4th edition

REPORT

“Transition from adolescence into adulthood”

LIS-N & LER-N

Educational meeting in SMA

2nd & 3rd of December, 2020

Biogen

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About spinal muscular atrophy

Spinal muscular atrophy (SMA) is characterised by degeneration and loss of motor neurons in the brain and spinal cord. The loss of functioning motor neurons leads to progressive muscle weakness and atrophy as muscles stop receiving signals from the central nervous system. SMA is caused by a mutation or deletion in the survival motor neuron 1 *(SMN1)* gene which encodes the survival motor neuron (SMN) protein. A second SMN gene *(SMN2)* produces a shortened and less functional SMN protein. SMA develops when the mutation or deletion is present on both copies of the *SMN1* gene, in which case there will be insufficient SMN protein levels for the motor neurons to survive.[1-3]

SMA with autosomal-recessive inheritance is classified into different subtypes according to age of onset and severity, with the most common subtypes being:[4-7]

- **SMA type 1**, the classic form of SMA also known as infantile-onset SMA or Werdnig-Hoffmann disease, typically manifests itself before the age of 6 months. SMA type 1 is the most severe form of SMA; if untreated, children with SMA type 1 will never be able to sit and their life expectancy is less than two years.
- **SMA type 2** typically appears between 6 and 18 months of age and is a less severe form of SMA. Children with SMA type 2 are able to sit independently but not walk; 70% of the patients are still alive at the age of 25.
- **SMA type 3**, or Kugelberg-Welander disease, develops in children older than 18 months. Children with SMA type 3 are typically able to walk independently and have a normal life expectancy. However, although SMA type 3 is a milder form of SMA, patients with SMA type 3 may progressively deteriorate as they grow older.

A typical presentation of SMA type 1 is muscle weakness and hypotonia, known as the "floppy baby syndrome." SMA is diagnosed based on the medical history and clinical presentation together with neurophysiological testing and DNA sequencing to confirm the *SMN1* gene mutation or deletion.[4,8]

Patients with SMA are treated with supportive interventions that focus on the quality of life, including physiotherapy, mobility assistance, and respiratory and nutritional support.[4,9-12] Until recently there was no effective drug treatment for SMA and the main focus was then on palliative interventions.

References:
1. Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell 1995;80:155-65. **2.** https://ghr.nlm.nih.gov/gene/SMN1. **3.** Kolb SJ, Kissel JT. Spinal muscular atrophy: a timely review. Arch Neurol 2011;68:979-84. **4.** Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018;28:103-115. **5.** Markowitz JA, Singh P, Darras BT. Spinal muscular atrophy: a clinical and research update. Pediatr Neurol 2012;46:1-12. **6.** Lunn MR, Wang CH. Spinal muscular atrophy. Lancet 2008;371:2120-33. **7.** Moosa A, Dubowitz V. Motor nerve conduction velocity in spinal muscular atrophy of childhood. Archives of Disease in Childhood 1976;51:974-977. **8.** D'Amico A, Mercuri E, Tiziano FD, et al. Spinal muscular atrophy. Orphanet J Rare Dis 2011;6:71. **9.** Lemoine TJ, Swoboda KJ, Bratton SL, et al. Spinal muscular atrophy type 1: are proactive respiratory interventions associated with longer survival? Pediatr Crit Care Med 2012;13:e161-5. **10.** Iannaccone ST. Modern Management of Spinal Muscular Atrophy. Journal of Child Neurology 2007;22:974-978. **11.** Oskoui M, Levy G, Garland CJ, et al. The changing natural history of spinal muscular atrophy type 1. Neurology 2007;69:1931-6. **12.** Chatwin M, Bush A, Simonds AK. Outcome of goal-directed non-invasive ventilation and mechanical insufflation/exsufflation in spinal muscular atrophy type I. Archives of Disease in Childhood 2011;96:426-432.

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Introduction

We are proud to share the 2020 LIS-N & LER-N report with you. This was the fourth LIS-N & LER-N meeting since the start of this initiative, and this year's theme was "Transition from adolescence into adulthood".

