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Evaluating disease progression and care provision in Spinal Muscular Atrophy

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Evaluating disease progression and care provision in Spinal Muscular Atrophy

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Per en Lluc, en Joan i … en Louie

.. per tot el temps robat

Declaration of authorship

To the best of the candidate's knowledge, this thesis contains no material previously published by another person, except where due acknowledgement has been made.

This thesis is the candidate's own work and contains no material which has been accepted for the award of any other degree or diploma in any institution.

Human Ethics: The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007). Specific ethics approvals were granted, as deemed necessary, by the human research and ethics committees of hospital clinics or centres assisting in recruitment and development of specific projects.

Mr. Robert Muní i Lofra Newcastle upon Tyne, 14th June 2022

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Finally, I would like to thank you … for being there, for your continuous support and for making me feel very lucky to have you as compagna di viaggio.

Abstract

Background: Spinal Muscular Atrophy is a group of rare genetic conditions characterised by progressive muscle wasting and weakness. SMA has a heterogenous clinical presentation ranging from severe infant onset to milder forms with childhood and adult onset. Disease progression has been described using multiple outcome measures, but some gaps and limitations have been identified.

The approval of new therapies over the last few years, has caused a paradigm shift in the way the disease is managed, and the potential implementation of Standards of Care revised in 2017

Aims: To explore patient's perspective on disease progression and access to Standards of Care, and to evaluate the capacity of specific items of the Revised Hammersmith Scale to quantify trunk involvement.

Methods: A combination of qualitative and quantitative methods were used to deliver three projects to achieve the three aims of the thesis. The first was based on a set of patient interviews to explore their life experiences. The second, is based on an online survey to evaluate experience of individuals with SMA regarding their care in the UK. The third, is an international multicentric collaboration to collect cross-sectional data on functional and respiratory data to explore the assessment of trunk involvement in SMA.

Results: Patient perspective about disease progression showed some relevant differences from the clinician's view. Access to Standards of Care appears to have significant limitations especially for certain professionals and in particular for the adult population. Capturing trunk involvement in SMA requires an integrated approach around motor performance, respiratory function, and spinal health.

Conclusions: Differences in patients' perspective on disease progression, in particular with the advent of novel therapies, and significant limitations in access to Standards of Care bring new challenges to the SMA community. Care also requires effective evaluation of all impacted body structures, and trunk involvement would benefit from further research to identify improved methods of assessment.

Foreword

The present thesis has been a significant achievement and personal journey that started when I was working as a physiotherapist in a domiciliary program for children with neuromuscular diseases. During those early stages of my career, I met for the first-time people living with Spinal Muscular Atrophy (SMA). Eva, Carla, Sandra, and Judit taught me so much about what appeared to me, to be a completely different way to approach life as they lived with SMA. Alongside these experiences, the more time I spent working with them, the more questions arose about what could be the best way to optimise their care. This was about our role as physiotherapists, and about how care was delivered and most importantly to me, what was the real impact on their disease progression.

The content of this thesis is a contribution to answering some of these questions. On one hand by contributing to a better understanding of how disease progresses over time, but also how can care provision, modify the natural course of the disease. This thesis includes several projects that aim to cover a variety of aspects of disease progression such as patient's perception about disease progression, access to Standards of Care (SoC) and development of new outcome measures to facilitate more informed clinical decisions.

La present tesi ha estat un èxit i un important viatge personal que va començar quan treballava com a fisioterapeuta en un programa domiciliari per a nens/es amb malalties neuromusculars. Durant aquelles primeres etapes de la meva carrera, vaig conèixer per primera vegada persones que vivien amb atròfia muscular espinal (SMA). L'Eva, la Carla, la Sandra i la Judit em van ensenyar molt sobre allò que em va semblar, que era una manera completament diferent d'abordar la vida com vivien amb SMA. Paral·lelament a aquestes experiències, com més temps passava treballant amb elles, més preguntes sorgien sobre quina podria ser la millor manera d'optimitzar la seva atenció. Eren al voltant del nostre rol com a fisioterapeutes, del model d'atenció que els donàvem i, el més important per a mi, de quin seria l'impacte real en la progressió de la seva malaltia.

El contingut d'aquesta tesi és una contribució per donar resposta a algunes d'aquestes preguntes. D'una banda, contribuint a una millor comprensió de com avança la malaltia al

llarg del temps, però també com pot el model d'atenció, modificar el curs natural de la malaltia. Aquesta tesi inclou diversos projectes que tenen com a objectiu cobrir diversos aspectes de la progressió de la malaltia, com ara la percepció del pacient sobre la progressió de la malaltia, l'accés a Standards of Care (SoC) i el desenvolupament de noves mesures de resultats per facilitar decisions clíniques més informades.

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List of abbreviations

10MWRT	Ten meters walk/run test
6MWT	Six minutes walking test
ACEND	Assessment of caregiver experience with neuromuscular disease
ACTIVE	Ability Captured Through Interactive Video Evaluation
ACTIVLIM	Active limb
ADLs	Activities of daily living
AFO	Ankle foot orthoses
ATEND	Adapted test of neuromuscular disorders
BMI	Body mass index
BPI	Brief Pain Inventory
BSID	Bayley Scales of Infant Development
BSITD III	Bayley Scales for Infant and Toddler Development, third edition
CAQDAS	Computer Assisted Qualitative Data Analysis Software
CHOP-INTEND	Children's hospital of Philadelphia Infant test of neuromuscular disorders
DMD	Duchenne Muscular Dystrophy
DMT	Disease modifying therapies
EK2	Egen Klassification 2
EQ-5D	Euro quality of life 5 dimensions
ES9HPT	Endurance shuttle 9-hole peg test
ESBBT	Endurance shuttle box and blocks
FEV1	Forced exhaled volume in one second
FIM	Functional Independency Measurement
FRV	Functional reaching volume
ppFRV	Percentage predicted Functional reaching volume
FSS	Fatigue Severity Scale
FVC	Forced vital capacity
GLI	Global Lung Initiative
GMFM	Gross Motor Function Measure
GOSH	Great Ormond Street Hospital
GRO	Neuromuscular Gross Motor Outcome
HFMS	Hammersmith functional motor scale
HINE-2	Hammersmith infant neurological examination 2
HMFSE	Hammersmith functional motor scale expanded
HRQoL	Health-related quality of life
HUI	Health utilities index
ICF	International Classification of Functioning, Disability and Health
iSMAC	International SMA Consortium

JWMDRC	John Walton Muscular Dystrophy Research Centre
KAFO	Knee ankle foot orthoses
MAA	Managed Access Agreements
MDUK	Muscular Dystrophy UK
MEP	Maximal expiratory pressure
MFM	Motor function measure
MIP	Maximal inspiratory pressure
MMT	Manual muscle testing
MRC	Medical Research Council
NIV	Non-invasive ventilation
NMD	Neuromuscular diseases
OMs	Outcome measures
PCF	Peak cough flow
PEDI-CAT	Pediatric evaluation of disability inventory computer adaptative test
PEDs QoL	Pediatric quality of life *Inventory*
PEG	Percutaneous Endoscope Gastrostomy
PRISM- SMA	Patient Reported Impact of Symptoms
PROMIS Fatigue SF	Patient reported outcomes measurement information system Fatigue short form
PROMs	Patient reported outcome measures
QoL-NMD	Quality of Life in Neuromuscular Diseases
RHS	Revised Hammersmith scale
RMI	Rivermead Mobility Index
ROM	Range of motion
RULM	Revised upper limb module
SD	Standard deviation
SF-36	Short form 36
SMA	Spinal muscular atrophy
SMA HI	Spinal muscular atrophy health index
SMAIS	Spinal muscular atrophy independence scale
SMAREACH UK	Spinal muscular atrophy research and clinical hub UK
SMN	Survival motor neuron
SNIP	Sniff nasal inspiratory pressure
SoC	Standards of care
TCT	Trunk control test
TFT	Timed function tests
TIMP	Test of infant motor performance
TIMPSI	Test of infant motor performance screening items
TLSO	Thoracic lumbar sacrum orthoses
TUG	Time up and go

UK	United Kingdom
ULM	Upper limb module
VAS	Visual analogue scale
WHO	World health organization
WHOQOL-BREF	World Health Organisation Quality of Life assessment
WPAI	Work productivity and activity impairment

List of authored publications and presentations

Publications

- Included in present thesis:
    - Muni-Lofra R, Murphy LB, Adcock K, Farrugia ME, Irwin J, Lilleker JB, et al. Real-World Data on Access to Standards of Care for People With Spinal Muscular Atrophy in the UK. Front Neurol. 2022;13(May)
- Related to SMA:
    - Wolfe A, Scoto M, Milev E, Muni Lofra R, Abbott L, Wake R, et al. Longitudinal changes in respiratory and upper limb function in a pediatric type III spinal muscular atrophy cohort after loss of ambulation. Muscle Nerve [Internet]. 2021 Nov 1 [cited 2022 Jan 18];64(5):545–51. Available from: https://pubmed.ncbi.nlm.nih.gov/34432301/
    - Trucco F, Ridout D, Scoto M, Coratti G, Main ML, Muni-Lofra R, et al. Respiratory trajectories in type 2 and non-ambulant 3 Spinal muscular atrophy in the iSMAC cohort study. Neurology [Internet]. 2020 Oct 16 [cited 2020 Oct 25];10.1212/WNL.0000000000011051. Available from: http://www.neurology.org/lookup/doi/10.1212/WNL.0000000000011051
    - Coratti G, Pera MC, Lucibello S, Montes J, Pasternak A, Mayhew A, et al. Age and baseline values predict 12 and 24-month functional changes in type 2 SMA. Neuromuscul Disord [Internet]. 2020 Jul 25 [cited 2020 Sep 14]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32900576
    - Coratti G, Messina S, Lucibello S, Pera MC, Montes J, Pasternak A, et al. Clinical Variability in Spinal Muscular Atrophy Type III. Ann Neurol [Internet]. 2020 [cited 2020 Oct 26]; Available from: https://pubmed.ncbi.nlm.nih.gov/32926458/
    - Pera MC, Coratti G, Mazzone ES, Montes J, Scoto M, De Sanctis R, et al. Revised Upper Limb Module for Spinal Muscular Atrophy: 12 month changes. Muscle Nerve [Internet]. 2019 Jan 24 [cited 2019 Feb 8]; Available from: http://doi.wiley.com/10.1002/mus.26419
    - Salazar R, Montes J, Young SD, McDermott MP, Martens W, Pasternak A, et al. Quantitative Evaluation of Lower Extremity Joint Contractures in Spinal Muscular Atrophy: Implications for Motor Function. Pediatr Phys Ther. 2018;30(3).

- Pera MC, Coratti G, Forcina N, Mazzone ES, Scoto M, Montes J, et al. Content validity and clinical meaningfulness of the HFMSE in spinal muscular atrophy. BMC Neurol [Internet]. 2017 Dec 23 [cited 2017 Feb 27];17(1):39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28231823

Conference poster presentations

- Presentation of preliminary results of Project C (Chapter 5)
  - R. Muni-Lofra, G. Coratti, D. Ramsey, F. Muntoni, E. Mercuri, A. Mayhew Trunk involvement in spinal muscular atrophy type 2 and 3, DOI: https://doi.org/10.1016/j.nmd.2020.08.096, volume 30, supplement 1, s73, October 01, 2020
- Presentation of preliminary results of Project A (Chapter 3)
  - R. Muni Lofra, M. Eagle, A. Fort, D. Ramsey, M. Scoto, F. Muntoni, K. Bushby, H. Lochmüller, V. Straub, A. Mayhew, Patient's perception around disease progression and influential factors in spinal muscle atrophy, DOI: https://doi.org/10.1016/j.nmd.2017.06.141, volume 27, supplement 2, s130, October 01, 2017

Invited lectures

- May 2022, *Rol del fisioterapeuta en malalties neuromsuculars (Physiotherapìst role in neuromusuclars diseases)*, Congrés internacional de fisioteràpia, Col·legi de fisioterapeutes de Catalunya, Barcelona
- April 2022, *Real-world data on access to Standard of Care for people with Spinal Muscular Atrophy in the UK*, Muscular Dystrophy UK Physiotherapy meeting, Birmingham, UK
- January 2022: *Current tools for assessment of muscle function in adults with SMA #254 Workshop* European Neuro Muscular Centre Workshop, Virtual Meeting.
- November 2021, *Orthopaedic management in SMA*, SMA Basecamp Neuromuscular Academy, Sheffiled, UK

- May 2021, *Rol del fisioterapeuta en assaigs clínics: experiència en pacients neuromsuculars* (*Physiotherapist role in clinical trials: experience with neuromsucular diseases)*, Jornada interhospitalària Societat Catalanobalear de Fisioteràpia, Barcelona
- December 2019, *UK network perspective,* International SMA Consortium Evaluator Meeting, Miami, Florida
- October 2019, *Motor development in SMA*, TreatNMD SMA Expert Masterclass, London, UK
- April 2019: *Escalas de valoración en DMD/AME (Outcome measures in DMD and SMA)*, XXIV Jornadas Sociedad Española de Rehabilitación Infantil, Valencia, Spain
- November 2018, *Overview of functional outcome measures in SMA*, TreatNMD masterclass, Rome, Italy
- June 2018, *Managing the neuromuscular disease foot and ankle*, Muscular Dystrophy UK Physiotherapy meeting, Birmingham, UK
- April 2018, *Quality of life scale in SMA: An update,* International SMA Consortium Evaluator Meeting, Orlando Florida.
- January 2018, *Overview of Clinical Functional Assessments for SMA patients*; *Considerations and Management of Adults SMA Patients*, SMA International meeting from Biogen, Krakow, Poland

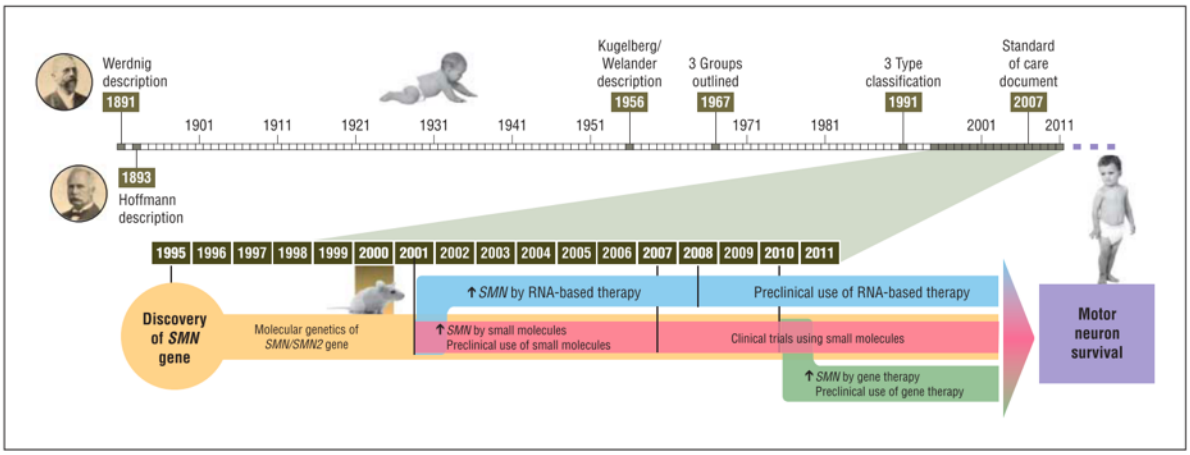
Chapter 1 Introduction

1.1 Spinal Muscular Atrophy

SMA refers to a group of genetic diseases that present with muscle atrophy and weakness primarily as a result of degeneration of the anterior horn cells. 95% of the cases are due to an homozygous deletion or mutation in the 5q13 survival motor neuron 1 (SMN1) gene (1) which is of autosomal recessive inheritance. The incidence of the condition is of 1:11000 live births and the prevalence of the carrier state is suggested to be around 1 in 54 (2).

The body of knowledge about SMA has evolved significantly over the years (see figure 1-1). The key milestones achieved were the early descriptions of cases by Werdnig (1891) and Hoffman (1893) and latterly by Kugelberg and Welander (1956) with what were thought to be different conditions (3). They were first considered to be all the same condition with a broad spectrum of clinical presentation by Dubowitz (4) and this was confirmed in one of the key moments of SMA history, with the discovery by Judith Melki's group of the disease causing gene in 1995 (5). After this, different therapeutic approaches were pursued aiming to increase the expression of SMN protein which has led to the current scenario (see section 1.4).

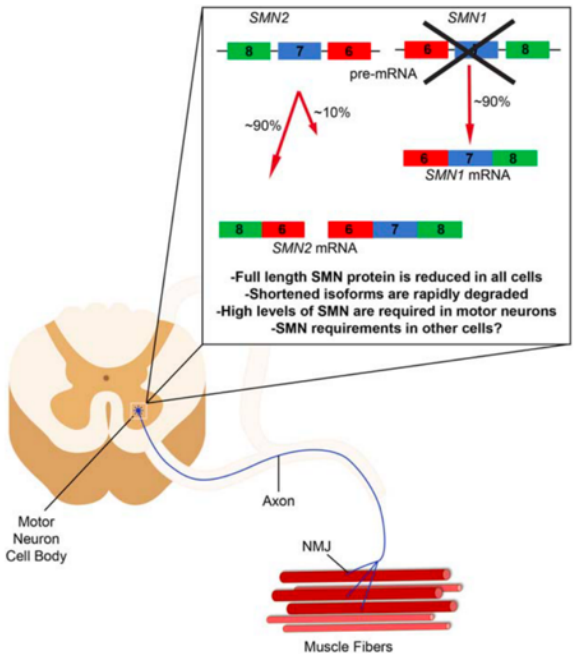
Figure 1-1 Timeline in SMA from Kolb et al 2011



In terms of clinical care, global experience and collaboration resulted in the Consensus statement document for SoC in SMA (6) first published in 2007. This document was then updated and extended with a more comprehensive version in 2017 (7,8).

One distinguishing aspect of SMA is the heterogenous clinical presentation. This was perhaps why it was so challenging initially to even reach the conclusion that the presenting phenotypes were the same condition, and later became key to delivering optimum care and developing suitable outcome measures (OMs) appropriate for different phenotypes. Disease severity is somewhat related to the proportion of SMN protein expressed (9). In humans, the expression of this protein is dependent on 2 forms of the SMN gene existing in each allele. A telomeric form (SMN1) and a centromeric form (SMN2) (see figure 1-2). Transcription of the SMN1 gene produces fully functional protein whilst the expression of SMN2 only produces around of 10% of fully functional protein. This is due to a substitution of a C to a T at position 840 that results in the exclusion of exon 7 during transcription (3).

Figure 1-2 SMN expression from Arnold et al 2011



(10)

All patients with SMA are missing the copy of SMN1 gene which makes them dependent on SMN2 gene function for the required SMN protein for survival. SMN protein

is known to have a role in RNA splicing but is also found in the axons of the motor neurons where it appears to have a crucial role not yet fully understood (3). This lack of protein leads to compromised growth and survival of motor neurons which is the reason for muscle weakness in people with SMA. The higher the number of copies of SMN2 that they have, the milder the phenotype they tend to present with, although there are exceptions and overlaps which are not yet fully understood (11).

With this diverse clinical presentation, one of the first challenges was to try to classify the disease continuum. This led to different opinions about the best way to classify a disease with the aim of better describing its different phenotypes and the variable prognosis. Some clinicians were in favour of maintaining a more descriptive subdivision (severe, intermediate and mild) based on clinical criteria such as motor function achieved whilst others preferred a numerical classification (1, 2 and 3) based on age of disease onset and age of death (12). Any classification encountered the limitation of how best to reflect the variability within the different subtypes. A proposed solution by Professor Victor Dubowitz was to use a decimal classification (type 1.1-1.9, type 2.1-2.9 and type 3.1-3.9) (13). The conclusion was a combination of the original two suggestions with 5 numerical types (0 to 4) with the addition of alphabetic subtypes (a, b, and c) based on a combination of highest motor milestone achieved and disease onset (see table 1-1)(10,11,14,15). Different types had been associated with a range of SMN2 copies (1,16) and estimated survival based on the so far known natural history data.

Table 1-1 SMA classification

Type	Onset	Highest function	Survival	SMN2 copies
0	Prenatal	Respiratory failure at birth	Weeks	1
1a	2 weeks	No head control ever achieved	< 1 year	1-3
1b	< 3 months	No ever to roll	< 1 year	1-3
1c	3-6 months	Unable to sit independently	Childhood	1-3
2a	>6 months	Able to sit	>25 years	3-4
2b	< 18 months	Able to stand or walk with support	>25 years	3-4
3a	< age 3	Able to walk	Adult	3-4
3b	> age 3	Able to walk	Adult	4
4	> age 30	Able to walk independently	Adult	4-8

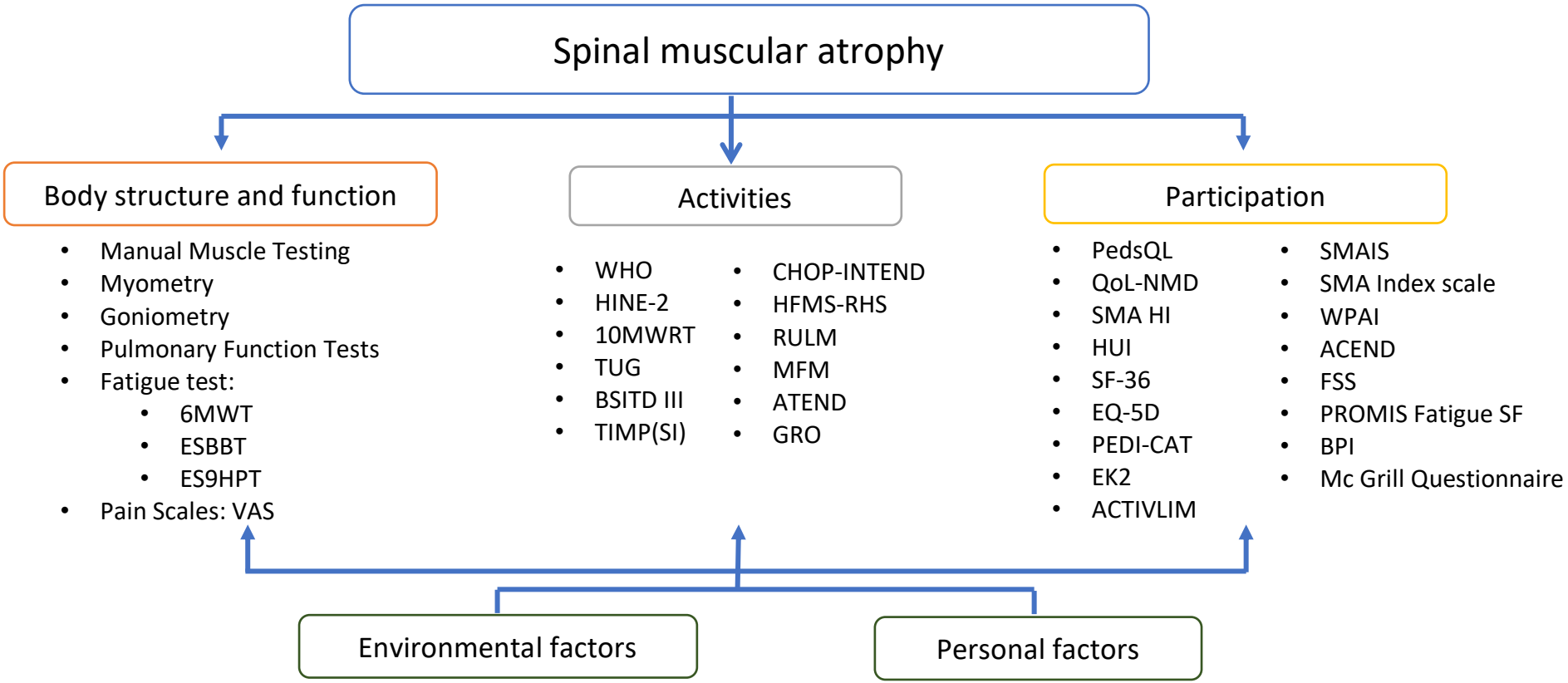
In clinical practise, subtypes are often limited to numerical categories (0-4) with limited exceptions being the use of subtypes which are mainly helpful to describe populations in natural history studies or clinical trials.

1.2 Current outcome measures for SMA

A review of the current OMs available for any condition requires set criteria for its classification to understand the scope and usage of each one of them. Here we use the International Classification of Functioning, Disability and Health (ICF) (17) as a framework.

The ICF describes 3 main domains: body part or function, activity, and participation. In addition, environmental and personal factors are also considered. The different outcome measures available for SMA will be referenced according to the three domains described above. A summary of the OMs discussed is presented in Figure 1-3.

Figure 1-3 Outcome measures in SMA according to ICF



ICF: International classification of functioning, 6MWT: 6 minutes walking test, ESBBT: Endurance shuttle box and blocks, ES9HPT: Endurance shuttle 9-hole peg test, VAS: Visual analog scale, WHO: World health organization, HINE-2: Hammersmith infant neurological examination 2, 10MWRT: 10 meters walk/run test, TUG: time up and go, BSITD III: Bayley Scales for Infant and Toddler Development, third edition, TIMP(SI): Test of infant motor performance screening items, CHOP-INTEND: Children's hospital of Philadelphia Infant test of neuromuscular disorders, HFMS-RHS: Hammersmith functional motor scale-Revised Hammersmith scale, RULM: Revised upper limb module, MFM: Motor function measure, ATEND: Adapted test of neuromuscular disorders, GRO: Neuromuscular Gross Motor Outcome, PEDs QoL: Pediatric quality of life Inventory,QoL-NMD: Quality of life in neuromuscular diseases, SMA HI: Spinal muscular atrophy health index, HUI: Health utilities index, SF-36: Short form 36, EQ-5D: Euro quality of life 5 dimensions, PEDI-CAT: Pediatric evaluation of disability inventory computer adaptative test, EK2: Egen Klassification 2, ACTIVLIM: Active limb, SMAIS: Spinal muscular atrophy independence scale, SMA Index scale: Spinal muscular atrophy index scale, WPAI: Work productivity and activity impairment, ACEND: Assessment of caregiver experience with neuromuscular disease, FSS: Fatigue severity scale, PROMIS Fatigue SF: Patient reported outcomes measurement information system Fatigue short form, BPI: Brief Pain Inventory

Outcome measures by body part and function

The use of an OMs aims to provide a precise and reliable evaluation of clinical data, which may be referenced against normative values and across individuals with the same condition. It is often difficult to find one aspect or scale that is a reliable reference for overall disease progression which limits their use for more general purposes (i.e., evaluation in drug trials). The result is that multiple measures are used in order to gain a better understanding of specific aspect of the condition which will help to explain potential variation in disease progression (18).

Manual muscle testing (MMT) or **myometry** are measures commonly used to assess muscle strength. MMT was developed by Lovett and described by Wright (19) in 1912. This has been reviewed and updated with different versions but the more commonly used, is the modified grading from the Medical Research Council (MRC) (20) which uses the score of 5 as a reference for "normal" strength. For myometry, there are specific publications with norm references values (21) which can be used to compare the most common muscle groups assessed. In the context of SMA, they have been both used to assess strength, in a qualitative or quantitative way, the current or progressive state of muscle weakness. More complex is to identify a suitable set of muscle groups that enable all individuals to be measured regardless of ability. MMT has mainly focused on higher functioning individuals (type IIIb) (22) or has assessed a very extensive number of muscle groups to describe the whole disease spectrum (23). The use of myometry follows the same pattern being either applied in isolation (24,25) or more commonly as a secondary endpoint in drug trials (26).

Contractures have been widely reported not only in SMA (27,28) but also in other neuromuscular diseases (29) and are a key part of disease management particularly in children (30–32). In this context, it is important to assess progression of range of motion with **goniometry** to track disease progression but also to measure the impact of interventions such as the use of orthotic devices. Despite being reported in different publications for this purpose (33,34), there is no standardised method to perform goniometry or to report the results (e.g. use of negative values to reflect presence of contractures). One of the most well defined and used in SMA publications is the one

proposed by Norkin (35), The Neutral Zero Method (36). Similar to myometry, there are published normative reference values by age groups for the main joints (21).

Respiratory involvement is one of the key features of SMA and consequently, the evaluation of respiratory function is one of the pillars of regular follow up. Standard **spirometry** techniques such as **forced vital capacity (FVC)** or sometimes **forced exhaled volume in one second (FEV_1)** are considered the gold standard to describe respiratory involvement (37–40). In more comprehensive studies, FVC and FEV1 have been conducted in combination with strength parameters such as **maximal expiratory pressure (MEP)** and **maximal inspiratory pressure (MIP)** (41) or **sniff nasal inspiratory pressure (SNIP)** (42). In addition, **peak cough flow (PCF)** has also been used particularly when evaluating effective cough and identifying the need for interventions to improve airway clearance (43,44). Respiratory parameters have also been used to assess the impact of scoliosis, spinal surgery (45) or bracing for spinal management (46,47). One of the main limitations of the respiratory tests is that their volitional nature is particularly challenging when looking at younger individuals and those with a more severe phenotype. For this purpose, exploratory outcome had been developed over the last few years aiming to better understand respiratory involvement in SMA type I (48). Normative values for lung function are well established and several versions have been used over the years but the most updated version is the Global Lung Initiative (GLI) (49). This has provided a list of reference values based on age and height (50) which is used to interpret the results of the different tests.

Fatigue is another clinical feature reported in individuals with SMA (51–53) despite the difficulties encountered to objectively assess it (54). The first important distinction is to separate *physiological fatigue* (decrease in level of performance over time in a prolonged activity) and *perceived fatigue*, which is a subjective measure that will be discussed with OMs by participation. There is also a third component, linked with physiological fatigue, which is *cognitive fatigability* which is measured by quantifying the decline in the capacity to process and maintain attention over a sustained complex information task (55). This will not be covered in the present review due to the lack of literature specific to SMA. In recent years however, different studies have determined the impact of physiological fatigue. For ambulant patients, the outcome measure used has been the 6 minutes walking test

(6MWT). Originally created to assess individuals with respiratory conditions (56) it has evolved from its original format of twelve minutes to six minutes as a "sensible" compromise between the twelve and two minutes versions proposed (57). Its validity, reliability and responsiveness was tested originally again in respiratory conditions (58,59) and later in SMA (60). It has also been used to objectively evaluate reduction in gait velocity as evidence of the impact of fatigue-related changes (61) and to identify individuals with SMA who have concurrent neuromuscular junction dysfunction (62). For non-ambulant patients, recent studies from a group in the Netherlands proposed the use of the nine-hole peg test (9HPT) as a repetitive task to identify fatigability in arm function (63). This was the proof of concept to then develop a set of endurance tests adapting the Endurance Shuttle Walk test (55). The results are the Endurance shuttle **Box and Block test (ESBBT)** and the **Endurance shuttle 9HPT (ES9HPT)** for proximal and distal arm function which have shown their validity and reliability to assess both ambulant and non-ambulant individuals (64).

Pain is another feature of SMA and has been described as significant in frequency and severity across many neuromuscular diseases (65,66). In SMA, it has been reported that the prevalence of pain is significantly lower for adults with SMA than in other neuromuscular conditions(65). However, hip pain has been identified as a significant feature in SMA (67). Objective OMs to assess pain are not available so here will be reported subjective OMs that aim to quantify it. The more commonly used scales used to describe pain intensity are Likert or numeric rating scales: **visual analogue scale (VAS)** or **faces pain scale** for pediatric patients. Reference cut-off points for VAS were suggested (68) based on criteria from Hirschfeld and Zerinkow (69) as follow: VAS ratings of 0 to 34 indicate mild pain, ratings between 35 and 59 indicate moderate pain and ratings of 60 or more indicate severe pain. Pain has also been assessed based on patient experience which will be reviewed later in this section when looking at OMs for participation.

Table 1-2 Summary of Outcome measures by body part and function

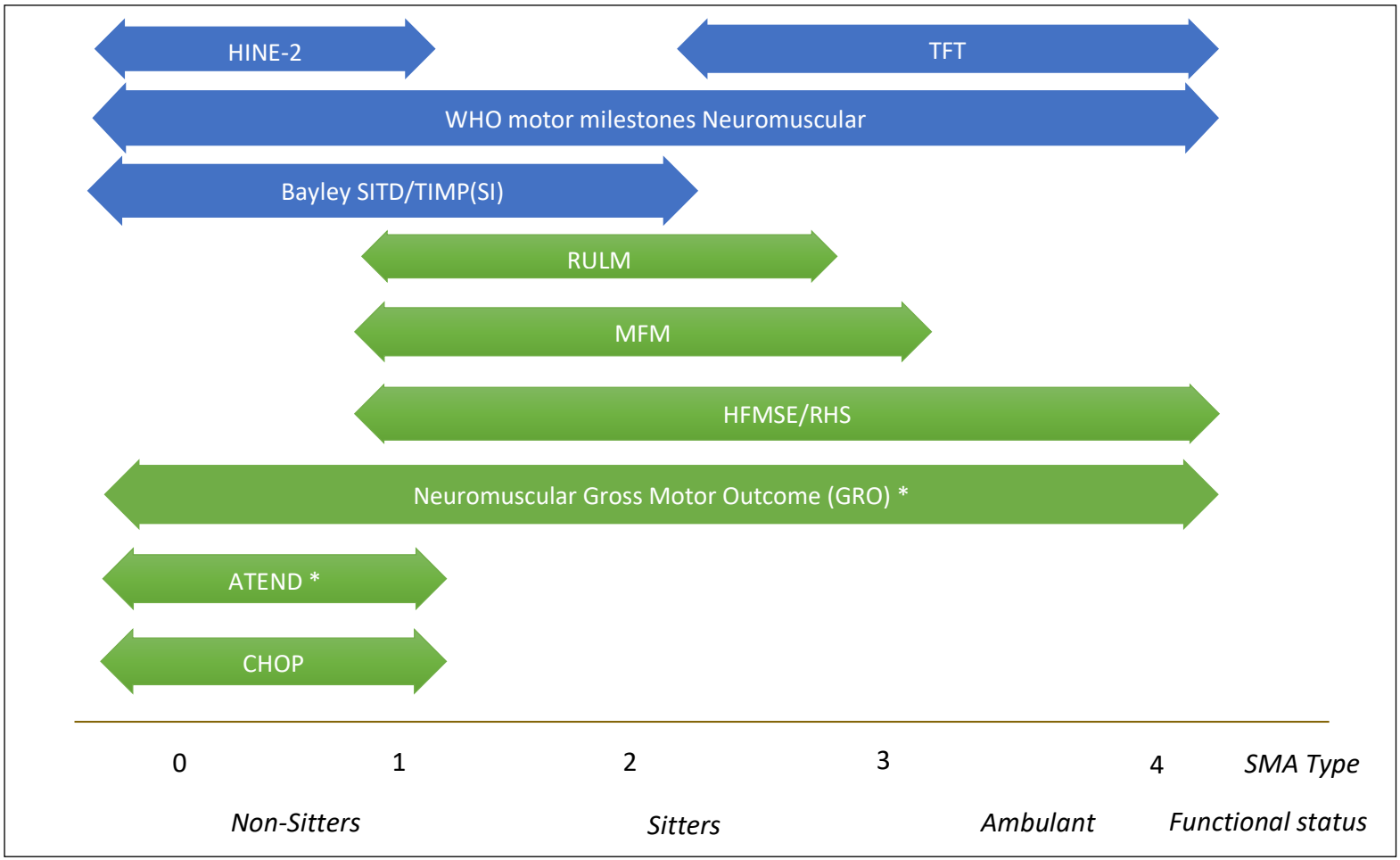
OMs	Scope of the assessment	SMA type/ functional status	Age range	Key related publications	
				Assessment	Use in SMA
Manual muscle testing	Strength testing	Nonspecific	To check	(19,20)	(22,23)
Myometry	Strength testing	Nonspecific	Above age 3	(21)	(24,25)
Goniometry	Range of motion	Nonspecific	All	(35,36)	(33,34)
Spirometry	Respiratory function	Nonspecific	Above age 3	(49,50)	(37–40)
Fatigue Scale	Physiological fatigue	Nonspecific	All	(55,56,63)	(60–62,64)
Pain scale	Pain intensity	Nonspecific	All	(68,69)	-

Outcome measures by activities

The use of OMs to assess activities, also named as functional OMs, have commonly been used to describe natural history of the disease and also more recently the impact of treatments. The challenge has been to find the right balance between suitability across a heterogenous phenotype and sufficient sensitivity to change for the individual. The result is a diverse set of different OMs that have been developed for slightly different purposes.

For this review, we will classify them in generic measures, referring to those develop to assess the general population and disease specific, for those that were developed specifically for SMA or neuromuscular diseases (NMD) with a similar phenotype. Here is a summary figure with the functional OMs presented (Figure 1-4).

Figure 1-4 Summary of functional outcome measures



Generic measures (blue), Disease specific measures (green), *under development

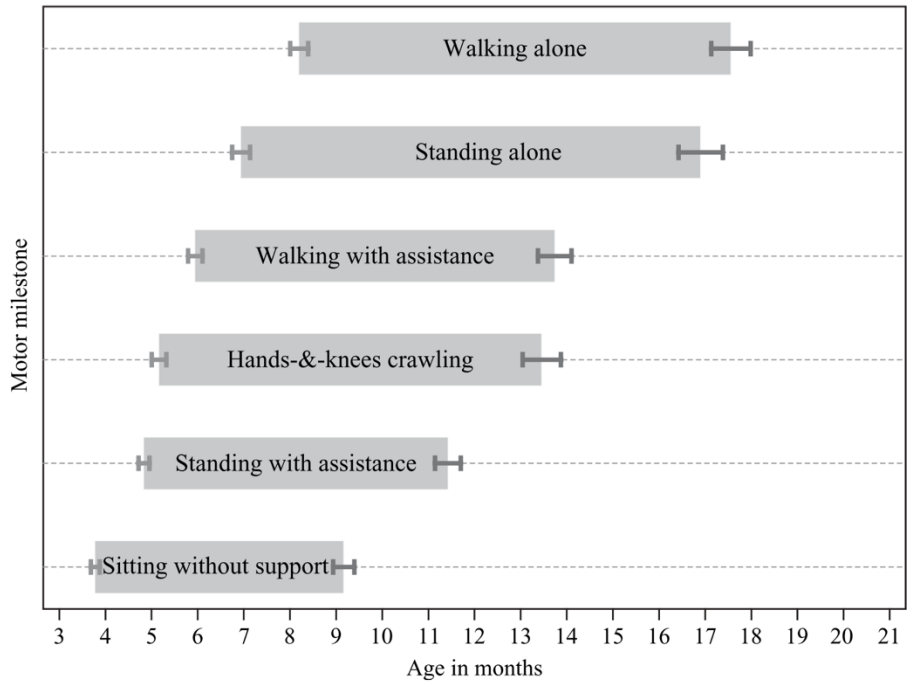
HINE-2: Hammersmith infant neurological examination 2, TFT: Timed functional tests, WHO motor milestones: World health organization motor milestones, BSITD III: Bayley Scales for Infant and Toddler Development, third edition, TIMP(SI): Test of infant motor performance screening items, RULM: Revised upper limb module, MFM: Motor function measure, HFMS-RHS: Hammersmith functional motor scale-Revised Hammersmith scale, GRO: Neuromuscular Gross Motor Outcome, ATEND: Adapted test of neuromuscular disorders, CHOP-INTEND: Children's hospital of Philadelphia Infant test of neuromuscular disorders

Generic measures

The role of generic measures is to be able to compare populations or individuals against general populations and for this reason some of them have normative values per age or for specific population subgroups. They are designed to be used across different subgroups of individuals and they tend to have common domains relevant to almost all individuals. Listed here are some of the generic outcome measure used in SMA for the purpose of this review but, by nature, many other could be used for the same purpose with different specifications.

