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UNDERSTANDING THE MFM AND THE SMAIS IN THE CONTEXT OF OUTCOME MEASUREMENTS IN SMA

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This brochure was developed by F. Hoffmann-La Roche Ltd in close collaboration with physiotherapists and spinal muscular atrophy (SMA) patient advocacy groups (PAGs).

This brochure was created to provide additional information about the Motor Function Measure (MFM-32) and the SMA Independence Scale (SMAIS) in the context of other outcome measures used in SMA. This brochure may be particularly useful for people living with SMA who are not familiar with these measures.

The included outcome measures are not exhaustive but are frequently used in clinical practice and in clinical trials. For each outcome measure, this brochure will cover what it assesses, why it is important for measuring motor function and functional independence, and its suitability to evaluate specific groups of people living with SMA. We will also discuss how changes in the scores for each outcome measure reflect changes in motor function ability or functional independence and the impact these changes have on the daily life of those living with SMA and their caregivers.

It is important for outcome measures to demonstrate excellent *reliability* and sound *validity*. Outcome measures should be appropriate and meaningful for those living with SMA and should be responsive to changes in function. This brochure will explain this in more detail.

This information may help the SMA community to understand more about the outcome measures that are being used to assess how their *disease trajectory* is changing over time.

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1. An overview of SMA

Spinal muscular atrophy, normally called 'SMA', is an inherited genetic condition with different degrees of severity, associated with the loss of *motor neurons* and disease-related complications that can affect the entire body.[1,2]

SMA develops when one of our genes called *SMN1* is missing or abnormal, i.e. it does not work properly.[2] This can cause symptoms such as muscle weakness and difficulties with *fine* and *gross motor function*, as well as problems with eating or breathing.[2]

The *SMN1 gene* carries the information needed to make a protein called survival of *motor neuron* protein or *SMN protein*.[2] This protein is important for keeping the nerves in the spinal cord that help to control muscles and coordinate movement, known as *motor neurons*, working.[2] *SMN protein* may also be important for other organs in the body.[2] When there is not enough functional *SMN protein, motor neurons* become damaged and cannot continue to function normally, eventually dying (**Figure 1**).[2,3]

SMN protein can also be produced by another *gene, SMN2* (**Figure 1**). However, this *gene* cannot produce enough *functional protein*.[2] As such, the severity of SMA may be dependent on how many copies of the *SMN2 gene* an individual has.[2] In some cases, the more copies a person has, the more protein that can be produced and the less severe the symptoms experienced.[2]

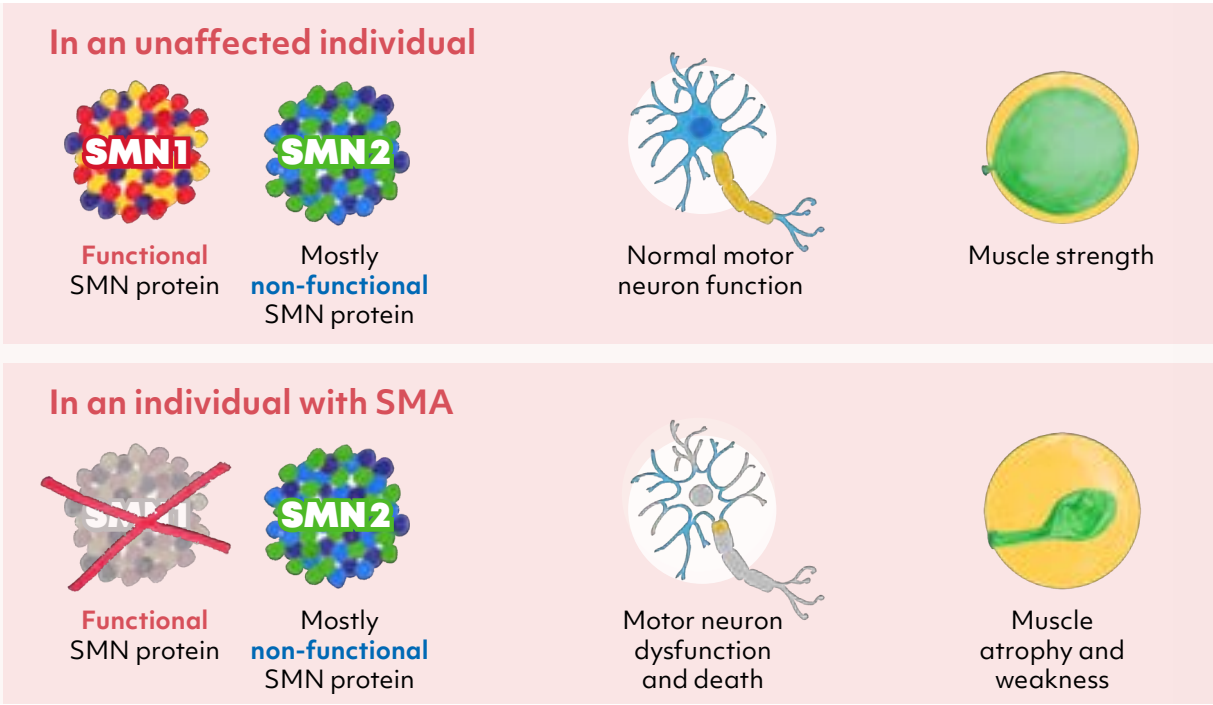


Figure 1 How the *SMN1* and *SMN2* genes work in unaffected individuals (top) and in those living with SMA (bottom)[2,3]

1. Shababi M et al. *J Anat* 2014;224:15–28
2. Farrar MA et al. *Ann Neurol* 2017;81:355–368
3. D'Amico A et al. *Orphanet J Rare Dis* 2011;6:71
4. Kolb SJ & Kissel JT. *Neurol Clin* 2015;33:831–846
5. Wang CH et al. *J Child Neurol* 2007;22:1027–1049
6. Mercuri E et al. *Neuromuscul Disord* 2018;28:103–115

In addition to the number of *SMN2 gene copies*, the definition and severity of SMA also depends on the age at diagnosis and the highest level of function achieved (i.e. motor milestones).[2] Traditionally, there are five types of SMA, ranging from Type 0, also known as neonatal SMA and considered the most severe form of the disease, to Type 4 or adult SMA, which, being the mildest form of the disease, is not life-threatening (**Table 1**).[2,4]

In recent years, the way healthcare professionals should care for people living with SMA has improved (due to use of a set of recommendations and guidelines known as *standards of care*), and treatments that change the course of the disease have become available.[6–9] As such, some individuals with SMA may be able to achieve certain milestones or have improvement in symptoms that would not have been previously expected.[10] For example, an infant living with Type 1 SMA receiving treatment might now be able to sit independently, which was a motor milestone not previously reported in studies of untreated infants living with Type 1 SMA.[10] This change in disease trajectories has also led to a change in the way the community classifies SMA. Nowadays, there is a shift towards a functional status definition, with people living with SMA classified according to the maximum milestone achieved (non-sitters, sitters, standers or walkers).[6]

Type		Characteristics of treatment-naïve individuals
Type 0 SMA[2]		• Prenatal age of symptom onset[2] • Infants are unable to sit or roll and experience respiratory insufficiency at birth[2]
Type 1 SMA[2,5]		• Symptoms appear in the first few months of life[5] • Infants are never able to sit without support[2,5]
Type 2 SMA[2,5]		• Symptoms appear between the age of 7 months and 18 months[5] • Individuals are never able to walk but can sit without support[2,5]
Type 3 SMA[2,5]		• Symptoms appear between the age of 18 months and 10 years[5] • Individuals are able to walk without support but may lose this ability over time[2,5]
Type 4 SMA[2,5]		• Symptoms usually appear between the age of 10 years and 30 years[2,5] • People with Type4 SMA are able to walk without support but motor function may be affected later in life[2,5]

Table 1 Classification of SMA

7 Biogen. Nusinersen Prescribing Information. 2019
8 AveXis. Onasemnogene abeparvovec-xioi Prescribing Information. 2019
9 Roche. Risdiplam Prescribing Information. 2020
10 Tizzano EF & Finkel RS. *Neuromuscul Disord* 2017;27:883–889

2. Motor function milestones in SMA

As explained in the previous chapter, there is large variability in the symptoms and motor function abilities of people living with SMA, including the highest motor milestone that they are able to reach.[1] Those living with SMA who have not received any treatment (treatment-naïve individuals) will typically not be able to reach the motor milestones achieved by unaffected children of a similar age and will lose motor function abilities over time.[1]

2.1. Growth and development: World Health Organization developmental motor milestones

The World Health Organization (WHO) has created a tool that assesses the acquisition of motor milestones.[2] This tool can be used as a reference to assess whether children are reaching their developmental milestones as expected.[2] An age range is provided to indicate at what stage in development each milestone should typically be achieved during the first months of life.[2] If a milestone is not achieved by the upper end of the expected age range, this may suggest a delay in the normal motor function development of the child;[2] this may prompt the need for medical tests and checks to understand the cause of such a delay.[2]

According to the WHO, there are six developmental motor milestones (**Figure 2**), some of which are similar to those used to classify the different types of SMA.[1,2] The WHO motor milestones have specific criteria.[2] While the corresponding motor milestones in SMA do not have specific definitions, they can be approximately mapped against the WHO motor milestones as shown in **Figure 2**.