The aim of the LIS-N & LER-N meeting is to provide a platform for healthcare professionals caring for patients with SMA in the Nordic countries to meet and interact across national borders, to share and promote knowledge and best practice with the ambition to improve competence in the management of SMA in the Nordic region. Because of the Covid-19 pandemic, the 2020 LIS-N & LER-N meeting was held digitally over two half-days. Another novelty this year was the addition of a physiotherapists' parallel session hosted by Anna-Karin Kroksmark, to expand the scope of the meeting to include a wider range of healthcare professionals. The 2020 LIS-N & LER-N meeting contained a comprehensive programme of lectures and discussions on a variety of topics, chaired and moderated by Professor Már Tulinius.

Dr Anna-Karin Kroksmark opened Day 1 with a lecture on *Outcome measures: current use and future needs*. This was followed by a tandem presentation by Professor Tulinius and Associate Professor Christopher Lindberg, who shared their perspectives on the *paediatric-adult transition process in SMA* from their respective centres in Gothenburg. Day 2 began with the invited guest speaker Professor Tim Hagenacker from University Hospital Essen in Germany who discussed *the natural history of SMA in adults*, highlighting that disease stabilisation is important to people living with later-onset (type 2 or 3) SMA; 81% of the patients in a recent study felt that disease stabilisation would represent major progress.[1] This was followed by Professor Reidun Førde who spoke on the topic of *Start and stop criteria: Ethical considerations*, while in parallel Dr Kroksmark hosted a break-out session for physiotherapists on *Habilitation and rehabilitation in spinal muscular atrophy*.

The two days of lectures by different speakers from different professions at the 2020 LIS-N & LER-N meeting had one message in common: today's treatment of SMA demands a new mindset and wider professional skills. Biogen will continue to support this process by sharing knowledge and experience around SMA, until all children and adults have access to treatment. A key element in this commitment is the organisation and funding of the annual LIS-N & LER-N meeting. We hope you will enjoy reading this report and that it will help you in your daily practice.

Peps Bengtsson, Biogen

References:
1. Rouault F, Christie-Brown V, Broekgaarden R, et al. Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients. Neuromuscul Disord. 2017;27(5):428-438. doi:10.1016/j.nmd.2017.01.018

Photo: Henrik Rådmark

ANNA-KARIN KROKSMARK

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Outcome measures: current use and future needs

Physiotherapists play a key role in the multidisciplinary team around SMA patients as clinical evaluators of motor function and muscle strength. A wide range of clinically relevant and validated tools and instruments are available for assessing various aspects of motor function such as mobility, posture, and range of movement.

As a research physiotherapist at Queen Silvia Children's Hospital, associate professor Anna-Karin Kroksmark has had extensive experience of working with children with neuromuscular disorders, both in routine practice and as clinical evaluator in research studies for new medical treatments. Her presentation at Lis-n & Ler-n 2020 reviewed a series of evaluation tools that are used both as outcome measures in studies and in routine clinical practice, and highlighted future needs.

CHOP INTEND

One of the most widely disseminated and recognised instruments for assessing SMA patients is the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), first published and validated around ten years ago as a tool for assessing the very weakest infants with SMA type 1.[1,2] CHOP INTEND captures a range of aspects of proximal and distal muscle strength in the upper and lower limbs, and evaluates motor function in the supine, prone and sitting position. The instrument itself comprises 16 items and a maximum score of 64 can be achieved. A longitudinal prospective natural history study of children with infantile-onset SMA published in 2017 showed that while healthy

> *"While healthy infants typically achieve optimal total CHOP-INTEND scores by the age of three to four months, infants with SMA 1 achieve significantly lower total scores which deteriorate over time."*

infants typically achieve optimal total CHOP-INTEND scores by the age of three to four months, infants with SMA 1 achieved significantly lower total scores which deteriorated over time.[3]

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Fatigue severity scale (FSS)

Read and circle a number.		Strongly Disagree ⟶ Strongly Agree						
1.	My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2.	Exercise brings on my fatigue.	1	2	3	4	5	6	7
3.	I am easily fatigued.	1	2	3	4	5	6	7
4.	Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5.	Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6.	My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7.	Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8.	Fatigue is among my most disabling symptoms.	1	2	3	4	5	6	7
9.	Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Table adapted from Werlauff U, Højberg A, Firla-Holme R, et al. 2014

A key advantage with CHOP INTEND is that it is responsive to change in SMA type 1 patients without any apparent floor or ceiling effects; however, Anna-Karin Kroksmark pointed out that this may be set to change as new medical treatments for SMA are bringing about changes in the natural history of SMA type 1. "CHOP INTEND has been used as an outcome measure in clinical research studies for new medical treatments for infantile-onset SMA," she said.