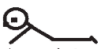
The **World Health Organisation (WHO) Motor Development Study** (70) provided definitions and normative windows of achievement for six gross motor milestones (sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone and walking alone). The achievement of the mentioned motor milestones is expected to happen within the first 18 months from birth but in the SMA context has been used primarily to define clinically SMA type (71) or to classify cohorts mainly in the context of clinical trials (72,73)(Figure 1-5).

Figure 1-5 WHO windows of milestones achievement from WHO study group



Another generic outcome measure used in SMA is the **Hammersmith Infant Neurological Examination (HINE)** (74). The HINE was designed to assess full-term and preterm infants and consist of 3 sections: Neurological examination, Developmental milestones, and Behaviour. It was developed to assess infants from 2 to 24 months and was validated in full-term and pre-term children (75). The use of the HINE has been mainly limited to Section 2 (Figure 1-6) that refers to motor milestones, and in a similar way to the WHO has helped to describe cohorts of patients but also to assess disease progression particularly in the more severe phenotypes such as Type 1 SMA (76). This has been used for natural history studies to confirm the absence of now motor milestones but also to measure the effect of treatments (77).

Figure 1-6 HINE-2 development milestones from Haataja et al.

Column	1	2	3	4	5	6
Head control	unable to mantain head upright (normal < 3 mo)	wobbles (normal at 4 mo)	all the time mantained upright (normal at 5 mo)			Observed: Reported (age):
12 m (%)			100			
18 m (%)			100			
Sitting	Cannot sit	With support  (normal at 4 mo)	Props  (normal at 6 mo)	Stable sit  (normal at 7 mo)	Pivots  (normal at 10 mo)	Observed: Reported (age):
12 m (%)				1	99	
18 m (%)					100	
Voluntary grasp	no grasp	uses whole hand	index finger and thumb but immature grasp	pincer grasp		Observed: Reported (age):
12 m (%)			3	97		
18 m (%)			2	98		
Ability to kick: (in supine)	no kicking	horizontally legs do not lift	upward (vertically)  (normal at 3 mo)	touches leg  (normal at 4-5 mo)	touches toes  (normal at 5-6 mo)	Observed: Reported (age):
12 m (%)					100	
18 m (%)					100	
Rolling	no rolling	rolling to side (normal at 4 mo)	prone to supine or supine to prone (normal at 6 mo)	supine to prone and prone to supine (normal at 7 mo)		Observed: Reported (age):
12 m (%)		1	1	98		
18 m (%)				100		
Crawling	Does not lift head	On elbow  (normal at 3 mo)	On outstretched hand  (normal at 4-5 mo)	Crawling flat on abdomen  (normal at 8 mo)	Crawling on hands and knees  (normal at 10 mo)	Observed: Reported (age):
			2	4	94	
					100	
Standing	Does not support weight	Supports weight (normal at 4-5 mo)	Stands with support (normal at 8 mo)	Stands unaided (normal at 12 mo)		Observed: Reported (age):
12 m (%)		3	18	79		
18 m (%)			2	98		
Walking		Bouncing (normal at 6 mo)	Cruising (walks holding on) (normal at 11 mo)	Walking (normal at 15 mo)		Observed: Reported (age):
12 m (%)		4	45	51		
18 m (%)			2	98		

The use of **timed function tests (TFT)** has been mainly as specific items included in other more comprehensive assessments (i.e., Time to rise from supine as part of RHS). However, there are a few specific publications. These are the Timed Up and Go test (TUG) and the 10 meters walk/run test (10MWR). TUG was originally use to test balance and functional mobility in elderly people (78,79) and has been used in ambulant SMA showing good correlation with strength (MMT) and functional assessments (80). A more recent publication looked at longitudinal natural history data for the 10MWR (81). The finding of this study describes a trajectory for this test in SMA population with a window between 3 to 8 years of age where the speed improves, becoming stable between 9 to 10 years of age and then progressive decline. Despite the availability of normative values for many functional tests (82,83), there have not been to date any comparative studies.

Finally, there are several currently available scales and tests with slightly different specifications that mainly assess motor development in children. The Bayley Scales of Infant Development (BSID) and the Test of Infant Motor Performance Screening Items (TIMPSI) are examples which have been used in SMA. Others such as the Peabody Developmental Motor Scales-2, Harris Infant Neuromotor Test, Alberta Infant Motor Scale or Gross Motor Function Measure amongst others, have also been used for the same purposes but less frequently. The BSID III concept was to "identify children with developmental delay and to provide information for intervention planning" (84) in an age range from 1 to 24 months. The **Bayley Scales for Infant and Toddler Development, third edition (BSITD III)** (85) implemented substantial changes from the first and second previous versions including new items, and creation of five distinct scales Cognitive (91 items), Language (97 items), and Motor scales (138 items), and caregiver ratings of Social-Emotional (35 items) and Adaptive Behaviour (241 items). The scale also provides normative data that has been validated in many different populations to minimise the limitations of cross-cultural differences (85). Despite these efforts, its capacity to detect potential developmental delays with its current criteria has been criticised and it has been suggested that normative data should be reviewed (86). In the context of SMA, the motor section of the BSITD III has been used to validate some of the new OMs for neuromuscular diseases such as the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP Intend) (87). It has also been used in clinical

trials (88,89) in combination with other disease specific OMs. The possibility of a positive impact of a new drug could potentially result in participants reaching a ceiling effect in disease specific outcomes designed for use in natural history studies or asymptomatic patients. The **Test of Infant Motor Performance (TIMP)** was designed in a similar way to BSITD III aiming to assess infants' development and detect potential developmental delays. In this case, mainly motor development with a combination of spontaneous observations and elicited motor behaviours (90) which was then used to create standard reference values to identify infants at risk of motor delay (91). Within this same aim, but as a screening tool the **TIMP Screening Items (TIMPSI)** was developed based on extensive psychometrics including Rasch analysis. The concept is that by using a reduced number of items, it may be possible to predict the outcome of the compete test (92). The TIMP (93) and the TIMPSI (94) have also been validated for its use in SMA I showing a good fit for severe disease phenotype (95).

Disease specific measures

Disease specific OMs, which are designed to capture disease progression mainly focus on muscle weakness in the upper and lower extremities and the trunk. Due to the significant variation in disease severity, it is quite challenging to find a scale with clinically meaningful sensitivity that is applicable across the different phenotypes.

Starting from the more severe phenotype and younger individuals, the **Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP Intend)** was designed to assess weak infants with NMD (87) and was validated to assess SMA I infants from 1.4 to 37.9 months without showing either ceiling or floor effect (96). Longitudinal data confirmed its applicability to assess disease progression in natural history studies for the severe end of the spectrum of the disease (97,98). The CHOP Intend has also been key in assessing the effectiveness of drug treatments over the last few years showing evidence of improvement in many (88,89,99). The main limitation of this scale is the age and size of the subject to evaluate. The scale consists of sixteen items assessed bilaterally that score quality of movement by segments in different positions. These include supine and semi-reclined position but also ventral and vertical suspension. As babies grow or become more able,

items can be impossible to perform and/or score. This compromises its applicability in older children but also adults.

The **Hammersmith functional motor scale (HFMS)** is discussed here alongside its adapted or different versions. The HFMS was originally developed based on clinical observations aiming to assess SMA II and III through 20 activities (100). The scoring system consisted of a three-point grading: 2 for when the activity was completed unaided, 1 when assistance is required or there are compensations and 0 when unable. The focus was mainly for those with limited ambulation (101) and an updated version was published to try to standardize and clarify operational and scoring criteria for its use in clinical trial settings (102). A third version was published soon after introducing modified items from the Gross Motor Function Measure (GMFM) aiming to target higher functioning individuals and resolve the ceiling effect that some ambulant patients presented with in previous versions of the scale (103). The **Hammersmith functional motor scale expanded (HFMSE)** scale was validated in SMA II and III showing significant associations with other measures of function and strength (GMFM, myometry) but was also able to discriminate patients based on their functional level, diagnosis and use of ventilation (104). This confirmed the HFMSE as one of the most consistently used scales to assess disease progression (23,105–108) but also effect of experimental drugs in clinical trials (109–111). The most updated version of the scale is the **Revised Hammersmith Scale (RHS)** which has been developed to improve its psychometric properties through Rasch analysis and suggestions from an international expert panel (112). The result is a more clinically robust scale to assess weak SMA II individuals as well as highly functional ambulant patients. The Hammersmith Scale with its different versions is a good example of how developing a consistent and clinically meaningful tool requires several steps and procedures. The resulting scales assess SMA II and III well, but it is not suitable for very weak individuals who cannot sit.

One effort to evaluate weaker SMA II was to focus on upper limb function as a potential way to assess disease progression. This was the aim of the **Upper Limb Module (ULM).** An initial set of 20 items mimicking activities of daily life with a three-point score system similar to the HFMS was suggested by a group of experts. Throughout the process several items were discarded to minimise variability in its use (i.e., putting a t-shirt on) or

minimise the impact on scoring of maturational status of the individual (i.e., using scissors). The finally suggested 9 item version required of a small set of equipment (pencil, coins, plastic cup, lamp, can and weights) and was used to assess people with SMA ranging from age 30 months to 27 years (113). Later, an updated version was published aiming to improve its consistency and validity for its use in clinical trials and to assess those with better arm function. The **Revised Upper Limb Module (RULM)** was piloted in a multicentre study (Rome, London, Newcastle), and using modern psychometric analysis demonstrated generally good item fit and improved targeting of patients when compared to its previous version (114). The RULM has also been used effectively to assess disease progression and together with the HFMS had been important in describing the functional trajectories in sitters and walkers (39,115,116) but also the benefits of disease modifying treatments (109,110,117).

In parallel to all these scales the **Motor Function Measure (MFM)** has also been used in specific studies for SMA. The scale was designed to assess a range of neuromuscular diseases and is composed of three dimensions (standing position and transfers, axial and proximal motor function and distal motor function) (118). An original set of 75 items was suggested based on previous scales (GMFM) and the experience of physiotherapists and clinicians. This was reduced to 32 items based on the feedback received after piloting it in forty-seven centres. The scale has a 4-point Linkert scale scoring system: 0, does not initiate movement or starting position cannot be maintained; 1, partially completes the exercise; 2, completes the exercise with compensations, slowness, or obvious clumsiness; 3, completes the exercise with a standard pattern. The scale was later validated in SMA II and III (119) and since then has been used in natural history studies (120,121) but also in a clinical trial setting (122). Additional work has also been done to correlate specific items of the scale with activities of daily living (ADLs) (123) and to determine the threshold considered meaningful for patients and caregivers (124). The scale has however shown some validity issues in SMA when compared to other scales and it was suggested additional items were required to address the floor effect in more severely affected SMA II (95).

As mentioned at the beginning of this section, the available OMs propose a diverse set of options in an attempt to cover the disease spectrum, but some gaps and discontinuities

have been identified (95). The main measurement gap identified is for older children and adults that present with a more severe phenotype and are unable to sit independently. This group of patients has shown a floor effect for HMFSE and MFM (14,115) which limits the capacity to assess disease progression to the RULM that only focuses on upper limb function. This has been perceived as a significant limitation in the current climate where new treatments have been introduced (see section 1.4). In particular due to the increased life expectancy of infants with severe forms of SMA but also to assess the impact of pharmaceutical interventions in older patients with access to treatment. To fill this gap, there is an ongoing project to develop a wheelchair based assessment called **Adapted Test of Neuromuscular Disorders (ATEND)** (125). The first step involved adapting items of the CHOP Intend to determine which items were feasible and appropriate to use in older individuals. Additional items from scales such as the RHS, RULM, MFM and Egen Klassification (EK) were included to mimic the construct of those items discarded from the CHOP Intend. The result is a 14-item scale which evaluates strength and function of the neck and trunk as well as distal strength of upper and lower limbs. Further validation and longitudinal studies are required to assess its potential use in this population.

Another potential way forward is the development of an assessment to use across the whole disease phenotype which has many advantages when comparing different populations. The team in Columbus, Ohio has led a recent initiative that goes in this direction. The **Neuromuscular Gross Motor Outcome (GRO)** aims to assess people living with SMA across all phenotypes (126). It is a 50-item assessment scored with a Likert scale ranging from 0 to 2. A score of 0 points indicates inability to perform the task, 1 point partially completes the task, and 2 completes the task with no compensations. The list of items covers activity in supine, in early supported sitting to standing and walking activities. Some additional items address wheelchair use aiming to cover more limited mobility in older patients. So far, the scale has only been used in a cohort of patients ranging from 8 days of life to 32 years and was reported to show no floor or ceiling effect. The scale was validated initially against CHOP, HFMSE, RHS and BSID III showing good correlation for the subjects eligible for each pf the mentioned scales. The scale showed promising results but

could benefit from being tested in bigger cohort and modern psychometric analysis as acknowledged by the authors.

Table 1-3 Summary of outcome measures by activities

OMs	Scope of the assessment	SMA type/ functional status	Age range	Key related publications	
				Assessment	Use in SMA
WHO Motor milestones	Achievement of 6 main gross motor milestones	All	0-18 months	(70)	(71–73)
Hammersmith Infant Neurological Examination (HINE)	Achievement of motor milestones	All	2-24 months	(75)	(76,77)
Time functional test (TFT)	Time of performance of specific tasks	Ambulant	Above age 3 years	(78,79,82,83)	(80,81)
Bayley Scales for Infant and Toddler Development, third edition (BSITD III)	Identify children with developmental delay and to provide information for intervention planning	All	1-24 months	(84,85)	(87–89)
Test of Infant Motor Performance (TIMP)/ TIMP Screening Items (TIMPSI)	Assess infant motor development and potential delays	All	1-5 months	(90–92)	(93–95)
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP Intend)	Assess motor function in weak infants with neuromuscular diseases	Non-sitters	1.4-37.9 months	(87)	(88,89,96–99)
Hammersmith functional motor scale (HFMS) to Revised Hammersmith Scale (RHS)	Assessment of motor function of SMA	Sitters and walkers	Above age 1 year 4 months	(100,104,112)	(23,105–111)
Upper Limb Module (ULM)/ Revised Upper Limb Module (RULM)	Assess upper limb function in SMA	All	Above 30 months	(113,114)	(39,109,110,115–117)
Motor Function Measure (MFM)	Assess motor function in neuromuscular diseases	Sitters and walkers	Above age 2 years	(118,122–124)	(119–122)
Adapted Test of Neuromuscular Disorders (ATEND)	Wheelchair based assessment of motor function in SMA	Non-sitters	All	(125)	-
Neuromuscular Gross Motor Outcome (GRO)	Assessment of motor function in SMA	All	Above age 8 days	(126)	-

Outcome measures by participation

OMs related to participation have been primarily used to assess perception of health-related quality of life (HRQoL), ability to perform daily life activities and caregiver burden but also specific aspects related to participation such as perceived fatigue or pain. The nature of these OMs is that they are mainly reported by people living with SMA or their carers, so for this reason they are often covered under the umbrella of patient reported outcome measures (PROMs). In a similar way to functional outcome measures, there is a co-existence of generic and disease specific PROMs but a much more limited range of validated PROMS. In a recent publication, a critical review of these OMs was published (127) which will be used for reference in this section but also additional OMs related to perceived fatigue will be added. It is also true that this field is experiencing an increasing interest with the appearance of DMT and the need to measure potential gains. For this reason, this review is likely to evolve rapidly with new OMs or additional versions or validation of existing ones.

It is important to remember that HRQoL is a multidimensional construct, consisting at least of physical, psychological (emotional and cognitive), and social health dimensions. This multidimensional construct implies that the range of potential scales or questionnaire that could be used is significant. In the mentioned review, Messina et al (127) selected up to eleven OMs but only two were reported to have been evaluated using modern psychometric analysis. The **Pediatric Quality of Life Inventory (PedsQL)** was designed to assess the common aspects related to HRQoL in a module approach with a 15-item core measure of global HRQoL and eight supplemental modules to assess specific symptoms or treatment domains (128). The PedsQL Generic Core Scales was specifically designed for both healthy and patient populations from age 2 to 18 years (129). It can either be self-reported by patients (age 5 to 18 years) or reported by caregivers (age 2 to 18 years) and has several items related to physical, emotional, social, and school functioning that patients or the caregiver score. The aim is to report how much each item has been a problem in a 5-point response scale with a simplified 3-point for younger children (5 to 7 years) with a “face scale” reference for each score. It was originally developed with cancer patients as a model but has been expanded with specific modules for other common diseases such as cerebral

palsy (130), diabetes (131), rheumatology (132) or asthma (133). In 2009 a module for neuromuscular diseases with SMA in the focus was validated (134). The PedsQL 3.0 Neuromuscular Module has since then been used in a number of clinical trials (135) but also to assess cohorts of patients with SMA (136–138).

The **Quality of Life in Neuromuscular Diseases (QoL–NMD)** (139) a questionnaire for adult patients with neuromuscular conditions. It is an evolution of the World Health Organisation Quality of Life assessment (WHOQOL-BREF)(140), after piloting it with 159 patients with neuromuscular conditions. The result is a selection of items, two general ones and 24 grouped in 3 domains: Impact of physical symptoms, self-perception and activities and social participation. The QoL-NMD showed adequate concurrent validity when compared to the WHOQOL-BREF when tested in a number of different neuromuscular condition including SMA (141). It is a practical and "clinically friendly" questionnaire due to the limited time required to be completed but still presents a major limitation as it has only been used in adults.

In addition, the **SMA Health Index (SMA HI)** since has been specifically designed for SMA. The SMA-HI was constructed based on the results of the PRISM- SMA (Patient Reported Impact of Symptoms) study (142). The PRISM-SMA is cross-sectional study aiming to understand the relative importance of the different symptoms experienced by adult people living with SMA. The study was performed through an international patient registry and 359 participants were recruited. An in-depth analysis of the most relevant symptoms reported led to the SMA-HI. The scale was later tested and confirmed to be valid, reliable, and relevant to assess people living with SMA. The process was done with semi-structured qualitative interviews and proved to be applicable not only for adults but also for older children and teenagers (8-15 years) (143).

Finally, the **Health Utilities Index (HUI)** has also been used in SMA although not yet fully validated. The HUI is composed of 3 stand-alone measurement systems named Mark 1, 2 and 3 respectively (144). HUI1 was designed to assess very-low birth-weight infants and is used infrequently. HUI2 aimed to assess global morbidity burden of childhood with cancer and covers seven aspects of QoL: vision, hearing, speech, mobility, emotion, cognition, self-care, pain, and fertility. HUI3 was developed to address some of the definition issues

encountered with HUI2 and to be used both in clinical settings and in general population studies (145). The HUI3 covers aspects of QoL with several of them overlapping with HUI2: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. HUI scores range from -0.36 which is associated with the worse possible health to 1.00 being perfect health, passing by 0.00 which is death. The assessment also provides categorical scores which are identified as a mild disability (ranging from 0.89 to 0.99), moderate disability (0.70 to 0.88) and severe disability (>0.70). The scale has been used for DMD (146,147)and SMA (148). In the context of SMA it only reported the results related to HUI3 which was considered by the authors as the most relevant system for the condition. The results showed good correlation with functional status and SMA type. For all participants, including SMA III who were able to walk independently at the time of the assessment, scores indicated severe disability levels (below 0.70). When looking at specific aspects, statistically significant differences were observed for speech by SMA type (Type I: 0.51, Type II 0.95 and Type III 0.99). The authors reported many positives in the use of the HUI in assessing disease progression or potential impact of treatment, however a significant limitation was identified as the HUI3 might not be able to capture subtle changes in motor ability.

It is not uncommon that PROMs aim to cover a combination of different aspects within the participation dimension. Two PROMs that fall under this category that have also been used in in clinical trials for SMA. In both cases they collect information about HRQoL and ADLs. The **Medical Outcomes Study 36-items short-form** (**SF-36)** was designed to be used in clinical practise and research to evaluate general populations (149). It is composed of a multi-item scale that assess eight health concepts: limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities because of emotional problems, vitality (energy and fatigue), and general health perceptions. Since its creation, it has become one of the most commonly used PROMs to report in overall HRQoL in neuromuscular patients (65,66,150) but also to assess impact of specific interventions such spinal surgery (151) or respiratory support (152). There are also a number of publications where the SF-36 has been used to describe SMA (153,154).

The second questionnaire that combined HRQoL and ADLs items is the **EuroQoL EQ-5D**. The EQ-5D is a generic measure of health status created by the international research EuroQol Group (155). This initiative started in 1987 with the aim to develop standardized, non-disease specific instruments to describe and quantify HRQoL. The EQ-5D concept was to be a simple descriptive index value to be used in clinical and in health-economics evaluation of health care and population health status. The assessment has two parts: firstly, the user self-classifies his/her health related to 5 domains (Mobility, Self-Care, Usual activities, Pain/discomfort, and Anxiety/depression) and secondly a visual analogue scale (VAS) score to reflect the overall impression of one's own health status. The initial version EQ-5D-3L, had 3 descriptors for each domain and on 2010, a new version was created with 5 descriptors (EQ-5D-5L9 to increase its sensitivity (156). Its simplicity and generic design has made it a good classifier of HRQoL used in many occasions to describe general population or cohorts of patients including neuromuscular patients (150). It has also been used in the context of clinical trial but its sensitivity to change appears to be limited although this has not been tested to date.

Messina et al identified up to five PROMs designed to assess ADLs that have been used at some point for SMA. This figure falls o only three when examining those that have been tested with modern psychometrics. We will however present the SMA Independence Scale which has been also developed specifically for SMA by one of the pharmaceutical companies after the review by Messina et al was published.

Firstly, the **Pediatric Evaluation of Disability Inventory Computer Adaptative Test (PEDI-CAT)** (157). As described in its name, it was conceived to assess a pediatric population with a variety of cognitive, motor, and behavioural difficulties and relies on caregiver reported information. The actual PEDI-CAT is an expanded version (276 items) of the original PEDI (197 items) and evaluates aspects such mobility, daily activities, social/cognition, and responsibility. It is intended to cover an age range from 1 to 21 years old. Another addition of the computerised version is that it contains item maps to reduce the number of items suggested for the subject assessed, based on relevance. The scale provides age percentiles and T-scores for 21 age groups which allow a comparison of individuals assessed with normative score from a range of healthy and individuals with disability (158). In the context

of SMA, the scale was evaluated using Rasch analysis process concluding that some additional items were required to detect small changes in order to increase its sensitivity in particular for mobility skills in types I and III (159) but at the same time the scale showed good capacity to detect limitations in the mobility and daily activity performance (160).

The second PROM suggested is the **Egen Klassification (EK)** that was originally designed to capture an overall picture of "own functioning" in non-ambulant individuals affected by Duchenne Muscular Dystrophy (DMD) or SMA (161). It was initially composed of 10 items: ability to use wheelchair, ability to transfer from wheelchair, ability to stand, ability to balance in a wheelchair, ability to move arms, ability to use hands and arms for eating, ability to turn in bed, ability to cough, ability to speak and physical well-being. This initial data set has 4 categories each for score ranging from 0 to 3 being a higher score and indicator of higher degree of disability. It was validated for both conditions, DMD and SMA, against muscle strength parameters, severity of contractures, respiratory involvement and years of wheelchair dependence as previously described as indicator factors of disease severity (161). All categories prove to be valid and relevant to discriminate between levels of functional performance in both cohorts of patients (160). Seven years later a second version was published (EK2) with the purpose of increasing the domains captured by the scale to better describe disease progression in the non-ambulant stages of the conditions (162). A group of 10 experts suggested up to 10 new items that were piloted in a cohort of SMA patients from Denmark, Italy, and the United Kingdom (UK). 7 were finally included after the pilot study that made the EK2 more comprehensive by including aspects such as head control, fatigue, hand function and different parameters related to bulbar function such as eating, swallowing, and chewing. This final version has been used in different cohorts of patients (163,164) but so far has not been included as an OMs in clinical trials.

The third PROM suggested is the **ACTIVLIM** questionnaire designed to assess activities limitations for children and adult with neuromuscular diseases (165). A total of 138 items were originally selected from previously used PROMs based on their potential suitability to assess disease progression. The list of items was submitted to a group of 32 experts healthcare professionals and 23 adults living with a NMD to evaluate their relevance for paediatric and adult patients but also to propose additional items for aspects not covered by

the suggested set of items. In addition, adults living with a NMD were asked to evaluate the perceived difficulty in performing each task. A final draft questionnaire with 91 items was suggested for adults after removing items considered as not relevant by the experts. Rasch analysis, performed with the responses from adult participants provided rationale to also remove items that did not provide any additional contribution to a unidimensional variable. The number of items for the pediatric questionnaire was reduced to 99 after the recommendations of the experts. Both sets of activities were tested in a sample of 369 patients (245 adults and 124 pediatric) who scored the level of difficulty to perform each task with a three-level scale: 0 for impossible, 1 for difficult, and 2 for easy. The results of the second Rasch analysis performed with the new responses not only reduced the number of suggested items to 22, but it also ensured that the questionnaire responses had the same capacity to discriminate across all items and there was no overlap between them. An additional step was performed to confirm its validity comparing the self-reported results from patients using the questionnaire with those observed by examiners in the clinical setting (166). After this a longitudinal study confirmed its validity in a cohort of different neuromuscular conditions (167).

Finally, the **SMA Independence Scale (SMAIS)** which was developed under the umbrella of Roche pharmaceutics and validated with data collected during several of their clinical trials (168). The SMAIS was developed to record meaningful changes in independence in ADLs. A total of 29 items were used to assess a range of 8 categories: Bathing/Hygiene, Dressing, Eating and Drinking, picking up, Moving objects, Mobility and Strength, Chores, and other tasks. The targeted population was non ambulant patients and was validated for individuals from age 2 and above. The scale was subjected to qualitative and quantitative analysis to ensure its validity for the targeted population. In the first part, qualitative interviews with people living with SMA and caregivers were conducted and in the second part, two rounds of Rasch analysis were used to test at item level the correct fit for score and item progression. In this second part, a sub-scale was created to focus on upper limb function (SMAIS UL) and it was also tested in a similar way to confirm it was fit for purpose (168). The publication of this paper was six months ago, and no further publications

have been found in relation to the SMAIS or its upper limb module version at the time of this review.

Of the PROMs that have been designed to assess caregiver burden and taking again Messina et al publication as reference, only 3 have been used in the context of clinical trials with none of those presented as having been evaluated using modern psychometric testing or validation. The **SMA Index Scale** has not been released for public use but has been included in two clinical trials. It is likely that it will be developed in a similar way of the previously mentioned SMAIS based on the clinical trial data collected but again, has not been published at the time of finishing the present review. Renaming the assessment may be advisable to avoid the coincidence in the acronym with SMAIS.

The second is the **Work Productivity and Activity Impairment (WPAI)** which, as its name states, focusses on evaluating the impact on work capacity of the individual. The WPAI was developed to evaluate time missed from work, impairment of work and common activities related to a health condition or symptoms but also, looking at measures of general health perception related to physical, emotional, pain, symptom severity (169). The assessment was designed to be self-reported and is represented as impairment percentages, where a higher number is an indicator of higher impairment and less productivity (148). The concept of the assessment is to evaluate the impact of health conditions; however, it has no specific questions related to the type of condition or employment, which makes it a generic tool to be used across different occupations and conditions. It has though been validated for specific conditions (170) and also used to assess SMA population (148). Both individuals with SMA and caregivers' perspectives were captured, and the results suggest that there are no statistical differences in the score/impact between the two groups. However, one of the limitations of the study was the limited representation of adults outside of school age which might underestimate the impact on work ability. The WPAI has been suggested to be an effective way to link a changing limitation on productivity for a specific condition and to be easily generalisable for different occupations and diseases (171). It may have some limitations as it does not differentiate between types of work and non-work-related tasks as they are assessed together.

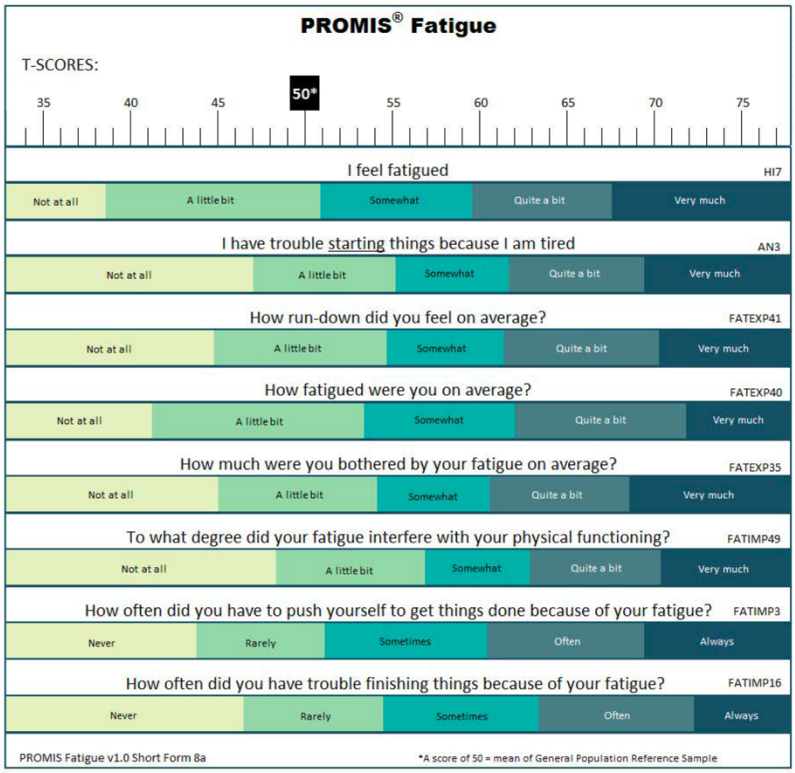
For assessment of caregiver burden the **Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)** is as stated in its name, is caregiver and neuromuscular focused and is intended to assess caregivers of individuals ranging from 4 to 18 years of age. The ACEND is structured in two domains: Physical and Caregiver impact. Physical domain contains four subdomains: feeding/grooming/dressing (6 items), sitting/play (5 items), transfers (5 items), and mobility (7 items). For Caregiver impact domain, 3 subdomains: time (4 items), emotion (9 items), and finance (5 items). An initial validation of the instrument was performed in 46 children with moderate-to-severe neuromuscular diseases and their parents comparing the results obtained in the ACEND with the Gross Motor Classification System IV/V showed limitations on the physical domain with a floor effect for participants with a higher degree of disability (GMFCS V) and some ceiling effect for more functional participants (GMFCS III). There were no reported limitations for caregiver impact domain (172) most likely due to the different construct of the compared assessments. In addition, participant's feedback was included about relevance (Mean 6.21 ± 0.37) and clarity of the scoring (Mean 6.68 ± 0.52) in a scale of 0 to 7. The ACEND has only been used in SMA in the context of a clinical trial and there are no results specifically about its findings at the time of completion of this review.

Two final dimensions of participation to explore are perceived fatigue and pain. Perceived fatigue has become of increasing interest due to the high prevalence in this group but also because current DMT seems to have a significant impact in this area. It is important to differentiate from physiological fatigue (covered in the OMs by body part or function) but it also fair to mention that it is slightly different from other PROMs mentioned in this section. Perceived fatigue is the subjective experience of feeling fatigue, and although has been effectively assessed in SMA, has not shown a direct correlation with physiological fatigue or function (173). At the same time, it is a common complaint present in many conditions and in the general population which means that there are many non-disease specific assessments available. For this review, we will discuss two scales that have been specifically used in SMA studies. The first one and most commonly used is the **Fatigue Severity Scale (FSS)**. The FSS was originally developed to assess the impact of fatigue on ADLs of multiple sclerosis and Systemic Lupus Erythematosus (174). It is a self-reported

questionnaire composed of 9 statements (e.g., Fatigue interferes with my physical functioning) to be scored with a 7-point Likert scale (1 strongly disagree to 7 strongly agree). The overall score is calculated by the mean of all the individual scores, with values above 4 an indicator of abnormal fatigue and equal or above 5, severe fatigue (175,176). The FSS has been tested and validated for a number of conditions (175,177–179) but also in healthy subjects (176). Identified by a group of experts as being potentially suitable for use in SMA (180) it was used to assess a cohort of SMA II (181). This study not only aimed to assess the population, but to also to evaluate the properties of the FSS in adult SMA. As suggested in previous studies, (182) the scale does not appear to be unidimensional as intended. The limitation is mainly around item one, (*My motivation is lower when I'm fatigued*) that captures the consequences of being fatigued and item 2, (*Exercise brings on my fatigue*), that captures potential causes of fatigue whilst the rest of the scale, captures different aspects of the experience of being fatigued. Werlauff at al suggested that removing the first two items improves the scale properties and content validity for its use in SMA (181). The FSS has also been used in the context of treated adults with nusinersen (183) reporting a transient benefit in reducing fatigue after the first 6 months but not after 10 months from the start of the treatment.

The **Patient Reported Outcomes Measurement Information System Fatigue Short Form (PROMIS Fatigue SF)** was developed under the umbrella of the Patient-Reported Outcomes Measurement Information System (PROMIS) project (184) which includes several other short forms for adults, pediatric and parent proxy reported questionnaires. The PROMIS Fatigue SF was developed to assess both perceived fatigue and impact of fatigue, aiming to minimise participant burden whilst completing it (185). The adult version has 8 items, the pediatric and parent-proxy version 10. Response scores are on a 5-point Likert scale (1= never to 5= always). Therefore, higher total score values are indicative of higher levels of fatigue. The scale provides T-score maps to compare individuals against normative data (186) (see Figure 1-5). Its use in SMA was performed in a project to assess QoL in 478 people living with SMA (148). The authors reported a clear higher level of fatigue when compared to general population but suggesting at the same time, that some of the questions used are not appropriate in the context of SMA.

Figure 1-7 PROMIS Fatigue SF T-score map



In relation to perceived pain, as mentioned previously in this section, pain has been reported as a frequent clinical feature in neuromuscular diseases (NMD) and SMA. Several scales have been used to look now at pain as an experience or as a factor that affects different aspects of ADLs or QoL starting with the impact of pain using the **Pain interference Scale**- a subscale of Brief Pain Inventory (BPI) (187,188). The SF-36 has questions relating to pain) (149) and some studies have employed the **McGill pain questionnaire** (189). However, none of these have been employed exclusively to measure pain in SMA but have been used in wider sets of neuromuscular conditions.

Table 1-4 Summary of outcome measure by participation

OMs	Scope of the assessment	SMA type/ functional status	Age range	Key related publications	
				Assessment	Use in SMA
Pediatric Quality of Life Inventory (PedsQL)	HRQoL	All	2-18 years	(128,129,134)	(135–138)
Quality of Life in Neuromuscular Diseases (QoL–NMD)	HRQoL	All	Adults	(139,140)	(141)
SMA Health Index (SMA HI)	HRQoL	All	Above age 8	(142)	(143)
Health Utilities Index (HUI)	HRQoL	All	Above age 5	(145)	(148)
Medical Outcomes Study 36-items short-form (SF-36)	HRQoL and ADLs	All	14 years and above	(149)	(153,154)
EuroQoL EQ-5D	HRQoL and ADLs	All	Adults	(156)	(150)
Pediatric Evaluation of Disability Inventory Computer Adaptative Test (PEDI-CAT)	ADLs	All	1-21 years	(157,158)	(159,160)
Egen Klassification (EK)	ADLs	All	Age 8 and above	(161,162)	(163,164)
ACTIVLIM	ADLs	All	Age 6 and above	(165,166)	(167)
SMA Independence Scale (SMAIS)	ADLs	All	Age 2 and above	(168)	-
SMA Index Scale	Caregiver burden	All	Not reported	-	-
Work Productivity and Activity Impairment (WPAI)	Caregiver burden	All	All	(169)	(148)
Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)	Caregiver burden	All	4-18 years	(172)	-
Fatigue Severity Scale (FSS)	Perceived fatigue	All	Adults	(174)	(181,183)
Patient Reported Outcomes Measurement Information System Fatigue Short Form (PROMIS Fatigue SF)	Perceived fatigue	All	All	(185)	(148)
Pain interference Scale	Perceived pain	All	Adults	(187,188)	-
McGill pain questionnaire	Perceived pain	All	Adults	(189)	-

HRQoL: Health related quality of life, ADLs: Activities of daily living

1.3 Paradigm shift in SMA treatments and management

A significant effort has been made over the years to progress the understand of the physiopathology, natural history, and effects of different interventions for people living with SMA. A good representation of this is the figure from Kolb presented in section 1.2 which was updated in 2011. However, since then, it is probably fair to say that a revolution has occurred with access to new treatments (Appendix A). On 23rd December 2016 the US Food and Drug Administration (FDA) and soon after, on 30th May 2017 the European Medicines Agency (EMA) approved Nusinersen (Spinraza) as the first available drug to treat SMA. The results obtained in the randomized, double-blind, sham-controlled, phase 3 efficacy and safety trial in infants with SMA (NCT02193074) showed significant differences in the treatment group in survival and an improvement in motor function (190). Soon after this, other therapeutics options (73,88) also proved to be effective, creating an unprecedented scenario where different therapeutic options coexist despite limited evidence of their efficacy at all ages or stages of the disease (191). With treatments, SMA is no longer the progressive disease that we knew and has become a treatable condition which has significant implications for life expectancy, epidemiology and also patient, relative and healthcare professional expectations.

This extraordinary moment was the result of a change in research and development in therapies for rare disease when in 1983, the United States Orphan Drug Act declared partial tax-incentives for investments in clinical development, market exclusivity and for assistance in the regulatory process of successful treatments (192). Other countries like Japan, in 1993, or Europe in 2000 followed the same example (193). Therefore, we are seeing a significant number of emerging therapeutics options, which has created the need for specialised centres to focus on these conditions. The main aim is to have a better understanding of the new natural history, optimise management and care provision whilst also have the capacity to test efficacy of new therapies.