1 Farrar MA et al. *Ann Neurol* 2017;81:355–368
2 WHO Multicentre Growth Reference Study Group. *Acta Paediatr Suppl* 2006;450:86–95

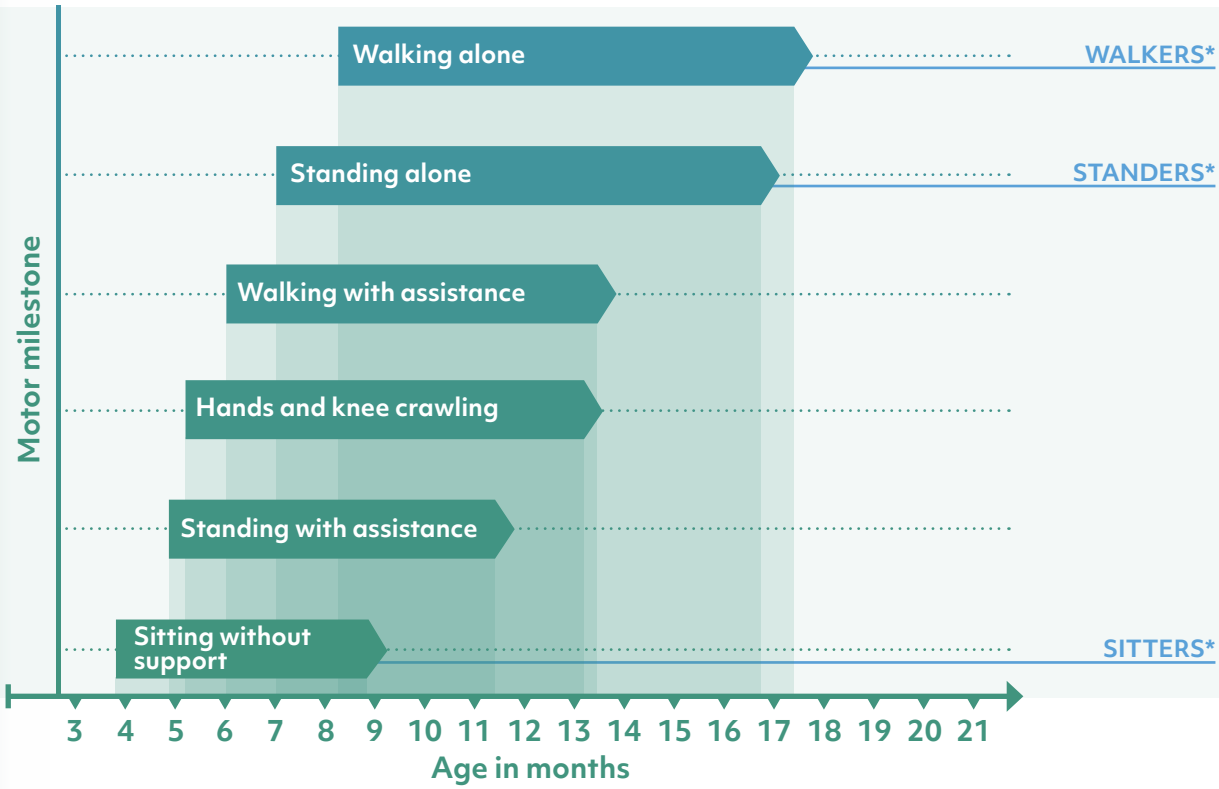


Figure 2 Age ranges for motor milestone achievement[1,2]

*Individuals with SMA who are described as sitters may achieve the WHO motor milestone 'sitting without support', those who are described as standers may achieve the WHO motor milestone 'standing alone' and those who are described as walkers may achieve the WHO motor milestone 'walking alone'. Adapted from the WHO Multicentre Growth Reference Study Group

2.2. Hammersmith Infant Neurological Examination, Module 2 (HINE-2)

The HINE-2 was designed to assess whether a child can achieve eight different motor milestones, ranging from head control to walking.[1,2] These age-appropriate milestones are based on what is expected from an unaffected child's development and allow the user to assess improvements for both weaker and stronger infants.[1,2]

In a study of untreated infants with Type 1 SMA aged 1–8 months at the onset of symptoms, none of the more severely affected infants achieved a major motor milestone assessed by the HINE-2, such as rolling over, independent sitting, crawling, standing or walking.[2]

What is assessed?[2]	The HINE-2 assesses if a child is able to achieve eight different motor milestones:
Key features[1–4]	• Offers a comparison with the motor function expected in infants without SMA[1,2] • Although not specifically designed for SMA, its use is well established in infants with Type 1 SMA[3,4]
Target population[1,2]	Non-sitters and sitters aged 2–24 months
How long does it take to perform?[4]	5–15 minutes
What equipment is used?[4]	Does not require any specific equipment
How many items are included?[1]	8

1. Haataja L et al. *J Pediatr* 1999;135:153–161
2. de Sanctis R et al. *Neuromuscul Disord* 2016;26: 754–759
3. Finkel RS et al. *N Engl J Med* 2017;377:1723–1732

2.2.1. What do the HINE-2 scores mean?

For each milestone (movement), the physiotherapist will decide the score to give from 0 to a maximum of 4, whereby 0 represents absence of activity.[2] Nevertheless, the maximum score allowed will vary per motor milestone.[2] For example, while the sitting and crawling tasks allow for a maximum score of 4 when the child is able to perform them, tasks like voluntary grasp and rolling only allow for a maximum score of 3.[2]

The scores for each item are combined to give an overall score out of a total of 26.[2]

(4) CureSMA. Best practices for physical therapists and clinical evaluators in spinal muscular atrophy (SMA). Available at: www.curesma.org/wp-content/uploads/2019/11/Cure-SMA-Best-Practices-for-PTs-and-CE-in-SMA-Clinical-Trials-Nov-2019.pdf, accessed December 2020

3. Measuring outcomes in people living with SMA

Outcome measures are tools usually used by healthcare professionals, including physiotherapists, nurses and neurologists, to assess and measure how a person feels, how they function and their survival, and to measure how someone responds to an intervention.[1] For individuals with SMA, these outcome measures largely assess motor and non-motor function, overall medical condition and quality of life.[2] Outcome measures can take many forms, including measurements of muscle strength, a set of activities one needs to perform that are assessed using an objective rating scale or a self-reported questionnaire, among others.[2,3]

In SMA, healthcare professionals consider both motor and non-motor outcome measures (e.g. assessing respiratory and *bulbar function*) to gain a holistic overview of where a person living with SMA is in their own disease path.[4]

3.1. Why is it important to measure motor function?

Motor development can be divided into two parts: gross motor development and fine motor development.[5]

- Gross **motor development** refers to the development of physical skills that involve the large muscles of the body. Some examples of gross motor activities include sitting, standing, walking and running[5]
- Fine **motor development** refers to the development of physical skills that involve the small muscles in the hands and fingers. Some examples of fine motor activities include writing, cutting with scissors and manipulating small objects[5]

Typical *motor development* involves a progressive and predictable gain of motor skills/function, that is, increasing movements and actions of the muscles, with gain of particular functions being associated with specific ages (**Figure 2**).[5,6]

Maintaining and gaining motor skills is one of the key treatment/care goals in SMA.[7] Motor function tests (or *assessment scales*) have an important role in routine clinical assessment and in clinical trials.[2,4] They can be used to monitor the natural progression of the disease and check if the symptoms of SMA are worsening over time; this is known as 'disease progression'.[2] They can also help doctors to determine if

1. FDA. Available at: www.fda.gov/media/84987/download, accessed December 2020
2. Montes J et al. *J Child Neurol* 2009;24:968–978
3. Trundell D et al. Presented at the Cure SMA Annual Conference, 14–17 June 2018, Dallas, TX, USA
4. Mercuri E et al. *Neuromuscul Disord* 2018;28:103–115
5. Early Childhood Intervention. Available at: http://blogs.ubc.ca/earlychildhoodintervention1/category/1-3-what-is-development-motor-development/, accessed December 2020
6. WHO Multicentre Growth Reference Study Group. *Acta Paediatr Suppl* 2006;450:86–95

the symptoms stabilise or improve due to medical treatments or other interventions such as physiotherapy; this is known as 'response to treatment'.[2] A response or lack of response to treatment is important when determining the effectiveness of a particular treatment, and will have an impact on whether a treatment will need to be adapted or discontinued. Furthermore, these response data will indicate whether a clinical trial has been successful and will be used as evidence to help regulatory bodies decide whether a new treatment will be approved (made available for use in a specific country) and/or reimbursed (funded by a healthcare provider in that country).[2,8] As such, it is important to use outcome measures that are widely accepted as being *valid* and *reliable*, so the effectiveness of a treatment being considered by a regulatory body can be measured in a standardised way.[2]

Clinical trials select a group of individuals to participate based on a particular set of disease characteristics, then changes in their response to a particular treatment are compared with the natural disease trajectory or with people receiving a placebo.[9] As such, individuals eligible to be enrolled in a clinical trial may not be fully representative of every person with SMA.[9] Similarly, the outcome measures that are used in these trials may be optimal for a particular group of individuals but not fully adapted to detect motor function changes in a more *heterogeneous population* with varied disease severity, age and motor function ability.[10]

3.2. How is motor function measured?

Everyone with SMA is unique and has different motor function abilities and goals.[7,11] For example, some people may be unable to hold their head upright for any length of time and are aiming to improve the endurance of their neck muscles. Some people may be able to walk but tire easily and have a goal of increasing the distance they can walk.[7] Others may be able to sit in a wheelchair and are working on improving the motor function in their hands to help with activities such as getting dressed or brushing their teeth.[7] This means there is not a single 'perfect' *assessment scale* that will work for everyone. Therefore, many different motor function *assessment scales* are used to evaluate the broad range of functional abilities that exist within the SMA population.[4] Each scale used in SMA is designed to test a specific set of motor skills, and the choice of scale used is based on a person's disease severity, age and motor function abilities (**Figure 3**).[2]

7. Cure SMA Voice of the patient report (2018). Available at: www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf, accessed December 2020
8. Havard Business School. Available at: www.isc.hbs.edu/health-care/value-based-health-care/key-concepts/Pages/measure-outcomes-and-cost.aspx, accessed December 2020
9. Al-Zaidy SA et al. *Pediatr Neurol* 2019;100:3–11
10. Vuillerot C et al. *Am J Phys Med Rehabil* 2013;94:1555–1561
11. Wang CH et al. *J Child Neurol* 2007;22:1027