HFMSE

Another important instrument in SMA clinical research and practice is the Hammersmith Functional Motor Scale (HFMS), which was developed in the early 2000s to evaluate motor ability and monitor clinical progress in children with SMA with no or limited ambulation.[4] In its initial version it contained 20 items which were scored as 0 (inability), 1 (ability with assistance) or 2 (ability unaided); in a later development a further 13 items were incorporated from the widely used Gross Motor Function Measure (GMFM) to make the HFMS suitable for both ambulant and non-ambulant patients.[5] Like CHOP INTEND, the expanded version (HFMSE) has been used as an endpoint in clinical research studies of new medical treatments for SMA.

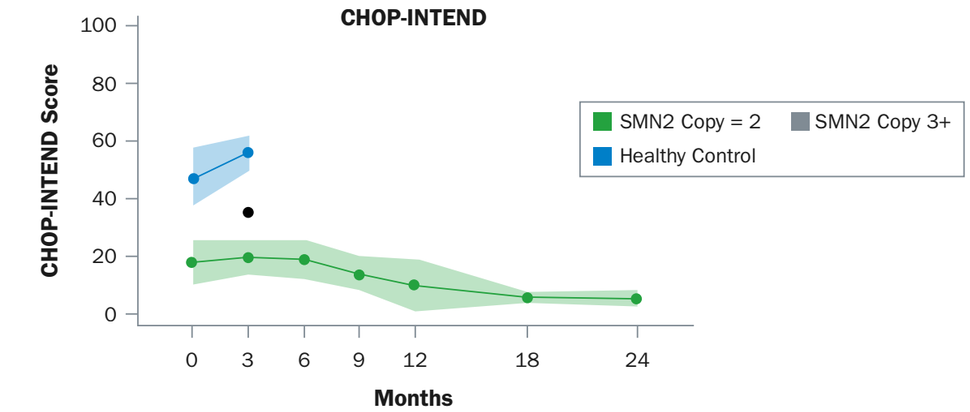
Other instruments

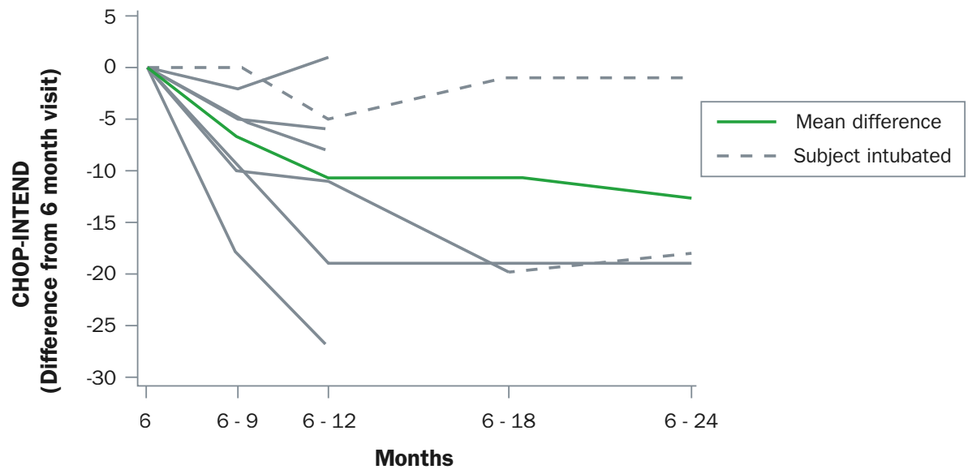
In addition to CHOP INTEND and HFMSE, Anna-Karin Kroksmark also mentioned WHO motor milestones, the Revised Upper Limb Module (RULM), and the six-minute walking test (6MWT) as instruments that are used both in routine clinical practice and

> *"The WHO motor milestones instrument is essentially a series of 'yes' or 'no' questions, since a milestone has been achieved or it has not."*

as evaluation tools in clinical research studies. The WHO motor milestones have the advantage of being easy to use. "This instrument is essentially a series of 'yes' or 'no' questions, since a milestone has been achieved or it has not," Anna-Karin Kroksmark

Longitudinal progression - CHOP INTEND





Figures adapted from Kolb et al; 2017

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said. "Of course, this relies on each milestone having a clear and specific definition." The RULM was developed in 2017 as a tool for evaluating upper extremity function in patients with SMA from 30 months of age;[6] it typically takes no more than 20 minutes to complete (less if the evaluator is highly experienced) and it is generally well tolerated by the patient, who can complete the test seated on a chair or in a wheelchair. Likewise, the 6MWT is an easy test to carry out, although it requires the patient to be of sufficient age and ability to walk at least ten metres unaided.