The new treatments have created multiple potential scenarios where several considerations must be taken into account. The epidemiology of the disease is destined to

change, considering 60% of the cases are linked to the most severe forms of the disease (194) that without treatment, has a significantly limited life expectancy. If treatment becomes accessible to all newly diagnosed SMA, it is highly likely that that the prevalence of the condition is going to grow considerably. This has implications for access to current treatments but also in supportive care provision and consequently in the number of professionals required with expertise in SMA. On the other hand, the potential impact of the new treatments in different forms of the condition is still unclear, leading to the use of terms such as “evolving phenotypes” or “new chronic forms”(195) to define novel clinical presentations of the disease which will require revision of current OMs and care provision. A particularly relevant example is the change in respiratory management and expectations with more aggressive screening and consequently more pro-active treatment for hypoventilation (196). It is also important to consider carefully supportive care, particularly with those interventions that aim to provide assisted positioning or promoting function where maximising active movement will become the top priority.

A far reaching implication for the current scenario is that all available treatments appear to be more effective (197) which makes the next step to take into consideration the general implementation of new-born screening.

Having presented the available measures for evaluating all aspects of SMA and with the significant impact that DMT may have on survival and the implications for this on care provision, next steps require us to understand better patient perspectives, access to care and gaps within our current battery of assessments.

1.4 Patient-perception on disease progression in SMA

Several outcome measures have been developed and used to assess the progression of function in SMA, particularly for type II (those who achieved sitting but not walking) and type III (those that achieved walking). These include a range of functional scales (107,112,119,198), hand held myometry (24,199) and endurance tests (61) (see section 1.3). Several natural history studies have looked at the relationship between function and weakness, with no clear conclusions. Some papers described a functional loss with stable strength measures and others reported a link between function and strength with a

confounding influence of other variables such as body mass index (BMI) and respiratory function (22,200–203). One recent paper, describing a large cohort of SMA patients has reported that SMA II patients younger than 5 years of age often gained motor skills, whilst children between 5 and 15 years of age were at a higher risk of losing motor function which tended to then stabilise beyond 15 years of age. For SMA III the risk of loss of ambulation is much higher if symptom onset was before the age of 3 years (SMA IIIa subtype) compared with patients whose symptoms did not present until after the age of 3 years (SMA IIIb) (105).

Several factors may contribute to the progressive loss of function and these include: weakness, contractures and joint hypermobility, respiratory capacity, growth, changes in weight, type of compensatory movements used and other factors often defined as "environmental" (204). There have already been many efforts to monitor these factors over time.

Despite numerous papers reviewing clinic-based assessments, disease progression has not been explored from an individual's perspective either in adults or children. Patient's perceptions are becoming increasingly important for regulatory authorities where clinically significant endpoints must be supported by Patient Reported Outcome Measures (PROMS). A recent study has contributed to this topic by linking the clinical meaningfulness of individual items of the Hammersmith Functional Motor Scale Expanded (HFMSE) to relevant tasks for everyday activities such as sitting on a chair or toilet, get dressed or tie shoes (106).

1.5 Access to Standards of Care for people with Spinal Muscular Atrophy

A Consensus document on SoC was published in 2007 (6) and updated in 2017 (7,8). The aim of these publications was to benchmark diagnosis and management of SMA. The process was performed over different rounds of Delphi survey and was based on the available evidence for diagnosis and interventions (30,135,205–209) but also providing expert based recommendations and a consensus statement where new advances in care were not reflected in the existing literature (7).

Nine topics were included in the updated document: 1. Diagnosis and genetics; 2. Physical therapy and rehabilitation; 3. Orthopaedic care, growth, and bone health care; 4. Nutrition; 5. Pulmonary care; 6. Acute care in the hospital setting; 7. Other organ system involvement; 8. Medication; 9. Ethics and palliative care. For all the relevant aspects of the condition a series of specific recommendations were made regarding management. These were presented as Neuromuscular and musculoskeletal evaluation, Rehabilitation, orthopaedic management, Nutritional management, swallowing and gastrointestinal dysfunction and finally pulmonary management. All these topics were generally summarized with specific recommendations according to the different functional subtypes: non-sitters, sitters, and walkers (Table 1-5).

Table 1-5 Summary of recommendations on SoC

(Adapted from Finkel et al 2017 and Mercuri et al 2017)

Neuromuscular and musculoskeletal evaluation		Assessment
All		Assessments of **strength and range of joint motion, relevant motor functional scales and timed tests** to monitor those aspects of function that reflect activities of daily living. These assessments should be performed routinely by **trained examiners** every **6 months.**
Rehabilitation		
Type	Assessment	Intervention
Non-sitters	Postural control Scoliosis Hip dislocation Sitting tolerance Chest deformities Contractures ROM, goniometry Muscle weakness antigravity movements Functional Scales CHOP Intend Motor development HINE	Positioning and bracing: Daily use of seating systems, postural Stretching: Daily use of orthosis (>60 min to overnight) Upper limb and AFO, KAFOS Braces (minimal frequency 5/week) TLSO Stretches (duration depending of specific patient needs) Promote function and mobility: Seating and mobility systems Mobile arm supports for upper extremity function
Sitters	Postural control Foot and chest deformities Scoliosis and pelvic obliquity Hip dislocation Contractures ROM, goniometry	Positioning and bracing: Thoracic bracing posture and promote function (minimal frequency 5 times/week) Cervical bracing for safety and transportation Stretching: Daily use of orthosis (>60 min to overnight) Stretches (Minimal frequency stretching 5-7/week)

	Functional Scales HFMSE, RULM, MFM Muscle weakness Strength tests	Supported standing (up to 60 min, minimal frequency 3-5/week, optimal 5-7 times/week) Promote function and mobility: Exercise for function, strength, ROM, endurance, ADLs, participation and balance Swimming, hippotherapy and wheelchair sport Electric/powered wheelchair with custom postural support Tilt/recline option and seta elevator sometimes necessary
Walkers	Mobility Timed tests Measure of endurance 6MWT Falls Functional Scales HFMSE, RULM Muscle weakness Strength tests Contractures ROM, goniometry Postural control Scoliosis Hip dislocation	Positioning and bracing: Lower limb orthosis for posture and function Thoracic bracing to promote posture in sitting Stretching: Stretches (Minimal frequency stretching 2-3/week, optimal 3-5 times/week) Use of orthoses according to specific needs Promote function and mobility: Exercise (minimal frequency 2-3 times/week, optimal 3-5) Maintain flexibility and balance exercises

Orthopedic Management		
Type	Assessment	Intervention
Non-sitters	Cobb angle Supine or sitting with trunk brace	Spine deformity management Specific rigid braces
Sitters	Inspection of spine Spine radiographs Hip instability Contractures Fractures	Spinal orthoses (Rigid or soft orthoses) For scoliosis >20 degrees specially with significant growth remaining Surgical intervention based on: Magnitude of curve (>50 degrees) Rate of progression (>10 degrees per year) Other factors Decreased respiratory function, parasol rib deformity, hyper kyphosis, pelvic obliquity, trunk imbalance) Delayed till age 4 years < 8 to 10 years old: “growth-friendly” instrumentation 8-12 years old variability in practice Hip instability: Only managed surgically in patients with significant pain Contractures: Surgical management of contractures to be considered when caused pain or impair function Fractures Closed treatment with cast for non-ambulant patients Avoid prolonger immobilization (> 4 weeks) Hip fractures: surgical stabilization
Walkers		Fractures Long bone benefit from surgical stabilization

Nutritional management, swallowing and gastrointestinal dysfunction		
Type	Assessment	Intervention
Non-sitters	Optimal care: 3-5 months children, annually by adults Video Fluoroscopic Swallow Study shortly after diagnosis Difficulties feeding Nutritional analysis of food records Longitudinal anthropometrics	Referral to specialist feeding therapy/modification Nasojejunal tube until gastric tube with Nissen fundoplication Adjust caloric, fluid, macronutrient, micronutrient and timing of feeds Minimize fasting during acute care (<6 h) Monitor Fluid intake, electrolyte, glucose level. Bowel regulation medications
Sitters	Minimum: evaluation by dietician shortly after diagnosis Optimal: evaluation every 3-6 months children, annually adults Symptoms of dysphagia/aspiration/difficulties feeding Video fluoroscopic swallow study if suggested by clinical signs Nutritional analysis of food records Longitudinal anthropometrics Specific acute care monitoring	If swallow safe, referral for feeding therapy/modifications If swallow failed, nasofeeding tube- long term gastric feeding tube Growth failure, supplemental nutrition products
Walkers	Dietician for nutrition Longitudinal anthropometrics	Provide macro/micronutrient intakes based on guidelines for healthy sedentary individuals Minimize fasting during acute care

Pulmonary management		
Type	Assessment	Intervention
Non-sitters	Initially every 3 months then 6 monthly Hypoventilation (End tidal CO2) Sleep study or pneumograms Clinical assessment of gastroesophageal reflux	Airway clearance with oronasal suction, physiotherapy/respiratory therapy, and cough augmentation to all non-sitters with ineffective cough Ventilation for all symptomatic patients Some experts recommend it before documented respiratory failure Judge start based on clinical observation for adequate gas exchange or during sleep study NIV interfaces fitted by skilled physiotherapist Customary immunizations, palivizumab and influenza + Mucolytics should not be used long-term
Sitters	6 monthly Same as above	Same as above
Walkers	Clinical evaluation for cough effectiveness or signs of hypoventilation	Supportive care when needed Customary immunizations, annual influenza and pneumococcal vaccination

The SoC have been widely adopted as a reference for implementation of care in SMA across the globe. The guidelines have also been used as a benchmark for care during clinical trials (7) and more generally with these treatments more recently becoming available via clinical care. The paradigm shift in SMA treatments with the appearance of new disease modifying therapies (DMT) and its progressive implementation (Appendix A) has raised some ethical questions on standardization of supportive care to evaluate its impact on DMT (210).

The implementation of these standards and adherence to them across different countries or regions is still unclear. Some studies have identified significant differences with implications on the age at which ambulation is lost (211). In the UK no information has been gathered as to the extent in which these SoC are being implemented or if care in the UK is meeting these standards. The current model in the UK relays on a dual care provision with tertiary centres across the country working alongside community and primary care services locally. Access to specialised care in tertiary centres is less frequent and often requires for part of the population then need of covering significant distances to be seen. On the other hand, community services are more numerous and as a consequence more equally distributed but lack the experience and knowledge for rare diseases. Evidence also suggests that there is a substantial psychosocial impact of living with SMA (212) which is an aspect of care that is not covered by the current SoC guidelines. Understanding the extent to which SoC are implemented will help identifying potential gaps.

1.6 Trunk assessment for SMA

Progressive muscle weakness impacts overall function (6,213–215) and the asymmetric involvement of trunk muscles also leads to scoliosis. In addition, respiratory impairment has been associated with reduced motor function (37,216). It is unclear what factors lead to the appearance and progression of spinal deformities. However several authors describe trunk weakness and muscular imbalances in the lower and upper extremities alongside contractures as being the main contributing factors (217,218). The impact of trunk deformity is considerable on everyday life due to the importance of trunk strength for stability in sitting (217) providing a platform on which other body parts rely,

optimising respiratory function, and ensuring postural stability in a variety of positions including when transitioning between positions.

The importance of assessing trunk function is relevant not only in relation to its impact on progression on scoliosis or respiratory function but also on informing management decisions such as spinal braces, postural support or, in later stages, spinal surgery.

Key outcome measures have been used in either clinical trials or for clinical purposes for SMA population as described in section 1.2. They all have been designed to assess motor function with different specifications. The CHOP-INTEND was designed for younger and severely affected individuals with SMA I and the RULM is focused on upper limb function. The HFMS was initially designed for the SMA population with limited ambulation (100) and later extended (HFMSE) to capture motor performance of stronger individuals with SMA III (103). The latest revision of the scale is the Revised Hammersmith Scale (RHS) which covers with its 36 items from very weak SMA 2 through to very strong SMA 3. It includes items in lying, sitting, standing and walking with transitions in between. For these reasons the various iterations of the Hammersmith scale make it the most adopted scale for clinical and clinical trial use.

Despite many of these scales having some items which involve trunk function, none of the mentioned outcome measures were specifically designed to assess trunk involvement. However, one group sought to evaluate trunk function in neuromuscular disease using the Trunk Control Test (TCT) (219). The TCT was originally developed to assess motor impairment after stroke. It is based on four items (see table 1-6) with scores of 0, 12 or 25 (220).

Table 1-6 Trunk Control Test items and scoring system from Collin et al.

Items	Description	Scoring	
1	Rolling to the left	25	Able to complete the movement normally
2	Rolling to the right	12	Able to perform movement, but in an abnormal style
3	Sitting from lying	0	Unable to perform movement without assistance
4	Sitting with feet unsupported	25	Able to sit independently for 30 seconds
		12	Requires upper limb support
		0	Unable to stay up by any means

In this paper, 66 adult ambulant patients with a diagnosis of Neuromuscular disease were assessed with the TCT, manual muscle test (trunk, upper and lower extremities), Motor Function Measurement (MFM), Functional Independency Measurement (FIM) and the Rivermead Mobility Index (RMI). Patients had diagnosis of Myopathies, Myotonic Dystrophy, Limb Girdle Muscular Dystrophy, Fascioscapulohumeral Dystrophy and Becker Muscular Dystrophy. The TCT showed good reliability and different degrees of correlation with other measures. For total MFM the correlation was moderate (r=0,57) and strong (r=0,62) for Dimension 2, which is specific for axial and proximal motor function. For the FIM was moderate (r=0,35) again for its total and strong (r=0,66) for the Motor items. For RMI the correlation was moderate (r=0.39) again and in relation to MMT the correlation was moderate for total muscle strength (r=0,40) and strong for the trunk tests (r=0,61). However, in this study no SMA patients were included.

It is also worth noting that the TCT has not been widely adopted by the neuromuscular community which may in part be due to the lack of disease specific adaptations and unspecified descriptions of compensations used.

Another publication approached this subject in a more empirical way aiming to understand the impact of surgery on trunk function. Dunaway et all (221) reviewed a cohort of 17 participants with SMA that had received spinal surgery. The outcome measure used to assess functional impact was the HFMSE and the overall conclusion was that there is an immediate negative impact on function after surgery. The authors suggest that instrumentation that includes pelvic fixation might limit the use of compensations post-surgery limiting strategies which might in turn compensate for progressive muscle weakness.

The current scenario in SMA, due to recent successful drug development, has led to evolving phenotypes amongst the population. The capacity to assess trunk function in addition to the collection of related clinical features such as appearance or degrees of scoliosis and spinal fractures, will be especially relevant to evaluate both disease progression and benefits of treatment in a more comprehensive way and to improve the evaluation of the impact and indication of spinal surgery. The link between motor

performance as measured by the HFMSE, MFM or the more recently developed scale RHS and ADLs confirms the importance of trunk stability to individuals with SMA.

Chapter 2 Scope of the research

2.1 Introduction

There is a significant body of evidence and clinical guidance to manage and support people living with SMA. However, some gaps have been identified and for this reason, the purpose of this research project is to deepen knowledge about disease progression for people living with SMA and better understand the impact of having access to the recommended SoC.

In 2016, When this thesis was conceived there were no treatments for SMA, and the main purpose of this research aimed at evaluating the impact of ROM on function and management which at the time was an important unanswered question. However, with the rapid pace of drug development and subsequent success of several different pharmaceutical alternatives an opportunity arose to re-focus the aims of this thesis making it highly relevant to the evolving face of SMA. In order not to lose this important clinical focus, an international collaboration was created which published their findings on lower limb ROM (34).

This research is composed of three separate projects aiming to contribute to current gaps in our knowledge.

The first component focuses on the patient's perception about disease progression. For too long the focus on progression has been about the clinician's objective clinic-based evaluation and has not taken into account the patients' perspective and how this changes with time and age and stage of the disease. There is an increasing interest in understanding how objective measurement correlates with PROMs and overall patient prospective. This specific project aims to give voice to a representative group of patients to highlight key aspects of their condition and how these have influenced the way their personal disease experience has evolved over time.

The second focus of this thesis relates to access to Standards of Care (SoC). As presented in the previous chapter they were first described in 2007 and updated in 2017 when this project had already started. The impact of a SoC can only be realised if patients

are able to access these standards, consequently it is key to understand better how they are implemented in the UK. In the current scenario of implementation of new DMT (see section 1.4 and Appendix A) there is a huge investment in providing and assessing the long-term effect of these new treatments. It is however unclear how accessible the recommended SoC are to the SMA populations. A significant difference is observed between the access for pediatric and adult populations in our clinical practise, but there are also significant gaps for specific interventions (such supported standing devices or powered wheelchairs). Having a more complete picture of the true access will not only help to identify gaps as a first step to resolve them but will also help to explain potential differences in the outcome of the evaluation of DMT. This is particularly relevant for adult patients that tend to have less engagement with care provision.

The third point of interest of this research specifically evaluates trunk weakness and function. As described in section 1.3, there are several current OMs to assess different aspects of the disease and yet gaps in assessing the continuum of disease are still present. It is also true that some aspects of the condition, might not be useful as indicators of disease progression but they still can have a significant role for specific decision making related to particular interventions. This is the case for trunk involvement where orthotics and respiratory management are often employed. It is also a key aspect of motor involvement that has direct implications for the acquisition of reaching (222) and sitting (223). Trunk function has also been a particular focus of interest in treated patients (224).

Combining these three topics has led to specific research aims which despite their apparent distinctive nature aim to better capture the assessment of key components that have not been explored fully or in detail, particularly in relationship to patient opinion and experience.

2.2 Research aims

a) To explore from a patient's perspective, which factors influence disease progression with a particular focus on physiotherapy and other non-pharmaceutical interventions
b) To describe the experience of individuals living with SMA regarding their specialist care in the UK in relation to the published SoC guidelines.
c) To evaluate the capacity of specific RHS items to describe and quantify trunk involvement in SMA population in relation to respiratory function.

Chapter 3 Methods

3.1 Patient-perception on disease progression in SMA

Design

Individuals were recruited at the John Walton Muscular Dystrophy Research Centre (JWMDRC) in Newcastle and at Great Ormond Street Hospital (GOSH) in London in September 2017. Participants with SMA II and III were identified to represent the whole spectrum of the condition from childhood to adulthood. Patients with SMA I were not included in the study due to the limited life experience available to be reported. Recruitment was carried out during the yearly clinical reviews at the JWMDRC and during the patient interest group meeting at GOSH. At the time of the interviews, no DMT were available for the SMA population (See Appendix A).

Qualitative methods with a narrative research approach were used. The research method paradigm used was constructivism which aims to explore patient's perspective through their life experiences. One-to-one semi-structured interviews were performed with each participant at a convenient location for them. Three interviews were performed during a family interest group meeting (at GOSH), three others over a web-based conference call and two at participant's home. All participants had previously consented for Spinal Muscular Atrophy Research and Clinical Hub UK (SMAREACH UK) study (REC#13/LO/1748) (Appendix D Study protocol). Patients were contacted to discuss their willingness to participate in this sub-study and provided with the relevant patient information sheet (PIS) (Appendix E) and reconsented under SMAREACH UK on the same day of the interview (Appendix F). Furthermore, the participant's understanding of the purpose of the study was ascertained before the interview and additional explanation was provided when necessary. For those participants under the age of 18 years, the interviews were performed in the presence of at least one of their parents or carers.

All interviews were performed by the same researcher (RM) and the same question framework was used, aiming to optimise internal validity. However, the fact that RM was a

known Neuromuscular Physiotherapist by the participants was assumed to be itself an influential factor and a limitation for the study.

Data collection and processing

The question framework included questions about disease progression over the last year, the last 5 years, the last 10 years, or longer periods of time if applicable. Specific factors were included such as joint mobility, strength, fatigue, and impact of interventions such as physiotherapy and surgical interventions. All participants were encouraged to add any additional information related to each domain or other topics if appropriate. See appendix B for a copy of the interview framework.

All the interviews were audio recorded and transcribed for further analysis.

Data analysis

Computer Assisted Qualitative Data Analysis Software (CAQDAS) was used to organize and analyse the data (NVIVO computer software, Version 11.3.2 1888) (225). The process of analysis started with an independent initial theme analysis carried out by two researchers (RM and AM) to identify distinct themes and quotes relevant for the purpose of the study. The second phase of the analysis was a joint discussion between both researchers to merge common themes identified from the initial analysis. After this, all the quotes were linked to different themes and subthemes in the NVIVO software.

A second review was performed to identify themes related to disease progression. Three categories were established: deterioration, stability, and improvement. It was also established if the identified factor was perceived by patients as negative, neutral, or positive.

For the purpose of the analysis, the different themes and subthemes were structured according to the International Classification of Functioning, Disability and Health (ICF) units (17).

The interpretation of the results was based on different criteria. First prevalence, considering which themes were most reported. Second was pertinence, when themes were

identified to belong to a participant's subgroup (e.g., SMA Type). Finally, themes were also analysed by relevance, looking at those considered most important by the participants.

3.2 Real-world data on access to Standards of Care for people with Spinal Muscular Atrophy in the UK

An online anonymized survey with a total of 31 questions was design on Survio [survio.com] for the purpose of this study. It was open from August 2020 to end of July 2021. The link inviting individuals to participate in this survey was sent out via patient organizations, the UK SMA Patient Registry, professional networks, and social media to reach the SMA population across the UK. Given the nature of data collection - via voluntary participation in an online survey with no direct contact with the participants no consent was implied and therefore no ethical approval was required.

The survey was structured in four main topics:

- **Demographic** profile (*Questions 1-9*)
    - Age, SMA type, functional status, and area of residence.
- **Range of professionals** involved in a patient's care (*Questions 10-13*)
    - General Practitioner (GP), Paediatrician, Neurologist, Nurse Specialist, Physiotherapist, Occupational Therapist, Speech and Language Therapist, Pulmonologist, Respiratory Physiotherapist, Orthotist, Dietician/Nutritionist, Care Advisor, Carer and Psychologist/Counsellor.
- **Interventions** that patients have access to (*Questions 14-26*)
    - Contracture management (Splints, Stretches, etc)
    - Postural management (Braces, Standing devices, etc)
    - Respiratory support (NIV, cough augmentation)
    - Exercise plan (Strengthening, Endurance, etc)
- **Access to mobility aids and home adaptations** (*Questions 27-30*)
    - Wheelchair access and home adaptations.

A final open text section was added for any additional comments.

Participants were asked about their access to services/care including location (*community, specialized centre, or both*) and frequency of their visits. To gather their perception, participants were asked to rate how important each professional was for their health and wellbeing (*1 meaning not at all and 10, most important*). Participants were also asked to rate how often they would like to see each professional if applicable for them (*Less often, as much as I'm seen now, more often*).

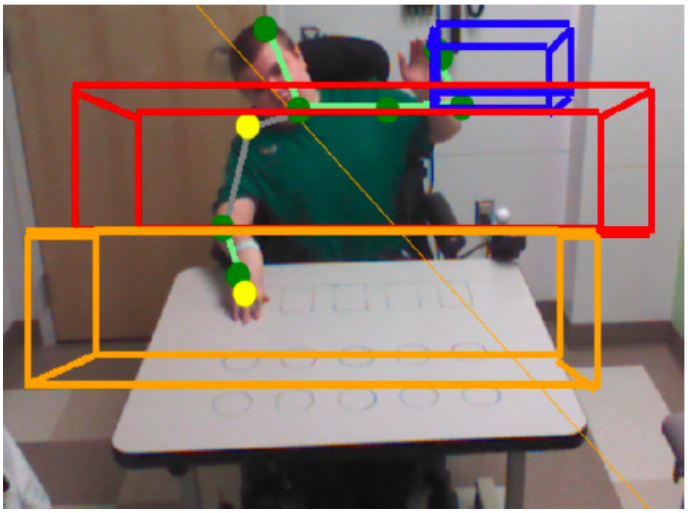
To ascertain interventions and access to mobility aids and home adaptations a similar approach was performed. First participants were asked about their access to each specific intervention and if applicable, its frequency of use. Afterwards, the relevance was rated (1-10 as previously) and their degree of satisfaction about access was requested (*I don't need it, I believe I do need it but can't get it, I do need it and can get it but with limitations, I do need it and I get what I need*).

3.3 Developing a trunk assessment for SMA

Pilot Study

A prior exploratory study to explore the use of a novel outcome measure to assess upper limb function in SMA – The Ability Captured Through Interactive Video Evaluation (ACTIVE) (226,227) led to the development of this chapter's focus. ACTIVE is a movement tracking video game that measures functional reach volume (FRV) developed by Dr Linda Lowes and her team in Nationwide's Hospital in Columbus (Ohio). FRV is defined by maximal reach of 6 regions: overhead, side-to-side, and forward for each side (see figure 3-1)(228). The raw functional reaching volume (FRV) is measured in cm3 and then converted to a percentage of the subjects predicted volume (ppFRV) based on their height.

Figure 3-1 ACTIVE regions from Lowes et al



The assessment will produce a summary of subject's performance reporting total volume reached (3 dimensions), percentage of the predicted volume and total surface covered (2 dimensions) and the corresponding percentage of the predicted area. In addition to this, trunk movement will be added up with lateral deviation (left and right) and central/forward leaning (see figure 3-2).

Figure 3-2 ACTIVE report sample

ACTIVE-seated Completion Report

Subject ID:	Visit Date: 10-12-2014
Ulna Length (cm): 24.1 (cm)	Brooke Level: 2
Diagnosis: BMD	Age (yr): 15

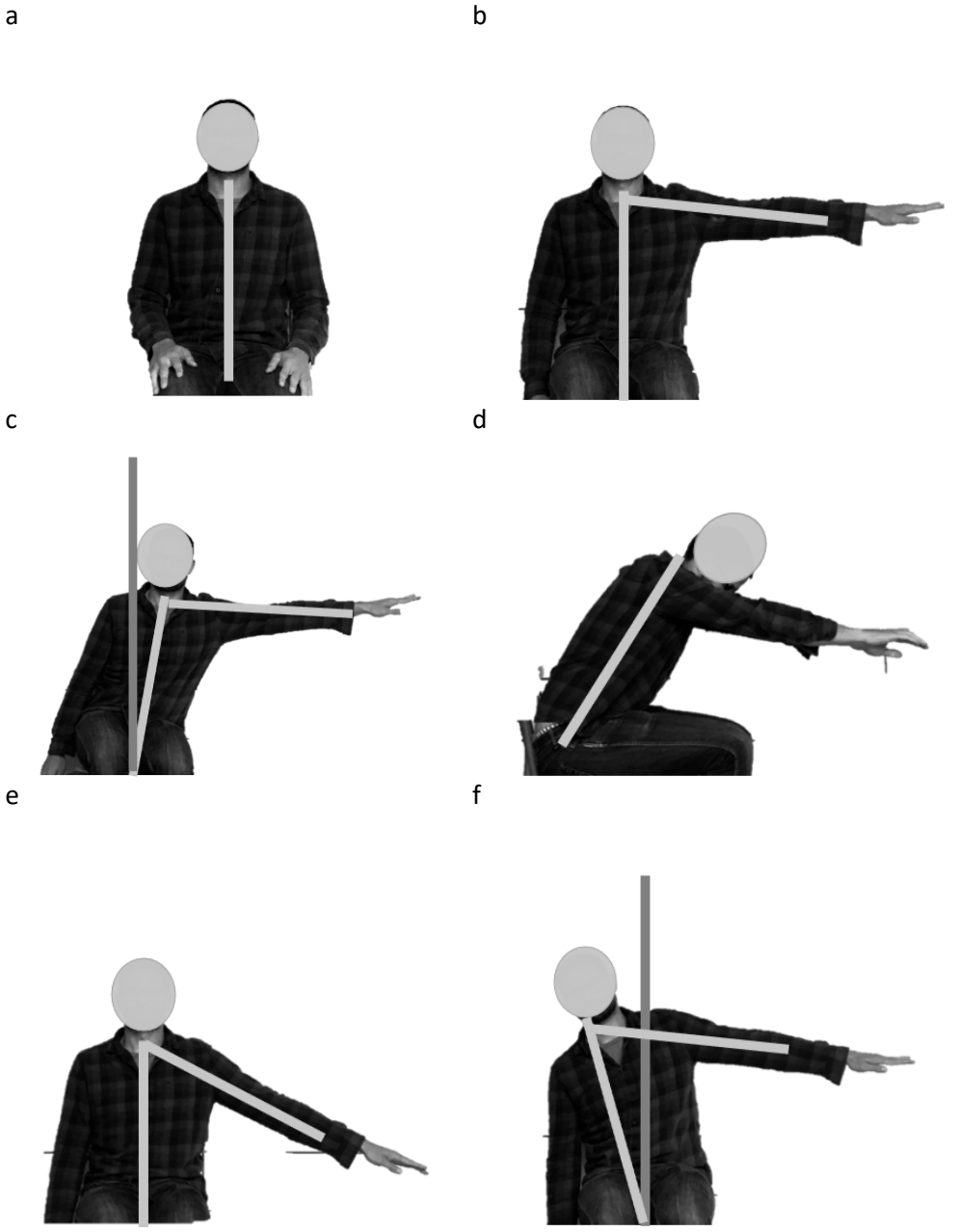
Last Successful Calibration: 10-12-2014T11:40:37

Trial Time	Total Volume (m^3)	Percent Predicted Volume	Total Surface Area (m^2)	Percent Predicted Area	Trunk Left	Trunk Center	Trunk Right
60	0.41	47.54	1.53	61.41	0.20	0.02	0.12
60	0.40	46.55	1.49	59.91	0.14	0.09	0.17

A pilot study conducted in Newcastle UK in September 2017 highlighted the importance of trunk functional ability to support arm function and how loss of trunk muscle strength impacts arm function and vice versa. It was clearly seen that reaching was highly influenced by trunk activation. When a participant with no proximal weakness is requested to reach from a sitting position, (figure 3-3a), reaching to the side (3-3b) is significantly

enhanced by the addition of trunk homolateral side flexion (3-3c). This is even more obvious when reaching forward with trunk flexion (3-3d). When proximal weakness is present, as in SMA, active range is limited (3-3e), but if good trunk control is preserved, this helps to increase active range by adding contralateral side flexion (3-3f).

Figure 3-3 Trunk involvement in reaching



Our first assessments showed that, because of progressive weakness, both proximal upper limb and trunk function adapt, creating different strategies to optimize function. These different strategies were particularly apparent in the group of patients included in our pilot making difficult to understand the role of trunk weakness when comparing upper limb activity (using the RULM) with ACTIVE.

This initial pilot study highlighted the need to explore ways to quantify trunk weakness in our population.

An examination of currently available functional outcome measures - presented previously (section 1.3) and learning from our experience with the ACTIVE, highlighted that there is no objective way to quantify trunk involvement in our cohort of patients. This was the challenge that this chapter aims to address.

Methods

Cross-sectional and longitudinal data were collected between September 2017 and September 2020. The project was developed under the umbrella of the International SMA Consortium (iSMAC) which includes networks from US, Italy, and UK. The study was approved by the Ethical Committee of each centre involved (IRCCS Bambino Gesù Children's, Catholic University of Sacred Heart, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, UCL Institute of Child Health & Great Ormond Street Hospital, Newcastle upon Tyne Hospital NHS Trust, Columbia University; Boston Children's Hospital, Stanford University; Children's Hospital of Philadelphia). Participants included in the UK sites were informed about the study protocol (Appendix D- SMA REACH UK Study Protocol v1.3 26.01.2015) (REC#:13/LO/1748) and provided with the relevant patient information sheet (PIS) (Appendix E- PIL 6-10 v1.1 3.12.2013; adult patents consented (that data was collected as part of their regular clinical assessment would be part of observational study to understand disease progression and they all provided informed consent/assent . They were advised that anonymised data would be shared at national and international levels for the purpose of the study. All patients had genetically confirmed diagnosis of SMA and, at the time of the study were not actively treated with disease modifying drugs (nusinersen, risdiplam or zolgensma). The inclusion criteria were having a clinical diagnosis of SMA type 2

(being able to sit independently) or Type 3 (able to walk independently) and being able to perform a reliable spirometry.

Patients were assessed using the RHS and respiratory function was captured via Forced Vital Capacity and its % predicted (FVC%) which was calculated according to their height and age. Gender, ambulatory status for type 3 individuals and previous spinal surgery were also collected for consideration in the analysis as they are key areas which may influence trunk function.

Revised Hammersmith Scale

The RHS is the last version of several different revisions of a scale developed to assess people living with SMA with different motor abilities (see section 1.2). It consists of 36 items which evaluate specific actions (see table 3-1 using a 3-point Likert scale, with a score of 2 for "performs without compensation",1 "performs with modification/adaption/ compensation" and 0 for "unable to perform the task". The only exception of this criteria is for items 8, 28 and 29 that have a score of 1 for competition of the task and 0 for being unable.

Table 3-1 RHS item description and score range

Item number	Description	Score range
1	Sitting	0-1-2
2	Hands to head in sitting	0-1-2
3	Sitting to lying	0-1-2
4	Adduction from crook lying	0-1-2
5	Right hip flexion in supine	0-1-2
6	Left hip flexion in supine	0-1-2
7	Lift head from supine	0-1-2
8	Supine to side-lying	0-1
9	Rolls from supine to prone	0-1-2
10	Lifting head from prone	0-1-2
11	In prone, prop on forearms	0-1-2
12	Four-point kneeling and crawling	0-1-2
13	Rolls prone to supine	0-1-2
14	Lying to sitting	0-1-2
15	Sit to stand	0-1-2
16	Cruising-Supported standing	0-1-2
17	Standing	0-1-2

18	Walking	0-1-2
19	Runs 10 meters	0-1-2
20	Squat down and up	0-1-2
21	Stand to sit on floor	0-1-2
22	High kneeling	0-1-2
23	High kneeling to right half kneel	0-1-2
24	High kneeling to left half kneel	0-1-2
25	Rise from floor	0-1-2
26	Stand on right leg	0-1-2
27	Stand of left leg	0-1-2
28	Hop on right leg	0-1
29	Hope on left leg	0-1
30	Ascends stairs	0-1-2
31	Descends stairs	0-1-2
32	Climbs box step leading with right leg	0-1-2
33	Descends box step leading with right leg	0-1-2
34	Climbs box step leading with left leg	0-1-2
35	Descends box step leading with left leg	0-1-2
36	Jump forward 30 cm	0-1-2

The total score is the sum of the items individual scores and ranges from 0 to 69 with a lower score indicative of lower levels of ability and vice versa.

Statistical analysis

Summary statistics (N, mean, SD, range) were used and main demographics were used to describe the cohort included in the project. Kendall's tau correlation coefficient was used to investigate the monotonous relationship between FVC percentage and each of the RHS items. The correlation was quantified as strong when $\tau \geq 0.55$, moderate when $0.55 > \tau \geq 0.3$ and weak when $\tau < 0.3$. Analyses were carried out using R (229) and results were regarded as significant when $p < 0.05$.

Chapter 4 Results

4.1 Patient-perception on disease progression in SMA

Demographics

A total of eight participants were interviewed in seven interviews. This was because two siblings were interviewed together. When participants were children, the interviews were performed together with parents or carers. Participant's demographics are listed in table 4-1.

Table 4-1 Demographics of interviewees

ID	Gender	Age	Location	SMA Type	Ambulant Status
01	Female	9	London	3	Transition
02	Male	11	London	3	Transition
03	Male	15	London	3	Non-Ambulant
04	Female	22	Newcastle	2	Non-Ambulant
05	Female	24	Newcastle	2	Non-Ambulant
06	Female	34	Newcastle	3	Transition
07	Male	34	Newcastle	2	Non-Ambulant
08	Male	47	Newcastle	3	Non-Ambulant

A total of twenty themes were identified during the initial theme analysis and classified using the ICF framework to assist in interpretation (Table 4-2).

Table 4-2 Themes classification and distribution

ICF Component	ICF Unit	Theme	Sources	References
Body Function	B760 Control of voluntary movement functions	Function	7	74
	B730-740 Muscle power-endurance functions	Strength-Fatigue-Endurance	7	44
	B720 Mobility of bone functions	Range of Motion (ROM)	4	43
	B126 Temperament and personality functions	Attitude-Mood	5	15
	B280 Sensation of Pain	Pain	5	8
	B550 Thermoregulatory functions	Thermoregulation-Circulation	3	5
	B530 Weight maintenance functions	Body Mass Index	2	9
	B6602 Functions related to childbirth	Childbirth	2	4
Activities-Participation	D9205 Socializing	Participation	5	6
	D160 Applying knowledge	Information- Knowledge	3	5
	D840 Work and employment	Work	4	4
	D550 Eating	Nutrition	2	4
Environmental Factor	E5800 Health Services	Exercises	7	48
	E1201 Assistive Products and technology for personal indoor and outdoor mobility and transportation	Mobility Aids	7	22
	E5800 Health Services	Spinal Management	4	23
	E5800 Health Services	Splints	5	14
	E5800 Health Services	Standing Frame	4	9
	E5800 Health Services	Other interventions	3	6
	E410 Individual attitudes of immediate family members	Parents	2	2
	E1101 Drugs	Drugs-Supplements	1	1

Body function

For Body Function, several themes were described (see Table 4-2 for classification and Table 4-3 for patients quotes).

Table 4-3 Patient Quotes for Body Function

ICF Component	Theme	Patient Quotes
Body Function	Function	"I probably just adapted to the way it works" "If I'm in the right position I can still cut my own food, it just takes a long time" "A loss and a gain"
	Strength and Fatigue	"I go to bed in the nighttime, and I wouldn't say that I'm tired from the whole day"
	Range of Movement	"The amount that it [the joint] goes is enough for what I do"
	Attitude-Mood	"I'll pass you the 'pop', and I'll say like no, no, I can get that myself" "I become more tired (…) and it affected my confidence a lot"
	Weight-BMI	"I think if he was a lot shorter it probably makes life a lot easier." "I really struggle to put on weight because as soon as I do, I feel almost immediately [a negative] effects on my muscle function"
	Childbirth	"What's been most influential is that I had two children and each time that I had been pregnant and had the child I've noticed a deterioration in my strength"

Function: Two different patterns of disease progression were identified. Adult participants with SMA III and young SMA II participants reported a progressive deterioration, whereas adults with SMA II reported no major changes over several years.

The most commonly reported factor influencing disease progression was increasing weakness. Specific events such as acute injuries or fractures, sprains and Achilles tendon surgery were often reported to have a dramatic impact on strength and function even precipitating the loss of ambulation.

Participants clearly identified the loss of a specific ability or function as hugely significant, more so than the fact that they might need to use compensatory strategies or that it requires longer time to achieve it a task.

Strength and Fatigue: Weakness was identified as the main limitation on function. Growth was reported as having a negative impact on strength and ultimately, function.