Motor function *assessment scales* are simply a set of items (or tasks) that measure how well a person can use their muscles to perform various actions or movements.[10] These items are often grouped into categories, or domains, such as head movement, rolling and sitting.[10,12] Practically, when a physiotherapist assesses someone living with SMA, they will examine each individual item included in a particular *assessment scale* and evaluate how well the person is able to perform it.[10] Depending on the scale, the level of functional ability is associated with a particular score for each item which, when taken collectively, gives the physiotherapist an idea of someone's overall motor function ability.[10]

3.3. Who measures motor function?

In SMA, it is important to monitor the various aspects that are known to be involved in disease progression and, when possible, provide anticipatory care.[4] As such, a multidisciplinary approach is key for managing the care of people living with SMA.[4] The multidisciplinary team, or MDT, is responsible for several aspects of care, including bone health, respiratory function, nutrition and motor function.[4] These can include neurologists, pulmonologists, orthopaedists, occupational therapists and physiotherapists, among other healthcare professionals.[4,20] The exact members of the team that a person will see depends on their disease presentation, age and immediate needs at a particular time.[4]

Physiotherapists are key members of the MDT.[4] Physiotherapists play an instrumental role in the management of those living with SMA by helping them reach their functional goals through a variety of modalities such as exercises and equipment, orthoses (braces to support arms or legs), mobility aids (e.g. wheelchairs) and domotics (assistive technology) to improve overall mobility and strength.[4,21] In addition, physiotherapists help to manage contractures—defined as the permanent tightening of tissues—and other symptoms of SMA.[4,21] The healthcare professionals who are involved in the SMA care listed here may include members of the MDT beyond physiotherapists, depending on the country.

Assessment of motor function is key in identifying the strengths and weaknesses of an individual with SMA and in facilitating an anticipatory rather than a reactive approach to management.[4] To evaluate motor function, physiotherapists rely on *fine* and *gross motor function assessment scales*, which use a series of tasks to document *disease trajectory* or the response to a particular treatment.[4]

(12) de Sanctis R et al. *Neuromuscul Disord* 2016;26: 754–759
(13) Bayley N. *J Psychoed Assess* 2007;25:180–198
(14) Glanzman AM et al. *Neuromuscul Disord* 2010;20: 155–161
(15) Trundell D et al. *Neurol Ther* 2020; Aug 27: doi: 10.1007/s40120-020-00206-3 [Epub ahead of print]
(16) de Lattre C et al. *Arch Phys Med Rehabil* 2013;94: 2218–2226
(17) O'Hagen JM et al. *Neuromuscul Disord* 2007;17: 693–697

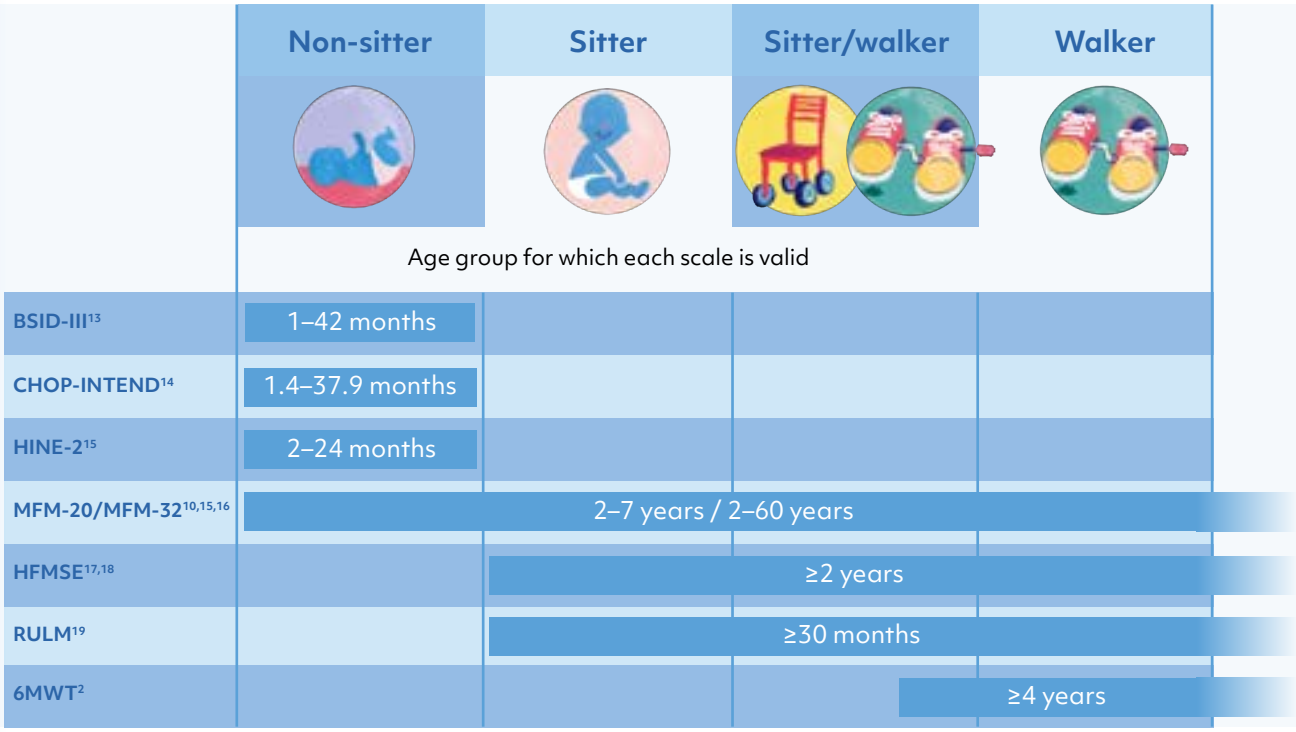


Figure 3 Different motor function *assessment scales* used in SMA

6MWT, 6-minute walk test; BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE-2, Hammersmith Infant Neurological Examination, Section 2; MFM, Motor Function Measure; RULM, Revised Upper Limb Module

18 Main M et al. Eur *J Paediatr Neurol* 2003;7:155–159
19 Mazzone E et al. *Muscle Nerve* 2017;55:869–874
20 Finkel RS et al. *Neuromuscul Disord* 2018;28:197–207
21 SMA UK. Available at: https://smauk.org.uk/whos-who-of-professionals, accessed December 2020

4. Motor function assessment scales in SMA

In the following pages, we will introduce the MFM-32 as well as other *assessment scales* that are frequently used in clinical practice and/or in SMA clinical trials. For each *assessment scale*, what type of motor function it measures, the number of items or tasks covered, the age group it is most appropriate for, the scoring system and the time it takes to complete will be discussed, among other things. A top-line overview of this information for each *assessment scale* can be found in **Table 3** in the summary section.

4.1. Motor Function Measure (MFM)

The MFM was developed to address a gap in the available motor function *assessment scales* for *neuromuscular disorders*:[1] other *assessment scales* were designed for a particular *phenotype* (e.g. sitters with strong motor function or walkers)[2,3] and to assess a particular type of motor function (e.g. *gross motor function*, upper limb function).[2,4]

Although not specifically designed to assess motor function in people living with SMA, the MFM has been validated for use in SMA and has been used in SMA clinical trials.[1,5] It assesses different types of motor function involving the head, trunk, arms and legs, in a broad range of disease severities and across a wide spectrum of ages.[1,6]

There are two versions of the MFM.[1,7] The MFM-32 is a 32-item scale which has been validated in individuals with SMA aged 2–60 years,[1,5] and the MFM-20 is a 20-item scale which has been validated in children with SMA aged 2–7 years.[7]

What is assessed?[1,7]	The MFM can be used to measure how the disease is changing over time by assessing three categories:  Standing position and transfers, i.e. how well a person can perform activities that involve standing  **Axial** and **proximal limb motor function**, i.e. how well a person can perform activities involving the trunk and the head (**axial function**), and the shoulders and the upper arms (proximal function)  **Distal limb motor function**, i.e. how well a person can perform activities involving their forearms, hands, fingers and feet
Key features[1,5,7]	• A scale that includes items for several types of motor function[1,7] • Very *reliable*[5] • Having two versions of this scale allows for age-appropriate measurements[1,7] • The MFM-32 assesses 32 items (for individuals aged 2–60 years)[1,5] • The MFM-20 assesses 20 items (for individuals aged 2–7 years)[7] • Suitable for individuals older than 2 years[5] • Suitable for weak and strong individuals[1]
Target population[1,5,7]	Non-sitters, sitters, standers and walkers aged 2–60 years
How long does it take to perform?[8]	MFM-20: 12–50 minutes MFM-32: 30–50 minutes
What equipment is used?[8]	Tennis ball, coins, CD, pencil, paper, stopwatch and other items found in therapy settings
How many items are included?[1,7]	32 for MFM-32[1] 20 for MFM-20[7]

4.1.1. What are the key differences between the MFM-20 and MFM-32 scales?

The MFM-32 has been validated for use in individuals with SMA aged 2–60 years.[1,5] The MFM-20 was adapted from the MFM-32 to create a scale that can be used specifically with young children aged 2–7 years.[7] The 12 items that were considered to be difficult for most of the children in this age range were removed from the 32-item scale, creating a shorter version that is targeted to younger children.[7] **Table 2** shows the number of items in each category for both versions of the MFM. The MFM-32 can also be used with young children and can be useful when assessing response to treatment and the gain of functions that otherwise may have been difficult to assess.[5] In cases where the MFM-20 is used in young children, it should be noted that it is not possible to translate an MFM-20 score into an equivalent MFM-32 score as the child gets older.[5] As such, it is advised that one scale is selected to assess the child throughout development.[5]

	MFM-20	MFM-32
Standing position and movement	8	13
Axial and **proximal limb motor function**	3	7
Distal limb motor function	9	12

Table 2 Number of items in each category for the MFM-20 and the MFM-32[7]

To assess the change in motor function abilities of a person with SMA, a physiotherapist will ask the person to perform (or try to perform) each item in turn.[1] The MFM-20 should take 12–50 minutes to complete, and the MFM-32 should take 30–50 minutes to complete.[8]