Outside of clinical research, other tools used to evaluate SMA patients include time tests, which involve simple stopwatch measurements of the time required to perform tasks such as walk or run 10 metres, stand up from the supine position, or climb up or down four standard stairs; myometric measurements of muscle strength which can be compared with reference values for healthy children to provide valuable information about asymmetries; and assessment of contractures using goniometry of the upper and lower limbs. Anna-Karin Kroksmark stressed that the latter should ideally be performed by two people. "Having two physiotherapists, or a physiotherapist and an occupational therapist, present for this procedure may not be feasible in some hospitals, but it is highly recommended for optimal reliability," she said.

Despite the many instruments and scales that are available to healthcare professionals caring for SMA patients, there are gaps and unmet needs that reflect the changing characteristics of this patient population. The current tools have to a large extent been developed for use with infants and children, and may be less suitable for use with teenagers and adults. Anna-Karin Kroksmark suggested implementing scales that have been developed and validated for adults with neuromuscular disorders, such as the EK scale[7] and/or the Motor Function Measure (MFM)[8] which have both been validated for patients with SMA.

> *"Our current evaluation instruments do not capture fatigue and perceived levels of energy."*

Another aspect of SMA that Anna-Karin Kroksmark believes should be evaluated and monitored in the era of effective medical treatments for SMA is fatigue. "Our current evaluation instruments do not capture fatigue and perceived levels of energy," she said. The Fatigue Severity Scale (FSS) has been used in clinical research to assess fatigue in SMA patients,[9] but has yet to be validated for this patient population.

References:

1. Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): Test development and reliability. Neuromuscul Disord 2010;20:155–161. Available at: https://doi.org/10.1016/j.nmd.2009.11.014. **2.** Glanzman AM, McDermott MP, Montes J, et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). Pediatr Phys Ther 2011;23. Available at: https://journals.lww.com/pedpt/Fulltext/2011/23040/Validation_of_the_Children_s_Hospital_of.2.aspx. **3.** Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. Ann Neurol 2017;82:883–891. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29149772. **4.** Main M, Kairon H, Mercuri E, et al. The Hammersmith Functional Motor Scale for Children with Spinal Muscular Atrophy: a Scale to Test Ability and Monitor Progress in Children with Limited Ambulation. Eur J Paediatr Neurol 2003;7:155–159. Available at: https://doi.org/10.1016/S1090-3798(03)00060-6. **5.** O'Hagen JM, Glanzman AM, McDermott MP, et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscul Disord 2007;17:693–697. Available at: https://doi.org/10.1016/j.nmd.2007.05.009. **6.** Mazzone ES, Mayhew A, Montes J, et al. Revised upper limb module for spinal muscular atrophy: Development of a new module. Muscle Nerve 2017;55:869–874. Available at: https://doi.org/10.1002/mus.25430. **7.** Steffensen B, Hyde S, Lyager S, et al. Validity of the EK scale: a functional assessment of non-ambulatory individuals with Duchenne muscular dystrophy or spinal muscular atrophy. Physiother Res Int 2001;6:119–134. Available at: https://doi.org/10.1002/pri.221. **8.** Vuillerot C, Payan C, Iwaz J, et al. Responsiveness of the Motor Function Measure in Patients With Spinal Muscular Atrophy. Arch Phys Med Rehabil 2013;94:1555–1561. Available at: https://doi.org/10.1016/j.apmr.2013.01.014. **9.** Werlauff U, Højberg A, Firla-Holme R, et al. Fatigue in patients with spinal muscular atrophy type II and congenital myopathies: evaluation of the fatigue severity scale. Qual Life Res 2014;23:1479–1488. Available at: https://doi.org/10.1007/s11136-013-0565-8.