Most participants reported that weakness had greater impact on function than fatigue. In addition, some SMA III participants mentioned fatigue, physical and mental as an additional limiting factor.

Range of Movement: SMA II participants described ROM as more stable over time as opposed to SMA III, who reported a pattern of deterioration over time. Some of the individuals perceived hypermobility positively due to the benefits it may provide on their ability to transfer. Other participants describe it negatively, particularly when related to hand function. In one case, hypermobility in the feet was reported as a key-limiting factor for ambulation. Other individuals described no impact.

A pattern of tight shoulders, hips, knees, and ankles combined with hypermobile fingers was often described in older individuals. Younger participants described a more generalised pattern of hypermobility. The only reported tightness in these cases was related to mild tightness in their ankles.

Individuals often reported hypermobility and contractures as “normal” although they were more likely to recognise these alterations in ROM when clinicians measured them.

Participants reported contractures as having a minimal or no impact on lower limbs function but as a limiting factor for specific tasks in the upper limbs. However, it was reported that certain tasks were facilitated by elbow contractures and on occasions could compensate limited ROM in shoulders.

Attitude-Mood: Two participants indicated it was important to remain positive and avoid accepting more adaptations than was necessary. One participant reported how important it was to keep as active as possible and another reported the on-going impact of disease progression on their mood.

Pain: Pain was reported, mainly in the back, hips, and feet. Back pain was associated with spinal surgery and reported to be perceived in different ways and at time points. Spinal surgery was described as a cause of pain but also as a means of pain management, after variable periods of time post-surgery. However, the overall benefit of such an

intervention was always highlighted. Hip pain because of hip subluxation and sore feet were mentioned by two participants. Foot pain was identified as a severe limiting factor for walking.

Thermoregulation: Hands and feet were predominantly reported to have poor thermoregulation which limited function in hands and fingers (I.e., steering a powered wheelchair). One participant mentioned the importance of keeping warm and wrapped up as a preventative measure.

Weight / BMI: Two participants reported on the negative influence of growth spurts resulting in the loss of ambulation over a period of growth. A parent of another participant mentioned that his tallness was a limiting factor as regards his functional ability.

With regards to BMI, an adult participant reported the negative impact of weight gain on function.

Childbirth: The experience of parenthood was reported by two of the participants, one female and one male. They both reported the negative impact of this on disease progression.

The impact of pregnancy (for the female participant) was accompanied by the burden of the childcare (mentioned by both participants) as having a detrimental influence on compliance with care interventions leading to disease progression.

Activities and participation

In relation to Activities and Participation, four themes were identified (see Table 4-2 for classification and Table 4-4 for patients quotes).

Table 4-4 Patient Quotes by Themes on Activities and Participation

ICF Component	Theme	Patient Quotes
Activities and Participation	Participation	"It has affected how I approach things. I am much less likely to do stuff that requires [me] to go out" "I'm getting a lot more help for feeding or drinking"
	Knowledge and Information	"I think sometimes too much information - it's not helped the children that is going through it now" "It's not really as much knowledge about SMA locally obviously"

	Work	"I think that overall, I would progress or [have] deteriorated slower if it wasn't for things like surgery, having children and having a busy job that sometimes I get overtired"
	Nutrition	"When I'm well nourished (…) I'm doing more of what I was able to do" "If I eat sugar (…) I know instantly it will wake me up but in half an hour I will feel really tired" "I have tried many times to be vegetarian (…) but if I go several months without eating meat, I can't handle that"

Participation: Participants highlighted the negative impact of disease progression on their social life limiting the level of participation in work and community related activities.

Knowledge and Information: Participants reporting using the internet and social networks to interact and compare themselves with other families and people affected with SMA and at the same time using these forums as a source of information. This was not always reported to have a positive effect.

In addition, participants reported a difference in level of care received in tertiary centres compare to non-specialised local services. This was reported as a limiting factor in access to specialised care. A family reported that a different approach to contracture management between two centres had a negative impact on ambulation as it had delayed intervention.

Work: Two participants reported that being professionally active, had a negative impact on overall fatigue management. Working from home was reported as helpful for fatigue management.

Nutrition: Two participants commented on the positive influence and importance of nutrition and specific foods on motor performance.

Environmental Factors

In relation to Environmental Factors, eight themes were identified (see Table 4-2 for classification and Table 4-5 for patients quotes).

Table 4-5 Patient Quotes by Themes on Environmental Factors

ICF Component	Theme	Patient Quotes
Environmental	Exercises	"It didn't really improve the strength, but it maintained, if I

Factors		stopped using them or when I didn't use my strength deteriorated" "When I left school, I had one session of Physiotherapy and she said she'll come back to me with another appointment, and I never heard from her back again." "It's a nice feeling because (…) I can actually stand up in the pool without anybody holding me" "No, no exercise. I just do all my everyday tasks" "If we work and they're long days sometimes we are tired, some days we don't do as much as other days"
	Spinal Management	"My brace was my godsend, but I needed it every day, I hated wearing it, but I hated not wearing it" "I don't think I can probably do half stuff of what I do if I didn't have my back rodded" "I sit straighter and better too and naturally that I can use my arms more prior to my operation" "[It] was a good investment thinking on a long-time basis but at the moment was … a bit going backwards"
	Splints	"I was wearing every day in my shoes, from getting out to bed to go to bed (…) I haven't had anything of those since I was 18" "All those threats that you'll never wear shoes again if you stop wearing your splints, that hasn't happened"
	Parents	"If I'm in anything close to being in a reasonable shape now it's pretty much due to my parents pushing us when I was a kid"

Exercise: Exercise was reported widely as an ongoing part of their routine for some of the participants but often with no clear structure. Use of stretches for flexibility was reported as beneficial if done daily and with the capacity to not only maintain ROM but to improve it. Stretches were reported as helpful for pain management and potentially as an alternative to the use of splints. One participant reported a positive role of endurance exercise using a cyclo-ergometer for upper and lower limbs. The use of elastic band and weights was reported as useful to maintain strength but not to improve it. Different specific exercises were mentioned reporting different frequencies and intensity. No clear universal guidance was identified.

Physiotherapy: Access for children was perceived as reasonably good, however adult services were perceived as nearly non-existent. Physiotherapy was reported as beneficial if done on a regular basis particularly during childhood.

Water based exercises: Regular access (twice a week) was considered beneficial. Occasional access was reported as a nice experience but with no influence on function.

Horse riding: Regular practise was reported as beneficial (≥2 times a week) but a more intense regime i.e., daily, was reported as a risk for increasing fatigue potentially resulting in a negative impact on function.

Some participants reported they undertook no formal exercise and perceived everyday tasks as exercise. Other participants reported that exercise helped to increase awareness of their capabilities in comparison with daily activities. Some participants mentioned the impact of their care and exercise on their careers.

Mobility Aids: The use of crutches, walkers, manual wheelchairs, and powered wheelchairs were mentioned depending on the level of mobility. Specific injuries and surgical interventions lead to increased use of mobility aids either temporarily or permanently. Keeping any support to a minimum was reported as beneficial to preserve strength and endurance.

Spinal Management: Spinal braces and spinal surgery were reported as being beneficial for posture, strength in upper limbs function, independence, and pain management. However spinal braces were reported to be uncomfortable before getting familiar with wearing them on a regular basis.

SMA III participants reported spinal surgery as an intervention that limits mobility and function in the short-term but provides them with more stability in the long-term. SMA II participants interviewed perceived spinal surgery as a positive intervention immediately.

Splints: Most individuals reported the use of splints being more accessible for paediatric participants other than in adults. The main factor for poor compliance in children was the discomfort.

In adult participants, splints were rarely used or rarely being even prescribed to them. However no major changes in ROM were perceived despite not using orthotics.

Standing Frame: Only paediatric participants reported using a standing frame or swivel walker and they reported their use having a positive impact on flexibility in their legs and on

circulation. It was reported as an especially enjoyable intervention for those who regularly used it.

Other Interventions: Airflow mattress and percutaneous endoscope gastrostomy (PEG) were both perceived as positive interventions.

Parents: Participants reported the benefit of parents encouraging them to be as active as possible and helping to maintain compliance with management strategies.

Drugs-Supplements: Iron supplements were the only reported to be used regularly by one patient and helping in reducing overall fatigue.

Disease progression and influencing factors

A second analysis was performed to determine within all references, which ones were related to disease progression. Out of 82 references identified, 58 (71%) described deterioration and these were reported by 7 participants. Several factors were linked to this deterioration (table 4-6), some of which were specific to the condition but also external factors such as workload or family responsibilities. It was on occasion linked to specific body parts (dominant hand, legs) but also generalised deterioration.

Table 4-6 Disease Progression-Deterioration quotes

Disease progression	Patient Quotes
Deterioration	"I have got more weakness on my left-hand side down my shoulder and my arm, I found that that over the last year is gone quite quickly"
	"It's more effort now but I can still do a lot of things that I used to do, just find it take longer to do certain things"
	"I thought my muscles have deteriorated a bit because I stop doing as much as I used to because I work at home"
	"I think that overall, I would probably progress or deteriorated slower if it wasn't for things like surgery, having children and having a busy job that sometimes I get overtired"
	"I mean, the less I have been able to do the more the stiffness comes into my shoulders you know"

Improvement was described by only 7 (9%) references out of 4 participants (table 4-7). These references were mainly related to specific time points or to interventions that were found to have a positive effect.

Table 4-7 Disease progression- Improvement quotes

Disease progression	Patient Quotes
Improvement	"I feel like I move better"
	"Every time I had a period off (hippotherapy session) I always go back to be very unbalanced and needing quite a lot of support to ride but then after a few months I always managed to get back to where I was"
	"There was a time when they were walking a bit more because they were developing, they were not progressing as quickly as their friends but getting a little bit stronger"

Finally, 17 (20%) references were linked with stability and were by 5 participants (table 4-8). It was often linked to specific function (i.e., ability to perform task in a certain way) and mostly for shorter periods of time (i.e., no changes observed over periods of 12 months).

Table 4-8 Disease Progression- Stability quotes

Disease progression	Patient Quotes
Stability	"I'm still feed myself; I've always been able to feed myself"
	"I don't think anything really has changed over the last year"
	"In the last 12 months … yeah … I think I've been pretty stable, and I think I had quite a deterioration … over a year ago and since then things have been reasonably stable"

When the analysis focused on influencing factors 89 references were made with either negative (*31*) or positive (*49*) being clearly more present than neutral (*9*).

Negative influences were linked to specific interventions but mainly to overall disease progression (table 4-9).

Table 4-9 Influences- Negative quotes

Influences	Patient Quotes
Negative	"I only go in once maybe twice while I am there because not only It's a lot of effort to get us in the pool, it's uncomfortable once I've been in cause with my hip problems I find I´m in lot of pain when I've been in the pool"
	"I think hyper mobility has influenced his lost the ability to walk, I think the flexibility in the ankle joints does play quite a large part of it"
	"And there's still certain things that I can't do now that I could do before. I don't suppose that I would be able to do those again."
	"It's something that I really … kind of … struggle to put on weight because a soon as I do, I feel almost immediately effect of my muscle function"
	"Strength is reduced, but equally at the same time his body mass has increased tremendously growing a lot"

There was no dominance of one specific subject or factors named across the group (figure 4-1).

Figure 4-1 Negative influences quotes word cloud

The mention of a neutral influence was anecdotical being linked to unclear influence of intervention or often linked with the presence of adaptation to overcome small changes with a neutral result table 4-10, figure 4-2).

Table 4-10 Influences- Neutral quotes

Influences	Patient Quotes
Neutral	"I only go in once maybe twice while I am there because not only It's a lot of effort to get us in the pool, it's uncomfortable once I've been in cause with my hip problems I find I´m in lot of pain when I've been in the pool"
	"I don't think that hyper mobility, I don't think has an influence in his function now"
	"I think that it's all right. I think that I just adapted to do those sorts of things. I probably just adapted to the way it works"

Figure 4-2 Neutral Influences quotes word cloud

Positive quotes were the most common ones within the influence theme. They were mainly linked to interventions with different degree of satisfaction reported and different timelines. One of the main recurrent topics is that positive changes were perceived but not linked with objective improvements with only a few exceptions (table 4-11 and figure 4-3).

Table 4-11 Influences- Positive quotes

Influences	Patient Quotes
Positive	“I would personally say the most helpful intervention for me it’s been horse riding”
	“I’m generally more comfortable and I don’t have the pain and I’m straighter. I can feel the benefit of it (spinal surgery) now over the years on”
	“I started taking iron tablets because one of the doctors, you know, Dr Wood she said that people with my condition are often anemic. So that explains a lot you know throughout my life about why I have often been tired. Ever since I started taking iron tablets regular, I have felt a lot better.”
	“The hydrotherapy pool loosens the muscles off and the joints, I was much better … I felt better after that”
	“I’m on support groups and stuff like on Facebook, and I look at some of them, and I’m like Jesus why am I so well”

Figure 4-3 Positive influence quotes word cloud

4.2 Real-world data on access to Standards of Care for people with Spinal Muscular Atrophy in the UK

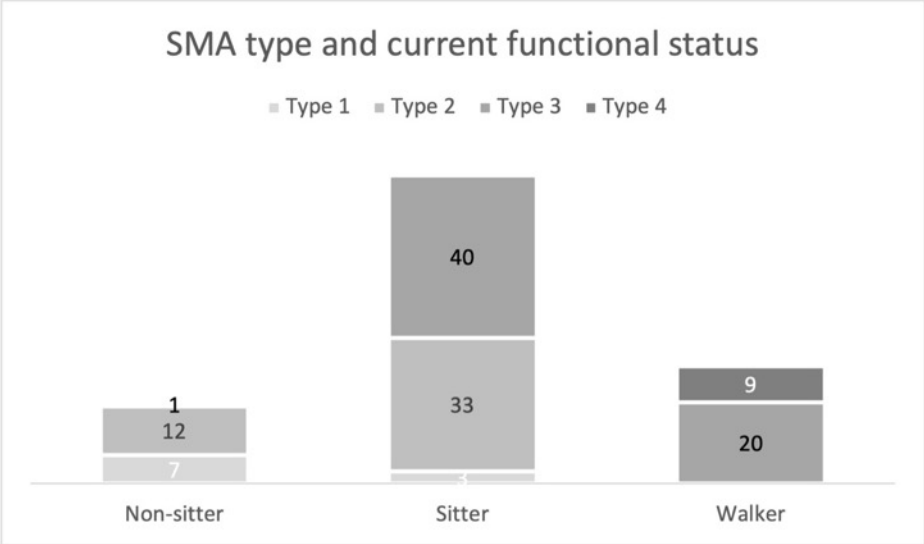
Demographics

A total of 128 responses were collected (3 excluded due to a non 5q SMA diagnosis reported). The majority of participants (68%) took between 10 to 30 min to complete the survey. Overall completion rate was 21% (635 total visits) and none of the surveys were left incomplete.

Median age was 34 years (range from 1 – 81 years of age) with good representation across the different age ranges (average 9 responses per group) and with 73% of participants being adults and 60% men. Responses from participants below age 14 were collected through parents or tutors. Above that age, responses were reported by patient themselves or jointly with parents or carers.

When analysed by current functional status, sitters were the most represented functional group (76%) (Figure 4-4)

Figure 4-4 SMA type and current functional status distribution



Most participants were based in England (85%) but also representation from Scotland, Wales, Northern Ireland, and Guernsey was collected. The sample from England was spread across 35 counties out of a total 48.

Access to professionals and interventions according to Standards of Care

Access to SoC was measured by the proportion of participants that reported access to the relevant professional or intervention and how often they were seen or received the care.

SoC recommendations include “neuromuscular and musculoskeletal evaluation by trained examiners every 6 months”. (7) Page 4

Table 4-12 Reported access by age and functional group for neuromuscular and musculoskeletal evaluation

Access reported to	Neurologist	Physiotherapist	Nurse
Pediatric	**97%**	**100%**	**76%**
Non-sitter	100%	100%	89%
Sitter	95%	100%	84%
Walker	100%	100%	33%
Adult	87%	41%	23%
Non-sitter	**91%**	**36%**	**45%**
Sitter	93%	44%	26%
Walker	70%	45%	4%
Grand Total	**90%**	**57%**	**48%**

A significant majority of the participants reported having access to a neurologist (Table 4-12). This was consistent across age and functional ability except for walkers who reported having better access in the pediatric group. 64% reported seeing a neurologist once or twice a year or more frequently however, a difference was observed between pediatric (94%) and adults (52%).

Access to a nurse specialist was reported by less than half of the participants again showing a discrepancy between pediatric (76%) and adult (23%) responders. Frequency of visits was reported to be once or twice a year or more by 57%.

In total, over half of the participants reported having access to a physiotherapist with a significant difference over pediatric and adult responders. 64% of participants reported seeing a physiotherapist once a year or more (81% pediatric, 38% adult). Only 14% reported regular access (once every two months or more) with a difference for age group (38% pediatric, 5% adult).

In the Rehabilitation section, recommendations are made for "positioning and bracing". These include: use of orthosis (splints) for more than 60 min or overnight, use of braces for non-sitters and sitters 5 times a week (7) Page 5

Table 4-13 Reported access by age and functional group for positioning and bracing

Access reported to	Splints	Spinal Braces	Stretches	Supported standing
Pediatric	**59%**	**15%**	**82%**	**53%**
Non-sitter	67%	22%	78%	33%
Sitter	53%	16%	89%	79%
Walker	67%	0%	67%	0%
Adult	**14%**	**13%**	**44%**	**7%**
Non-sitter	18%	18%	57%	0%
Sitter	14%	16%	47%	7%
Walker	13%	4%	30%	9%
Grand Total	**26%**	**14%**	**54%**	**19%**

The use of splints was reported by just over quarter of all participants with non-sitters using them most compared to sitters and walkers (Table 4-13). The frequency and duration of use was reported to be for an hour a day or more by 43% of the users - non-sitters (63%) followed by walkers (55%) and sitters (30%).

Spinal braces were reported to be used by a minority of the overall participants being mainly non-sitters and sitters with 73% reporting using them more than 3 hours a day.

Also in the rehabilitation section, stretches are recommended with different regimes depending on functional status: to be adapted to patients needs for non-sitters, 5-7 times a week for sitters and 2-3 to 3-5 times a week for walkers (7) Page 5

Over half of the participants reported doing stretches with higher rate for non-sitters, followed by sitters and walkers (Table 4-13). Looking at performing stretches by age group, pediatric participants have a higher rate than adults.

The use of supported standing devices is recommended in addition to stretches for sitters for 60 min, 3-5 to 5-7 times a week.(7) Page 5

A supported standing device (Standing frame or KAFOS) is used by a minority of participants (Table 4-13); 20% of these reported using this device for an hour a day or more as recommended in SoC. The most commonly reported use was for an hour almost every day (43% of the users).

In the rehabilitation section several interventions are recommended to “promote function and mobility”. Introduction of home adaptations, mobility aids and exercises are recommended with different specifications depending on the functional type. It is suggested that exercise can have an effect on function, strength, ROM, endurance for sitters. Walkers are encouraged to perform aerobic and general conditioning exercise (at least for 30 min per session). Some examples of specific exercises are suggested for both types including swimming hippotherapy, wheelchair sports, walking, rowing, cycling, yoga, etc. (7) Page 5

Table 4-14 Reported access by age and functional group for promote function and mobility

Access reported to	Occupational Therapist	Mobility aids	Home adaptations	Exercise
Pediatric	**88%**	**91%**	**62%**	**91%**
Non-sitter	100%	89%	89%	78%
Sitter	89%	100%	47%	95%
Walker	63%	67%	67%	100%
Adult	**53%**	**86%**	**88%**	**62%**
Non-sitter	55%	100%	91%	73%
Sitter	63%	100%	98%	54%
Walker	26%	43%	61%	74%
Grand Total	**62%**	**87%**	**81%**	**70%**

Access to occupational therapy is reported to be available to over half of the participants with much higher proportion in pediatrics in comparison to adults (Table 4-14). Frequency of once a year or more was reported by 26% of the users with “being seen when needed” the most common response (65% overall, 50% of pediatric, 73% of adults).

Mobility aids and home adaptations are accessible to the great majority of the participants with higher access for more severe phenotypes (Table 4-14).

Home adaptations are spread across different dimensions. 54% of participants have access to mobility adaptations (handrails, stair lifts, ramps, etc), 62% for selfcare (toilet, shower, wet room, etc), 48% for transfers (hoist, sliding board, etc) (75% for non-sitters, 57% of sitters and 7% walkers) and 22% accessories (adapted cutlery, trays, adapted clothes, etc.) (30% of non-sitters, 26% of sitters and 7% walkers).

Access to any form of exercise was reported by most of the participants with much higher rate for pediatrics (Table 4-14). Endurance exercise was accessible for 20% (5% of non-sitters, 17% of sitters, 38% of walkers and 38% of pediatrics, 13% of adults). Mixed exercise (yoga, Pilates, etc.) was accessible by 6% of the participants (9% pediatric and none of the adults).

In the Nutrition section, optimal evaluation was recommended to be for non-sitters and sitters from 3 to 6 months for children and yearly for adults. (7) Page 8

Table 4-15 Reported access by age and functional group for nutrition section

Access reported to	Dietician/ Nutritionist	Speech and Language Therapist
Pediatric	**47%**	**44%**
Non-sitter	67%	78%
Sitter	42%	36%
Walker	33%	0%
Adult	**11%**	**10%**
Non-sitter	36%	27%
Sitter	11%	10%
Walker	0%	0%
Grand Total	**21%**	**16%**

Access to dietician or nutritionist and speech and language therapist is reported to be available to a minority of the participants with more than double the proportion for pediatrics in comparison to adults. Access was more present also for more severe phenotypes (Table 4-15). The frequency most reported for visits to dietician or nutritionist was “when needed” for pediatrics (69%) and once or twice a year for adult users (60%). For speech and language therapist, 35% of the users reported to be seen at least once a year in

(38% pediatrics, 30% adults), with “being seen when needed” the most common result for pediatrics (62%) and less than once a year (40%) for adults.

In the respiratory section, the SoC recommendation suggests regular assessment for non-sitters (3-6 monthly) and sitters (6 monthly) and access when needed for walkers. It is also recommended to have access to support for airway clearance, physiotherapy/respiratory therapy and ventilation for all symptomatic patients.(8) Page 3

Table 4-16 Reported access by age and functional group for respiratory section

Access reported to	Pulmonologist	Respiratory physiotherapist	Ventilator	Airway clearance
Pediatric	**60%**	**54%**	**32%**	**38%**
Non-sitter	100%	100%	89%	89%
Sitter	53%	53%	11%	26%
Walker	29%	0%	17%	0%
Adult	**42%**	**26%**	**19%**	**21%**
Non-sitter	82%	73%	73%	64%
Sitter	42%	27%	16%	21%
Walker	22%	0%	0%	0%
Grand Total	**47%**	**34%**	**22%**	**26%**

Access to pulmonologist is reported by nearly half of the participants and in slightly lower proportion for respiratory physiotherapist (Table 4-16). There were differences for both professionals when comparing pediatric and adult participants. As seen previously, access was also higher for more severe phenotypes being nearly inexistent for walkers. Frequency of visits was reported to be for once or twice a year or higher in 80% of the users for pulmonologist and by 59% for respiratory physiotherapist.

Access to ventilation and airway clearance is reported by nearly a quarter of the participants with differences by functional level (Table 4-16). Again, more severe phenotype reported higher rate of access. For ventilation, the most common frequency if use was “every night” (48%) with 33% of non-sitters reporting additional daytime use. For airway clearance the frequency of use most reported was “twice a day” by non-sitters (47%) and “when needed” by sitters (41%).

In addition to the professionals included in the SoC document, access to psychological support was reported to as available by 14% of the participants with a reported frequency of visits “when needed” by 44%.

Participant's perception

Participants rated the importance of having access to different professionals and interventions represented by age and functional group (Table 4-17 and 4-18).

Table 4-17 Rate of importance by professionals by age and functional group

Mean, SD	General Practitioner		Pediatrician		Neurologist		Nurse Specialist		Physiotherapist		Occupational Therapist		Speech and Language Therapist		Pulmonologist		Respiratory physiotherapist		Orthotist		Dietician/ Nutritionist		Care Advisor		Carer		Psychologist/ emotional support/ counsellor	
Pediatric	**5.1**	**2.9**	**5.4**	**3.4**	**8.9**	**2.2**	**6.7**	**3.2**	**9.2**	**1.6**	**8.6**	**2.0**	**3.4**	**3.5**	**5.8**	**4.0**	**5.9**	**4.1**	**7.7**	**2.5**	**4.7**	**3.5**	**4.1**	**4.0**	**2.6**	**3.3**	**3.1**	**3.2**
Non-sitter	5.3	2.6	5.3	3.5	8.6	2.6	7.4	2.7	8.6	1.9	7.7	2.8	4.9	3.8	8.3	2.2	8.4	2.2	6.4	2.4	4.7	3.2	3.4	3.9	5.0	4.7	2.2	2.2
Sitter	5.5	3.2	5.9	3.6	8.9	2.3	7.6	2.7	9.9	0.3	9.0	1.7	3.5	3.6	5.7	4.3	6.2	4.2	8.0	2.8	4.4	3.6	4.3	4.1	1.8	2.3	2.4	2.6
Walker	3.8	2.2	3.8	2.4	9.0	1.7	2.8	2.9	7.8	2.4	8.5	0.8	1.0	0.0	2.3	2.2	1.2	0.4	8.5	1.0	6.0	4.1	4.7	4.4	1.3	0.8	6.8	3.7
Adult	**6.4**	**2.9**	**1.8**	**2.3**	**7.9**	**2.4**	**3.9**	**3.4**	**6.7**	**3.4**	**5.6**	**3.2**	**2.4**	**2.5**	**5.2**	**3.9**	**4.3**	**3.8**	**3.0**	**3.0**	**4.0**	**3.5**	**3.8**	**3.5**	**6.2**	**4.3**	**4.4**	**3.6**
Non-sitter	7.8	1.7	2.5	3.4	8.2	1.9	4.5	3.5	6.0	3.4	5.5	2.8	2.8	2.8	8.9	1.6	6.9	3.3	4.2	3.8	5.3	3.6	3.6	3.3	9.1	2.7	5.0	3.8
Sitter	6.6	2.9	1.9	2.4	7.9	2.4	4.7	3.6	7.1	3.4	6.2	3.0	2.7	2.8	5.7	3.9	5.0	4.0	2.9	2.9	4.5	3.6	4.5	3.6	6.9	4.1	4.7	3.7
Walker	5.3	3.1	1.3	1.5	7.9	2.6	1.8	1.9	6.2	3.4	4.4	3.6	1.3	0.9	2.1	2.3	1.4	1.0	2.4	2.8	2.4	2.9	2.0	2.7	2.9	3.4	3.4	3.5
Total	**6.1**	**2.9**	**2.8**	**3.1**	**8.2**	**2.4**	**4.7**	**3.6**	**7.4**	**3.2**	**6.4**	**3.2**	**2.6**	**2.8**	**5.4**	**3.9**	**4.8**	**3.9**	**4.2**	**3.6**	**4.2**	**3.5**	**3.9**	**3.6**	**5.2**	**4.3**	**4.1**	**3.6**

1 (black) = not at all important and 10 (white) = most important.

Table 4-18 Rate of importance by intervention by age and functional group

Mean, SD	Splints		Back braces		Supported standing		Ventilator		Cough augmentation		Stretches		Strengthening exercises		Endurance exercise		Mixed exercise		Other exercise		Mobility devices		Home adaptations	
Pediatric	**7.2**	**3.2**	**4.3**	**4.2**	**6.3**	**4.0**	**4.4**	**4.1**	**5.2**	**4.4**	**9.0**	**1.2**	**8.6**	**2.5**	**7.8**	**3.0**	**6.8**	**3.6**	**6.4**	**3.9**	**9.5**	**1.8**	**9.1**	**2.0**
Non-sitter	7.0	2.7	3.6	4.4	6.0	3.7	8.9	1.7	9.5	1.1	8.7	1.1	8.0	3.2	7.6	3.3	7.9	3.2	5.6	4.3	9.0	3.0	9.4	1.3
Sitter	7.5	3.2	5.5	4.3	7.5	3.6	2.4	3.1	4.2	4.3	9.4	1.1	8.8	2.5	7.8	3.1	7.2	3.5	7.5	3.6	9.9	0.2	9.4	2.1
Walker	6.2	4.1	1.0	0.0	1.0	0.0	2.8	3.5	1.0	0.0	7.8	1.3	8.4	1.5	8.2	2.7	4.0	3.9	3.8	4.1	8.8	2.0	7.8	2.4
Adult	**2.9**	**3.1**	**2.3**	**3.1**	**2.4**	**2.9**	**3.4**	**3.7**	**4.0**	**4.1**	**6.8**	**3.2**	**6.7**	**3.3**	**5.9**	**3.7**	**5.3**	**3.8**	**5.6**	**3.9**	**8.4**	**3.2**	**9.0**	**2.1**
Non-sitter	4.2	4.1	2.8	3.6	2.3	3.0	8.1	3.2	7.9	3.4	7.4	3.0	5.8	3.8	4.7	3.9	3.8	3.2	4.4	3.6	10	0.0	8.9	2.0
Sitter	2.8	2.9	2.8	3.5	2.8	3.2	3.2	3.6	4.3	4.2	7.0	3.2	6.6	3.4	5.4	3.9	5.4	4.0	5.9	4.0	9.7	1.4	9.7	1.0
Walker	2.6	3.2	1.0	0.0	1.5	2.1	1.0	0.0	1.0	0.0	6.1	3.3	7.4	2.9	7.5	2.7	6.0	3.7	5.7	3.9	4.5	3.8	7.3	3.2
Total	**4.2**	**3.7**	**2.9**	**3.5**	**3.6**	**3.7**	**3.7**	**3.8**	**4.3**	**4.2**	**7.5**	**2.9**	**7.3**	**3.2**	**6.5**	**3.6**	**5.8**	**3.8**	**5.9**	**3.9**	**8.7**	**2.9**	**9.0**	**2.1**

1 (black) = not at all important and 10 (white) = most important

Participant perception about current access was also captured with scores ranging from not applicable, to satisfied with current access, would like to see/receive the intervention more often or less often. The option "less often" was only reported by one individual consistently across different professionals involved. This option has been excluded from the table to limit iteration of a column with minimal significance.

Table 4-19 Reported frequency of access satisfaction by age and functional group for neurologist, nurse specialist, physiotherapist, and occupational therapist.

	Neurologist			**Nurse specialist**			**Physiotherapist**			**Occupational Therapist**		
Frequency satisfaction	More often	Not applicable for me	As much as I'm seen now	More often	Not applicable for me	As much as I'm seen now	More often	Not applicable for me	As much as I'm seen now	More often	Not applicable for me	As much as I'm seen now
Pediatric	**26%**	**9%**	**66%**	**23%**	**23%**	**54%**	**57%**	**3%**	**40%**	**23%**	**9%**	**69%**
Non-sitter	11%	11%	78%	11%	11%	78%	67%	0%	33%	22%	0%	78%
Sitter	26%	11%	63%	21%	21%	58%	53%	5%	42%	21%	11%	68%
Walker	43%	0%	57%	43%	43%	14%	57%	0%	43%	29%	14%	57%
Adult	**49%**	**5%**	**46%**	**23%**	**60%**	**17%**	**66%**	**16%**	**17%**	**34%**	**32%**	**35%**
Non-sitter	36%	0%	64%	18%	55%	27%	36%	18%	45%	45%	18%	36%
Sitter	47%	5%	48%	29%	51%	20%	76%	12%	12%	36%	22%	41%
Walker	61%	9%	30%	9%	87%	4%	57%	26%	17%	22%	61%	17%
Grand Total	**43%**	**6%**	**51%**	**23%**	**50%**	**27%**	**64%**	**13%**	**24%**	**31%**	**25%**	**44%**

Over half of the participants reported satisfactory access to a neurologist with only a minority reporting they role wasn't applicable to them (Table 4-19). The was a difference when comparing pediatric participants to adults.

Access to a nurse specialist was reported to be not applicable by half of the participants being much higher for adult participants when compared to pediatrics. These differences meant that most of the pediatric participants were satisfied with current access

and most adults reported the role not applicable for them. Most participants reported insufficient access to a physiotherapist with a slightly higher rate within adult participants. Access to occupational therapist was nearly split in thirds for each category with satisfactory access being most reported. This proportion was higher for pediatric participants.

Table 4-20 Reported frequency of access satisfaction by age and functional group for nutrition and respiratory section

	Dietician/ Nutritionist			**Speech and Language Therapist**			**Pulmonologist**			**Respiratory Physiotherapist**		
Frequency satisfaction	More often	Not applicable for me	As much as I'm seen now	More often	Not applicable for me	As much as I'm seen now	More often	Not applicable for me	As much as I'm seen now	More often	Not applicable for me	As much as I'm seen now
Pediatric	**20%**	**46%**	**34%**	**3%**	**69%**	**29%**	**6%**	**43%**	**51%**	**20%**	**43%**	**37%**
Non-sitter	22%	33%	44%	11%	33%	56%	0%	0%	100%	33%	0%	67%
Sitter	16%	53%	32%	0%	74%	26%	11%	47%	42%	21%	42%	37%
Walker	29%	43%	29%	0%	100%	0%	0%	86%	14%	0%	100%	0%
Adult	**29%**	**60%**	**11%**	**8%**	**82%**	**11%**	**20%**	**49%**	**32%**	**23%**	**57%**	**21%**
Non-sitter	30%	20%	50%	0%	64%	36%	27%	0%	73%	27%	18%	55%
Sitter	36%	56%	8%	9%	81%	10%	24%	44%	32%	27%	51%	22%
Walker	13%	87%	0%	9%	91%	0%	5%	86%	9%	9%	91%	0%
Grand Total	**27%**	**56%**	**17%**	**6%**	**78%**	**16%**	**16%**	**47%**	**37%**	**22%**	**53%**	**25%**

Most of the participants rated access to a dietician/nutritionist and speech and language therapist as not applicable with small differences in between pediatric patients and adults (Table 4-20).

Over half reported that access to a Pulmonologist was applicable with slightly higher proportion of adult willing to see them more often (Table 4-20). By functional status, the role had clear trends for non-sitters where they had satisfactory access, whereas walkers find the role not relevant. When looking at sitters, there is more spread across the three categories with predominance of the role not being applicable for nearly half of the

participants. Respiratory Physiotherapist access follows a similar pattern with a slightly higher rate of unsatisfied participants (Table 4-20).

48% of participants reported that access to psychologist or emotional support was applicable, with 38% willing to see them more often. Of those accessing this support 79% said that would like to receive this support more frequently either for themselves or their child.

Participant's perception around access to specific interventions is reported again with the most common option selected with additional distinction by age group or functional status when significant differences were noted.

Table 4-21 Reported frequency of access satisfaction by age and functional group for positioning and bracing

	Splints				Spinal braces				Stretches				Supported standing			
Frequency satisfaction	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it
Pediatric	**12%**	**21%**	**38%**	**29%**	**3%**	**15%**	**12%**	**71%**	**9%**	**41%**	**44%**	**6%**	**6%**	**12%**	**38%**	**44%**
Non-sitter	0%	33%	33%	33%	0%	22%	0%	78%	11%	33%	33%	22%	11%	22%	11%	56%
Sitter	16%	16%	42%	26%	5%	16%	21%	58%	5%	42%	53%	0%	5%	11%	63%	21%
Walker	17%	17%	33%	33%	0%	0%	0%	100%	17%	50%	33%	0%	0%	0%	0%	100%
Adult	**8%**	**12%**	**8%**	**73%**	**3%**	**5%**	**5%**	**86%**	**26%**	**29%**	**19%**	**26%**	**10%**	**3%**	**5%**	**81%**
Non-sitter	18%	0%	18%	64%	9%	0%	9%	82%	27%	27%	18%	27%	9%	0%	0%	91%
Sitter	9%	12%	7%	72%	4%	9%	7%	81%	28%	32%	18%	23%	14%	5%	5%	75%
Walker	0%	17%	4%	78%	0%	0%	0%	100%	22%	22%	22%	35%	0%	0%	9%	91%
Grand Total	**9%**	**14%**	**16%**	**61%**	**3%**	**8%**	**7%**	**82%**	**22%**	**32%**	**26%**	**21%**	**9%**	**6%**	**14%**	**71%**

Most of the participants reported not needing access to splints with a significant contribution of adult participants (Table 4-21). When looking at the proportion separately, the majority of pediatric patient reported getting what they need.

Access to spinal braces was perceived as not needed by most of the participants with only pediatric sitters the ones to report higher rates for satisfactory access and access with limitations.

Access to stretches was perceived as needed by the majority reporting a similar degree of satisfaction with current access across different functional status. Pediatric patients had a higher degree of satisfaction.

Most of the participants reported not needing access to a supported standing devices, with much higher proportion for adults. This was particularly true for walkers with sitters being the functional group with higher degree of satisfaction.

Table 4-22 Reported frequency of access satisfaction by age and functional group for mobility, promoting function and respiratory interventions

	Mobility aids				Home adaptations				Ventilation				Cough augmentation			
Frequency satisfaction	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it
Pediatric	**6%**	**44%**	**44%**	**6%**	**29%**	**26%**	**38%**	**6%**	**0%**	**6%**	**35%**	**59%**	**6%**	**9%**	**29%**	**56%**
Non-sitter	0%	56%	33%	11%	22%	33%	44%	0%	0%	11%	89%	0%	11%	11%	67%	11%
Sitter	0%	42%	53%	5%	26%	26%	37%	11%	0%	5%	16%	79%	5%	11%	21%	63%
Walker	33%	33%	33%	0%	50%	17%	33%	0%	0%	0%	17%	83%	0%	0%	0%	100%
Adult	**1%**	**48%**	**37%**	**13%**	**16%**	**46%**	**30%**	**8%**	**0%**	**0%**	**19%**	**81%**	**8%**	**1%**	**23%**	**68%**
Non-sitter	0%	64%	36%	0%	18%	55%	27%	0%	0%	0%	64%	36%	9%	0%	73%	18%
Sitter	0%	58%	39%	4%	16%	53%	30%	2%	0%	0%	18%	82%	11%	2%	23%	65%
Walker	4%	17%	35%	43%	17%	26%	30%	26%	0%	0%	0%	100%	0%	0%	0%	100%
Grand Total	**2%**	**47%**	**39%**	**11%**	**20%**	**41%**	**32%**	**7%**	**0%**	**2%**	**23%**	**75%**	**7%**	**3%**	**25%**	**65%**

Access to mobility devices was reported to be widely accessible with a similar distribution for those who have access with some limitations and those who have access to what they need (Table 4-22). There were no major differences in between functional or age group with the only exception of adults' walkers where the majority reported not needing mobility aids.