4.1.2. What do the MFM scores mean?

For each item, the physiotherapist will decide the score to give, from 0 to a maximum of 3:[6]

- A score of 0 means the person was not able to start the movement or maintain the starting position
- A score of 1 means the person was able to partially perform the movement
- A score of 2 means the person was able to complete the movement but with difficulty, without complete control or with some help
- A score of 3 means the person was able to complete the movement

The scores for each item are combined to give an overall score out of a total of 60 (MFM-20) or 96 (MFM-32).[6,7] These scores are then converted to a 0–100 scale.[5] The mean (average) MFM-32 score out of a maximum of 100 is 40 in individuals with Type 2 SMA and 70 in individuals with Type 3 SMA.[1]

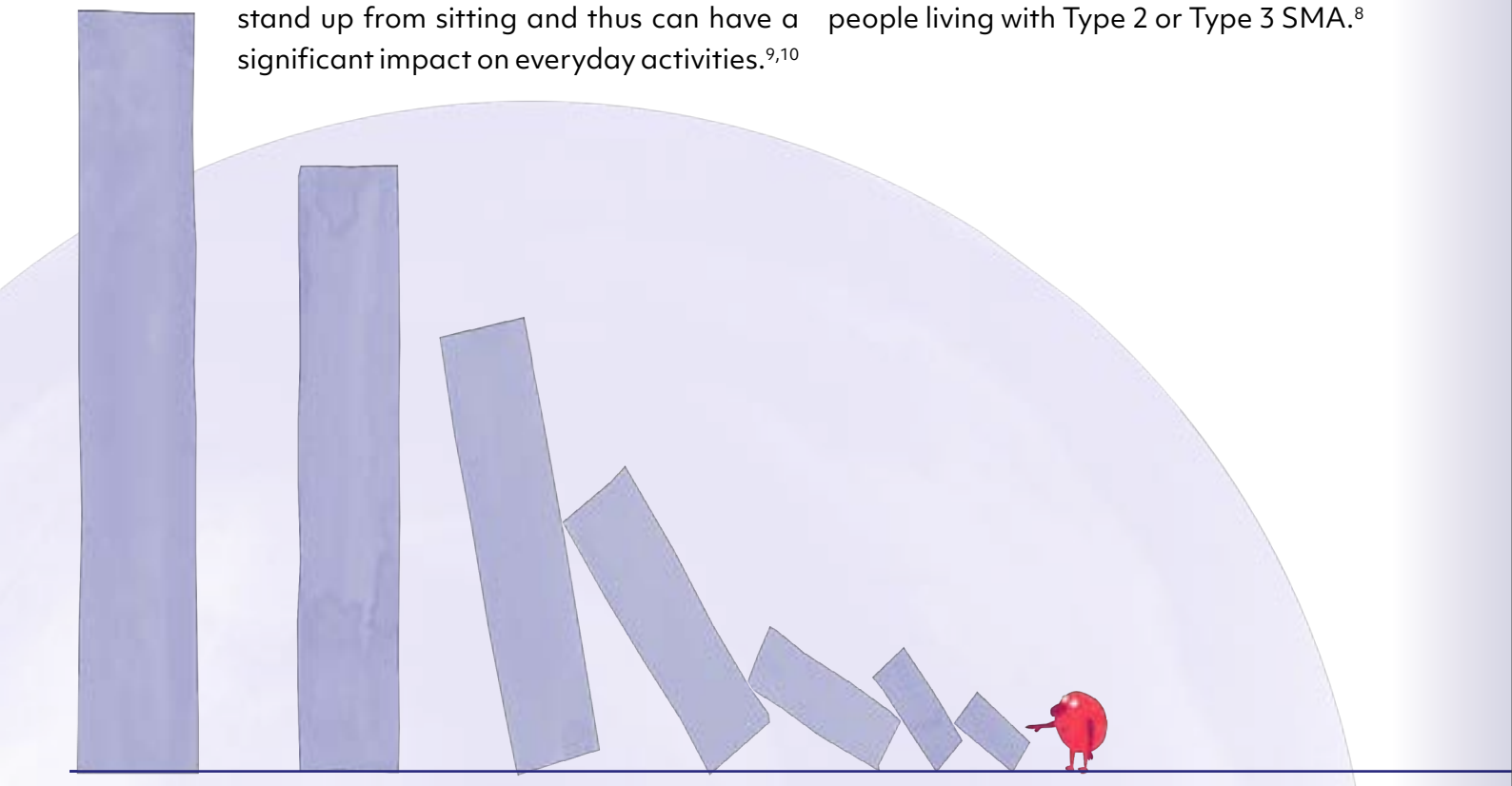
The items in the MFM-32 do not follow a linear pattern of progression.[1] This means that it is possible for a person to have a change in score on one item at the same time as their score changes on another item, even if the items require a different level or type of muscle function.[1] This is because each item is scored between 0 and 3, allowing small intermediate changes in functional abilities to be measured.[1]

A study has been carried out to explore how the abilities assessed in the MFM-32 scale are considered to be related to important *activities of daily living*, or *ADLs*, from the perspective of individuals with Type 2 or Type 3 SMA and their caregivers.[9] The results of this study are shown in **Figure 4**, which demonstrates that all items on the MFM-32 can be considered to be related to at least one important *ADL*.[9] A different study evaluated the level of change on the MFM-32 that could be considered to be meaningful to people living with Type 2 or Type 3 SMA aged 2–25 years.[10] Overall, the study showed that disease stabilisation is considered to be a meaningful outcome and that even small improvements may represent a substantial level of change for these individuals.[10] In addition, the results demonstrate that a 2- to 3-point improvement in the MFM-32 total score represents a substantial level of improvement across people living with Type 2 or Type 3 SMA aged 2–25 years.[10] As stabilisation is considered to be a meaningful outcome for individuals with SMA, a 2- to 3-point improvement in the MFM-32 total score may be viewed as a higher threshold against which to assess improvement. When looking more closely at different age groups within the 2–25 years age range, smaller changes are meaningful in late childhood and for adolescents and adults with a more progressed disease.[10]

Therefore, a small change in score for just one item could have a meaningful impact on the daily life of a person living with SMA.[9] For example, item 24 measures the ability to stand up from sitting on a chair, which requires upper and lower body mobility.[9,11] A score of 0 means the person is not able to stand from sitting, while a score of 1 means that the person is able to stand up when using a table for support.[11] A score of 2 means that the person can stand without using their arms to support them, but uses compensatory movements (such as tilting their trunk) to help them stand.[11] A score of 3 means the person can stand from sitting without needing to use their arms, meaning they would be able to stand while holding objects such as books or a mug without having to put any objects down first.[11] This demonstrates that even a small change on an item can influence how much assistance a person needs to stand up from sitting and thus can have a significant impact on everyday activities.[9,10] Such activities include the ability to use the toilet independently, which is a task of high importance to people living with SMA.[12]

Another example is item 7 which assesses an individual's ability to roll from lying on their back to their front and requires trunk (torso) strength to initiate and complete.[9,11] A score of 0 means the individual cannot start to roll, while a score of 1 means the individual can roll partially.[11] A score of 2 means the individual can turn over onto their front with difficulty, and a score of 3 means the individual can roll onto their front completely, freeing their arms from underneath them.[11] How much assistance a person needs to roll over has a significant impact on how independently they are able to perform important daily tasks such as rolling over in bed at night.[12]

Overall, the results of this study support the relevance of the motor functions assessed by the MFM-32 to the *ADLs* of people living with Type 2 or Type 3 SMA.[8]



ADL category:	MFM-32 item number	What does the item measure?	Which ADL(s) was most likely to be related to this item?
Dressing 	4	Pulling up the foot	Putting on shoes
	3	Bringing the knee to the chest	Dressing lower body
	6	Raising the pelvis	Putting on pants
	5	Bringing one hand to the opposite shoulder	Dressing upper body
	26	Standing on one foot	Dressing lower body
Mobility/ transferring 	7	Roll from lying on front to back	Turning and moving in bed to change positions
	8	Lying down to sitting up	Getting out of bed
	11	Sit to stand	Stand after a fall/from sitting on the floor
	1	Turning head	Adjusting position in bed
	2	Lifting head	Lifting head to move pillow/ getting out of bed
	25	Stand without support	Stand from sitting
	29	Walking in a straight line	Walking around the house
	12	Sitting down on a chair from standing	Sitting down when tired/ unsteady
	24	Standing up from sitting on a chair	Stand up from sitting at dinner table/to change position/when carrying objects
Self-care 	15	Bring arms up to place both hands on top of the head	Brushing hair
	5	Bringing hand to opposite shoulder	Itching/scratching

ADL category:	MFM-32 item number	What does the item measure?	Which ADL(s) was most likely to be related to this item?
Self-feeding 	23	Place forearms and/or hands on table	Eating independently
	21	Turning a ball over in hand	Picking up food when eating
	16	Extending elbow to touch a pencil	Picking food off a table without help
	20	Tearing a sheet of paper	Opening a wrapper/food packaging
	13	Maintain a seated position	Eating while seated
Reaching, picking up and holding objects 	17	Picking up coins	Picking up and holding small items
	9	Sitting on the floor	Holding objects in a seated position
	10	Leaning towards a ball	Reaching an object
	27	Touching the floor while standing	Touching the floor to pick up something
	32	Squatting	Picking something up from the floor
Physical activity 	28	Walking on heels	Walking
	30	Running	Exercising
	31	Hopping	Exercising/playing sport/hopping
	29	Walking in a straight line	Walking
	26	Standing on one foot	Taking a step/walking
Writing and technology use 	22	Pointing at drawings	Using a phone or other device/touchscreen device
	18	Going around the edge of a CD	Using a touchscreen device
	19	Picking up a pencil and drawing loops	Writing/drawing with a pen
	20	Tearing a sheet of paper	Using your hands to tear a piece of paper

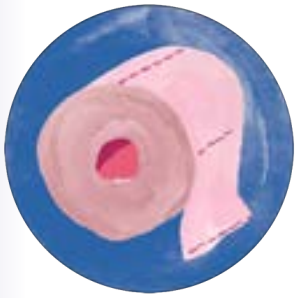
ADL category:	MFM-32 item number	What does the item measure?	Which ADL(s) was most likely to be related to this item?
Social contact/ engagement 	14	Raise the head from the chest	Having a conversation/ engaging with others
	1	Turning head	Looking around the room
	2	Lifting head	Looking around the room
Toileting 	25	Stand without support	Using a toilet independently
	12	Sitting down on a chair from standing	Using a toilet independently
	24	Standing up from sitting on a chair	Standing from sitting on the toilet
Performing work/ school activities 	13	Maintain a seated position	Doing work/schoolwork while seated

Figure 4 Most frequently reported **ADLs** in relation to each MFM-32 item[9]

The MFM-32 is one *assessment scale* among several others that are used to measure motor function changes in people with SMA.[1] Each *assessment scale* is unique in terms of the type of motor function that is measured and the population in which the *assessment scale* was designed to be used.[1] The next sections will provide an overview of additional motor *assessment scales*.