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Paediatric-adult transition: Experiences from Gothenburg

When young SMA patients in Gothenburg are ready to transition from the paediatric neurology department to the adult clinic, the healthcare teams in both settings work hard to ensure the process is as easy and smooth as possible for the patients and their families. As Sahlgrenska University Hospital is a major referral centre for SMA in Sweden, careful coordination with local caregivers and regional rehabilitation teams is key to a successful transition process.

Transitioning from a children's hospital or clinic to adult healthcare services can be a major challenge for young patients with life-limiting conditions such as SMA, and for their families. There is increased recognition among healthcare professionals caring for SMA patients that advances in medical therapy and clinical care will result in greater numbers of children reaching adulthood with SMA, which means there is a growing need for coordination between paediatric and adult services and support to ensure smooth transitions for these children.[1] Sahlgrenska University Hospital is one of the foremost centres of excellence in the Nordic region for the treatment and follow-up of patients with SMA. In a tandem presentation at Lis-n & Ler-n 2020, paediatric neurologist Professor Már Tulinius and adult neurologist Dr Christopher Lindberg described how their respective departments work in increasingly close collaboration to support children with SMA and their families during the transition into adult care.

In terms of paediatric care, the team at the Neuromuscular Centre at Queen Silvia Children's Hospital is responsible (together with Astrid Lindgren Children's Hospital in Stockholm) for diagnosing children with neuromuscular disorders and maintaining follow-up programmes for monitoring their long-term health and wellbeing. A total of 325 children are currently being cared for at Queen Silvia Children's Hospital, 70 of whom have been diagnosed with SMA. The centre is also a clinical research centre and has participated in several large international studies to document new medical treatments for SMA and other neuromuscular disorders. Children with SMA who receive treatment at the centre are monitored at regular intervals, from one to three times a year depending on SMA type and duration of treatment, by regional rehabilitation teams comprising paediatricians, physiotherapists, occupational therapists and dieticians. As one of only two SMA centres of excellence in Sweden, the paediatric neuromuscular centre at Queen Silvia

> *"A key task for the team is to coordinate with the regional rehabilitation teams work to minimise long-distance travel for patients and families."*

Children's Hospital cares for patients within a large geographic uptake area, and a key task for the treatment team is to coordinate with the regional rehabilitation teams work to minimise long-distance travel for patients and families.

Once SMA patients reach the age of 18 they are referred to the adult neuromuscular centre at Sahlgrenska University Hospital. The actual transition takes place in multidisciplinary team conferences which are held once or twice a year as required. In these conferences, the two teams of paediatric and adult physicians, nurses, physiotherapists and occupational therapists meet either face to face or, more recently, digitally to introduce and plan the handover of care of those patients who will turn 17 or 18 in the coming calendar year. In Gothenburg, on average five to ten patients have transitioned to adult care through this process in recent years. In some cases, if deemed helpful for social or other reasons, an adult physiotherapist and/or occupational therapist may also attend the patient's final paediatric follow-up visit to further ease transition. At the patient's first visit to the adult neuromuscular centre, all diagnostic tests and assessments are completed in one day, and a treatment and rehabilitation plan is devised which is passed to the local caregiver. Each patient is then cared for and monitored by the multidisciplinary team at the adult neuromuscular centre through regular follow-up visits at intervals of one to three years, depending on the type and severity of SMA. The multidisciplinary team, which in addition to a neurologist, nurse, physiotherapist and occupational therapist also can consult with a dietician, speech therapist, social worker etc if required, follows up on patients' motor function and makes referrals as necessary to minimise complications and optimise health-related quality of life. In the same way as the paediatric services, all care is delivered in close cooperation with the patient's local healthcare professionals.

All patients cared for at the adult neuromuscular centre are entered into the Swedish neuromuscular registry to facilitate clinical care monitoring and dissemination of knowledge on neuromuscular disorders in Sweden.[2] At present, the team follows up a total of 20 patients with SMA type 3 and seven patients with SMA type 2 every year. Of these, two patients in each group are receiving medical treatment and undergo annual evaluations to confirm eligibility for continued treatment. In the same way as the paediatric neuromuscular centre at Queen Silvia Children's Hospital, the adult neuromuscular centre at Sahlgrenska is one of only two centres in Sweden to perform these evaluations.