For home adaptations the distribution of responses was similar to that of mobility aids but showing a higher rate of participants with no access.

Access to Ventilation was reported as accessible when needed with a small proportion having access with limitations. It was clearly less needed for less severely affected participants. Airway clearance devices follow a similar pattern but with a higher rate of participants reporting no access despite needing it (Table 4-22).

Table 4-23 Reported frequency of access satisfaction by age and functional group for strengthening, endurance and mixed exercises

	Strengthening exercises				**Endurance exercises**				**Mixed exercises (Ioga, Pilates)**			
Frequency satisfaction	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it
Pediatric	**15%**	**44%**	**32%**	**9%**	**21%**	**35%**	**26%**	**18%**	**21%**	**15%**	**6%**	**59%**
Non-sitter	11%	33%	22%	33%	22%	22%	22%	33%	33%	0%	0%	67%
Sitter	11%	53%	37%	0%	16%	42%	26%	16%	11%	16%	11%	63%
Walker	33%	33%	33%	0%	33%	33%	33%	0%	33%	33%	0%	33%
Adult	**36%**	**25%**	**15%**	**23%**	**34%**	**19%**	**15%**	**32%**	**24%**	**13%**	**10%**	**53%**
Non-sitter	27%	27%	0%	45%	27%	18%	0%	55%	9%	0%	9%	82%
Sitter	40%	26%	12%	21%	40%	16%	9%	35%	26%	16%	7%	51%
Walker	30%	22%	30%	17%	22%	26%	39%	13%	26%	13%	17%	43%
Grand Total	**30%**	**30%**	**20%**	**19%**	**30%**	**23%**	**18%**	**28%**	**23%**	**14%**	**9%**	**54%**

In relation to access to exercise, endurance, strengthening, and mixed exercise were reported as not being accessible by a similar proportion of participants with slightly higher rates for adults (Table 4-23). Access with limitations or satisfactory access was reported to be higher in pediatric patients for strengthening and endurance exercise, whilst having similar figures for mixed exercise. The proportion of participants that reported not needing each form of exercise was again higher for adults and gradually increasing overall from strengthening, endurance to mixed having the highest proportion.

4.3 Developing a trunk assessment for SMA

A total of 219 assessments were collected from 138 unique participants with additional 81 assessments from a second visit.

For visit one, the mean age was 17.56 years (SD 13.76; max 73.89, min 2.8) (figure 4-5) and 49% of females. For the SMA type, 61 (44%) were reported to be Type 2 and 77 (56%) were Type 3. From this group, 41 (53%) were ambulant (see figure 4-6) leaving a total of 97 sitters combining type 2 and 3.

Figure 4-5 Age distribution for visit 1

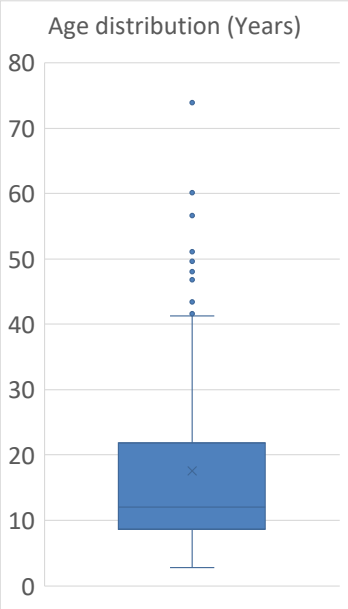
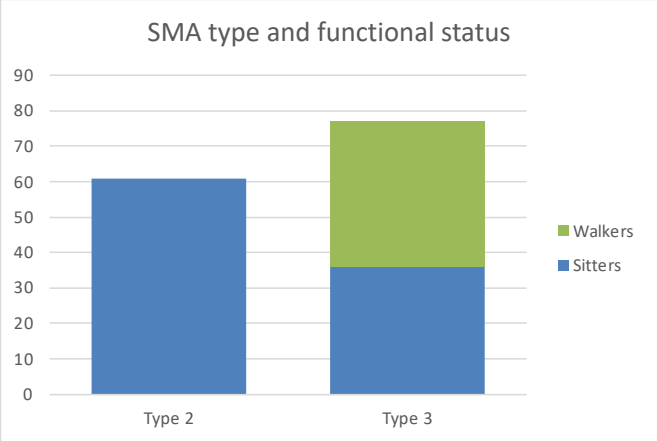
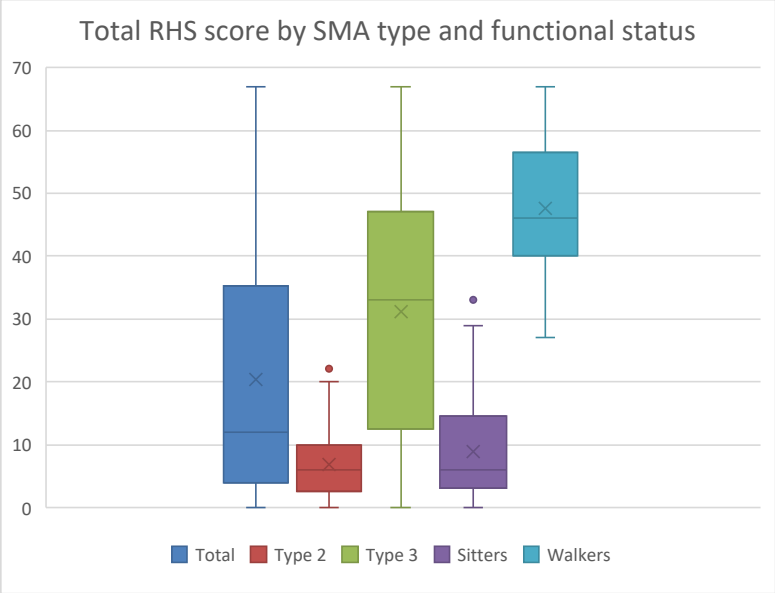


Figure 4-6 SMA type and functional status



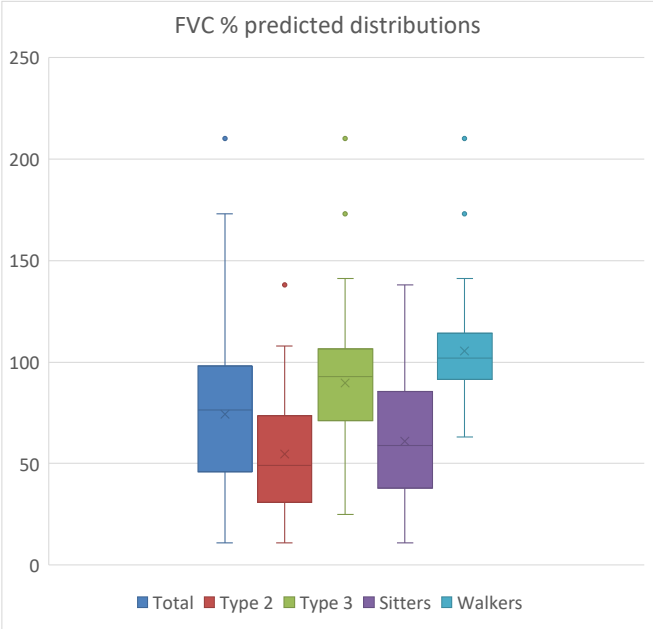
The functional profile was distinct as expected across the different subgroups (see figure 4-8). All participants had a mean for RHS total score of 20.4 (SD 19.8, max 67, min 0). When looking at SMA type, SMA 2 – a mean RHS total score of 6.8 (SD 5.7, max 23, min 0) and for SMA 3 - 31.2 (SD 20.4, max 67, min 0). The functional differences were more evident when separating by current functional status. Mean RHS total score for sitters 8.9 (SD 8.02, max 34, min 0) and for walkers 47.5 (SD 11, max 67, min 27).

Figure 4-7 Total RHS score by subgroups and total



Regarding respiratory data, differences were present also but more subtle (see figure 4-9). The mean FVC% for the whole cohort was 74.2 (SD 34.3, max 210, min 11). For SMA Type 2 mean FVC% was 54.6 (SD 28.3, max 138, min 11) and for Type 3 - 89.7 (SD 30.5, max 210, min 25). Functional status demonstrated more distinct groups. Sitters had a mean of 61 for FVC% (SD 28.4, max 138, min 11) and for walkers - 105.4% (SD 26, max 210, min 63).

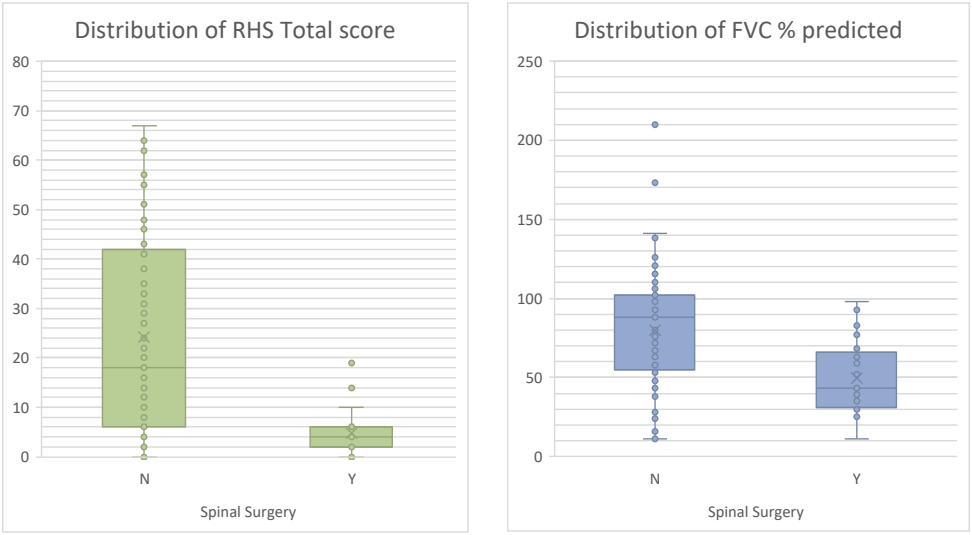
Figure 4-8 FVC percentage predicted by subgroups and total



Regarding spinal surgery, 27 participants had spinal surgery with all being non-ambulant at the time of the assessment as expected (figure 4-10). Their RHS total score and

FVC% distribution showed a more severely affected profile. The mean for RHS total score was 4.7 (SD 4.3, max 19, min 0). Mean for FVC% was 49.8 (SD 23.1, max 98, min 11).

Figure 4-9 Distribution of FVC% and RHS total for Spinal surgery participants



Using cross-sectional data from the first visit only, six items demonstrated strong positive correlations ($n = 138, 0.55 \leq \tau \leq 0.60,\ p < 0.001$) indicating that higher RHS individual item scores were likely to be associated with higher FVC%. These items from the RHS are presented here (Table 4-24).

Table 4-24 Top correlated items FVC % pred-RHS

		Correlation (P-value <0.001)			
Item	**Descriptor**	**Total V1**	**Total V2**	**Sitters**	**Walkers**
3	Sitting to Lying	0.6035	0.6065	0.5122	0.0667
13	Rolls prone to supine	0.5979	0.5988	0.4884	0.0780
11	In prone, prop on forearms	0.5939	0.6257	0.4515	NA
9	Rolls from supine to prone	0.5822	0.5708	0.4628	0.0833
14	Lying to sitting	0.5573	0.6037	0.3512	0.1160
10	Lifting head from prone	0.5543	0.5896	0.3941	0.2136

Correlation coding: green strong, orange medium, yellow weak or no correlation, NA: not applicable

The analysis was then repeated for subsets of this data as well as for data collected on the patient's second visit. All 6 items continued to demonstrate strong correlations with FVC%.

For the subgroup of sitters, the correlations between FVC% and RHS items remained significant only for item 3. For RHS items 13, 11, 9, 14 and 10 the correlations dropped to moderate ($n = 97, 0.57 \leq \tau \leq 0.60,\ p < 0.001$). For the subgroup of walkers, none of the six items correlated with FVC% and for item 11 the correlation was not possible due to uniform scoring from all participants ($n = 41, 0.21 \leq \tau \leq 0.11,\ p < 0.05$).

Chapter 5 Discussion

This present project started in 2017 as an evolution of a proposal that was more focused on evaluation of upper limb function in SMA. The original proposal's objective was to describe the influence of weakness, anthropometrics, age, and management on arm function in non-ambulant individuals with SMA. The proposal aimed to assess the impact of management of ROM on function, to explore patients' perception of disease progression and to explore relationship of current functional outcome measures with novel outcome measures in non-ambulant patients with SMA.

Several changes have been introduced for different reasons. The first one, relates to the preliminary findings regarding current contracture management in the UK population. Measuring joint range with the necessary precision proved difficult and a lack of information on the prevalence of contractures was required before a study was undertaken. As a result, a joint study with international colleagues which examined lower limb contractures was developed to partially resolve this limitation (34) .

The second major factor has been the approval and introduction of the first DMT for SMA. As mentioned in section 1.4, this has changed the management and care provision together with patient's and professional expectations. It is for this reason that the inclusion of the second objective of the present research was found of key relevance.

In summary, the present thesis is a reflection of two of the main challenges that are intimately linked with working with rare diseases. The description of general clinical features and care provision is often lacking and becomes a first step to describe the current situation before other more specific projects can proceed. Second, is the need of international collaborations to deliver any substantial piece of work. The low prevalence of these diseases makes the population of a single centre, insufficient to report on disease progression or characteristics.

Taking these general aspects into account, each of the projects has generated various learning points.

5.1 Patient-perception on disease progression in SMA

In this qualitative study we report the outcome of semi-structured interviews in SMA II and III patients to evaluate patient perceptions with regards to various interventions and their impact on disease progression before the advent of DMT (Appendix A). The results show similarities with previous studies with regards to perceptions and impact of strength and function (22,200–203). In relation to overall disease progression, participants reported the same rate of deterioration (71%), stability (20%) and improvement (9%) in their interviews as in a previous study with larger natural history sample (106). The different patterns of disease progression for young SMA II and adult SMA III patients in comparison with adults with SMA II as defined by the individuals in this study has also been reported by other authors (105,138). Weakness is widely accepted as an inevitable part of the disease trajectory of this condition without treatments (22,200–203). Individuals in this study report a perceived loss of strength within the context of other factors such as growth or weight gain.

The presence of fatigue, physical and mental was mainly reported by SMA III participants. This could be related to this group being more active in comparison to SMA II.

The ROM limitations have been reported previously (27,28) and in this study its progression was comparable with the reported literature being more stable for SMA II and more progressive for SMA III (107). In this study only non-ambulant or transitioning patients were included; this could have an impact on patient perception about the relevance of contractures in upper limbs compared to lower limbs. The impact of ROM management, especially orthotics, on ROM is also of interest with patients reporting that well-fitting splints could help manage ROM but stopped using them in adulthood with no further impact on ROM. An explanation for this could be that during childhood, splints are necessary due to growth, but their role is less relevant once growth has stopped.

There is limited literature regarding the impact of pregnancy and childbirth on disease progression in SMA (230–234). Several case reports regarding anaesthetic aspects of delivery in SMA have been published about this population (235–240). One paper (n=12)

(241), reported an exacerbation of weakness over the second trimester which did not improve after delivery for 50% of the patients. This concurs with our limited findings which also highlighted the issue of parenthood impacting levels of fatigue.

Patients reported limited access to physiotherapy when reaching adulthood. This has been clearly identified in the Muscular Dystrophy UK (MDUK) report to Parliament titled "Overstretched" which highlights as well the need of up-skilling the community staff (242). Similarly, patients reported a disparity of knowledge and care provided in the various centres across the country.

Patients described physiotherapy and exercise and activity as beneficial if done regularly. This is supported by evidence which suggests that regular exercise is beneficial either as strengthening and aerobic exercises (3 times a week) (206,243) or as hydrotherapy (2 times a week) (207,208). Exercise interventions and its potential benefits should be evaluated further with attention to exercise prescribed in a more systematic way.

The overall impact of spinal surgery was perceived as beneficial. In SMA II participants the benefit was reported to be immediately post-surgery, however SMA III participants reported an initial functional loss post-surgery as described in two previous publications (244,245). This study has highlighted the need of a better understanding of the consequences of spinal surgery on function.

The small cohort assessed in this study could be a limiting factor when extrapolating the results and may influence external validity. Internal validity could also have been affected by the influence of the profile of the researcher (a neuromuscular physiotherapist) and for some individuals by the presence of parents during the interviews. However, every effort was made to reduce this influence and the study has benefited from the neuromuscular physiotherapy background of the researcher to gain in-depth information about the interventions discussed.

Overall, the results and conclusions have contributed to a better understanding of patient perception of disease progression and the factors which influence that natural history progression. The main limitation of the project was the sample size which made it difficult to generalise the findings. However, it is possible that the main reason that

publication was not achievable was the lack of interest from journal editors in a combination of qualitative research observations, on rare disease with focus on non-pharmacological interventions. This conclusion was reached after journals mainly focused on qualitative research rejected the publication of this project but also after more quality-of-life focus journals took long periods of time to find reviewers on the subject. After different attempts and over two years of resubmissions the group of authors considered the project outdated after the appearance of a much bigger cohort of patients interviewed with similar purpose. This was in a project sponsored by pharma companies presented at the Cure SMA Researcher meeting, 23rd International SMA Research Meeting, 28th June to 1st July 2019 (https://bit.ly/2XmApaf). The result of this project was linked to the introduction of DMT which were introduced after the completion of our project. The rapidly evolving landscape with the approval of DMT, clearly changed the scene and made our results outdated and insufficient for future publication.

Since then, patient reported outcome measures has attracted increasing interest with special relevance when it comes to evaluating treatment efficacy with DMT. The current project has the potential to be considered a landmark on patient's perception before the implementation of DMT in the general population. The increasing access to more treatment has, with no doubt, impacted patient's perception regardless of if they are having access to any of the DMT.

Future qualitative research projects would certainly help in the ascertainment of patient perception about disease progression from this new perspective. Increasing sample size and focussing on specific aspects of care will generate better opportunities for generalisation of the results.

5.2 Real-world data on access to Standards of Care for people with Spinal Muscular Atrophy in the UK

The aim of this project was to describe the experience of individuals living with SMA regarding their specialist care in the UK in relation to the published SoC guidelines. As mentioned in chapter 2, the introduction of this project was an attempt to set the scene with the rapidly changing scenario in SMA with newly approved DMT.

This study made use of an online survey technique to capture participants who were representative of different areas, ages and SMA types. The overall response rate of 21% which is slightly lower than reference values of 25-30% (246) was considered acceptable in the context of rare diseases. The sample included individuals aged between 1-81 years with a bias towards adult participants over pediatric ones. In relation to the SMA type, type 3 seems to be overrepresented when compared to the current figures from different registries where type 2 is often the more represented type (211). One of the potential explanations of this bias is that during the time the survey was open (August 2020-June 2021), the managed access agreement didn't include non-walkers SMA type 3 (Appendix A). This was perceived from patient organisation as one of the potential explanations for the higher participation of type 3 in the survey.

The SoC for SMA defines which professionals should be accessible to individuals with this condition. This survey highlights that certain professionals are not accessible to patients and underscores the striking differences in access to certain specialties between pediatric and adult patient populations. Figures range from 59% difference for access to physiotherapy (100% pediatric, 41% adults) to 15% difference for access to a neurologist (85% pediatric and 70% adults). This holds true for access to interventions, ranging from 46% difference for access to supported standing (53% pediatric, 7% adult) and 45% difference for access to splints (59% pediatric, 14% adult) to 5% difference for access to mobility aids (91% pediatric, 86% adults). Because SMA is a progressive disease regardless of age (14), this implies that these differences will ultimately create a significant gap in care and provision for adults with SMA. However, this is not to say that access meets the SoC in children, although the level of care is better. On the other hand, access to specific professionals or interventions follows a clear pattern that correlates with disease severity.

Access to pulmonologist and respiratory physiotherapist are a good examples of this (See Table 4-6).

Limited access to care and provision recommended within the SoC document were regularly reported, with half of the study population consistently not accessing full multidisciplinary care. Regular follow up by a neurologist was accessible by most of the participants but more limited to other members of the MDT team (nurse specialist and physiotherapist). When looking at the frequency of visits, only around 65% of the participants are seen once or twice a year which confirms, even for those accessing specialists such as neurologists that SoC are unfortunately not being met.

The SoC document outlines the importance of access to interventions for contracture management however, this study highlights significant limitations to this access. This is particularly evident around access to spinal braces and supported standing which was only available to less than 20% of the participants but also for splints (26%). It would appear from this data that if a patient has access to a spinal brace or standing device that they are likely to make use of them. However, this is less true if you are provided with splints. This poor uptake of use may be associated with limited capacity for follow up from multidisciplinary team as highlighted above (i.e., follow up to ensure good fit).

Performing stretches is probably one of the clearer examples of an intervention where it is difficult to predict the specific needs for specific age groups or even specific individuals, or patients with a particular functional status. However only 17% of the participants reported doing more than 3 hours a week of stretches. There are different reasons that might influence the limited undertaking of these interventions but is also important to identify factors that might limit the relevant support required to ensure its recommended use such as access to more regular physiotherapy.

Exercise is widely accessible for many survey participants, but limited frequency of use raises questions as to why those with SMA do not exercise more frequently. In a similar way that the performance of stretches can be limited due to limited support, access to adapted facilities within a relatively short distance of patients can be a significant factor to limits other forms of exercise. Exercise, in its many different forms, was highly valued by

participants which infers an understanding of the benefit of exercise among the SMA population and therefore may have great potential for improvement in this aspect of care.

Mobility aids and home adaptations appeared to be widely available and were also reported as the most valued type of intervention across age and functional groups. Access to occupational therapy was reported as being limited but 65% reported they had access when needed which might be the explanation for the good accessibility to mobility aids and the relevant home adaptations as in the UK occupational therapists are often providers of mobility and adaptations rather than providing specific support and practice for activities of daily living.

Access to nutritional support or speech and language therapy appears only to be available for a small proportion of the participants. The fact that this access decreases with age and disease severity is of some concern given the importance of these interventions within the SoC document.

Access to respiratory care was good especially when looking at the more severe forms of SMA, which is reassuring due to the predominance of respiratory issues as the disease progresses (37). However limited or no access to cough augmentation was reported by 15% of the non-sitters and sitters which raises the question of equitable access across the UK. Due to the limited representation of participants from each region of the UK it is not possible to identify if this proportion of participants is representative of specific regions of the country.

One of the main limitations of this study is the small sample recruited in comparison to the estimated SMA population in the UK. Up to 3 attempts were undertaken to reach the targeted population through patient registry, patient organizations and social media and increase participation. The limited number of responders may skew the results as the methods used will not include those with no access to technology. It is difficult therefore to infer this survey population is truly representative of the overall population of SMA in the UK, however clear trends within age groups and functional status were observed.

Being able to quantify access to SoC in SMA from data provided by patients has been one of the most valuable learning points of this project. It has helped to highlight significant

limitations, in particularly regarding the adult population. As well as limited access to several different health professionals such as occupational therapists and physiotherapists, it is also concerning that a significant proportion of the adult population do not consider splints to be part of useful care (73%). It is difficult to interpret if this is due to the longstanding lack of access to orthotics or if there is a lack of understanding of their role in contracture management. Another interesting finding has been how highly participants rated the importance of stretches to their care but the significant limitations on accessing stretches (22% no access, 32% access with limitations). In both cases, it is clear the need to advocate so that subjects have better and regular access to supportive care in the community. This is particularly relevant when a substantial amount of public funding is supporting access to drug treatments which could in turn benefit from access to necessary SoC so best function is achieved. If there was a moment in history where having the right support could make a difference for people living with SMA it is now.

Another learning point of the project has been the importance of understanding the implications of the rapidly evolving scenario in the SMA field. With the rapid introduction of new treatments, people living with SMA, and their relatives have quickly shifted their expectations but also, their willingness to bring their condition to a more central role in their life. This has become apparent when performing this project as the unexpected bias towards SMA III in the response rate was thought to be linked to the limited access to nusinersen for this group of patients. The results were still valuable, due to the significant trends in some of the aspects covered, but it was difficult to effectively make conclusions with the sample size and representation. In future projects, exploring general patients' perceptions would benefit from incorporating the impact of ongoing treatment on changes in progression for better or worse and also to focus on more specific aspects such as bulbar function.

Now that the manuscript related to access to SoC is published, it is important that next steps now deliver these findings to organisations and care providers and that action is taken to reduce gaps in provision to ensure quality care of all individuals with SMA regardless of their access to DMT.

5.3 Developing a trunk assessment for SMA

The aim of the third project was to evaluate the capacity of specific items RHS to describe and quantify trunk involvement in SMA population.

The results of this cross-sectional analysis identified a sub-set of 6 items which had a strong correlation with FVC%. No correlation was identified when looking separately at functional groups (sitters and walkers). These results suggest that looking at a subset of items of the RHS could be of interest when assessing trunk weakness in SMA patients.

The sample collected, was similar in functional profile to the natural history published by Ramsey et al (112) which is suggestive of effective recruitment for the purpose of the research. The significant difference in the functional profile of walkers and sitters is a confirmatory finding of the natural history data. This is consistent with the recent trend to define patients more by their functional status rather than the initial SMA type used in the past.

The suggested list of correlative items in this project, has some clear overlaps with the ones identified by Dunaway et al (221) (see table 5-1). In their publication, Dunaway et al used the individual scores of the HMFSE to report on the impact of spinal surgery on motor abilities. Due to the similarity of the items of the HFMSE with the items in the RHS, a comparison can be made. Items such as “rolling from supine to prone” and “prop on forearms in prone” are present in both, but there are discrepancies such as “hands to head” or “hip flexion”. These differences are likely due to the limited impact that respiratory function can have on upper limb function (as captured by Item 3 and 4-hands to head) or low back/hip strength (as captured by Item 21 and 22-hip flexion) but which are heavily influenced by the presence of spinal fixation.

Table 5-1 Sub-set of Items compared with Dunaway et al

Sub-set of items with strong correlation	
RHS Item	**Descriptor**
3	Sitting to Lying
9	Rolls from supine to prone
10	Lifting head from prone

Sub-set of items suggested by Dunaway et al	
HFMSE Item	**Descriptor**
2	Long sitting
3 and 4	Hands to head in sitting
5, 8 and 9	Rolls supine to prone

11	In prone, prop on forearms
13	Rolls prone to supine
14	Lying to sitting

11	In prone, props on elbows
21 and 22	Hip flexion in supine

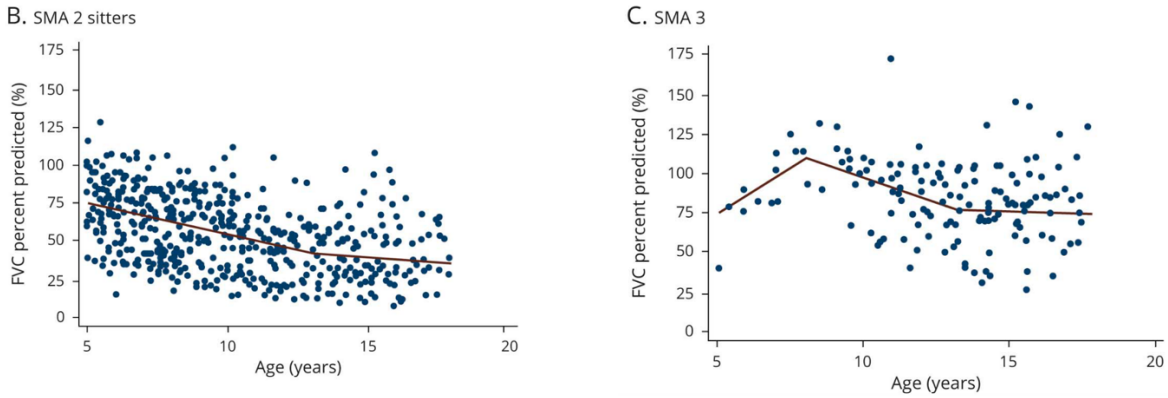
It is difficult to establish clear conclusions due to the limited number of subjects included in Dunaway's project (n=17). Further work could examine the relationship between all these variables. One of the limitations of the present study is that detailed information on spinal surgery was not collected or analysed (such the date of the surgery as compared to the date of the assessment). This limits the extent to which the impact of the procedure can be reported on.

Looking at the data collected and comparing the two groups, it becomes apparent that both variables (RHS and FVC%) had different degree of progression for similar clinical presentations (see figures 5-3 and 5-4). This was particularly evident when comparing sitters and walkers where functional data was much more discrete between the two groups whilst respiratory data overlapped more (top quartile).

This created significant doubts on the capacity of the FVC% to act as a gold standard for trunk involvement and therefore its ability to act as a point of construct validity for a potential subset of items of the RHS that could act as "trunk assessment items".

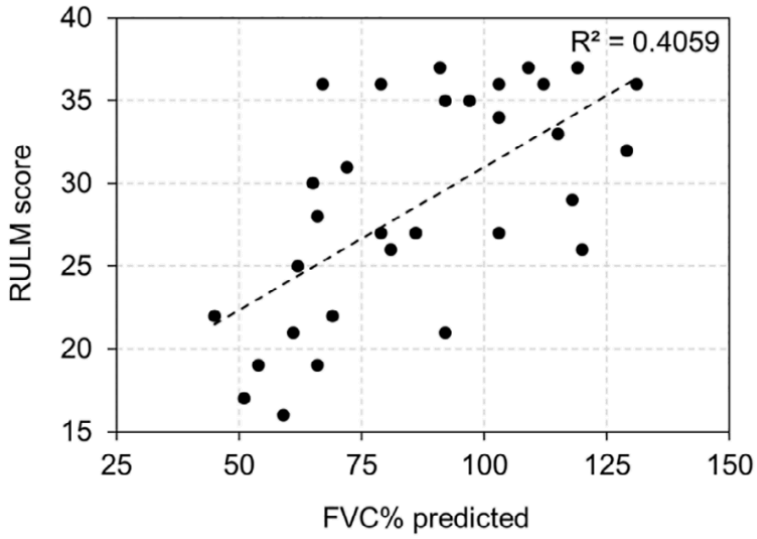
After the results of this projects were collected, our research group contributed to a joint project with international networks aiming to collected bigger datasets to gain a more in-depth understanding of pattern of respiratory involvement in SMA. The result of the initiative is the publication from Trucco et al (38) from 2020 which describes respiratory trajectories in SMA 2 and non-ambulant type 3 which is the group with a higher discrepancy between functional and respiratory data from our cohort (see figure 5-1).

Figure 5-1 Respiratory trajectories in SMA 2 and non-ambulant 3 from Trucco et al.



Despite the study being focused on pediatric data, it became more apparent that the range of respiratory progression is much milder than that of function when looking at our data. Trucco et al also reported a positive correlation of FVC% with total score of the HFMSE and RULM which is consistent with our data. For SMA, type 3 individuals who had lost ambulation our research group contributed to a similar study which examined the relationship of upper limb function as measured using the RULM and FVC% in a cohort of 16 individuals. This (39) demonstrated a positive correlation with total score of the RULM and FVC%, albeit in a much smaller cohort of patients (see figures 5-2).

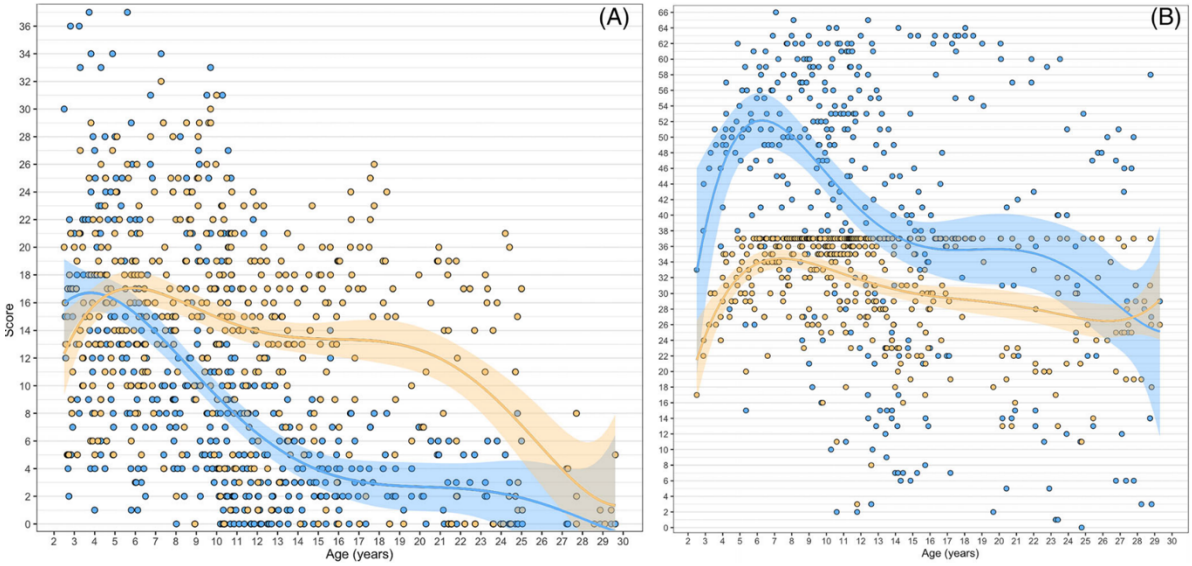
Figure 5-2 RULM and FVC % Predicted correlation from Wolfe et al.



Both publications, contributed to a better understanding of the progression of respiratory involvement and its correlation with total scores on functional scales however, in 2021 when Coratti et al (115) published functional trajectories for HFMSE and RULM in

this patient group (under the same international network) the relationship become clearer. In 364 patients' different trends in score and point of slope change for the two scales were noted. When change over one year was examined the two scales moved in the same direction in 57% and in 40% one scale remained stable and the other changed. This suggests that both scales are needed to capture progression effectively.

Figure 5-3 Functional trajectories in SMA 2 and 3 from Coratti et al.



Distribution of scores according to age and total score for SMA 2 patients (panel A) and SMA 3 patients (panel B). Color coding = blue: HFMSE, orange: RULM. Blue line: polynomial line for HFMSE (ribbon: 95% confidence interval [CI]). Orange line: polynomial line for RULM (ribbon: 95% CI). Polynomial line describes progression overtime, local maxima of the curve is indicative of the point of slope

Comparing the trajectories observed in Trucco (figure 5-9) and Coratti's publications (figure 5-3), it is apparent that they follow a different rate of progression and makes it even more questionable the capacity of the FVC% to predict functional deterioration. Whilst functional data showed different rates of progression by age groups: slight initial improvement up to age 5-6 for sitters and 7-8 years for walkers, to then general rapid deterioration. Respiratory data maintains a more sustained progression over decades even reaching normative values for a length of time in walkers.

One of the main learning points of the project has been the importance of data collection within the international network iSMAC. Collaborations with the PNCR (US network) and the Italian network together with the national network in the UK (SMAReach)

had been crucial to gather a significant sample size for the project. Understanding data sharing agreements and audit process has been a journey itself but has also created a more established path for future research projects and collaborations.

The second learning point is related to the specific aim of the project as, the aim to develop a new trunk assessment will require further steps to be completed. Learning how different functional assessments scores progress in SMA with age, has been mainly conducted using the total score as a unique indicator. The initial concept of using a specific sub-set of items to act as a surrogate to assess specific dimensions such as trunk involvement remains of interest. This is particularly true given the number of functional scales that patients are expected to perform at each clinical visit. A smaller subset could be evaluated more quickly and potentially remotely. Next steps could potentially promote current assessment to be a gold standard for validation of novel measures or perhaps, especially given the Coratti paper around the usefulness of using two scales to assess progression, combining items from across scales could assist in targeted trunk evaluation as well as the evaluation pre and post intervention similar to Dunaway's paper (221).

Future research projects could explore the role and progression of suggested sub-sets of items but also, explore how these integrate with techniques such as ACTIVE as a joint assessment of trunk and upper limb abilities. Lowes group had published data regarding the validity of ACTIVE to quantify meaningful change in SMA when compared with total scores of the HMFSE and RULM (227) which suggests that further research in this direction should also be considered.

In summary, the current body of knowledge has significantly progressed since the start of this project which makes the conception of further research to understand trunk involvement in SMA much clearer albeit more complicated in that multiple factors must be considered.

Chapter 6 Conclusions

Evaluating disease progression in a condition like SMA is a significant challenge due to the number of variables in action. First, the heterogeneity in the severity and type of symptoms affecting this disease population. Evaluation is also made more difficult as it is a disease that affects infants, children, and adults and this implies that developmental maturation, puberty, and old age need to be considered. It is also a rare disease, which means reaching conclusions from a single centre experience is unlikely to be generalisable. We have sought to reflect this in the chapters presented and outlined the learning points that we have experienced.

Gathering the patient voice and experience has helped us to understand the difference between their view and our clinical view. This relates not to just perception of progression but perception of benefit and use of management strategies around SoC.

Patients describe a similar pattern of disease progression as recorded by clinician rated outcomes, however the patients perceived the presence of contractures and hyperlaxity as being 'normal'. Individuals also perceive the ability or inability to perform a task, as much more important than the time it takes to do a task or the use of compensatory movements to achieve it. This could impact on how measurement scales are constructed and used within clinical trials with the loss of a function (often scored as 0) being giving greater significance than evidence that a particular task is more difficult (often scored as 1).

Patients reported benefit from many interventions when performed regularly (splints, stretches, physiotherapy, physical activity) however, they also reported poor access to these, in particular when reaching adulthood and variation in delivery of services in childhood. This study also highlighted the need to assess interventions such as exercise with attention given to duration, intensity, and frequency. In relationship to spinal surgery the immediate and long-term impact of spinal surgery appears to be different across the SMA sub-types. The impact on trunk function makes the timing of spinal surgery worthy of further exploration.

These insights from a patient's perspective will help us better understand disease progression in terms of natural history and should help guide us as we construct patient

reported outcomes in the new world of DMT. Insights from these interviews regarding management and exercise can contribute to refining our models of care for this group and led us to question patient access to SoC. The patient perspective in this chapter, has been one of the contributing factors which led to the project presented in the next chapter regarding real-world access to SoC.

Access to standards of care has probably been assumed to be delivered in a country with one of the wealthiest economies in the world, but most clinicians involved in the clinical field know that adequate care is often not implemented.

The results of our study suggest the need of further research to gain a better understanding of the limiting factors for contracture management. It is important to identify potential solutions related to training needs, additional budget allocated to community services or the increase overall awareness about SMA. This is crucial due to the impact of these aspects of care in conjunction with disease modifying treatments. For similar reasons it is recommended to undertake further investigations around effects and uptake of exercise for individuals with SMA.

There are pockets of good practice in the UK such as access to respiratory care or neurologist that align with the SoC documents. However, access is not equal for adults and children and access to certain healthcare professionals like physiotherapist, SALT or nutritionist is significantly limited. This creates a limitation in supportive care which is not reflected by the natural history of the disease.