1. Vuillerot C et al. *Arch Phys Med Rehab* 2013;94: 1555–1561
2. O'Hagen JM et al. *Neuromuscul Disord* 2007;17: 693–697
3. Montes J et al. *Neurology* 2010;74:833–838
4. Mazzone E et al. *Neuromuscul Disord* 2011;21:406–412
5. Trundell D et al. *Neurol Ther* 2020; Aug 27: doi: 10.1007/s40120-020-00206-3 [Epub ahead of print]
6. Bérard C et al. *Neuromuscul Disord* 2005;15:463–470
7. de Lattre C et al. *Arch Phys Med Rehabil* 2013;94: 2218–2226
8. CureSMA. Best practices for physical therapists and clinical evaluators in spinal muscular atrophy (SMA). Available at: www.curesma.org/wp-content/uploads/2019/11/Cure-SMA-Best-Practices-for-PTs-and-CE-in-SMA-Clinical-Trials-Nov-2019.pdf, accessed December 2020
9. Duong T et al. Manuscript in submission
10. Duong T et al. Manuscript in submission
11. Roche. Data on file
12. Cruz R et al. *Clin Ther* 2019;41:943–960

4.2. Hammersmith Functional Motor Scale Expanded (HFMSE)

The HFMSE is an *assessment scale* that was developed specifically for SMA.[1] Therefore, the items are ordered by increasing level of difficulty to reflect the sequence of motor function improvements expected from those living with this disorder.[2] The HFMSE is useful to assess gross motor skills in stronger individuals who are able to sit or walk.[1,3]

What is assessed?[1,3]	The HFMSE assesses 33 gross motor skills split into different categories, including:  Lifting head (prone/supine)  Sit to and from lying  Lying and rolling  Propping on arms  Crawling and kneeling  Sitting  Standing  Taking steps  Walking, running and jumping
Key features[1,3]	● Very *reliable*[1] ● SMA-specific *assessment scale*[1] ● Does not include many items to assess arm, forearm and *fine* motor skills[1,3] ● Suitable for stronger individuals with Type 2 SMA and individuals with Type 3 SMA[1]
Target population[1]	Sitters and walkers aged ≥2 years
How long does it take to perform?[4]	10–30 minutes
What equipment is used?[4]	Mat, adjustable bench, stairs, tape and ruler
How many items are included?[4]	33

4.2.1. What do the HFMSE scores mean?

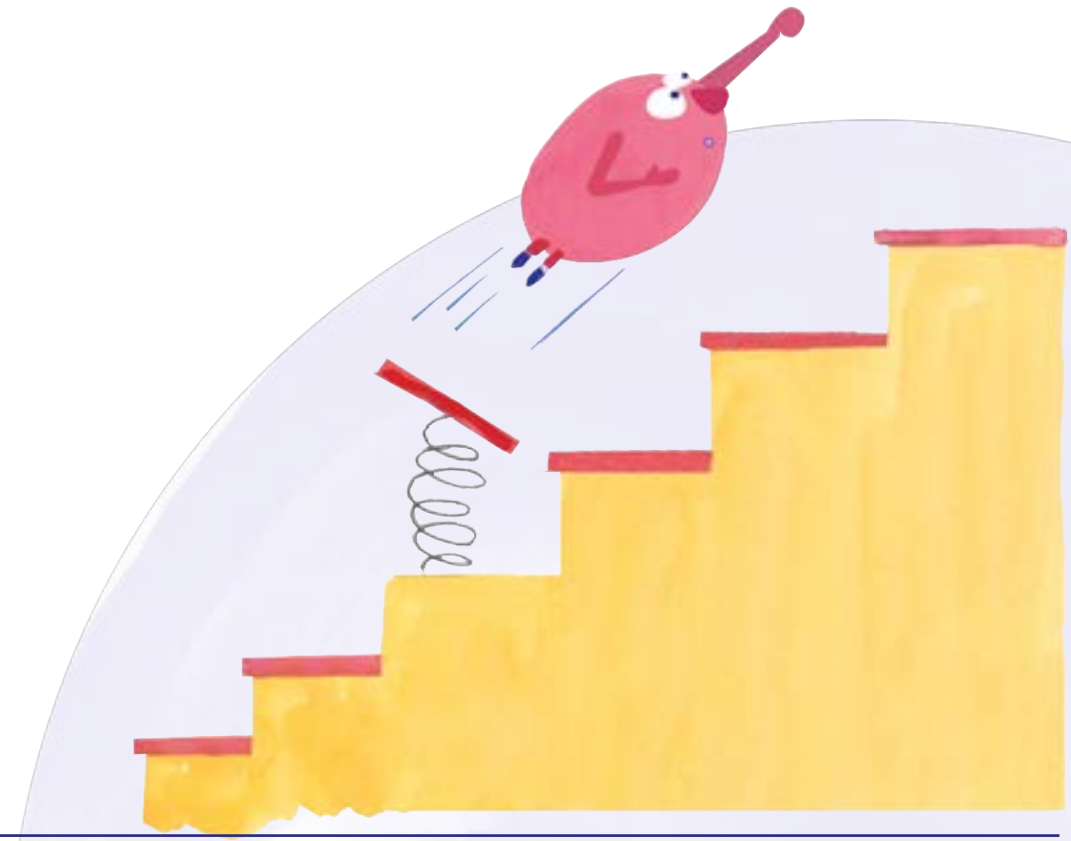
For each item, the physiotherapist will decide the score to give, from 0 to a maximum of 2:[1,3,4]

- A score of 0 means the person was not able to perform the item
- A score of 1 means the person was able to partially perform the item or to perform the item with difficulty or assistance
- A score of 2 means the person was able to complete the item

The scores for each item are added up to give an overall score out of a total of 66.[4]

A study used focus groups and surveys to explore the views of people with SMA and their caregivers about the clinical relevance of the HFMSE.[5] The results from this study suggested that small improvements in the HFMSE total score (even improving by just one or two points) could result in a meaningful change for people with SMA.[5]

For more information on the HFMSE, please visit: www.smareachuk.org/smaoutcomemeasures/the-hammersmith-scale-what-is-it



1. O'Hagen JM et al. *Neuromuscul Disord* 2007;17: 693–697
2. Glanzman AM et al. *J Child Neurol* 2011;26:1499–1507
3. Main M et al. *Eur J Paediatr Neurol* 2003;7:155–159
4. CureSMA. Best practices for physical therapists and clinical evaluators in spinal muscular atrophy (SMA). Available at: www.curesma.org/wp-content/uploads/2019/11/Cure-SMA-Best-Practices-for-PTs-and-CE-in-SMA-Clinical-Trials-Nov-2019.pdf, accessed December 2020
5. Pera MC et al. *BMC Neurol* 2017;17:39

4.3. Revised Upper Limb Module (RULM)

The RULM is an SMA-specific scale used to assess motor function of the arm, forearm and hand from the age of 30 months.[1,2]

This scale was designed for use alongside the HFMSE, which predominantly assesses *gross motor function*, to provide an assessment of upper limb function.[1,3] People who have very limited mobility may not be able to complete many items of the HFMSE, so the RULM allows upper limb function to be assessed when lower limb function is lacking or when severe contractures and/or scoliosis impact the assessment of *gross motor function*.[2–4] The items of the RULM have been designed to assess abilities that are needed to perform *ADLs*.[1]

What is assessed?[2]	The RULM assesses upper limb strength and function, with individuals scored on their ability to complete a series of tasks. Items are ordered to assess *distal* finger tasks first (including tracing a path using a pencil or picking up coins) followed by increasingly larger arm movements (including lifting various weights or opening plastic containers)
Key features[1,2]	• Includes items reflective of meaningful *ADLs*, such as bringing a cup to the mouth, opening a plastic container and lifting different weights to and above shoulder height[2] • SMA-specific *assessment scale*[1] • To be used as an add-on module to the HFMSE[1]
Target population[1]	Sitters aged ≥30 months
How long does it take to perform?[5]	10–15 minutes
What equipment is used?[5]	Plastic cup, button light, calibration weights, sand weights, pencil, plastic container, paper
How many items are included?[2]	20 (the entry item does not contribute to the overall score)

4.3.1. What do the RULM scores mean?

The first (entry) item is used as a starting question to determine the maximum level of upper limb function.[2] It does not contribute to the total score.[2] For the remaining scorable items, 18 of the 19 items are given a score from 0 to a maximum of 2:[2]

- A score of 0 means the person was not able to start the movement
- A score of 1 means the person was able to complete the movement with some modification (e.g. if the person stops part-way through the action)
- A score of 2 means the person was able to complete the movement with no difficulty

The remaining item is scored as either able or unable to achieve the task, with 1 as the highest score (able to achieve as per the criteria).[2] The scores for each item are totalled to give an overall score out of 37.[2]

For more information on the RULM, please visit: https://smanewstoday.com/news-posts/2019/02/18/rulm-can-assess-arms-function-in-wider-spectrum-sma-patients

1. Mazzone E et al. *Neuromuscul Disord* 2011;21:406–412
2. Mazzone E et al. *Muscle Nerve* 2017;55:869–874
3. O'Hagen JM et al. *Neuromuscul Disord* 2007;17: 693–697
4. Mercuri E et al. *Neuromuscul Disord* 2018;28:103–115
5. CureSMA. Best practices for physical therapists and clinical evaluators in spinal muscular atrophy (SMA). Available at: www.curesma.org/wp-content/uploads/2019/11/Cure-SMA-Best-Practices-for-PTs-and-CE-in-SMA-Clinical-Trials-Nov-2019.pdf, accessed December 2020

4.4. 6-Minute Walk Test (6MWT)

For people with SMA who can walk, reducing fatigue (or tiredness) is an important outcome.[1] The 6MWT evaluates physical function by assessing how far someone can walk (endurance) and how tired a person becomes when walking for 6 minutes.[2] This is specific for individuals who are able to walk.[2]

What is assessed?[3]	Individuals are asked to walk as fast as possible for 6 minutes (or for as long as they can, without sitting down) along a 25-metre course. At the end of 25 metres, they should walk around a cone and return to the start of the course. They should repeat this as many times as they can within 6 minutes
Key features[2,3]	• Well established in SMA and similar conditions[2,3] • Suitable for individuals who are able to walk[2]
Target population[4]	Walkers aged ≥4 years
How long does it take to perform?[5]	10 minutes
What equipment is used?[5]	Clear 30-metre walkway, tape measure, stopwatch, two orange cones, post-it flags
How many items are included?[3]	1

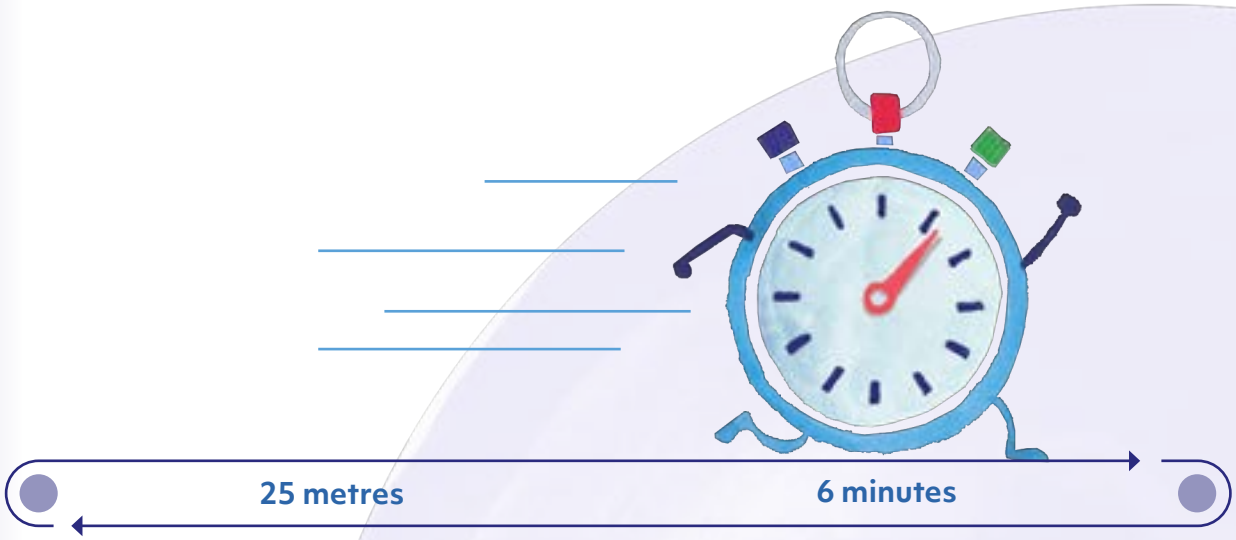
4.4.1. What do the 6MWT scores mean?

The physiotherapist may record:

- The total distance walked in 6 minutes[3]
- The distance walked in each minute[3]
- The average stride length per 25 metres[3,6]

The total distance walked in 6 minutes can help the physiotherapist to see if the person has improved their ability to walk or if their walking has become more impaired since their last visit.[3] By comparing the distance walked in the 1st minute with the distance walked in the 6th minute, the physiotherapist will be able to measure how fatigued, or how tired, the person became over the duration of the task.[3] The average stride length per 25 metres is also used to measure fatigue, as the more a person's stride length decreases over the 6 minutes, the more tired they are becoming.[6]

For more information on the 6MWT, please visit: https://smanewstoday.com/six-minute-walk-test



1. Cure SMA. Voice of the patient report. 2018. Available at: www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf, accessed December 2020
2. Montes J et al. *Neurology* 2010;74:833–838
3. Young SE et al. *Muscle Nerve* 2016;54:836–842
4. Montes J et al. *J Child Neurol* 2009;24:968–978
5. CureSMA. Best practices for physical therapists and clinical evaluators in spinal muscular atrophy (SMA). Available at: www.curesma.org/wp-content/uploads/2019/11/Cure-SMA-Best-Practices-for-PTs-and-CE-in-SMA-Clinical-Trials-Nov-2019.pdf, accessed December 2020
6. Montes J et al. *Muscle Nerve* 2011;43:485–488

4.5. Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)

The BSID-III uses a series of play tasks to assess the development of infants aged 1–42 months; it was developed to test if children could perform activities similarly to others their own age.[1] The scale covers five sections: thinking (cognitive), language (communication), movement (motor), social skills (emotion) and responding (adaptation).[1] A modified version of the movement section is used in a clinical trial for infants with SMA who are non-sitters.[2] In this modified version, tasks have been reordered to reduce tiredness and the scale has been adapted to better study the development of infants with SMA who are non-sitters.[2] This modified version is not permitted to be used outside of a clinical trial setting.[2]

What is assessed?[1]	The BSID-III motor scale includes assessment of fine (66 items) and gross motor skills (72 items). During the assessment, infants, toddlers and preschool age children are asked to perform different tasks and their ability to do so or not is recorded.  **Fine motor function:** tests how well a child can use their hands and fingers  **Gross motor function**: tests how well a child can move their body
Key features[1,3]	• Suitable for individuals aged <42 months[1] • Score can be compared with norms from typically developing children of the same age[3]
Target population[1]	Infants and children aged 1–42 months
How long does it take to perform?[1]	50–90 minutes*
What equipment is used?[3]	Bayley kit and score sheets, large room without distractions, floor mat, and a chair or bench at an appropriate height
How many items are included?[1]	138

*Time to complete reflects administration of all five scales and varies by age of the individual.

4.5.1. What do the BSID-III scores mean?

For each item, the physiotherapist will decide the score to give on a 0–1 scale:[1]

- A score of 0 means the infant was not able to perform the movement
- A score of 1 means the infant could complete the movement

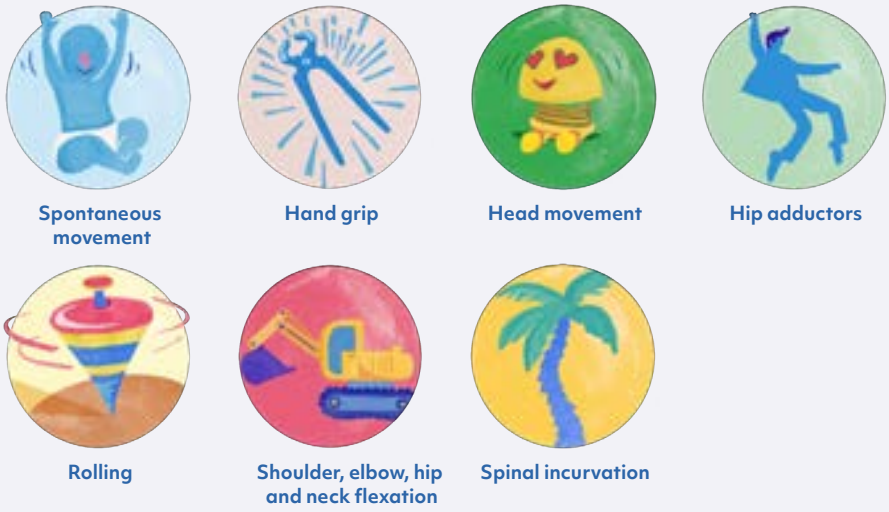
The scores for each item are combined to give an overall score out of a total of 138. A total score can also be given for the fine motor skills section (out of a total of 66) or the gross motor skills section (out of a total of 72).[1]

1. Bayley N. Harcourt Assessment 2006;25:180–198
2. Rose K et al. Presented at the Cure SMA Annual Conference, 28 June–1 July 2019, Anaheim, CA, USA
3. CureSMA. Best practices for physical therapists and clinical evaluators in spinal muscular atrophy (SMA). Available at: www.curesma.org/wp-content/uploads/2019/11/Cure-SMA-Best-Practices-for-PTs-and-CE-in-SMA-Clinical-Trials-Nov-2019.pdf, accessed December 2020

4.6. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)

The CHOP-INTEND was developed to assess motor function in infants with *neuromuscular disorders*. This scale is designed so that even children who have limited mobility will be able to complete some of the items.[1]

CHOP-INTEND scores have been observed to decrease over time in untreated infants with Type 1 SMA.[2] A CHOP-INTEND score over 40 is rarely seen in treatment-naïve infants with Type 1 SMA.[2]

What is assessed?[1]	The CHOP-INTEND assesses motor function across seven categories, with a total of 16 items:  Spontaneous movement Hand grip Head movement Hip adductors Rolling Shoulder, elbow, hip and neck flexation Spinal incurvation
Key features[1]	• Used in infants who are non-sitters and other conditions that affect muscles and nerves[1] • *Reliable* measure in infants who are weak and get tired easily[1] • Suitable for non-sitters[1]
Target population[1]	Non-sitters aged 1–38 months
How long does it take to perform?[1,3]	15–40 minutes
What equipment is used?[3]	Mat, standardised toys in a clinical trial setting (rattle, Sophie the Giraffe, toy phone)
How many items are included?[2]	16