Exercise and rehabilitation are particularly important to maximize the benefits of disease modifying therapies. This is particularly relevant not only to have access but to have the supportive care to ensure consistency in their practise. From this study it is clear that this is not in place for the UK.

The opportunity to publish information on real-world details of SoC provision in the UK will assist in the promotion of discussions on this subject with wider patient groups, clinicians, charities, funders, and care providers which will hopefully, with the right drivers and advocates, lead to a better care provision. Importantly addressing some of the significant disparities between provision for children and adults.

Developing new outcome measures to respond to specific clinical needs, requires extensive landscaping work and ensuring outcomes are relevant to patients as well.

Despite the initial encouraging finding of a sub-set of items of the RHS with a strong correlation with the FVC % predicted, the potential usability remains unclear due to the poor correlation with functional subgroups.

The clinical relevance of this subset of items is to be explored. One of the first potential uses might be to evaluate the impact of spinal surgery. A similar approach to the Dunaway et al paper looking at pre- and post-surgery scores would be of interest. Another potential focus of interest would be looking at differences observed when implementing regular use of spinal braces or positioning systems that are expected to weaken the trunk muscles.

The data presented here have contributed to the understanding some of the factors that influence disease progression in SMA and have led to positive collaborations with other researchers. The results have added a substantial body of knowledge to the understanding of the complex relationship between aspects such motor performance, respiratory function, and spinal health.

This research has identified avenues for future research in the evaluation of disease progression and care provision in SMA together with making contributions to patients prospective, access to standards of care and assessment of trunk weakness.

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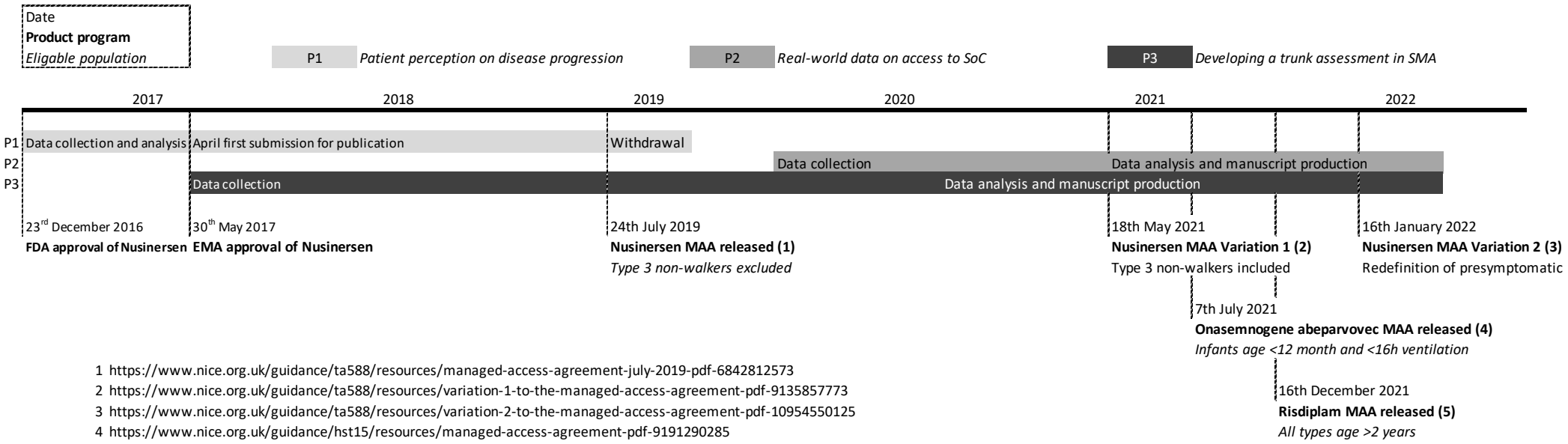
Appendix A Timeline with DMT implementation and project development



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Appendix B Interview framework for patient-perception project

Thank you for taking the time to participate in this interview to answer to the following questions. There are no right or wrong answers. We are here to better understand how we can improve our practice with SMA patients. We would like to know how patients and families feel about it.

We are going to ask you about your thoughts about what factors influence your ability to do everyday activities. By factors we mean anything that can change the way you manage a task.

The interview will be recorded so that we can transcribe it accurately and be able to review and analyse all relevant data. Once transcribed it will be erased.

Patient details:	ID: _____ Age: _____ Parents/Carers present: Yes No SMA type: I II III Functional Status: ambulant non-ambulant
Question 1:	Which is your general perception about the progression of your condition in the last year, last 5 years (Improving, stable, deterioration)? And during the last 10 years?
Question 2:	In your view, there's any activities / functions of daily life that had changed in the past 1 year, 5 years? And during the last 10 years?
Question 3:	One of the aspects that the Standards of Care are focused on is keeping joints mobile and preserving strength as much as possible (slow down the progressions of the weakness). Have you had any treatment or found anything helpful to keep your joints mobile and/or to preserve strength?
Question 4:	How effective (useful) have these been from your point of view?
Question 5:	Do you think that there's any intervention or strategy that has been or is particularly effective?
Question 6:	Thinking about the flexibility of your joints, do you have any tightness or contractures in your joints? Are these mainly arms or legs?
Question 7:	Are some of your joints very flexible (called hypermobility)?
Question 8:	Do you feel the tightness in your joints affects you to perform activities? Are they helpful for you, have no impact or do they constrict?
Question 9:	Do you think that hypermobility affects you in the same way?
Question 10:	We are trying to understand the relationship between strength and function (how you do things). Have you a perception of increasing weakness in the last 1 year, 5 years? And in the last 10 years?
Question 11:	How do you notice that? (e.g., Changes in function)
Question 12:	Sometimes when we talk about weakness people see this as including fatigue or tiredness or see this as something separate. Does fatigue affect how you function in everyday life?
Question 13:	Do you have any suggestion to improve the Standards of Care?
Question 14:	Any other comments?

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Real-World Data on Access to Standards of Care for People With Spinal Muscular Atrophy in the UK

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Spinal Muscular Atrophy (SMA) is characterized by muscle atrophy and weakness and has an incidence of 1:11. 000 live births which projects an estimated population in the UK of 650–1,300 affected patients. Standards of Care (SoC) were updated in 2017 and they have been widely adopted as a reference for implementation of care in SMA across the globe. The effectiveness of implementation and adherence to these standards across different countries is unclear. The aim of this study is to describe the experience of individuals with SMA regarding their care in the UK. An online anonymised survey was sent out *via* patient organizations, the UK SMA Patient Registry, professional networks, and social media to reach across the UK. The survey captured demographic profile, professionals involved in a patient's care, Interventions and access to mobility aids and home adaptations. Participants responded about their access to services and to rate how important each professional and intervention was for their health and wellbeing. One hundred and twenty-eight responses were collected with a median age of 34 years (1–81). Seventy-three percent of participants were adults and 60% men. Overall good access to neurologist (>90%) but limited to nurse specialist (48%) and physiotherapist (57%). Good access to respiratory support was reported but limited for interventions for positioning and bracing and exercise. This survey highlights that access to certain professionals for people with SMA is limited in the UK. Striking differences were noted between pediatric and adult populations. Limited access to care were regularly reported, with half of the study population consistently not accessing full multidisciplinary care. Access to interventions for contracture management were recorded to have significant limitations. Mobility aids and home adaptations are widely available and were also reported as the most valued interventions. Access to nutritional support or speech and

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language therapy appears only to be available for a small proportion of the participants. Access to respiratory care was good especially in severe forms of SMA. We found pockets of good practice in the UK that align with the SoC. However, access is not equal for adults and children and access to certain professionals is significantly limited.

Keywords: spinal muscular atrophy, standards of care, neuromuscular diseases, real-world data, United Kingdom

INTRODUCTION

Spinal Muscular Atrophy (SMA) is characterized by muscle atrophy and weakness secondary to a degeneration of the motor neurons in the reduction of SMN protein (1). SMA has an incidence of 1:11.000 live births (2) and a prevalence of 1–2:100.000 (3) which projects an estimated population in the UK of 650–1,300 affected patients.

A Consensus document on Standards of Care (SoC) was published in 2007 (4) and updated in 2017 (5, 6). The aim of these publications was to benchmark diagnosis and management of SMA. The process was performed over different rounds of Delphi survey and was based on the available evidence for diagnosis and interventions (7–13) but also providing expert based recommendations and a consensus statement where new advances in care were not reflected in the existing literature (5).

Nine topics were included in the updated document: (1) Diagnosis and genetics; (2) Physical therapy and rehabilitation; (3) Orthopedic care, growth, and bone health care; (4) Nutrition; (5) Pulmonary care; (6) Acute care in the hospital setting; (7) Other organ system involvement; (8) Medication; (9) Ethics and palliative care. For all the relevant aspects of the condition a series of specific recommendations were made regarding management. These were presented as Neuromuscular and musculoskeletal evaluation, Rehabilitation, orthopedic management, Nutritional management, swallowing and gastrointestinal dysfunction and finally pulmonary management. All these topics were generally summarized with specific recommendations according to the different functional subtypes: non-sitters, sitters, and walkers (**Table 1**).

The SoC have been widely adopted as a reference for implementation of care in SMA across the globe. The guidelines have also been used as a benchmark for care during clinical trials (5) and more generally with these treatments more recently becoming available *via* clinical care. The paradigm shift in SMA treatments with the appearance of new disease modifying therapies (DMT) has raised some ethical questions on standardization of supportive care to evaluate its impact on DMT (14).

The implementation of these standards and adherence to them across different countries or regions is still unclear. Some studies have identified significant differences with implications on the age at which ambulation is lost (15). In the UK no information has been gathered as to the extent in which these SoC are being implemented or if care in the UK is meeting these standards. Evidence also suggests that there is a substantial psychosocial impact of living with SMA (16) which is an aspect of care that is not covered by the current SoC guidelines.

Understanding the extent to which SoC are implemented will help identifying potential gaps.

The aim of this study is to describe the experience of individuals living with SMA regarding their specialist care in the UK in relation to the SoC as described in published documents. This includes which health professionals they have access to, how often they are seen, access to interventions and management and patient satisfaction with their current level of care. In addition, information about psychological or emotional support and carers was added to capture aspects of care not described in the SoC documents.

METHODS

An online anonymized survey with a total of 31 questions was design on Survio (survio.com) for the purpose of this study. The link inviting individuals to participate in this survey was sent out *via* patient organizations, the UK SMA Patient Registry, professional networks, and social media to reach the SMA population across the UK. Given the nature of data collection—*via* voluntary participation in an online survey with no direct contact with the participants no consent was implied and therefore no ethical approval was required.

The survey was structured in four main topics:

- **Demographic** profile (*Questions 1–9*)
  - Age, SMA type, functional status, and area of residence.
- **Range of professionals** involved in a patient's care (*Questions 10–13*)
  - General Practitioner (GP), Pediatrician, Neurologist, Nurse Specialist, Physiotherapist, Occupational Therapist, Speech and Language Therapist, Pulmonologist, Respiratory Physiotherapist, Orthotist, Dietician/Nutritionist, Care Advisor, Carer and Psychologist/Counselor.
- **Interventions** that patients have access to (*Questions 14–26*)
  - Contracture management (Splints, Stretches, etc.)
  - Postural management (Braces, Standing devices, etc.)
  - Respiratory support (NIV, cough augmentation)
  - Exercise plan (Strengthening, Endurance, etc.)
- **Access to mobility aids and home adaptations** (*Questions 27–30*)
  - Wheelchair access and home adaptations.

A final open text section was added for any additional comments.

TABLE 1 | Summary of recommendations on SoC.

Neuromuscular and musculoskeletal evaluation	**Assessment**
All	Assessments of **strength and range of joint motion, relevant motor functional scales and timed tests** to monitor those aspects of function that reflect activities of daily living. These assessments should be performed routinely by **trained examiners** every **6 months.**
Rehabilitation	
Type / **Assessment**	**Intervention**

Non-sitters
- Postural control
- Scoliosis
- Hip dislocation
- Sitting tolerance
- Chest deformities
- Contractures
  ○ ROM, goniometry
- Muscle weakness
  ○ antigravity movements
- Functional Scales
  ○ CHOP Intend
- Motor development
  ○ HINE
	- *Positioning and bracing:*
	  ○ Daily use of seating systems, postural
	- *Stretching:*
	  ○ Daily use of orthosis (>60 min to overnight)
	  ▪ Upper limb and AFO, KAFOS
	  ○ Braces (minimal frequency 5/week)
	  ▪ TLSO
	  ○ Stretches (duration depending of specific patient needs)
	- *Promote function and mobility:*
	  ○ Seating and mobility systems
	  ○ Mobile arm supports for upper extremity function

Sitters
- Postural control
- Foot and chest deformities
- Scoliosis and pelvic obliquity
- Hip dislocation
- Contractures
  ○ ROM, goniometry
- Functional Scales
  ○ HFMSE, RULM, MFM
- Muscle weakness
  ○ Strength tests
	- *Positioning and bracing:*
	  ○ Thoracic bracing posture and promote function (minimal frequency 5 times/week)
	- Cervical bracing for safety and transportation
	- *Stretching:*
	- Daily use of orthosis (>60 min to overnight)
	- Stretches (Minimal frequency stretching 5–7/week)
	- Supported standing (up to 60 min, minimal frequency 3–5/week, optimal 5–7 times/week)
	- *Promote function and mobility:*
	  ○ Exercise for function, strength, ROM, endurance, ADLs, participation and balance
	  ▪ Swimming, hippotherapy and wheelchair sport
	  ○ Electric/powered wheelchair with custom postural support
	  ▪ Tilt/recline option and seta elevator sometimes necessary

Walkers
- Mobility
- Timed tests
- Measure of endurance
  ○ 6 MWT
- Falls
- Functional Scales
  ○ HFMSE, RULM
- Muscle weakness
  ○ Strength tests
- Contractures
  ○ ROM, goniometry
- Postural control
- Scoliosis
- Hip dislocation
	- *Positioning and bracing:*
	  ○ Lower limb orthosis for posture and function
	  ○ Thoracic bracing to promote posture in sitting
	- *Stretching:*
	  ○ Stretches (Minimal frequency stretching 2–3/week, optimal 3–5 times/week)
	- Use of orthoses according to specific needs
	  ○ *Promote function and mobility:*
	  ○ Exercise (minimal frequency 2–3 times/week, optimal 3–5)
	  ▪ Maintain flexibility and balance exercises

Orthopedic Management	
Non-sitters - Cobb angle - Supine or sitting with trunk brace	○ Spine deformity management ○ Specific rigid braces

Sitters
- Inspection of spine
- Spine radiographs
- Hip instability
- Contractures
- Fractures
	- Spinal orthoses (Rigid or soft orthoses)
	  ○ For scoliosis >20 degrees specially with significant growth remaining
	- Surgical intervention based on:
	  ○ Magnitude of curve (>50 degrees)
	  ○ Rate of progression (>10 degrees per year)
	  ○ Other factors
	  ▪ Decreased respiratory function, parasol rib deformity, hyper kyphosis, pelvic obliquity, trunk imbalance)
	  ○ Delayed till age 4 years
	  ○ <8–10 years old: "growth-friendly" instrumentation
	  ○ 8–12 years old variability in practice

(Continued)

TABLE 1 | Continued

Type	Assessment	Intervention

		- Hip instability:
		  ○ Only managed surgically in patients with significant pain
		- Contractures:
		  ○ Surgical management of contractures to be considered when caused pain or impair function
		- Fractures
		  ○ Closed treatment with cast for non-ambulant patients
		  ▪ Avoid prolonger immobilization (> 4 weeks)
		  ○ Hip fractures: surgical stabilization

Walkers		- Fractures ○ Long bone benefit from surgical stabilization
Nutritional management, swallowing and gastrointestinal dysfunction		
Non-sitters	- Optimal care: 3–5 months children, annually by adults - Video Fluoroscopic Swallow Study shortly after diagnosis - Difficulties feeding - Nutritional analysis of food records - Longitudinal anthropometrics	- Referral to specialist feeding therapy/modification - Nasojejunal tube until gastric-tube with Nissen fundoplication - Adjust caloric, fluid, macronutrient, micronutrient and timing of feeds - Minimize fasting during acute care (<6 h) - Monitor Fluid intake, electrolyte, glucose level. - Bowel regulation medications
Sitters	- Minimum: evaluation by dietician shortly after diagnosis - Optimal: evaluation every 3–6 months children, annually adults - Symptoms of dysphagia/aspiration/difficulties feeding - Video fluoroscopic swallow study if suggested by clinical signs - Nutritional analysis of food records - Longitudinal anthropometrics - Specific acute care monitoring	- If swallow safe, referral for feeding therapy/modifications - If swallow failed, nasofeeding tube- long term gastric feeding tube - Growth failure, supplemental nutrition products
Walkers	- Dietician for nutrition - Longitudinal anthropometrics	- Provide macro/micronutrient intakes based on guidelines for healthy sedentary individuals - Minimize fasting during acute care
Pulmonary management		

Non-sitters	- Initially every 3 months then 6 monthly
	- Hypoventilation (End tidal CO_2)
	- Sleep study or pneumograms
	- Clinical assessment of gastroesophageal reflux
		- Airway clearance with oronasal suction, physiotherapy/respiratory therapy, and cough augmentation to all non-sitters with ineffective cough
		- Ventilation for all symptomatic patients
		  ○ Some experts recommend it before documented respiratory failure
		  ○ Judge start based on clinical observation for adequate gas exchange or during sleep study
		  ○ NIV interfaces fitted by skilled physiotherapist
		- Customary immunizations, palivizumab and influenza + Mucolytics should not be used long-term

Sitters	- 6 monthly - Same as above	- Same as above
Walkers	- Clinical evaluation for cough effectiveness or signs of hypoventilation	- Supportive care when needed - Customary immunizations, annual influenza and pneumococcal vaccination

Adapted from Finkel et al. (14) and Mercuri et al. (5).

Participants were asked about their access to services/care including location (*community, specialized center, or both*) and frequency of their visits. To gather their perception, participants were asked to rate how important each professional was for their health and wellbeing (*1 meaning not at all and 10, most important*). Participants were also asked to rate how often they would like to see each professional if applicable for them (*Less often, as much as I'm seen now, more often*).

To ascertain interventions and access to mobility aids and home adaptations a similar approach was performed. First participants were asked about their access to each specific intervention and if applicable, its frequency of use. Afterwards, the relevance was rated (1–10 as previously) and their degree of satisfaction about access was requested (*I don't need it, I believe I do need it but can't get it, I do need it and can get it but with limitations, I do need it and I get what I need*).

RESULTS

Demographics

A total of 128 responses were collected (3 excluded due to a non-5q SMA diagnosis reported). The majority of participants (68%) took between 10 and 30 min to complete the survey. Overall completion rate was 21% (635 total visits) and none of the surveys were left incomplete.

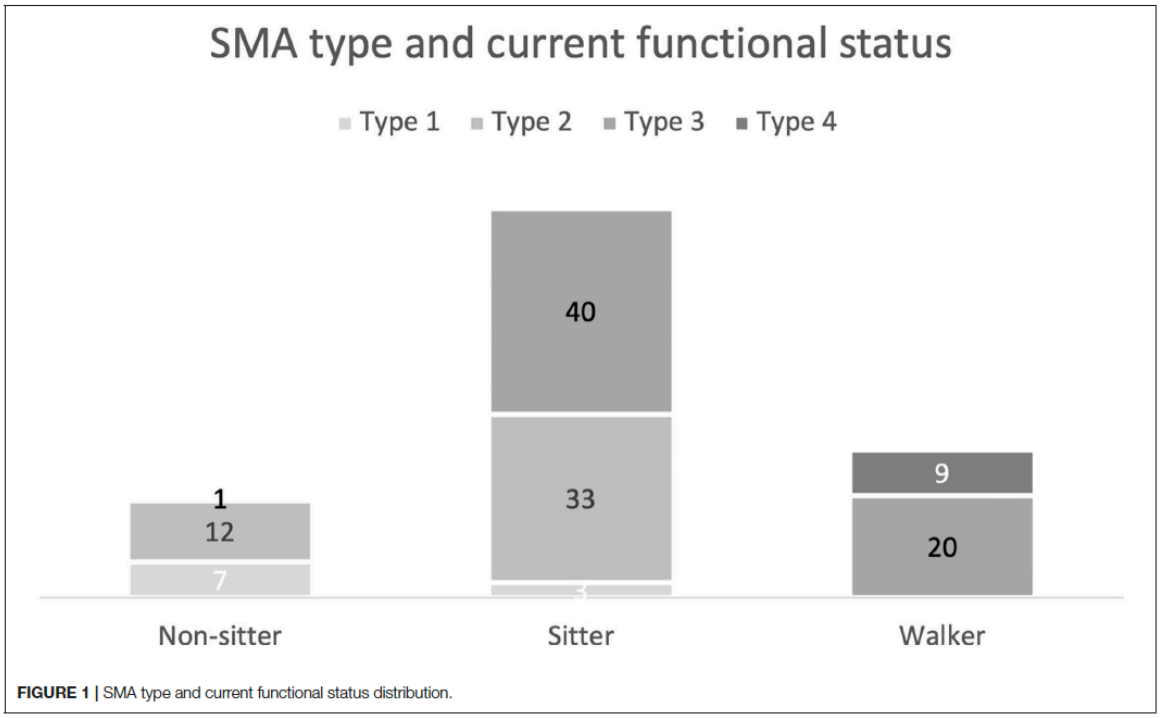

FIGURE 1 | SMA type and current functional status distribution.

Median age was 34 years (range from 1 to 81 years of age) with good representation across the different age ranges (average 9 responses per group) and with 73% of participants being adults and 60% men. Responses from participants below age 14 were collected through parents or tutors. Above that age, responses were reported by patient themselves or jointly with parents or carers.

When analyzed by current functional status, sitters were the most represented functional group (76%) (**Figure 1**).

Most participants were based in England (85%) but also representation from Scotland, Wales, Northern Ireland, and Guernsey was collected. The sample from England was spread across 35 counties out of a total 48.

Access to Professionals and Interventions According to Standards of Care

Access to SoC was measured by the proportion of participants that reported access to the relevant professional or intervention and how often they were seen or received the care.

SoC recommendations include "neuromuscular and musculoskeletal evaluation by trained examiners every 6 months". (5) *Page 4*

A significant majority of the participants reported having access to a neurologist (**Table 2A**). This was consistent across age and functional ability except for walkers who reported having better access in the pediatric group. Sixty-four percent reported seeing a neurologist once or twice a year or more frequently however, a difference was observed between pediatric (94%) and adults (52%).

Access to a nurse specialist was reported by less than half of the participants again showing a discrepancy between pediatric (76%) and adult (23%) responders. Frequency of visits was reported to be once or twice a year or more by 57%.

In total, over half of the participants reported having access to a physiotherapist with a significant difference over pediatric and adult responders. Sixty-four percent of participants reported seeing a physiotherapist once a year or more (81% pediatric, 38% adult). Only 14% reported regular access (once every 2 months or more) with a difference for age group (38% pediatric, 5% adult).

In the Rehabilitation section, recommendations are made for "positioning and bracing". These include: use of orthosis (splints) for more than 60 min or overnight, use of braces for non-sitters and sitters 5 times a week. (5) *Page 5*

The use of splints was reported by just over quarter of all participants with non-sitters using them most compared to sitters and walkers (**Table 2B**). The frequency and duration of use was reported to be for an hour a day or more by 43% of the users—non-sitters (63%) followed by walkers (55%) and sitters (30%).

Spinal braces were reported to be used by a minority of the overall participants being mainly non-sitters and sitters with 73% reporting using them more than 3 h a day.

TABLE 2 | Reported access by age and functional group.

(A)

Access reported to	Neurologist	Physiotherapist	Nurse
Pediatric	**97%**	**100%**	**76%**
Non-sitter	100%	100%	89%
Sitter	95%	100%	84%
Walker	100%	100%	33%
Adult	**87%**	**41%**	**23%**
Non-sitter	91%	36%	45%
Sitter	93%	44%	26%
Walker	70%	45%	4%
Grand total	**90%**	**57%**	**48%**

(B)

Access reported to	Splints	Spinal braces	Stretches	Supported standing
Pediatric	**59%**	**15%**	**82%**	**53%**
Non-sitter	67%	22%	78%	33%
Sitter	53%	16%	89%	79%
Walker	67%	0%	67%	0%
Adult	**14%**	**13%**	**44%**	**7%**
Non-sitter	18%	18%	57%	0%
Sitter	14%	16%	47%	7%
Walker	13%	4%	30%	9%
Grand total	**26%**	**14%**	**54%**	**19%**

(C)

Access reported to	Occupational therapist	Mobility aids	Home adaptations	Exercise
Pediatric	**88%**	**91%**	**62%**	**91%**
Non-sitter	100%	89%	89%	78%
Sitter	89%	100%	47%	95%
Walker	63%	67%	67%	100%
Adult	**53%**	**86%**	**88%**	**62%**
Non-sitter	55%	100%	91%	73%
Sitter	63%	100%	98%	54%
Walker	26%	43%	61%	74%
Grand total	**62%**	**87%**	**81%**	**70%**

(D)

Access reported to	Dietician/nutritionist	Speech and language therapist
Pediatric	**47%**	**44%**
Non-sitter	67%	78%
Sitter	42%	36%
Walker	33%	0%
Adult	**11%**	**10%**
Non-sitter	36%	27%
Sitter	11%	10%
Walker	0%	0%
Grand total	**21%**	**16%**

(Continued)

TABLE 2 | Continued

(E)

Access reported to	Pulmonologist	Respiratory physiotherapist	Ventilator	Airway clearance
Pediatric	**60%**	**54%**	**32%**	**38%**
Non-sitter	100%	100%	89%	89%
Sitter	53%	53%	11%	26%
Walker	29%	0%	17%	0%
Adult	**42%**	**26%**	**19%**	**21%**
Non-sitter	82%	73%	73%	64%
Sitter	42%	27%	16%	21%
Walker	22%	0%	0%	0%
Grand total	**47%**	**34%**	**22%**	**26%**

The bold values indicates the overall figures for pediatric, adult and grand total of the cohort (in opposition to breakdown by functional status for the same groups).

Also in the rehabilitation section, stretches are recommended with different regimes depending on functional status: to be adapted to patients needs for non-sitters, 5–7 times a week for sitters and 2–3 to 3–5 times a week for walkers. (5) *Page 5*

Over half of the participants reported doing stretches with higher rate for non-sitters, followed by sitters and walkers (**Table 2B**). Looking at performing stretches by age group, pediatric participants have a higher rate than adults.

The use of supported standing devices is recommended in addition to stretches for sitters for 60 min, 3–5 to 5–7 times a week. (5) *Page 5*

A supported standing device (Standing frame or KAFOS) is used by a minority of participants (**Table 2B**); 20% of these reported using this device for an hour a day or more as recommended in SoC. The most commonly reported use was for an hour almost every day (43% of the users).

In the rehabilitation section several interventions are recommended to "promote function and mobility". Introduction of home adaptations, mobility aids and exercises are recommended with different specification depending on functional type. It is suggested that exercise can have an effect on function, strength, ROM, endurance for sitters. Walkers are encouraged to perform aerobic and general conditioning exercise (at least for 30 min per session). Some examples of specific exercises are suggested for both types including swimming hippotherapy, wheelchair sports, walking, rowing, cycling, yoga, etc. (5) *Page 5*

Access to occupational therapy is reported to be available to over half of the participants with much higher proportion in pediatrics in comparison to adults (**Table 2C**). Frequency of once a year or more was reported by 26% of the users with "being seen when needed" the most common response (65% overall, 50% of pediatric, 73% of adults).

Mobility aids and home adaptations are accessible to the great majority of the participants with higher access for more severe phenotypes (**Table 2C**).

Home adaptations are spread across different dimensions. Fifty-four percent of participants have access to mobility adaptations (handrails, stair lifts, ramps, etc), 62% for selfcare (toilet, shower, wet room, etc), 48% for transfers (hoist, sliding board, etc.) (75% for non-sitters, 57% of sitters and 7% walkers) and 22% accessories (adapted cutlery, trays, adapted clothes, etc.) (30% of non-sitters, 26% of sitters and 7% walkers).

Access to any form of exercise was reported by most of the participants with much higher rate for pediatrics (**Table 2C**). Endurance exercise was accessible for 20% (5% of non-sitters, 17% of sitters, 38% of walkers and 38% of pediatrics, 13% of adults). Mixed exercise (yoga, Pilates, etc.) was accessible by 6% of the participants (9% pediatric and none of the adults).

In the Nutrition section, optimal evaluation was recommended to be for non-sitters and sitters from 3 to 6 months for children and yearly for adults. (5) *Page 8*

Access to dietician or nutritionist and speech and language therapist is reported to be available to a minority of the participants with more than double proportion for pediatric in comparison to adults. Access was more present also for more severe phenotypes (**Table 2D**). The frequency most reported for visits to dietician or nutritionist was "when needed" for pediatrics (69%) and once or twice a year for adult users (60%).

For speech and language therapist, 35% of the users reported to be seen at least once a year in (38% pediatrics, 30% adults), with "being seen when needed" the most common result for pediatrics (62%) and less than once a year (40%) for adults.

In the respiratory section, SoC recommendation suggest regular assessment for non-sitters (3–6 monthly) and sitters (6 monthly) and access when needed for walkers. It is also recommended access to support for airway clearance, physiotherapy/respiratory therapy and ventilation for all symptomatic patients. (6) *Page 3*

Access to pulmonologist is reported by nearly half of the participants and in slightly lower proportion for respiratory physiotherapist (**Table 2E**). There were differences for both professionals when comparing pediatric and adult participants. As seen previously, access was also higher for more severe phenotypes being nearly unexciting for walkers. Frequency of visits was reported to be for once or twice a year or higher in 80% of the users for pulmonologist and by 59% for respiratory physiotherapist.

Access to ventilation and airway clearance is reported by nearly a quarter of the participants with differences by functional level (**Table 2E**). Again, more severe phenotype reported higher rate of access. For ventilation, the most common frequency if use was "every night" (48%) with 33% of non-sitters reporting additional daytime use. For airway clearance the frequency of use most reported was "twice a day" by non-sitters (47%) and "when needed" by sitters (41%).

In addition to the professionals included in the SoC document, access to psychological support was reported to as available by 14% of the participants with a reported frequency of visits "when needed" by 44%.

Participant's Perception

Participants rated the importance of having access to different professionals and interventions represented by age and functional group (**Tables 3, 4**).

Participant's perception about current access was also captured with scores ranging from not applicable, satisfied with current access or access with limitations. For the professional this was reported with the options "would like to see them" more often or less often. The option "less often" was only reported by one individual consistently across different professionals involved. This option has been excluded from the table to limit the presence of a column with minimal significance.

Over half of the participants reported satisfactory access to a neurologist with only a minority reporting they role wasn't applicable to them (**Table 5A**). The was a difference when comparing pediatric participants to adults.

Access to nurse specialist was reported to be not applicable by half of the participants being much higher for adult participants when compared to pediatrics. This differences made that most of the pediatric participants were satisfied with current access and most adults reported the role not applicable for them. Most participants reported insufficient access to physiotherapist with slightly higher rate within adult participants. Access to occupational therapist was nearly splint in thirds for each category being satisfactory access the most reported one. This proportion was higher for pediatric participants.

Most of participants rated access to a dietician/nutritionist and speech and language therapist as not applicable with small differences in between pediatric patients and adults (**Table 5B**).

Over half reported that access to a Pulmonologist was applicable with slightly higher proportion of adult willing to see them more often (**Table 5B**). By functional status, the role had clear trends for non-sitters where they had satisfactory access and walkers that find the role not relevant. When looking at sitters, there more spread across the three categories with predominance

TABLE 3 | Rate of importance by professionals by age and functional group.

Mean, SD	General practitioner	Pediatrician	Neurologist	Nurse specialist	Physiotherapist	Occupational therapist	Speech and language therapist	Pulmonologist	Respiratory physio, therapist	Orthotist	Dietician/ nutritionist	Care advisor	Carer	Psychologist/ emotional support/ counselor
Pediatric	**5.1**	**5.4**	**8.9**	**6.7**	**9.2**	**8.6**	**3.4**	**5.8**	**5.9**	**7.7**	**4.7**	**4.1**	**2.6**	**3.1**
Non-sitter	5.3	5.3	8.6	7.4	8.6	7.7	4.9	8.3	8.4	6.4	4.7	3.4	5.0	4.7	2.2
Sitter	5.5	5.9	8.9	7.6	9.9	9.0	3.5	5.7	6.2	8.0	4.4	4.3	1.8	2.3	2.4
Walker	3.8	3.8	9.0	2.8	7.8	8.5	1.0	2.3	1.2	8.5	6.0	4.7	1.3	0.8	6.8
Adult	**6.4**	**1.8**	**7.9**	**3.4**	**6.7**	**5.6**	**2.4**	**5.2**	**4.3**	**3.0**	**4.0**	**3.8**	**6.2**	**4.3**	**4.4**
Non-sitter	7.8	2.5	8.2	4.5	6.0	5.5	2.8	8.9	6.9	4.2	5.3	3.6	9.1	2.7	5.0
Sitter	6.6	1.9	7.9	4.7	7.1	6.2	3.0	5.7	5.0	2.9	4.5	4.5	6.9	4.1	4.7
Walker	5.3	1.3	7.9	1.8	6.2	4.4	1.3	2.1	1.4	2.4	2.4	2.0	2.9	3.4	3.4
Total	**6.1**	**2.8**	**8.2**	**4.7**	**7.4**	**6.4**	**2.6**	**5.4**	**4.8**	**4.2**	**4.2**	**3.9**	**5.2**	**4.3**	**4.1**

Mean, SD	General practitioner	Pediatrician	Neurologist	Nurse specialist	Physiotherapist	Occupational therapist	Speech and language therapist	Pulmonologist	Respiratory physio, therapist	Orthotist	Dietician/ nutritionist	Care advisor	Carer	Psychologist/ emotional support/ counselor
Pediatric	**2.9**	**5.4**	**3.4**	**2.2**	**6.7**	**3.2**	**1.6**	**8.6**	**2.0**	**3.4**	**3.5**	**4.0**	**2.5**	**4.7**	**3.5**	**4.1**	**4.0**	**2.6**	**3.3**	**3.1**	3.2
Non-sitter	2.6	5.3	3.5	2.6	7.4	2.7	1.9	7.7	2.8	4.9	3.8	2.2	8.4	2.2	6.4	2.4	4.7	3.2	3.4	5.0	4.7	2.2	2.2
Sitter	3.2	5.9	3.6	2.3	7.6	2.7	0.3	9.0	1.7	3.5	3.6	5.7	4.3	6.2	4.2	8.0	2.8	4.4	3.6	4.3	4.1	1.8	2.3	2.4	2.6
Walker	2.2	3.8	2.4	9.0	1.7	2.8	2.9	7.8	2.4	8.5	0.8	1.0	2.3	2.2	1.2	0.4	8.5	1.0	6.0	4.1	4.7	4.4	1.3	0.8	6.8	3.7
Adult	**2.9**	**1.8**	**2.3**	**7.9**	**2.4**	**3.4**	**6.7**	**3.4**	**5.6**	**3.2**	**2.5**	**3.9**	**3.8**	**3.0**	**3.0**	**4.0**	**3.5**	**3.8**	**3.5**	**6.2**	**4.3**	**4.3**	**4.4**	**3.6**
Non-sitter	1.7	2.5	3.4	8.2	1.9	4.5	3.5	6.0	3.4	5.5	2.8	2.8	8.9	1.6	6.9	3.3	4.2	3.8	5.3	3.6	3.6	3.3	9.1	2.7	5.0	3.8
Sitter	2.9	1.9	2.4	7.9	2.4	4.7	3.6	7.1	3.4	6.2	3.0	2.7	5.7	2.8	5.0	4.0	2.9	3.9	4.5	3.6	4.5	3.6	6.9	4.1	4.7	3.7
Walker	3.1	1.3	1.5	7.9	2.6	1.8	1.9	6.2	3.4	4.4	3.6	1.3	2.1	0.9	1.4	2.3	2.4	2.8	2.4	2.9	2.0	2.7	2.9	3.4	3.4	3.5
Total	**2.9**	**2.8**	**3.1**	**8.2**	**2.4**	**4.7**	**3.6**	**7.4**	**3.2**	**6.4**	**3.2**	**2.6**	**5.4**	**2.8**	**4.8**	**3.9**	**3.6**	**4.2**	**3.5**	**3.9**	**3.6**	**5.2**	**4.3**	**4.1**	3.6

1 (black) = not at all important and 10 (white) = most important. The bold values indicates the overal figures for pediatric, adult and grand total of the cohort (in opposition to breakdown by functional status for the same groups).

TABLE 4 | Rate of importance by intervention by age and functional group.

Mean, SD	Splints	Back braces	Supported standing	Ventilator	Cough augmentation	Stretches	Streng -thening exercises	Endurance exercise	Mixed exercise	Other exercise	Mobility devices	Home adaptations
Pediatric	**7.2**	**3.2**	**4.3**	**4.2**	**6.3**	**4.0**	**4.4**	**5.2**	**4.1**	**4.4**	**9.0**	**1.2**	**8.6**	**2.5**	**7.8**	**3.0**	**6.8**	**3.6**	**6.4**	**3.9**	**9.5**	**1.8**	**9.1**	**2.0**
Non-sitter	7.0	2.7	3.6	4.4	6.0	3.7	8.9	9.5	1.7	1.1	8.7	1.1	8.0	3.2	7.6	3.3	7.9	3.2	5.6	4.3	9.0	3.0	9.4	1.3
Sitter	7.5	3.2	5.5	4.3	7.5	3.6	2.4	4.2	3.1	4.3	9.4	1.1	8.8	2.5	7.8	3.1	7.2	3.5	7.5	3.6	9.9	0.2	9.4	2.1
Walker	6.2	4.1	1.0	0.0	1.0	0.0	2.8	1.0	3.5	0.0	7.8	1.3	8.4	1.5	8.2	2.7	4.0	3.9	3.8	4.1	8.8	2.0	7.8	2.4
Adult	**2.9**	**3.1**	**2.3**	**3.1**	**2.4**	**2.9**	**3.4**	**4.0**	**3.7**	**4.1**	**6.8**	**3.2**	**6.7**	**3.3**	**5.9**	**3.7**	**5.3**	**3.8**	**5.6**	**3.9**	**8.4**	**3.2**	**9.0**	**2.1**
Non-sitter	4.2	4.1	2.8	3.6	2.3	3.0	8.1	7.9	3.2	3.4	7.4	3.0	5.8	3.8	4.7	3.9	3.8	3.2	4.4	3.6	10	0.0	8.9	2.0
Sitter	2.8	2.9	2.8	3.5	2.8	3.2	3.2	4.3	3.6	4.2	7.0	3.2	6.6	3.4	5.4	3.9	5.4	4.0	5.9	4.0	9.7	1.4	9.7	1.0
Walker	2.6	3.2	1.0	0.0	1.5	2.1	1.0	1.0	0.0	0.0	6.1	3.3	7.4	2.9	7.5	2.7	6.0	3.7	5.7	3.9	4.5	3.8	7.3	3.2
Total	**4.2**	**3.7**	**2.9**	**3.5**	**3.6**	**3.7**	**3.7**	**4.3**	**3.8**	**4.2**	**7.5**	**2.9**	**7.3**	**3.2**	**6.5**	**3.6**	**5.8**	**3.8**	**5.9**	**3.9**	**8.7**	**2.9**	**9.0**	**2.1**

1 (black) = not at all important and 10 (white) = most important. The bold values indicates the overal figures for pediatric, adult and grand total of the cohort (in opposition to breakdown by functional status for the same groups).

of the role not being applicable for nearly half of the participants. Respiratory Physiotherapist access follows a similar pattern with slightly higher rate of unsatisfied participants (**Table 5B**).