1. Glanzman AM et al. *Neuromuscul Disord* 2010;20: 155–161
2. Finkel RS et al. *Neurology* 2014;83:810–817

4.6.1. What do the CHOP-INTEND scores mean?

For each item, the physiotherapist will assign a score from 0 to a maximum of 4 according to the degree of success performing a particular task.[1,3]

- A score of 0 means the infant was not able to perform the movement
- A score of 1 means the infant was able to perform a minimal part of the task with gravity eliminated
- A score of 2 means the infant was able to perform the task completely with gravity eliminated
- A score of 3 means the infant was able to partially complete the task, moving against gravity
- A score of 4 means the infant was able to perform the task completely, moving against gravity

The scores for each item are combined to give an overall score out of a total of 64.[2]

(3) CureSMA. Best practices for physical therapists and clinical evaluators in spinal muscular atrophy (SMA). Available at: www.curesma.org/wp-content/uploads/2019/11/Cure-SMA-Best-Practices-for-PTs-and-CE-in-SMA-Clinical-Trials-Nov-2019.pdf, accessed December 2020

5. People living with SMA/caregiver perspectives on treatment/care goals and meaningful outcomes

With the development of *SMN protein*-restoring therapies and the implementation of *standards of care*, treatment expectations in SMA have evolved.[1] Individuals living with SMA and their caregivers now may expect disease-modifying outcomes, including improvements in overall survival, motor and respiratory function, and overall quality of life.[2] Nevertheless, treatment expectations are subjective and vary between each individual person living with this disorder.[2] As such, to make sure we set the right treatment expectations, a broad and holistic understanding of each person's needs is required.[3] Patient-reported outcome measures, such as the SMA Independence Scale described in the next section, provide useful insights into what is meaningful for people living with SMA;[4] however, there are other outcomes that are meaningful to people with SMA, such as having more energy, that are not captured by existing outcome measures.[5]

Surveys and meetings have been conducted by Cure SMA and SMA Europe, which aimed to obtain the perspective of people with SMA and their caregivers on the impact of SMA on their daily lives, among other topics.[2,6,7] These initiatives were completed or attended by people with Types 1, 2 or 3 SMA and their caregivers across a wide age range, and identified several outcomes to be meaningful to the lives of people living with SMA.[2,6,7]

For caregivers of infants diagnosed with Type 1 SMA, meaningful outcomes may include:[2,6,7]

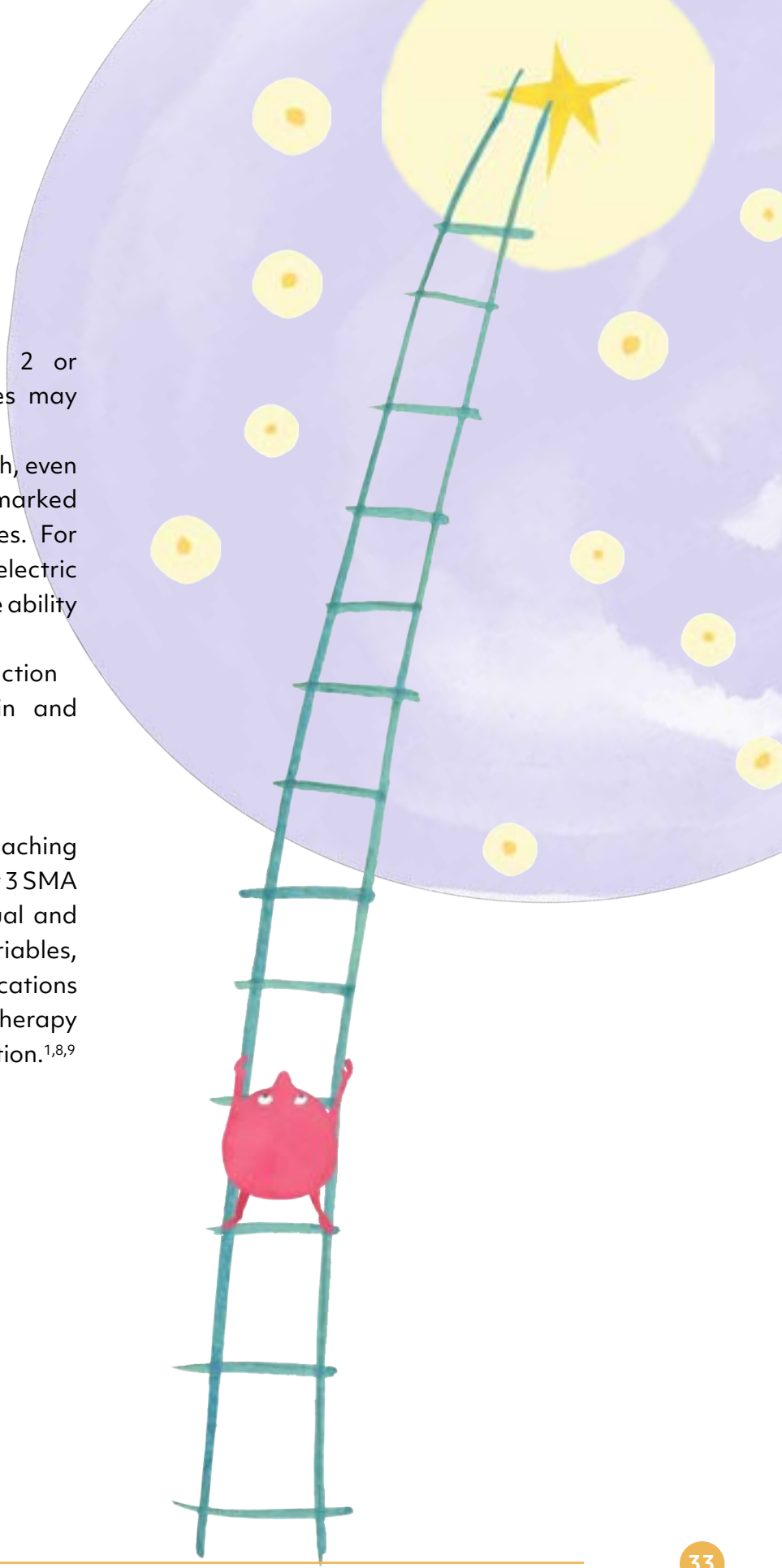
- Improvements in survival
- Improvements in respiratory and swallowing function
- Reaching motor milestones that historically are not reported in untreated infants, including sitting without support and standing

1. Tizzano EF & Finkel RS. *Neuromuscul Disord* 2017;27:883–889
2. Cure SMA. Voice of the patient report. 2018. Available at: www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf, accessed December 2020
3. Finkel RS et al. *Neuromuscul Disord* 2018;28:197–207
4. Trundell D et al. Presented at the Cure SMA Annual Conference, 14–17 June 2018, Dallas, TX, USA
5. Duong T et al. Manuscript in submission
6. Rouault F et al. *Neuromuscul Disord* 2017;27:428–438

For people living with Type 2 or Type 3 SMA, meaningful outcomes may include: [2,6,7]

- Improvements in muscle strength, even if small, as these may have a marked impact on day-to-day activities. For example, the ability to drive an electric wheelchair, which may mean the ability to have a job
- Improvements in respiratory function
- Improvements in fatigue, pain and psychological problems
- Disease stabilisation

It is important to highlight that reaching any of these milestones in Type 1, 2 or 3 SMA will vary from individual to individual and will be dependent on different variables, including disease duration, complications already present, functional level at therapy initiation and timing of therapy initiation.[1,8,9]



(7) Gusset N on behalf of SMA Europe. Pre-publication summary EUPESMA-2019 [manuscript in preparation]
(8) Dangouloff T & Servais L. *Ther Clin Risk Manag* 2019;15:1153–1161
(9) Mercuri E et al. *Neuromuscul Disord* 2018;28:103–115

6. Assessing what matters to those living with SMA and their caregivers

As described in the previous chapters, maintaining or gaining motor function is a key treatment/care goal in SMA; therefore, measuring motor skills and development is a primary focus in SMA.[1,2] Nevertheless, it is also important to understand how improvement in motor function can translate to increased independence and the ability to perform *ADLs*.[1,3] The CureSMA 'The Voice of the Patient Report' highlights how important being independent and able to perform *ADLs* is to people with SMA.[1] This may include tasks such as getting dressed or brushing your teeth.[1]

Several measures/instruments (i.e. questionnaires) have been developed in order to collect patient-reported data on functional independence, health-related quality of life and functional ability.[3–7] These include:[3–7]

Measure/instrument	Outcome measure assessed	Validated in SMA
SMA Independence Scale[4]	Level of functional independence	Yes
Pediatric Quality of Life Inventory™ 3.0 Neuromuscular Module[5]	Health-related quality of life	No
Pediatric Quality of Life Inventory™ 4.0 Generic Core Scales[5]	Health-related quality of life	No
Autoquestionnnaire Qualite' de Vie Enfant Image[5]	Health-related quality of life	No
RAND 36-Item Short Form Health Survey[5]	Health-related quality of life	No, but recommended for use in infants with SMA aged <2 years
Pediatric Quality of Life Inventory[5]	Health-related quality of life	No
Pediatric Evaluation of Disability Inventory–Computer Adaptive Test (PEDI-CAT)[6]	Level of functional ability	Yes
Egen Klassifikation Scale[7]	Level of functional ability	Yes
Web-based questionnaire[5]	Level of functional ability	No
Personal Adjustment and Role Skills Scale[5]	Level of functional ability	No
Revised Rutter Scale[5]	Level of functional ability	No

Nevertheless, most of these existing outcome measures lack specificity for SMA.[5] In the next section, we will be discussing the SMA Independence Scale in more detail; this scale was developed specifically to assess the level of functional independence of people living with Type 2 or 3 SMA and used as an outcome measure in the SUNFISH trial.[3,8]

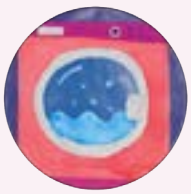
1. Cure SMA. The Voice of the Patient Report for Spinal Muscular Atrophy. 2018
2. Montes J et al. *J Child Neurol* 2009;24:968–978
3. Trundell D et al. Presented at the Cure SMA Annual Conference, 14–17 June 2018, Dallas, TX, USA
4. Staunton H et al. Presented at the Cure SMA Annual Conference, 8–12 June 2020, virtual meeting
5. Risson V et al. PSY200. *Value in Health* 2018;21:S1–S481
6. Pasternak A et al. *Muscle Nerve* 2016;54:1097–1107
7. Steffenson B et al. *Physiother Res Int* 2001;6:119–163
8. ClinicalTrials.gov NCT02908685, accessed December 2020

6.1. SMA Independence Scale (SMAIS): Assessing independence in those living with SMA

In 2019, Roche developed the SMAIS in partnership with the scientific community and Patient Advocacy Groups (PAGs) – SMA Europe and Cure SMA.[1] This scale is designed to measure the level of functional independence in people with SMA (sitters) based on their assessment of how much help they need to perform certain *ADLs*.[2] A version with a set of items that assess *ADLs* more relevant to individuals living with SMA who are able to walk is currently being developed.[1]

Two versions of the SMAIS have been developed with identical items:[2,3]

- One to be completed by individuals with SMA aged 12 years and older
- One to be completed by caregivers of individuals with SMA aged 2 years and older

What is assessed?[3]	The SMAIS includes 29 items assessing the level of independence when completing **ADLs**, for example:  Eating and drinking  Bathing/hygiene  Dressing  Picking up/moving objects  Chores  Mobility/strength
Key features[2]	● People living with SMA and caregivers can use the scale ● Focusses on *ADLs* that matter to those living with SMA and caregivers ● Not used so far in all SMA types (used in sitters only, not non-sitters and walkers)
Target population[3]	Sitters aged ≥2 years (caregiver reported) or ≥12 years (patient reported)
How long does it take to perform?[1]	5–7 minutes
What equipment is used?[2]	SMAIS questionnaire
How many items are included?[3]	29

6.1.1. What do the SMAIS scores mean?

The first version of the SMAIS developed with patient and caregiver input included 29 items scored on a scale of 0–4.[3] Validation studies indicated that people with SMA and their caregivers had difficulty distinguishing between the five response options and that all 29 items were not measuring a single concept.[3] In SUNFISH and JEWELFISH, a 22-item upper limb function total score was used and items were scored based on a re-scoring to a 3-point response option scale (range: 0-44 with higher scores indicating greater independence and less assistance required).

Subsequently for any future studies, the SMAIS has been updated to a 22-item measure (SMAIS-ULM) of upper limb (arm forearm and hand) function scored on a 0–2 scale where 0=cannot do this at all without help, 1=need some help and 2=do not need help. The other seven items (relating to mobility and chores/shopping) are scored on the same scale (0–2) but act as stand-alone items not included in the total score.[3]

This version of the SMAIS has demonstrated a high reliability and validity and can detect meaningful within-patient changes.[1,3,4]

1. Roche. Data on file
2. Trundell D et al. Presented at the Cure SMA Annual Conference, 14–17 June 2018, Dallas, TX, USA
3. Staunton H et al. Presented at the Cure SMA Annual Conference, 8–12 June 2020, virtual meeting
4. Staunton H et al. MDA Annual Conference, March 2021, virtual meeting

7. Summary

Outcome measures are important because they are used in clinical practice to measure how a person's disease is changing over time and in clinical trials to determine the effectiveness of a particular treatment.[1] The MFM and the SMAIS are among several different outcome measures used in SMA (**Table 3**).[1–3] Each one is suitable for a specific population, so it is important to choose the most appropriate *assessment scale* to measure the disease progression of a person with SMA, based on that person's age, disease severity and motor function ability.[1] For example, a scale that focusses on movements of the lower limbs (such as standing or walking) would not be suitable for a person who is unable to stand.[1]

Data collected by the different outcome measures will also be used as evidence to help regulatory bodies decide whether a new treatment is *valid* and can therefore be approved for the management of SMA.[4] As such, it is important to use outcome measures that are sound, *reliable* and detect changes that are truly meaningful for people living with SMA.[1,4] For example, a study evaluated the level of change on the MFM-32 that could be considered to be meaningful to people living with Type 2 or Type 3 SMA aged 2–25 years.[5] Overall, the study showed that disease stabilisation is considered to be a meaningful outcome and that even small improvements may represent a substantial level of change for these individuals.[5] In addition, the results demonstrate that a 2- to 3-point improvement in the MFM-32 total score represents a substantial level of improvement across people living with Type 2 or Type 3 SMA aged 2–25 years.[5]

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Assessment scale	Age group	Type of SMA	Number of items	Maximum total score	Time to complete	Average score per SMA type
Motor function assessment scales						
MFM[2,6–9]	2–60 years[2,6,7]	Non-sitters, sitters and walkers[2,6,7]	32 for MFM-32 20 for MFM-20[2,7]	96 for MFM-32 60 for MFM-20[7,8]	MFM-20: ~25 minutes[9] MFM-32: ~35 minutes[9]	Mean score of 40 for individuals with Type 2 SMA (n=44) and 70.1 for Type 3 SMA (n=59)[2]
HFMSE[9,10]	≥2 years[10]	Sitters and walkers[10]	33[9]	66[9]	10–30 minutes[9]	Mean score of 50.1 for individuals with Type 3 SMA (n=17) and 27.7 when pooling individuals with Type 2 and Type 3 SMA (n=38)[10]
RULM[9,11–13]	≥30 months[11]	Sitters and walkers[11]	19[12]	37[12]	10–15 minutes[9]	Mean score of 14.8 for people with Type 2 SMA (n=60), mean score of 27.4 in non-ambulant individuals with Type 3 SMA (n=22) and 34.2 in ambulant individuals with Type 3 SMA (n=32)[13]
6MWT[9,14,15]	≥4 years[14]	Walkers[14]	1[14]	N/A	10 minutes[9]	Mean distance of 343 m (1125 ft) walked in 6 minutes for ambulant individuals with Type 3 SMA (n=18)[15]
BSID-III[16,17]	1–42 months[16]	Non-sitters, sitters and walkers[16]	138 overall (66 items for fine motor subset and 72 for gross motor subset)[16]	Overall score is based on the number of items completed in each subset[16]	50–90 minutes[16]	Infants with Type 1 SMA are not expected to achieve the milestones evaluated, including independent sitting[17]
CHOP-INTEND[9,18–20]	1–38 months[18]	Non-sitters and sitters[18]	16[19]	64[19]	15–40 minutes[9]	A score of >40 is rare for infants with Type 1 SMA (mean score of 21.4 [n=23])[19,20]
HINE-2[9,17,21]	2–24 months[21]	Non-sitters, sitters and walkers[21]	8[21]	26[17]	5–15 minutes[9]	A score of 0 for items such as sitting, crawling and walking is expected for infants with Type 1 SMA (n=33)[17]
Functional independence assessment scales						
SMAIS[22,23]	≥2 years (caregiver reported) or ≥12 years (patient reported)[22]	Sitters[22]	29[22]	44 (for the 22 items related to upper limb function)[22]	5–7 minutes[23]	N/A

Table 3 An overview of the key characteristics for *assessment scales* used in clinical practice for SMA and/or in SMA clinical trials

8. Glossary

Activities of daily living (ADL)	the skills needed to manage basic physical needs, including personal hygiene, dressing, using the toilet, transferring and eating
Assessment scale	a set of items or questions that measure how well a person can use their muscles to perform various actions or movements
Axial muscle function	the ability of a person to perform activities or movements involving the torso or head
Bulbar function	function relating to swallowing and speech
Disease trajectory	the expected future outcomes of a person's disease based on previous measurements in populations with similar characteristics
Distal limb motor function	the ability of a person to perform activities or movements involving the forearms, hands, fingers or feet
DNA	the genetic code that determines all the characteristics of a living organism
Fine motor function	abilities or precise/small movements that use small muscles in the wrists, hands, fingers, feet and toes
Functional protein	a protein that can carry out a specific function
Gene	the basic unit of *DNA* instructions. Each gene has a very specific job to do; some carry the instructions for making proteins (the building blocks for cells) or for turning *DNA* off or on, whereas others carry the instructions for how to modify other proteins or *DNA* within a cell
Gene copies	the number of times a gene is repeated in the *DNA*
Gross motor function	abilities or movements that use the large muscles in the torso, arms and legs
Heterogeneous population	a group of people with varied characteristics

Motor development	the development of a child's bones, muscles and ability to move around and interact with their environment
Motor neurons	nerve cells that control muscle movement. Upper motor neurons send messages from the brain to the spinal cord, and lower motor neurons send messages from the spinal cord to the muscles. They form part of the neuromuscular system and are essential for day-to-day activities like breathing, holding your head up, walking and even holding a book
Neuromuscular disorders	conditions that affect the functioning of the muscles
Phenotype	the observable characteristics of an individual resulting from genetic and environmental influences
Proximal limb motor function	the ability of a person to perform activities or movements involving the shoulders, upper arms, pelvic muscles or thighs
Reliable/reliability	the ability of an outcome measure to produce stable and consistent results
SMN protein	a protein that helps nerves in the spinal cord (known as *motor neurons*) to survive, which helps to control muscles and coordinate movement
SMN1/2	genes that produce *SMN protein*. *SMN1* produces lots of *SMN protein* but *SMN2* only produces a small amount
Standards of care (in SMA)	the set of recommendations and guidelines for the care of a person with SMA that a healthcare professional should follow where possible. In SMA, this includes care of the person's motor function, breathing and swallowing, as well as many other types of care
Valid/validity	the ability of an outcome measure to assess the parameter it was designed to evaluate

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