Forty-eight percent participants reported that access to psychologist or emotional support was applicable, with 38% willing to see them more often. Of those accessing this support 79% said that would like to receive this support more frequently either for themselves or their child.

Participant's perception around access to specific interventions is reported again with the most common option selected with additional distinction by age group or functional status when significant differences were noted.

Most of the participants reported not needing access to splints with a significant contribution of adult participants (**Table 5C**). When looking at the proportion separately, the majority of pediatric patient reported to get what they need.

Access to spinal braces was perceived as not needed by most of the participants being only pediatric sitters the ones to report higher rates for satisfactory access and access with limitations.

Access to stretches was perceived as needed by the majority reporting a similar degree of satisfaction with current access across different functional status. Pediatric patients' higher degree of satisfaction age group.

Most of the participants reported not needing access to a supported standing devices, with much higher proportion for adults. This was particularly true for walkers being sitters the functional group with higher degree of satisfaction.

Access to mobility devices was reported to be widely accessible with a similar distribution for those who have access with some limitations and those who have access to what they need (**Table 5D**). There were no major differences in between functional or age group with the only exception of adults walkers where the majority reported not needing mobility aids.

For home adaptations the distribution of responses was similar to mobility aids but showing higher rate of participants with no access.

Access to Ventilation was reported as accessible when needed with a small proportion having access with limitations. It was clearly less needed for less severely affected participants. Airway clearance devices follow a similar pattern but with a higher rate of participants reporting no access despite needing it (**Table 5E**).

In relation to access to exercise, endurance, strengthening and mixed exercise were reported as not being accessible by a similar proportion of participants with slightly higher rates for adults (**Table 3E**). Access with limitations or satisfactory access was reported to be higher in pediatric patients for strengthening and endurance exercise, whilst having similar figures for mixed exercise. The proportion of participants that reported not needing each form of exercise, it was again higher for adults and gradually increase overall from strengthening, endurance to mixed having the highest proportion.

DISCUSSION

This study made use of an online survey technique to capture participants who were representative of different areas, ages and

TABLE 5 | Reported frequency of access satisfaction by age and functional group.

(A)

	Neurologist			Nurse specialist			Physiotherapist			Occupational therapist		
Frequency satisfaction	**More often**	**Not applicable for me**	**As much as I'm seen now**	**More often**	**Not applicable for me**	**As much as I'm seen now**	**More often**	**Not applicable for me**	**As much as I'm seen now**	**More often**	**Not applicable for me**	**As much as I'm seen now**
Pediatric	**26%**	**9%**	**66%**	**23%**	**23%**	**54%**	**57%**	**3%**	**40%**	**23%**	**9%**	**69%**
Non-sitter	11%	11%	78%	11%	11%	78%	67%	0%	33%	22%	0%	78%
Sitter	26%	11%	63%	21%	21%	58%	53%	5%	42%	21%	11%	68%
Walker	43%	0%	57%	43%	43%	14%	57%	0%	43%	29%	14%	57%
Adult	**49%**	**5%**	**46%**	**23%**	**60%**	**17%**	**66%**	**16%**	**17%**	**34%**	**32%**	**35%**
Non-sitter	36%	0%	64%	18%	55%	27%	36%	18%	45%	45%	18%	36%
Sitter	47%	5%	48%	29%	51%	20%	76%	12%	12%	36%	22%	41%
Walker	61%	9%	30%	9%	87%	4%	57%	26%	17%	22%	61%	17%
Grand total	**43%**	**6%**	**51%**	**23%**	**50%**	**27%**	**64%**	**13%**	**24%**	**31%**	**25%**	**44%**

(B)

	Dietician/nutritionist			Speech and language therapist			Pulmonologist			Respiratory physiotherapist		
Frequency satisfaction	**More often**	**Not applicable for me**	**As much as I'm seen now**	**More often**	**Not applicable for me**	**As much as I'm seen now**	**More often**	**Not applicable for me**	**As much as I'm seen now**	**More often**	**Not applicable for me**	**As much as I'm seen now**
Pediatric	**20%**	**46%**	**34%**	**3%**	**69%**	**29%**	**6%**	**43%**	**51%**	**20%**	**43%**	**37%**
Non-sitter	22%	33%	44%	11%	33%	56%	0%	0%	100%	33%	0%	67%
Sitter	16%	53%	32%	0%	74%	26%	11%	47%	42%	21%	42%	37%
Walker	29%	43%	29%	0%	100%	0%	0%	86%	14%	0%	100%	0%
Adult	**29%**	**60%**	**11%**	**8%**	**82%**	**11%**	**20%**	**49%**	**32%**	**23%**	**57%**	**21%**
Non-sitter	30%	20%	50%	0%	64%	36%	27%	0%	73%	27%	18%	55%
Sitter	36%	56%	8%	9%	81%	10%	24%	44%	32%	27%	51%	22%
Walker	13%	87%	0%	9%	91%	0%	5%	86%	9%	9%	91%	0%
Grand total	**27%**	**56%**	**17%**	**6%**	**78%**	**16%**	**16%**	**47%**	**37%**	**22%**	**53%**	**25%**

(C)

	Splints				Spinal braces				Stretches				Supported standing			
Frequency satisfaction	**I believe I do need it but can't get it**	**I do need it and can get it but with limitations**	**I do need it and I get what I need**	**I don't need it**	**I believe I do need it but can't get it**	**I do need it and can get it but with limitations**	**I do need it and I get what I need**	**I don't need it**	**I believe I do need it but can't get it**	**I do need it and can get it but with limitations**	**I do need it and I get what I need**	**I don't need it**	**I believe I do need it but can't get it**	**I do need it and can get it but with limitations**	**I do need it and I get what I need**	**I don't need it**
Pediatric	**12%**	**21%**	**38%**	**29%**	**3%**	**15%**	**12%**	**71%**	**9%**	**41%**	**44%**	**6%**	**6%**	**12%**	**38%**	**44%**

(Continued)

TABLE 5 | Continued

Frequency satisfaction	Splints				Spinal braces				Stretches				Supported standing			
	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it
Non-sitter	0%	33%	33%	33%	0%	22%	0%	78%	11%	33%	33%	22%	**11%**	**22%**	**11%**	**56%**
Sitter	16%	16%	42%	26%	5%	16%	21%	58%	5%	42%	53%	0%	**5%**	**11%**	**63%**	**21%**
Walker	17%	17%	33%	33%	0%	0%	0%	100%	17%	50%	33%	0%	**0%**	**0%**	**0%**	**100%**
Adult	**8%**	**12%**	**8%**	**73%**	**3%**	**5%**	**5%**	**86%**	**26%**	**29%**	**19%**	**26%**	**10%**	**3%**	**5%**	**81%**
Non-sitter	18%	0%	18%	64%	9%	0%	9%	82%	27%	27%	18%	27%	**9%**	**0%**	**0%**	**91%**
Sitter	9%	12%	7%	72%	4%	9%	7%	81%	28%	32%	18%	23%	**14%**	**5%**	**5%**	**75%**
Walker	0%	17%	4%	78%	0%	0%	0%	100%	22%	22%	22%	35%	**0%**	**0%**	**9%**	**91%**
Grand total	**9%**	**14%**	**16%**	**61%**	**3%**	**8%**	**7%**	**82%**	**22%**	**32%**	**26%**	**21%**	**9%**	**6%**	**14%**	**71%**

(D)

Frequency satisfaction	Mobility aids				Home adaptations				Ventilation				Cough augmentation			
	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it
Pediatric	**6%**	**44%**	**44%**	**6%**	**29%**	**26%**	**38%**	**6%**	**0%**	**6%**	**35%**	**59%**	**6%**	**9%**	**29%**	**56%**
Non-sitter	0%	56%	33%	11%	22%	33%	44%	0%	0%	11%	89%	0%	11%	11%	67%	11%
Sitter	0%	42%	53%	5%	26%	26%	37%	11%	0%	5%	16%	79%	5%	11%	21%	63%
Walker	33%	33%	33%	0%	50%	17%	33%	0%	0%	0%	17%	83%	0%	0%	0%	100%
Adult	**1%**	**48%**	**37%**	**13%**	**16%**	**46%**	**30%**	**8%**	**0%**	**0%**	**19%**	**81%**	**8%**	**1%**	**23%**	**68%**
Non-sitter	0%	64%	36%	0%	18%	55%	27%	0%	0%	0%	64%	36%	9%	0%	73%	18%
Sitter	0%	58%	39%	4%	16%	53%	30%	2%	0%	0%	18%	82%	11%	2%	23%	65%
Walker	4%	17%	35%	43%	17%	26%	30%	26%	0%	0%	0%	100%	0%	0%	0%	100%
Grand Total	**2%**	**47%**	**39%**	**11%**	**20%**	**41%**	**32%**	**7%**	**0%**	**2%**	**23%**	**75%**	**7%**	**3%**	**25%**	**65%**

(Continued)

TABLE 5 | Continued

(E)

Frequency satisfaction	Strengthening exercises				Endurance exercises				Mixed exercises (loga, Pilates)			
	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it	I believe I do need it but can't get it	I do need it and can get it but with limitations	I do need it and I get what I need	I don't need it
Pediatric	**15%**	**44%**	**32%**	**9%**	**21%**	**35%**	**26%**	**18%**	**21%**	**15%**	**6%**	**59%**
Non-sitter	11%	33%	22%	33%	22%	22%	22%	33%	33%	0%	0%	67%
Sitter	11%	53%	37%	0%	16%	42%	26%	16%	11%	16%	11%	63%
Walker	33%	33%	33%	0%	33%	33%	33%	0%	33%	33%	0%	33%
Adult	**36%**	**25%**	**15%**	**23%**	**34%**	**19%**	**15%**	**32%**	**24%**	**13%**	**10%**	**53%**
Non-sitter	27%	27%	0%	45%	27%	18%	0%	55%	9%	0%	9%	82%
Sitter	40%	26%	12%	21%	40%	16%	9%	35%	26%	16%	7%	51%
Walker	30%	22%	30%	17%	22%	26%	39%	13%	26%	13%	17%	43%
Grand total	**30%**	**30%**	**20%**	**19%**	**30%**	**23%**	**18%**	**28%**	**23%**	**14%**	**9%**	**54%**

The bold values indicates the overall figures for pediatric, adult and grand total of the cohort (in opposition to breakdown by functional status for the same groups).

SMA types. The overall response rate of 21% which is slightly lower than reference values of 25–30% (17) was considered acceptable in the context of rare diseases. The sample included individuals aged between 1 and 81 years with a bias toward adult participants over pediatric ones. In relation to the SMA type, type 3 seems to be overrepresented when compared to the current figures from different registries where type 2 is often the more represented type (15). One of the potential explanations of this bias is since during the time that the survey was open (August 2020–April 2021), managed access agreement didn't include SMA type 3. This was perceived from patient organization as one of the potential explanations for the higher participation rate in the survey.

The SoC for SMA defines which professionals should be accessible to individuals with this condition. Our survey highlights that, certain professionals are not accessible to patients and underscores the striking differences in access to certain specialties between pediatric and adult patient populations. Figures range from 59% difference for access to physiotherapy (100% pediatric, 41% adults) to 15% difference for access to a neurologist (85% pediatric and 70% adults). This holds true for access to interventions, ranging from 46% difference for access to supported standing (53% pediatric, 7% adult) and 45% difference for access to splints (59% pediatric, 14% adult) to 5% difference for access to mobility aids (91% pediatric, 86% adults). Because SMA is a progressive disease regardless of age (18), this implies that these differences will ultimately create a significant gap in care and provision for adults with SMA. However, this is not to say that access meets the SoC in children although the level of care is better. On the other hand, access to specific professional or interventions follow a clear pattern that correlates with disease severity. Access to pulmonologist and respiratory physiotherapist are a good example of this.

Limited access to care and provision recommended within the SoC document were regularly reported, with half of the study population consistently not accessing full multidisciplinary care. Regular follow up by a neurologist was accessible by most of the participants but more limited to other members of the MDT team (nurse specialist and physiotherapist). When looking at the frequency of visits, only around 65% of the participants are seen once or twice a year which confirms, even for those accessing specialists such as neurologists that SoC are unfortunately not being met.

The SoC document outlines the importance of access to interventions for contracture management however, this study highlights significant limitations to this access. This is particularly evident around access to spinal braces and supported standing which was only available to <20% of the participants but also for splints (26%). It would appear from this data that if a patient has access to a spinal brace or standing device that they are likely to make use of them. However, this is less true if you are provided with splints. This poor uptake of use may be associated with limited capacity for follow up from multidisciplinary team as highlighted above (i.e., follow up to ensure good fit).

Performing stretches is probably one of the clearer examples of an intervention where it is difficult to predict the specific

needs for specific age groups or even specific individuals, or patients with a particular functional status. However, only 17% of the participants reported doing more than 3 h a week of stretches. There are different reasons that might influence the limited undertaking of these interventions but is also important to identify factors that might limit the relevant support required to ensure its recommended use such as access to more regular physiotherapy.

Exercise is widely accessible for many survey participants, but limited frequency of use raises questions as to why those with SMA do not exercise more frequently. In a similar way that the performance of stretches can be limited due to limited support, access to adapted facilities within a relatively short distance of patients can be a significant factor to limits other forms of exercise. Exercise, in its many different forms, was highly valued by participants which infers an understanding of the benefit of exercise among the SMA population and therefore may have great potential for improvement in this aspect of care.

Mobility aids and home adaptations appeared to be widely available and were also reported as the most valued type of intervention across age and functional groups. Access to occupational therapy was reported as being limited but 65% reported they had access when needed which might be the explanation for the good accessibility to mobility aids and the relevant home adaptations as in the UK occupational therapists are often providers of mobility and adaptations rather than providing specific support and practice for activities of daily living.

Access to nutritional support or speech and language therapy appears only to be available for a small proportion of the participants. The fact that this access decreases with age and disease severity is of some concern given the importance of these interventions within the SoC document.

Access to respiratory care was good especially when looking at the more severe forms of SMA, which is reassuring due to the predominance of respiratory issues as the disease progresses (19). However, limited access or no access to cough augmentation was reported by 15% of the non-sitters and sitters which raises the question of equitable access across the UK. Due to the limited representation of participants from each region of the UK it is not possible to identify if this proportion of participants is representative of specific regions of the country.

One of the main limitations of this study is the small sample recruited in comparison to the estimated SMA population in the UK. Up to 3 attempts were undertaken to reach the targeted population through patient registry, patient organizations and social media and increase participation. The limited number of responders may skew the results as the methods used will not include those with no access to technology. It is difficult therefore to infer this survey population is truly representative of the overall population of SMA in the UK, however clear trends within age groups and functional status were observed.

This study also suggests the need of further studies to gain a better understanding of the limiting factors for contracture management. It is important to identify potential solution related to training needs, additional budget allocated to community services or the increase overall awareness about SMA. This is crucial due to the impact of these aspects of care in conjunction with disease modifying treatments. For similar reasons it is recommended to undertake further investigations around effects and uptake of exercise people with individuals with SMA.

There are pockets of good practice in the UK such as access to respiratory care or neurologist that align with the standards of care documents. However, access is not equal for adults and children and access to certain healthcare professionals like physiotherapist, SALT or nutritionist is significantly limited. This creates a limitation in supportive care which is not reflected by the natural history of the disease.

Exercise and rehabilitation are particularly important to maximize the benefits of disease modifying therapies. This is particularly relevant not only to have access but to have the supportive care to ensure consistency in their practice. From this study it is clear that this is not in place for the UK.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

RM-L, CM-B, and AMa contributed to the concept and design of the study. RM-L and AMa wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of Interest: LR was employed by SMAUK. JI was employed by Treat SMA and KA was employed by MDUK.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix D SMA REACH UK Study Protocol

Study Protocol v1.4 02.08.2016

PROTOCOL

Title: Spinal Muscular Atrophy Research and Clinical Hub UK (SMA REACH UK)

UK Sponsor	GOSH
Funder	The SMA Trust
Chief UK Investigator	Professor Francesco Muntoni Dubowitz Neuromuscular Centre
Newcastle Principal Investigator	Professor Kate Bushby Newcastle University
Co-Investigator	Professor Eugenio Mercuri Rome University

TITLE:

Improving standards of care and Translational Research in Spinal Muscular Atrophy

Introduction

Spinal Muscular Atrophy (SMA) is an autosomal recessive genetic disease that affects the motor neurons of the voluntary muscles that are used for activities such as crawling, walking, head and neck control, and swallowing. Approximately 1 in 6000 babies born are affected and about 1 in 40 people are genetic carriers. Childhood SMA can be divided into three subtypes depending on disease onset and severity but all patients suffer from degeneration of motor neurons controlling voluntary muscles with proximal limb and trunk muscle weakness leading to respiratory distress and in the most severe cases, ultimately death. Approximately half SMA children have the severe infant form, named SMA type I that is associated with severe respiratory problems and affected children are never able to sit on their own. The others have SMA type II or type III, defined by the ability to sit or to stand and walk, at some time in the course of development. The clinical course is unusual for a degenerative disease with a prolonged plateau or slowly declining phase after an initial more rapid period of declining function.

The disease is caused by the absence of the SMN1 gene resulting in the production of low levels of a protein (SMN) necessary for the survival of motor neurons. Progressive loss of motor neurons in the spinal cord causes muscle atrophy that can lead to fatal respiratory problems, difficulties eating and swallowing and skeletal deformities. Regular pulmonary, nutritional, orthopedic and orthotic assessments and monitoring are necessary for the lifetime of the condition since diagnosis. The impact of this disorder in clinical practice is huge as the management of SMA patients requires a multidisciplinary approach involving specific professions including paediatric neurologists, specialist nurses, physiotherapists, speech and language therapists, dieticians, orthopedic surgeons and orthotics, gastrointestinal surgeons, care advisors. The involvement of the palliative care unit is also required, especially when dealing with SMA type I.

Recent investigations into the pathogenesis of childhood SMA have raised hopes that a specific therapy might be possible. The recent identification of SMA as the disease closest to a treatment out of nearly 600 neurological disorders (2009 the National Institute of Health in America) along with the growing anticipation of both patients and families, and the rapid discoveries and advancements in the science toward several drugs suitable for clinical trials on the horizon, has pushed SMA clinical trials to pick up momentum in the last few years. In preparation for the inevitable upcoming clinical trials in SMA there is the need for a robust clinical and research Network poised for designing valid outcome measures for clinical trials, in non-ambulant and ambulant patients, and identifying possible bottlenecks.

Some important steps have already been taken in capturing data in SMA patients with the development of the SMArtnet and SMA registry databases. SMArtnet is mainly a large collection of clinical and physiotherapy assessment information while the SMA registry is mainly a genetic database; both these databases, despite providing unique information, are incomplete due to the lack of mutual integration. Furthermore the longitudinal data collected has never been implemented or undergone full validation with RASCH analysis so it has never been reviewed and audited. Now that pharmacological interventions and genetic based approaches are being successfully studied in preclinical models, further implementation of these databases and leading coordination becomes crucial to ensure that patient information and physiotherapy data are integrated in order to put into place the first data management system across the UK and Europe. This will both improve our knowledge of the natural history of SMA, with the clear consequence of implementing improved standards of care, as well as facilitate the preparation of personalized national and international clinical trials.

Aims

The primary aim of this project is to establish the first national clinical and research network named SMA REACH UK (SMA Research And Clinical Hub UK) to establish a national agreement on clinical and physiotherapy assessment and standards of care. We propose designing, piloting and expanding an electronic database created to streamline the collection of data for patients with SMA. This UK SMA database would be a unique infrastructure started at GOSH and Newcastle which would soon be built up and accessible to specialist centres across the UK who treat patients with SMA.

The Dubowitz Neuromuscular Centre at Great Ormond Street Hospital is well suited to lead this project joined by the Newcastle neuromuscular team. The dedicated multidisciplinary team has a history of leadership and experience with the related existing resources, specifically SMArtnet, North Star and SMA Patient registry. The SMA REACH UK project will begin with garnering a clear picture of the available patient pool, which is likely to be around 90 patients at GOSH (0-19 years) and 30-40 in Newcastle (paediatric and adult patients). Information about these patients will be collated from clinical charts and records. Once patients are identified, they will be invited to participate in the collection of harmonized data by enrolling in the SMA REACH UK. This database will be designed, created and run with help from a well-known software engineering company with experience in organizing healthcare systems. The long term aim is to utilize this streamlined assessment tool throughout the SMA community. For this project, we aim to enrol 50% of the available patient population at GOSH within the first year and at least 2/3rds by the end of the project. Enrolment of the majority of patients seen at the 2 larger UK sites will provide enough resource to allow for proper trial and reflection on the functionality of the SMA REACH UK before being expanded to additional sites.

The secondary aim of the project is to utilize the SMA REACH UK database as a longitudinal data house where information can be audited and reviewed. This will provide clinicians and researchers a rich resource of available information on a large collection of SMA patients, in collaboration with another International centre of excellence in SMA research and treatment located in Rome at the Catholic University, thereby facilitating translational research for this common neuromuscular disease in preparation to design National and International clinical trials. Once the system is finalised, additional national sites that have a history of successful SMA enrolment will be invited to participate and collect high quality longitudinal data. This work will be an invaluable tool for the centres

likely to be involved in upcoming SMA multicentre randomised clinical trials in SMA type I, II and III.

Further aims of the project are to ensure the functional scales used are suitable and clinically relevant for future trials.

Methodology

Location

This project is designed as a large multi-institution study including up to 20 centres in the UK led by GOSH in London in conjunction with Newcastle University. In view to extend this project to an international level, another European centre in Italy (Paediatric Neurology Division at the Policlinco University Hospital in Rome) has been invited to co-operate with designing and piloting the physiotherapy tools.

Inclusion criteria:

All patients with genetically confirmed SMA type I, II and III aged between 3 months and adult age will be recruited. The diagnosis of SMA must be documented by the absence of SMN1 on standard genetic tests for the disorder, and the determination of type I, II and III SMA by the ability to maintain a sitting position when placed, and if they are ambulant/non-ambulant. When possible, each patient should also have the determination of the SMN2 copy number.

Exclusion criteria

There are no exclusion criteria if a genetic diagnosis of SMA has been confirmed

Involvement in clinical trials is not an exclusion criterion nor is having had surgical procedures. Patients who are participating in clinical trials with novel treatments will also be included in the database although the data from this subgroup won't be analysed in the natural history study. Patients who have had orthopaedic surgery will also be eligible as this will further inform the natural history of the condition after surgery. Participants currently or previously taking a treatment intended to effect change in SMA (i.e. salbutamol, hydroxyurea, valrpoic acid, carnitine, etc) will also be included in the study as no effective treatment has been identified to date. The use of concurrent medications will be recorded at each visit.

Patient selection criteria/Number of patients/Methods for identifying and recruiting patients

Patients will be selected amongst those attending standard follow up clinics in the participating centres according to the mentioned inclusion criteria. We do not foresee many difficulties in recruiting patients as the project does not require any extra appointments for the patients and their families and the assessment does not require any extra invasive procedure on top of the standard clinical procedures. It does, however, include an extended physiotherapy assessment.

We anticipate that we will be able to enrol approximately 70 patients in the first year in the UK. We do not anticipate any difficulties in recruiting patients as this project does not require any additional appointments/procedures outside of routine clinical care.

Medical Assessment/Physical Examination

Standard clinical procedures for all patients will include the recording of the following parameters at each visit (every 7 months +/- 4 weeks) (Consensus Statement for Standard of Care in Spinal Muscular Atrophy, Ching H. Wang,et al, Journal of Child Neurology Volume 22 Number 8 August 2007 1027-1049):

Height (standing or arm-span), weight and blood pressure

Physical examination

Pulmonary function test (Spirometry) will be also performed at each visit (forced expiratory vital capacity, FVC as percent predicted). No additional tests are required.

In young children (<5 years) or when there is no compliance, or following clinical indication (daytime hypercapnia or FVC<60% at the spirometry), regular overnight sleep studies might be indicated as part of the current standard of care. No additional tests are required.

ECGs are usually performed at the first appointment and repeated every few years as follow-up or more often if there is a clinical indication.

Additional ECG will be performed prior commencing Salbutamol therapy and after three months of being on therapy. Follow-up ECGs are performed once a year in all patients receiving salbutamol therapy.

Bloods are taken on average once a year to monitor the Vitamin D level and electrolytes in patients on Salbutamol. No additional bloods are required.

Whole spine X-ray will be performed following the clinical indication (i.e. presence of spinal curve, back pain) and repeated follow-up will depend on the scoliosis progression. No further tests other than what is required for clinical care will be requested.

Lumbar spine or total body DEXA scan are not regularly performed and are requested following a clinical indication (bones fractures following minimal trauma, back pain, low vitamin D level, pre-op for spinal surgery). No additional DEXA scans other than those required as part of routine clinical care are required as part of this project.

Speech and language therapy and dietician review will be recorded when requested following a clinical indication.

Physiotherapy Assessment

All patients regardless of SMA type or ambulation status will receive a physiotherapy assessment in keeping with standard clinical practice for children and young people with SMA. This will involve gathering a thorough physiotherapy subjective history (current concerns/changes regarding mobility, falls, fatigability, endurance/exercise tolerance, equipment and orthotics evaluation, discussion of orthopaedic concerns, pain, activities of daily living, environmental concerns and home modifications); and an objective assessment of motor development, muscle length/contractures, joint range of movement, muscle strength (myometry- Lafayette myometer) and posture involving spine, head, lower and upper limbs. For the ambulant population further assessment of higher level motor functions such as gait, standing posture, stairs, 10 metres run/walk test etc. will be part of the routine assessment.

In addition to the standard physiotherapy assessment several functional measures will be used to assess current level of physical functioning. Due to the nature of this project and the current work being done in developing more sensitive SMA specific scales it is likely that that the protocol will be drawn from but not exclusively involve the scales mentioned below. Novel outcome measures may also be trialled and form part of the protocol.

Functional Scales for Non-Ambulant Patients

SMA Type 1

Due to the nature of this form of SMA and the young age of the child usually one of the below assessments will be completed, only in exceptional circumstances both will be completed. Length of time to complete these assessments will vary, but can be estimated to take 30 minutes.

CHOP INTEND (The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) – this is a scale used for the assessment of movement and function of very weak infants with SMA type 1. It consists of 16 items of motor function graded 0-4 with a maximum achievable score of 64 (Glanzman et al, 2010).

TIMPSI (Test of Infant Motor Performance Screening Items) – this scale assesses motor performance in infants born pre-term to 4 months of age, it has been recently described to be reliable in assessing motor function in infants with type 1 SMA (Krosschell et al, 2013). It consists of 29 items, with 3 item sets (screening, easy and hard sets).

SMA Type 2/3 non-ambulant

Hammersmith Functional Motor Scale Expanded (HFMSE) (O'Hagen et al, 2007) – this scale assesses motor function in patients with SMA, the original 20 item HFMS (Main et al, 2003) was expanded to include 13 additional adapted items from the Gross Motor Function Measure to

enable the scale to be more sensitive to the higher functioning ambulant population. It is an ordinal scale with 33 items, with a 3 point scoring system (2 unaided, 1 with assistance, 0 unable); the items are ordered to become progressively more difficult. The maximum score achievable is 66, the minimum 0. It includes items in supine, prone, sitting, four point kneeling, standing, walking and stepping in addition to transitional movements such as rolling and transferring from the floor/chair to standing. All items are to be tested without use of orthotics (spinal and lower limb). It takes approximately 15-25 minutes to complete.

Upper Limb Module for SMA (ULM for SMA) – this tests items which reflect the functional limitations observed in the arm function of patients with SMA (Mazzone et al, 2011). The 2013 version contains 9 core items and 7 extra items (see appendix for current working manual) testing upper limb function. It is recommended for use in children greater than 30 months. It involves items which test both proximal and distal motor function of the arm.

Performance of the Upper Limb Module for DMD (PUL for DMD) – this is designed to test upper limb function in patients with Duchenne Muscular Dystrophy (Mayhew et al, 2013). It consists of 21 items testing shoulder, elbow and distal upper limb performance which aim to reproduce functional tasks.

For the purposes of this protocol the ULM for SMA and the PUL for DMD will be completed at the same time, using one proforma in order to avoid unnecessary repetition of items and fatigue. The total time to complete both of these assessments will be approximately 20 minutes.

Functional Scales for Ambulant Patients

In addition to the HFMSE, ULM and PUL ambulant patients will have 2 further assessments -

6 Minute Walk Test (6MWT) – this is a measure of functional exercise capacity and in SMA it used as a measure of endurance/fatigue. It is able to identify a functional deterioration in the ambulant population and identify differences between type 3a and 3b SMA (Montes et al, 2011; Mazzone et al, 2013). It involves walking up and down a 25 metre track without aids or orthotics for as fast as possible for 6 minutes. Lap splits, minute splits and total distance are recorded, in addition to any rests and falls. The exact protocol regarding the 6MWT is to be confirmed but is likely to be a modified version of the American Thoracic Society guidelines. It takes approximately 15-20 minutes to complete.

North Star Ambulatory Assessment for SMA (NSAA for SMA) – The NSAA was originally developed to assess ambulant individuals with Duchenne Muscular Dystrophy it was then modified to be used for the assessment of ambulant individuals with type 3 SMA. It tests ambulatory function with 17 items including walking, stepping on and off a box, jumping and running (Cano et al, 2013). It takes approximately 15-20 minutes to complete.

Parent Reported/Patient Reported Outcome Measures (PROM)

In addition to the functional outcome measures and clinical assessments described we will be requesting the parents and children/young people themselves to comment on their abilities through use of PROM scales, these are likely to also comment on aspects of wellbeing and quality of life. There are not currently any SMA specific PROM scales and therefore we will be looking at a variety of scales to determine their suitability of use and these may be adapted into a more specific scale, it is likely that the protocol is drawn from but not exclusive to measures described below. We also hope to involve patients in the redesign of SMA specific patient

reported questionnaires in order to gain an accurate representation of items which are meaningful for children/young people with SMA and their families.

Pediatric Outcomes Data Collection Instrument (PODCI) – This was developed by the American Academy of Orthopaedic Surgeons, it consists of a child (< 10 years, parent reported) and adolescent version (11-18 years, self and parent reported). It is a questionnaire which assesses overall health, pain and ability to participate in activities of daily living. It can be scored relating to eight scales – upper extremity and physical function, transfers and basic mobility, sports/physical functioning, pain/comfort, treatment expectations, happiness, satisfaction with symptoms, global functioning. It is likely that this scale may require modifying for the UK population as it is written in American terminology; it was initially designed to monitor orthopaedic interventions and so modifications may be required to make the questions relevant for children and young people with SMA.

Egan Klassification Scale (EK2) – This will be used for non-ambulant patients and consist of a series of 17 questions reporting on physical function including ability to transfer, cough, swallowing, fatigue and arm function. The EK measure has been determined to be valid for use in non-ambulatory individuals with SMA (Steffensen et al., 2001).

It will take approximately 10 minutes to complete both of these questionnaires.

Patient Interviews:

In addition to these questionnaires, individual interviews with selected patients will be done with the specific purpose of understanding patient´s perception about the condition, interventions performed and Standards of Care. The patients will be selected depending on availability and willingness to participate.

The interviews will be recorded for the purpose of being transcribed. Once transcribed, they will be destroyed only keeping the written transcription as part of the SMAReach data for further analysis.

The interviews will be performed at the most convenient time for the patient. They will be done either face to face, through a phone call or videoconference.

Approximate length of assessment (physiotherapy subjective, objective & functional assessments)

Infant (type 1) – 30 minutes, assessments of infants may take more or less time than that stated.

Non ambulant (type 2 & 3) – 1 - 1 hour 30 minutes.

Ambulant (type 3) – 1- 2 hours.

Informed consent

The study does not require any invasive techniques. However, patients and their families will be informed of this study verbally and with a patient information sheet, and they will be asked to sign an informed consent/assent form before entering the study to allow the entry of their data into the new database including the extended physiotherapy assessment. They will be registered on the new database using an anonymous code number. The code number will be maintained as

it was in patients previously consented for SmartNet. New consented patients will have a progressive number according with the current SmartNet database. This will be transferred to a SMA REACH UK registration number once the new database is operational.

Sub-study: Strength and function tests in ambulant and non-ambulant SMA 2/3

We would like to collect information on upper limb strength and function tests in a Sub study of 5-10 patients with SMA II and III, aged 6-15 years to relate to data collected using the above mentioned functional scales. This optional assessment will take place on the same day as routine clinics every 6 months. Data collected as part of this sub study will be anonymised and sent to France for analysis. The analysis will be conducted by The Institute of Myology and the equipment developers' Sysnav navigation technologies using their high-tech software which is necessary to interpret the data. Further to analysis, data collected from these tools will be shared and correlated with data stored on the SMA REACH UK database.

Moviplate, Handgrip and Pinchgrip (Appendix II) - 30 min.

These are three non-invasive new tools recently developed at the Institut de Myologie (Paris) specifically designed for the quantified measurement of the upper limb motor abilities. The Moviplate test is performed with the patient sitting at a table on which the Moviplate apparatus has been placed or if the patient is unstable on a chair, the device is placed on the table of their wheelchair. This machine consists of a plate with two small elevated platforms, which the patient must touch alternately. The patient performs the test sitting down with the forearm placed on a table that has been adjusted to the patient's height. The aim of the test is to tap alternately the two platforms a maximum number of times in 30 seconds, using a co-ordinated extension movement of the wrist and fingers.

The hand-grip and pinch tests are dynamometric measurements of maximum palmar grip and thumb index pinch strength. These are obtained using the handgrip and pinch dynamometers, with the forearm placed on the table and the dynamometer held by the evaluator.

All strength and function tests will be repeated twice per upper limb and during each evaluation session. If the lowest measurement does not fall within the [90% highest measurement-110% highest measurement] interval, patients are allowed to repeat the tests a third time. The highest value achieved in the two or three tests is recorded.

Accelerometry - ActiMyo (Appendix II)

ActiMyo was developed by Sysnav and the Institute of myology

Actimyo is a wireless system. It consists of two 28g watches that contain three axis accelerometers, three axis gyroscopes and one magnetometer. The two watches continuously

record linear accelerations and angular velocity. They have an 18 hour autonomy. The patients are provided with the system and a written patient-directed instruction sheet. Physiotherapists who provide the patient with the actimyo also receive a health care provider-directed instruction sheet.

The system continuously records data during the day time. Watches must be replaced on the docking station every evening, for two purposes: power supply filling, and data uploading. Data are stored on a USB stick which is not accessible to the patient. Then, if the patient has access to a wireless internet connection point, data may be transferred by internet to the central center for analysis, namely the Institute of Myology. It must be noted that the data are a non-understandable anonymous list of points, and that nothing allows the patient to be identified, which guarantees patient privacy. Data are recognized as issued from a specific Actimyo (every actimyo is labelled and sends its label with the data) during a certain period of time. If the patient has no internet connection, data can be collected by the investigation center and upload by the center.

Study design

We propose to deliver this project over a phased time period of two years:

Phase 1 (First year).

Objectives:

a. Identify and describe SMA patients population seen at GOSH and Newcastle
b. Establish a merged database with clinical end genetic data
c. Piloting standardized assessment database for SMA patients
d. Begin recruitment of patients at GOSH and Newcastle using the newly developed database
e. Pilot new physiotherapy assessment tools
f. Organize a patient/parent focus group with clinicians aimed to update on standards of care.

The early implementation of the SMA REACH UK database will begin in a small number of Centres in UK, which have significant number of patients and have been recognized as centre of excellence for SMA management and research nationally and internationally. The Dubowitz Neuromuscular Centre at GOSH is well suited to lead this project, as being already provided the clinical and academic leadership for the UK North Star Network and SMArtnet, in conjunction with Newcastle University.

a. Clinical information of patients with SMA seen at GOSH is recorded in patient charts. A means of easily collating this data does not exist, therefore the first aim of this project will be to identify and describe the SMA population seen at GOSH and Newcastle thereafter.

b. Establish a merged database with clinical and genetic data collating the existing registries (SMARTnet and SMA registry) and grow the collaboration within the National Neuromuscular Database (NaND). The data collected would be jointly administered by the Dubowitz Neuromuscular Centre and MRC Neuromuscular Centres in London and Newcastle. Designing the database will be done with the assistance of Certus, database engineers who have considerable experience designing, building and supporting adaptable software and services, to assist healthcare organizations in the management of complex data and processes.

c. Piloting standardized assessment database for SMA patients to characterize the course of SMA patients and to report data on clinical and biological outcomes for use in trial planning. We will make use of the SMArtnet and SMA Registry infrastructure to create a data house where these measures can be assessed, housed and added to.

d. Patients with genetically confirmed SMA followed at GOSH and Newcastle, will be consented to be recruited into a longitudinal natural history study and sample size will be based on the figures determined from the point a. (identify and describe SMA patients population seen at GOSH and Newcastle). The recruitment period will be 6 months and the planned full assessment (clinical and physiotherapy) will be performed at baseline, 6 months and 12 months (for most of the patients these latter assessment will fall in to the second year). In parallel to these first UK sites, other international centres with high expertise in SMA care and clinical trials will run parallel projects also recruiting SMA patients to piloting the new tools during their physiotherapy assessment. The principal sites, including the international sites running parallel projects, will meet before the recruitment begins at each site to discuss practical issues and to perform training sessions and inter-observer reliability studies among all the examiners involved. Before starting the recruitment, a designed External Advisory Board will be consulted on the aims of the project and will be invited to attend the Focus group. After 6 months of recruitment period, the data related to the baseline physiotherapy assessments will be shared within the three Centres and analysed to evaluate feasibility of the new tools, their integration in to the clinical assessment and potential use for clinical trials.

e. As described above in the physiotherapy assessment section, various physiotherapy assessment tools will be will be piloted during an extended physiotherapy assessment. The SMA REACH UK study will run alongside parallel projects in Italy and USA which will use the same outcome measures, giving a larger dataset which will allow for more rigorous Rasch and psychometric analysis in order to develop robust outcome measures to assess the physical abilities of patients with SMA, thus ensuring the UK is clinical trial ready and aligned to the international agenda.

f. The first focus group will be hosted by GOSH and UCL Institute of Child Health and will occur with the funding and organizational assistance of the well-known UK SMA charity, the Jennifer Trust. As discussed in past SMA conferences, the patient population is eagerly awaiting clinical trials. There is a need to identify what study parameters the patient population find feasible and acceptable. This focus group will be focused to identify the degree to which each outcome measure is tolerated, the acceptable frequency of visits, the duration of each visit and length of the study, as well as the general feelings towards study design (i.e. is a traditional 1:1 placebo: active study design acceptable or should alternative study methodology be considered). This information will be collected and analysed after the focus group and will serve as advice for clinical trials, with the attempt to tailor study design to meet patient/family needs and expectations.

Phase 2 (second year). Objectives:

a. first longitudinal data analysis collected for one year to monitor standard of care and change if needed
b. organise a second workshop and training in preparation to expand the Network to the remaining UK Centres

The first longitudinal data analyses will be performed once all recruited patients will have completed at least six months in the study. We will establish the distribution of scores and variability observed over the period from the started recruitment. At this stage the final database amendments will be completed before the network is expanded to national level and remaining centres will be invited to participate to the standardized collection of data. The sites involved will meet before the recruitment is expanded to discuss practical issues and to perform training sessions and inter-observer reliability studies among all the examiners involved.

This second phase will include the provisions of national network workshop and training, equipment and consumables.

This project is expected to be extended further to allow the following objectives:

a. Initiation and maintenance of the broader network

b. Second longitudinal data analysis collected for at least 18 months

c. Organize a second patient/parent focus group with clinicians aimed to discuss implications of potential upcoming therapies; dissemination of results.

This third and last phase shall focus on the maintenance of the broader network after each site have begun recruitment to ensure that individual Clinical Network Centres provide longitudinal data collection for at least 18 months. As there is no pharmacology involved, there is no need to limit the recruitment period. As such, patients will be recruited and enrolled up until the end of the study, allowing us to add as many data points as possible. This will strengthen the adherence of each centre to recognized standards of care, will allow national and international audits and will monitor the impact of evolving standards of care on the natural history of the condition but will also facilitate SMA patient recruitment into clinical trials. In the third year a second patient/parent focus group with clinicians aimed to discuss implications of potential upcoming therapies will be organized and hosted in one of the main UK Centres, with the participation of relevant international clinicians and researchers in order to lay the groundwork to expand the UK Network to other International Centres of excellence in management and research in SMA.

Application of the outcome measures.

In each centre the physiotherapy assessments will be completed by a designated physiotherapist who will be fully trained in the specific clinical outcome measures used. The medical assessment will be completed by a designated doctor trained in the specific assessment required for children and young people with SMA.

Where informed consent has been acquired the physiotherapy assessments may be videoed in order to determine inter and intra-rater reliability, and to give the possibility of second evaluations of the scores by another investigator. In addition to videoing, where informed consent has been acquired photographs will be taken during the physical assessment in order to construct manuals for the physical assessments/outcome measures.

Revised Hammersmith Scale for SMA: The Revised Hammersmith Scale (RHS) is a newly developed outcome measure for SMA. Training on the RHS will be conducted in a UK cohort of neuromuscular physiotherapists; physiotherapists of the UK SMArtNet/NorthStar Clinical Network. It is anticipated that, following further testing, the RHS will be embedded as one of the data collection forms for the SMA REACH UK database. Once SMA REACH UK

is rolled out nationally, we would expect physiotherapists trained on the revised scale to adopt it as a tool to be used in routine clinical practice and research.

Physiotherapists will be trained to assess type 2 & 3 SMA patients using the RHS and will additionally be required to conduct inter- and intrarater reliability testing procedures for this scale. Training, and inter- and intrarater reliability testing will involve the analysis of the patient videos collected as part of SMA REACH UK. The videos will be stored in keeping with the strict UK data protection laws and kept on a secure UCL IDHS (data safe haven) server which conforms to the NHS information governance toolkit. As inter- and intrarater reliability testing will involve NHS Staff as subjects, a detailed application for these assessments has been made to the UCL Research Ethics Committee, The inter- and intrarater reliability testing of the RHS in a UK cohort of neuromuscular physiotherapists will form part of an Advanced Physiotherapy MSc project conducted by the SMA REACH physiotherapist.

There will be specific forms for medical practitioners and physiotherapists. Recording of the information will initially involve use of the current SMARTnet scannable key medical information and medical assessment forms for the medical assessment/physical examination. Regarding the physiotherapy assessment a newly created SMA REACH UK trial worksheet will be created. Once the outcome measures have been refined and clarified, and by the time of the expansion of the study nationally, the finalised SMA REACH UK proformas for the medical and physiotherapy assessments will be used.

Information from both assessments will be uploaded to the anonymised SMA REACH UK database. Patients will be identified by an anonymised SMA REACH UK code, the master key information will be available to specific members of the research team and the clinic administrator. In the initial stages this will involve the use of the previous SMArtnet system and where the SMArtnet system does not allow for the recording of new outcome measures a separate database for novel outcomes will be kept. Following the initial pilot of outcomes the SMA REACH UK database will then be created and all anonymised assessment information will be stored here.

Figure 1. Schedule of events for SMA REACH UK

Year I and II	Milestones	Time frame by which the milestone should be achieved
0-4 months	Identify and describe SMA patients population seen at GOSH (London) and Newcastle	By the end of month 2
	National "kick-off" meeting for clinical agreement (evolved use of Smartnet-→ UK SMA Platform)	By the end of month 2
	Piloting standardised physio assessment database for SMA patients	By the end of month 4
4- 10 months	Begin recruitment at GOSH (expected to recruit 2-4 patients per month) and Newcastle (expected to recruit 1 patient per month)	Expected to have minimum eighteen patients recruited at month 10
	Establish a merges database with clinical and genetic data	By the end of month 10
10- 14 months	First parent/patient focus group with clinicians aimed to update on standards of care	Between Months 10-12
	Continue recruitment and data collection in London, Newcastle.	Ongoing
15-24 months	First Longitudinal analysis on data collected to monitor the standard of care (this first analysis will be performed once all recruited patients between month 4 and 10 will have completed 6 months in to the study)	By the end of month 16
	Continue recruitment and data collection in London, Newcastle.	Ongoing
	Training for other UK centres in preparation for expansion of the Network to other UK centres	Between month 20 and 22
	Second longitudinal analysis on data collected to monitor the standard of care (this first analysis will be performed once all recruited patients between month 4 and 10 will have completed one year in to the study)	Between month 21 and 23
	Discussion on standard of care and dissemination with the possibility to change if needed	At month 24
Month 24 onwards	Continue with recruitment/data collection and publication of data	

Discussion of the Results.

The participating centres will meet before starting the recruitment and one year after the recruitment has started to discuss the state of the recruitment and to plan further steps. A final meeting will be held after the results of the statistical analysis will be available.

Further Statistical Design/Analysis.

The distribution of each of the outcome variables will be assessed. Appropriate descriptive statistics (means and standard deviations for normally distributed data, medians and ranges for data not normally distributed) of each of the measures at each time point will be compared. Also, the mean and standard deviation of change from baseline to 6 months and 1 year will be calculated for each measure. The sample size should provide sufficient precision in the estimates of the means and standard deviations.

Descriptive analysis will be carried out by computing means and medians of continuous variables (as appropriate according to the type of distribution, i.e. whether approximately normal or not), together with ranges, standard deviation and standard errors. Proportions and 95% confidence intervals will be computed for categorical variables.

The Cronbach's alpha will be used to assess the internal consistency of each test. The inter− and intra−rater reliability will be evaluated through the Intraclass Correlation Coefficient (ICC).

Appropriate statistics for repeated measures study design (ANOVA and multivariable mixed effects regression modelling) will be used to assess changes of scores in each scale over time (baseline, 6 and 12 months).

More in-depth examination of scale robustness will be performed via RASCH analysis.

The data elicited from the patient interview will be analysed with qualitative methods according with the specific purpose of the set of interviews.

Confidentiality of Personal Data

Personal data which will be stored for routine clinical purposes will only be accessible to authorized individuals in this study. Personal data will not be entered into the database as part of this research. The clinical data collected will only be linked to the patient by a study code number and will contain no personal identifiers. Informed consent/assent will be obtained from participants to collect and retain this data. The data that will be used for analysis and dissemination for research purposes will be completely anonymised. All staff in

UK NHS Trusts are obliged to adhere to their Duty of Confidentiality, the Data Protection Act 1998 and Caldicott Principles.

Potential Risks to Participants and Researchers

There are no extra invasive procedures involved in this research protocol. Assessments will be designed to minimize fatigue for individuals and hospital attendance.

Potential Benefits for Participants

The information collected in the database will lead to a better monitoring of current standards of care and improving where needed. Furthermore this may facilitate future patient recruitment in clinical trials.

Participants will not receive any payments specifically for taking part in this study. We expect to conduct the assessment in coincidence with the clinical appointment (every 7 months +/- 1 month), however due to the slightly extended time needed for the assessment, refreshments for patients will be provided. It is unlikely the assessments will fall outside the clinical appointment but whenever this will occur, travel costs or reimbursements will be available for families.

Ethical Issues

No specific issues have been identified to arise from this study. Informed consent/assent will be documented using the information sheet and consent/assent form, and the Data Protection Act 1998 will be adhered to as per routine clinical care. All data held and disseminated for research purposes will be anonymised, containing no personal identifiers.

The study protocol and associated documents for use in the study will be reviewed and approved by the Research Ethics Committee. The commencement of the study at each UK site will be subject to NHS R&D management approval.

Safety Monitoring plan

The study does not foresee any safety issues as the patients will undergo assessments that are similar to those used in routine clinical practice.

Dissemination of Results:

Approximately 3 months will be left to allow for the end of study analysis, data synthesis and publication preparation. The results of the study will be published in peer-reviewed scientific journal(s) and reported as part of submissions to regulatory bodies (NHS

R&D offices and Research Ethics Committee).The results of the study are likely to be published in peer-reviewed scientific journal(s) and reported at relevant scientific and patient conferences. Although there may be no direct benefit to those enrolled, this work will result in a clearer picture of long term natural history of SMA in preparation for the inevitable and rapidly approaching clinical trials.

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APPENDIX I

For the functional outcome measure manuals please see the additional folder titled protocol appendix with the manuals/proformas for the scales mentioned in the physiotherapy assessment section. (Protocol v1.0 Appendix_manuals&proformas.zip)

APPENDIX II

Myotools and ActiMyo

Figure 1: Moviplate

This is called a Moviplate and looks at how fast your child can move their fingers up and down.

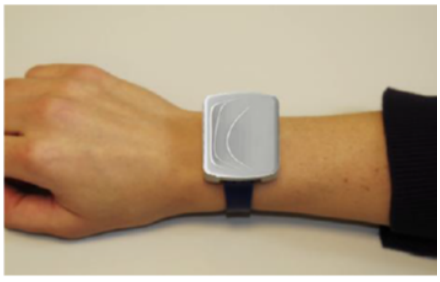
Figure 2:Handgrip

This is called the Handgrip. Your child will be asked to pull the handle as hard as they can to show us the strength of their grip.

Figure 3: Pinch Grip

This is called the pinch grip: your child will be asked to pinch the silver plate as hard as possible and the machine will measure how strong their fingers are.

Figure 4: ActiMyo



This equipment is called ActiMyo; it looks like a watch and measures level of activity over time.

Appendix E SMA REACH UK Study Patient information sheets

PIL 6-10 v1.1 3.12.2013

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NHS Foundation Trust

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Queen Victoria Road
Newcastle upon Tyne
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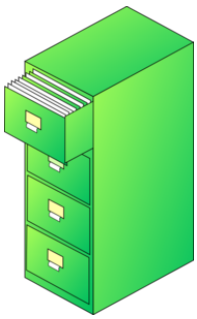
Tel: 0191 233 6161
Fax: 0191 201 0155

INFORMATION SHEET FOR CHILDREN (6-10 YEARS)

Chief Investigator: Professor Francesco Muntoni

Recording information on the management of your Spinal Muscular Atrophy in the UK – SMA REACH UK Database in association with the Neuromuscular Clinical UK Network

Please go through this leaflet with your parent or guardian.



You are being invited to take part in a research project as you have Spinal Muscular Atrophy. Research is a way we try to find out the answers to questions. Before you decide whether you want to take part, it is important to understand why the research is being done and what it will involve.

What is it about?

We would like to collect and record information which will help us to improve the care for all children with SMA in the UK. We would like to look at how SMA changes over time and keep a record in a database.

A database is like a filing cabinet where we can keep a lot of information all in one place. The database is called the SMA REACH UK Database. All children with SMA who

attend clinics at Great Ormond Street Hospital in London and in Newcastle will also be invited to take part.

Do I have to take part?

No, it is up to you to decide if you want take part. We will still look after you even if you say no.

What will I be asked to do if I take part?

You and your parents will fill out some forms to say you want to take part. You will be asked to come to hospital every 6 months as you do for your normal clinic appointments.

The only difference is that when you come to physio, it may take a little longer than usual as we will be doing a few more things and we would like to video you. You can still be put on the database if you do not want to be videoed.

We would like to collect and save information each time you are seen in clinic. The project will last for 2 years. You and your parents/carer may also be invited to one or two group meetings to talk about your SMA assessments if you would like to. At some point you might be asked to do an interview, together with your parents, to give us your point of view about how the management and time may have affected you.

Will joining in with this help me?

It may not help you but may help improve the care of children with SMA in the future.

Will my medical details be kept private if I take part? Will anyone else know I'm doing this?

We will only tell the people who need to know like the doctors taking care of you. We will only put information on the database or share it once your name and address has been removed.

How can I find out more?

You can talk to your parents about the project and ask them any questions that you have. If

they don’t know the answer you can ask your doctor, or your parents can ask your doctor for you.

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Royal Victoria Infirmary
Queen Victoria Road
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NE1 4LP

Tel: 0191 233 6161
Fax: 0191 201 0155

INFORMATION SHEET FOR CHILDREN (11-15 YEARS)

Chief Investigator: Professor Francesco Muntoni

Recording information on the management of your Spinal Muscular Atrophy in the UK – SMA REACH UK Database

in association with the Neuromuscular Clinical UK Network

Explanation (11-15 years old), Why are we doing this research?

You are receiving the expert care of medical and therapy teams for the long-term management of your Spinal Muscular Atrophy. We would like to collect and record information which will help us to improve and deliver the best care for all children with Spinal Muscular Atrophy in the UK.

This leaflet explains why we are asking your permission to record clinical information into a database called the SMA REACH UK Database.

What is the SMA REACH UK Database?

The SMA REACH UK database is a way that we can save all the information that is collected about your SMA in one place. The data collected would be jointly

looked after by the Dubowitz Neuromuscular Centre and MRC Neuromuscular Centres in London and Newcastle.

What is the SMA REACH UK Network?

The SMA REACH UK Network, supported by the SMA Trust, is a national and international partnership between doctors and therapists involved in the care of children with SMA.

Why have I been invited to take part?

You have been invited to take part in this research study because you have SMA and we would like to study how your condition changes over time. All children with SMA who attend clinics in Great Ormond Street Hospital in London and in Newcastle will be invited to take part in this study.

Do I have to take part?

No, it is entirely up to you to decide if you want take part. If you do decide to take part, your doctor or physio will ask you to sign a form called an assent form and your parents/guardians will need to sign a consent form. By signing the form you are agreeing to take part in the study. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop, this will not affect the care you receive in any way.

What will happen to me if I take part? What will I be asked to do?

You will be asked to come to hospital every 6 months as you do for your normal clinic appointments. The only difference will be that some of your physiotherapy assessments may be a little longer. The study will last for 2 years but may be extended in the future. At some point you

might be asked to do an interview to give us your point of view about how management and time may have affected you.

What information will we collect?

We would like to record:

- Your NHS number
- Name and date of birth
- General information about your condition for example your age at diagnosis and problems resulting from SMA
- Results of muscle, heart, breathing, growth and general health testing from medical assessments
- Some additional physiotherapy assessment measures.

We will also ask you for your permission to videotape you while the physical assessments are carried out. This will allow another physiotherapist to view the recordings. You can still be registered on the database if you do not wish to be videotaped.

Why are we collecting this information?

We will use the information we collect to help us:

- Collect accurate details about SMA
- Monitor medical and therapy care to make sure it is always up to date.
- Plan and develop services for better management of SMA
- Try out and develop new SMA assessment tools
- Create reviews and reports that will improve what we know about SMA and the current standards of care

- Compare information with data from other international sites
- Prepare for clinical trials

Who collects the information?

The hospital staff at the clinic will collect this information. This will usually be your doctor, physiotherapist or nurse or may be one of the designated research team: a doctor, physiotherapist or study coordinator.

When and how will you collect the information?

Information will be collected from the medical and therapy records and updated at every clinic visit. We will also invite you and your parents/carer to attend one or two group sessions in the coming months. This will allow you, your parents/carer and researchers and doctors to discuss the most useful assessment tools for families.

Who will see the information?

Only the NHS staff that care for you will see personal information like your name, date of birth and they will keep all this information private. Any information that is stored on the database will be password protected and saved on a safe system. We will only put information on the database or share information once your name and address removed.

What is the consent procedure?

If you are happy to be a part of this study you will be asked to sign an assent form. You will be given a copy of this information sheet and an assent form to keep.

Can I see the records on the database?

Yes, you can have a copy of the information we have about you. To do this, please talk to the doctor in charge.

Are there any benefits or disadvantages to taking part?

There are no direct benefits to you for taking part but we expect that the research will help to improve the

standards of care for SMA, and may also benefit children with SMA in the future.

Who is organising and funding the research?

This study is funded by a charity called the SMA Trust

Who has reviewed the study?

All research in the NHS is looked at by a group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favorable opinion by the London- Bromley Research Ethics Committee.

How can I find out more about the study?

Please talk to the doctor in clinic if you:

- Would like more information
- Have any questions or concerns
- Visit our website www.SMAREACHUK.com

Thank you for taking the time to read this information sheet

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
NE1 4LP

Tel: 0191 233 6161
Fax: 0191 201 0155

INFORMATION SHEET FOR PARTICIPANTS AGED 16-18+ YEARS

Chief Investigator: Professor Francesco Muntoni

Recording information on the management of your Spinal Muscular Atrophy in the UK – SMA REACH UK Database

in association with the Neuromuscular Clinical UK Network

You require the expert care of medical and therapy teams for the long-term management of your Spinal Muscular Atrophy. We would like to collect and record information, which will help us to deliver the best care to all children with SMA in the UK.

This leaflet explains why we are asking your permission to record clinical information into a database; the SMA REACH UK Database.

What is the SMA REACH UK Network?

The SMA REACH UK Network is a national and international partnership between doctors and therapists involved in the care of children with Spinal Muscular Atrophy. This Network is supported by the SMA Trust.

What is SMA REACH UK Database?

The SMA REACH UK Database is an internet based system which can save information about your diagnosis, assessment and management of SMA. Into this new database we aim to put clinical and genetic data from two existing databases (SMARTnet and the SMA registry). The data collected would be jointly managed by the Dubowitz Neuromuscular Centre and MRC Neuromuscular Centres in London and Newcastle.

Why have I been invited to take part?

You have been invited to take part in this research study because you have SMA and we would like to study how your condition changes over time. All children with SMA who attend clinics in Great Ormond Street Hospital in London and in Newcastle will be invited to take part.

Do I have to take part?

No, it is entirely up to you to decide. If you do decide to take part, your doctor or physio will ask you to sign a consent form. By signing the form you are agreeing to take part in the study. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop, this will not affect the care you receive in any way.

What will happen to me if I take part? What will I be asked to do?

We would like to collect and save information each time you are assessed in clinic. You will be asked to come to hospital every 6 months as you do for your routine clinic appointments. The only difference will be that some of your physiotherapy assessments may be a little longer. The study will last for 2 years but may be extended in the future. At some point you

might be asked to do an interview to give us your point of view about how management and time may have affected you.

What information will we collect?

We would like to record:

- Your NHS number
- Name and date of birth
- General information about your condition for example your age at diagnosis, any results of gene testing, and problems resulting from SMA Results of muscle, heart, breathing, growth and general health testing from medical assessments
- Some extra physiotherapy assessment measures.

We will also ask you for your permission to videotape you while the physical assessments are carried out. This will allow another physiotherapist to view the recordings. You can still be registered on the database if you do not wish to be videotaped.

Why are we collecting this information?

We will use the information we collect to help us:

- Collect accurate details about SMA and how it changes over time
- Monitor medical and therapy care to make sure it is always up to date.
- Plan and develop services for better management of SMA
- Try out new assessment tools with the aim to develop more sensitive SMA specific scales.
- Undertake reviews and produce reports that will improve our knowledge of the natural history of SMA
- Improve and monitor the standards of care
- Start to prepare for clinical trials.
- Compare information on SMA from this database with data from other international sites

Who collects the information?

The hospital staff at the clinic will collect this information. This will usually be your doctor, physiotherapist or nurse or may be one of the designated research team: a doctor, physiotherapist or study coordinator. A designated database manager may also help with recording information.

When and how will you collect the information?

The information will be collected and updated at every clinic visit. We will collect the information from the medical and therapy records.

We will also invite you and your parents/carer to be involved in one or two group sessions in the coming months. These sessions will allow you, your parents/carer, researchers and doctors to discuss the most useful assessment tools for families.

Who will see the information?

All information will be stored on a secure system and password protected. Only the NHS staff that care for you will see your details. There are strict regulations controlling who has access to personal information like your name, date of birth or NHS number. By law, everyone who works for the NHS must keep all personal information confidential and the trust has strict confidentiality and security procedures in line with the data protection act (1998). Only anonymised data will be shared with other institutions (SMA Registry, MRC database) and international centres.

What is the consent procedure?

If you are happy for your details to be stored on the database and used for clinical care and research purposes please give your permission on the consent form. A signed copy of your consent form and a copy of this information sheet will be given to you for your information.

Can I see the records on the database?

Yes, you can get a copy of the information we have about you. To do this, please ask the doctor in charge.

Are there any benefits or disadvantages?

You may not directly benefit from the database system; however it might help to improve the standards of care for SMA in clinics in the UK and may benefit children with SMA in the future. This research could also help to prepare for and design clinical trials for SMA in the future.

What if there is a problem?

You may contact one of the study team by email or telephone using the contact details at the end of this leaflet. If you are not happy about your treatment and you wish to complain, you should contact the PALS service at Newcastle upon Tyne NHS Hospitals Foundation Trust by phone: 0800 0320202 (direct line) or by email: northoftynepals@nhct.nhs.uk so that they can advise you about the steps to take as well as being able to give you the contact details for the appropriate people in the hospital.

Who is organising and funding the research?

This study is funded by the SMA Trust.

Who has reviewed the study?

Before any research is allowed to happen, all research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favorable opinion by the London- Bromley Research Ethics Committee.

How can I find out more about it?

Please talk to the doctor in clinic if you:

- Need more information
- Have any questions or concerns

Or contact one of the study team by email or telephone:

Dr Anna Mayhew: anna.mayhew@ncl.ac.uk

Research Office: 01912418663

Or visit our website www.SMAREACHUK.com

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Royal Victoria Infirmary
Queen Victoria Road
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NE1 4LP

Tel: 0191 233 6161
Fax: 0191 201 0155

INFORMATION SHEET FOR PARENTS/GUARDIANS

Recording information on the management of your child with Spinal Muscular Atrophy in the UK – SMA REACH UK Database in association with the Neuromuscular Clinical UK Network

Your child requires the expert care of medical and therapy teams for the long-term management of Spinal Muscular Atrophy. To help deliver the best care, we would like to collect and record information, which will help us optimise management, not only for your child, but also for all children/adults with Spinal Muscular Atrophy in the UK.

This leaflet explains why we are asking your permission to record clinical information into a database specially designed for use in the hospitals participating in the UK Neuromuscular Clinical Network (NMCN) and more specifically the SMA REACH UK Database.

What is the SMA REACH UK Network?

The SMA REACH UK network is a national and international collaboration supported by SMA Trust, between doctors and therapists involved in the care of children with Spinal Muscular Atrophy. We would also like to grow the collaboration within the National Neuromuscular Database (NaND), a network of doctors and therapists involved in the care of children with neuromuscular conditions which is supported by the Jennifer Trust for Spinal Muscular Atrophy and the UK Muscular Dystrophy Campaign. The data collected would be jointly administered by the Dubowitz Neuromuscular Centre and MRC Neuromuscular Centres in London and Newcastle.

What is the SMA REACH UK Database?

The SMA REACH UK Database is an internet web based system which can save information about diagnosis, assessment and management of Spinal Muscular Atrophy. Into this new database we aim to merge clinical and genetic data collating the existing registries (SMARTnet and SMA registry).

What information will we collect?

We would like to record:

- Your child's NHS number
- Name and date of birth of your child
- General information about your child's condition – e.g. age at diagnosis, results of gene testing, and problems resulting from Spinal Muscular Atrophy
- Results of muscle, heart, breathing, growth and general health testing from medical assessments
- In addition to the standard physiotherapy assessment, some additional functional measures will be used to assess current level of physical functioning.
- At some point you might be asked to do an interview to give us your point of view about how management and time may have affected your child.

You will be asked to give your permission for us to videotape your child whilst parts of the physical assessments are carried out. This will allow another physiotherapist to view the recordings and provide a second evaluation of your

child's scores for each assessment. Your child can still be registered in the database if you do not wish your child to be videotaped. You will be asked to give your permission for us to inform your child's GP that he/she is taking part in this study.

The study will last for 2 years but may be extended in the future. We would like to continue to collect and save information each time your child is assessed in clinic. Your child will be asked to come to hospital every 6 months as per usual for routine clinic appointments. The only difference will be that some physiotherapy assessments may be a little longer.

Why are we collecting this information?

We will use the information we collect to help us:

- Collect accurate details about the course of Spinal Muscular Atrophy, and its response to management.
- Monitor medical and therapy care to make sure it is always up to date.
- Plan and develop services for better management of Spinal Muscular Atrophy
- Pilot new assessment tools with the aim to develop more sensitive SMA specific scales.
- Undertake audits, and produce reports that will improve our knowledge of the natural history of SMA, with the clear consequence of implementing the National standards of care, as well as facilitate the preparation of personalized national and international clinical trials.

Who collects the information?

The hospital staff at the clinic will collect this information. This will usually be the doctor, physiotherapist or nurse or may be one of the designated research team: a doctor, physiotherapist or study coordinator. A designated database manager may also help with recording information.

When and how will you collect the information?

The information will be collected and updated at every clinic visit. We will collect information from the medical and therapy records. At times, the

doctor/physiotherapist may enter the information directly into the database system, and produce a record for the hospital case notes.

We will also invite you to be involved in one or two focus groups in the coming months. These focus groups will facilitate a discussion between parents, patients, researchers and doctors and will help researchers to design clinical assessment measures which are meaningful to your family.

Who will see the information?

Only the NHS staff who care for your child will see all the details. There are strict regulations controlling access to personal information like your child's name, date of birth or NHS number. By law, everyone who works for the NHS must keep all personal information confidential and the trust has strict confidentiality and security procedures in line with the data protection act (1998). Only anonymised data will be shared with other institutions (SMA Registry, MRC database).

What is the consent procedure?

If you are happy for your child's details to be used for clinical care purposes, analysis such as audits to improve clinical care or service delivery, and for clinical information to be transferred between hospitals looking after your child, please give your consent. A signed copy of the consent form and a copy of this information leaflet will be given to you for your information. Your child is free to stop taking part at any time during the research without giving a reason. If you decide to withdraw your child at any point this will not affect the care they receive in any way.

Can I see the records on the database?

Yes, you can get a copy of the information we have about your child. To do this, please talk to the doctor in charge.

Are there any benefits or disadvantages?

Your child may not personally benefit directly from the database system; however it is anticipated that audit of this data within, and across, neuromuscular clinics in the UK will improve the standards of care for Spinal Muscular Atrophy, and may also benefit children with Spinal Muscular Atrophy in the future. This will provide clinicians and researchers with a rich resource of available information on a large collection of SMA patients, ensuring the functional scales used are suitable and clinically relevant, facilitating translational research in preparation to design National and International clinical trials.

Once the database system has been developed and the information has been appropriately collected, it may provide an accurate and graphic report of the course of the condition, and its response to treatment in the individual child.

What if there is a problem?

You may contact one of the study team by email or telephone using the contact details at the end of this leaflet. If you are not happy about your treatment and wish to complain, you should contact the PALS service at Newcastle upon Tyne NHS Hospitals Foundation Trust by phone: 0800 0320202 (direct line) or by email: northoftynepals@nhct.nhs.uk so that they can advise you about the steps to take as well as being able to give you the contact details for the appropriate people in the hospital.

Expenses and payments

There will be no reimbursements for taking part in this research study as there are no additional appointments outside routine clinic appointments. Refreshments may be offered during the extended physio assessments.

Who is organising and funding the research?

This study is funded by the SMA Trust.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the London- Bromley Research Ethics Committee. This research was checked by the **NRES Committee London Bromley 13/LO/1748**.

How can I find out more about it?

Please talk to the doctor in clinic if you:

- Need more information
- Have any questions or concerns

Or contact one of the study team by email or telephone:

Dr Anna Mayhew: anna.mayhew@ncl.ac.uk

Research Office: 01912418663

Or visit our website www.SMAREACHUK.com

Appendix F SMA REACH UK Study Assent and consent forms

ASSENT form age 6-15 v1.3 28.10.2016

Assent for recording information in the SMA REACH UK Database in association with Neuromuscular Clinical Network	
Patient Details (or pre-printed label) Hospital Number …… Patient's Surname …… Patient's first names …… Date of birth …… **NHS number** ……	Responsible health professional …… Job title …….. Patient's other requirements ……

Please check Yes or No if you agree/disagree with the following statements

I agree to have medical information about me kept on the database	☐Yes	☐No
I agree to be videoed during the physiotherapy assessments	☐Yes	☐No
I agree to let my doctor (GP) know that I am taking part in this study	☐Yes	☐No
I agree to be involved in a group meeting to talk about my assessments	☐Yes	☐No
I agree to be contacted for an interview to talk about SMA and management and if agreed to participate, I agree to be recorded for analysis purposes.	☐Yes	☐No

If you don't want to take part in this study, do not write your name.
If you **do** want to take part, you can write your name below

Your name:_____ Date:_____

Practitioner Section:
I have given the parent/guardian the information sheet entitled: Recording information on the management of my Spinal Muscular Atrophy in the UK – SMA REACH UK Database in association with Neuromuscular Clinical Network.

I have explained to the above patient the purpose of collecting and recording clinical information in the database.

…… ……
Signature Date

…… ……
NAME (BLOCK CAPITALS) Job title

CONSENT form age 16-18+ v1.3 28.10.2016

Consent for recording information in the SMA REACH UK Database in association with Neuromuscular Clinical Network	
Patient Details (or pre-printed label) Hospital Number …… Patient's Surname …… Patient's first names …… Date of birth …… **NHS number** ……	Responsible health professional ……. Job title …….. Patient's other requirements ……

Medical Diagnosis: ……

Please Initial

I agree that clinical information about me will be collected and saved in the SMA REAC Database. ☐

I agree to be videotaped during part of the physical assessments.
(if you refuse, you may still take part in the study). ☐

I agree that my GP will be informed that I am taking part in this study ☐

I agree to be involved in a patient/parent/researcher focus group ☐

I agree to be contacted for an interview to talk about SMA and management and if agreed to participate, I agree to be recorded for analysis purposes. ☐

…… ……
Signature (patient) Date

Practitioner Section:
I have given the parent/guardian the information sheet entitled: Recording information on the management of my Spinal Muscular Atrophy in the UK – SMA REACH UK Database in association with Neuromuscular Clinical Network.

I have explained to the above patient the purpose of collecting and recording clinical information in the database.

…… ……
Signature Date

…… ……
NAME (BLOCK CAPITALS) Job title

Consent for recording information in the SMA REACH UK Database in association with Neuromuscular Clinical Network

Patient Details (or pre-printed label)
Hospital Number ……
Patient's Surname ……
Patient's first names ……
Date of birth ……

NHS number ……

Responsible health professional ……
Job title ……..

Patient's other requirements ……

Medical Diagnosis: ……

Please Initial

I agree that clinical information about my child will be collected, recorded and saved in the SMA REACH UK Database. ☐

I agree for my child to be videotaped during the physiotherapy assessments (if you refuse, your child may still take part in the study). ☐

I agree for my child's GP to be informed of his/her participation in this study ☐

I agree to be involved in a parent/patient/researcher focus group ☐

I agree to be contacted for an interview to talk about SMA and management and if agreed to participate, I agree to be recorded for analysis purposes. ☐

…… ……
Signature (parent / guardian) Date

…… ……
NAME (BLOCK CAPITALS) Relationship to patient

Practitioner Section:
I have given the parent/guardian the information sheet entitled: Recording information on the management of your child with Spinal Muscular Atrophy in the UK – SMA REACH UK Database in association with Neuromuscular Clinical Network.

I have explained to the above parent / guardian the purpose of collecting and recording clinical information in the database.

…… ……
Signature Date

…… ……
NAME (BLOCK CAPITALS) Job title

Terms definitions

The list of terms is a combination of standard definitions for reference terms but also additional terms specific to this thesis (i.e., mixed exercises).

Neuromuscular diseases: Range of conditions characterised by the impairment of muscle function, either directly affecting muscle fibres or indirectly affecting peripheral nervous system or neuromuscular junction.

Outcome measures: endpoint, effect measure within clinical or research practise used to measure natural history or effect of an intervention or treatment.

Disease modifying therapies: Term used to describe pharmacological treatment with the potential to modify the natural course of a disease.

Generic outcome measures: Outcome measures developed to assess general population.

Disease specific outcome measures: Outcome measures designed to capture particular clinical features of a condition or group of conditions.

International Classification of Functioning, Disability and Health (ICF): Classification of health and health-related domains used as international standard to describe and measure health and disability. ICF is structured in two parts: Functioning and disability which includes, body function and structure, activities, and participation. Contextual factors, that include environmental and personal factors.

Body structure and function: Component of the ICF that looks at the anatomical and physiological aspects of body systems.

Activities: Component of the ICF that looks at actions and tasks executed by individuals.

Participation: Component of the ICF related to involvement in life situations.

Environmental factors: Component of the ICF that looks at physical, social, and attitudinal environment in which people live. They can be classed as facilitators when having a positive influence in their functioning and barriers if they lower their level of performance.

Personal factors: Component of the ICF related to the individual such as gender, age, race, lifestyles, habits, education, and profession. Like with environmental factors, they can be classed as facilitators or barriers.

Myometry: A quantitative and objective method for assessment of muscular strength using a dynamometer.

Goniometry: The art and science of measuring the joint ranges in each plane of the joint.

Spirometry: Pulmonary function tests that measures lung function, specifically the amount and/or speed of air that can be inhaled and exhaled.

Forced vital capacity (FVC): The determination of the vital capacity from a maximally forced expiratory effort.

Vital capacity: Volume of air breathed out after the deepest inhalation.

Forced expiratory volume in one second (FEV1): Volume that has been exhaled at the end of the first second of forced expiration.

Maximum inspiratory pressure (MIP): Measure of the strength of inspiratory muscles, primarily the diaphragm, and allows for the assessment of ventilatory failure, restrictive lung disease and respiratory muscle strength.

Maximum expiratory pressure (MEP): Measures the maximum positive pressure that can be generated from one expiratory effort starting from total lung capacity.

Sniff nasal inspiratory pressure (SNIP): Measurement of pressure through an occluded nostril during sniffs performed through the contralateral nostril.

Peak cough flow (PCF): Maximum air flow generated during a cough.

Physiological fatigue: Decrease in level of performance over time in a prolonged activity.

Perceived fatigue: Subjective experience of feeling fatigue, tiredness, lack of energy or exhaustion.

Cognitive fatigability: Decline in the capacity to process and maintain attention over a sustained complex information task.

Non-Sitters: Functional category to describe individuals unable to sit independently.

Sitters: Functional category used to describe individuals able to sit independently but unable to walk without support.

Walkers: Functional category used to describe individuals that are able to walk independently.

Non-ambulant: Functional category used to describe individuals that are unable to walk independently.

Ambulant: Functional category used to describe individuals that retain the capacity to walk independently.

Activities of Daily living: Group of activities that individuals perform regularly for their daily care, used often as a measure of their abilities.

Timed function tests: Specific functions or tasks assessed with a measure of time to evaluate individual's abilities.

Health care related quality of life: Multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning considered to have an influence on individuals' well-being.

Patient Reported Outcome Measures: Variables used to assess individuals' health based on their own perspective and self report.

Caregiver burden: The strain or load borne by a person who cares for a chronically ill, disabled, or elderly family member.

Qualitative research: Type of research that involves collecting and analysing non-numerical data (e.g., text, video, or audio) to understand concepts, opinions, or experiences.

Exercise: Any bodily activity that enhances or maintains physical fitness and overall health and wellness.

Water based exercise: Type of exercise done in a body of water with the aim to use buoyancy as a facilitator or resistance as part of it.

Splints: A rigid or flexible device that maintains in position a displaced or movable part of the body.

Spinal brace: Device designed to limit the motion of the spine in cases of bone fracture or in post-operative spinal fusion, as well as a preventative measure against some progressive conditions or to correct patient posture.

Mobility aids: device designed to assist walking or otherwise improve the mobility of people with a mobility impairment.

Home adaptations: Changes made at individuals' home with the aim to make it safer and/or easier to move around and do everyday tasks.

Standing frame: Assistive device that provides positioning support in the standing position.

Real-world data: Data derived from a number of sources that are associated with outcomes in a heterogeneous patient population in real-world settings, including but not limited to electronic health records, health insurance claims and patient surveys.

Standards of care: Legal term that define the degree of care and skill of the average health care provider who practices in the provider's specialty, taking into account the medical knowledge that is available in the field.

Stretching exercises: a form of physical exercise in which a specific muscle or tendon (or muscle group) is deliberately flexed or stretched in order to improve the muscle's felt elasticity and achieve comfortable muscle tone.

Strengthening exercises: Exercises which are designed to increase the strength of specific or groups of muscles.

Endurance exercises: Exercises which are designed to increase the ability of an individual to exert itself and remain active for a long period of time.

Mixed exercises: Exercises which have a mixture of physical capacities involved with no clear dominance of one over the other one (i.e., yoga, Pilates).