An important aspect of follow-up of patients with neuromuscular disorders is to monitor biomarkers in the cerebrospinal fluid. At Queen Silvia Children's Hospital this is an integral part of the regular follow-up at the paediatric neuromuscular centre. Biomarkers in the cerebrospinal fluid that are of particular interest in patients with SMA include neurofilament light protein (NFL) and microtubule-associated protein tau which are established biomarkers for neurodegeneration in a range of neurodegenerative disorders;[3,4] and glial fibrillary acidic protein (GFAP) which is a biomarker for astrocytic degeneration.[5] Ongoing clinical research studies led by Professor Tulinius investigate the use of NFL as a biomarker for monitoring the response to medical treatment in SMA patients.

References:

1. Together for Short Lives: Improving Transitions for Young People Fund. https://www.togetherforshortlives.org.uk/changing-lives/developing-services/transition-adult-services/awards-programme/. **2.** National Quality Registry for Neuromuscular Diseases. https://kvalitetsregister.se/englishpages/findaregistry/registerarkivenglish/nationalqualityregistryforneuromusculardiseases2192.html. **3.** Zetterberg H. Neurofilament Light: A Dynamic Cross-Disease Fluid Biomarker for Neurodegeneration. Neuron. 2016;91(1):1-3. doi:10.1016/j.neuron.2016.06.030 **4.** Miller N, Feng Z, Edens BM, et al. Non-aggregating tau phosphorylation by cyclin-dependent kinase 5 contributes to motor neuron degeneration in spinal muscular atrophy. J Neurosci. 2015;35(15):6038-6050. doi:10.1523/JNEUROSCI.3716-14.2015 **5.** Bignami A, Eng LF, Dahl D, Uyeda CT. Localization of the glial fibrillary acidic protein in astrocytes by immunofluorescence. Brain Res. 1972;43(2):429-435. doi:https://doi.org/10.1016/0006-8993(72)90398-8

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TIM HAGENACKER

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Adult SMA: natural history

The availability of new and effective medical treatments for SMA is changing the nature and presentation of the disease in the clinic. Neurologists, including those looking after adult patients, need to adapt and to some extent upgrade their understanding of the disease and their approach to its management and care, to meet the needs of SMA patients in the future.

The correlation between levels of the ubiquitously expressed SMN protein and clinical manifestations of SMA is well understood among neurologists caring for SMA patients – defects in SMN expression lead to motor neuron loss and skeletal muscle atrophy, while complete deletion is fatal.[1] In his overview of the natural history of adult SMA at Lis-n & Ler-n 2020, Professor Tim Hagenacker from the Department of Neurology at the University Hospital of Essen in Germany postulated that as effective medical therapies for SMA become more widely available, adult neurologists will begin to see new phenotypes of SMA patients in their practice, including patients with SMA type 1 who have received treatment and older adult SMA patients.

Much less is known about the natural course and progression of later-onset SMA (type 2 and 3) compared with the early-onset type 1 variety. Professor Hagenacker attributed this lack of knowledge to the fact that adult neurologists tend to regard adult SMA as a 'stable' condition, a perception which he stressed is incorrect. "We lack knowledge about adult SMA mainly because as a rule, adult patients are cared for by primary care practitioners rather than neurologists," said Professor Hagenacker. "Neurologists tend to believe there is nothing that can be done for these patients." However, natural history studies have shown that patients with SMA type 2 and 3 lose a mean of 1.71 points off their HFMSE score in 36 months;[2] similarly, adult patients with SMA type 3 have been shown to lose almost 10 metres off their six-minute walking test result in the course of a year.[3] "It is important to remember that SMA is a progressive disease across all disease types and all ages," said Professor Hagenacker. "And halting this progression should be a key therapeutic goal."

> *"We lack knowledge about adult SMA mainly because in the main, adult patients are cared for by primary care practitioners rather than neurologists."*

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Just like childhood-onset SMA, later-onset SMA is associated with unique challenges that need to be taken into account when devising treatment and rehabilitation plans. While disease progression tends to be slower in later-onset SMA, and the impact on motor development and achievement of motor milestones less detrimental, complications such as scoliosis and spinal surgery are features of adult SMA that cannot be fully captured with the current validated assessment tools for SMA, yet have a profound impact on patients' everyday lives. In a survey of European patients with SMA type 2 and 3 that was published in 2017, more than 80% of patients agreed with the statement that a medication that could stabilise their current clinical condition would represent 'important progress' in the care of their disease.[4] Professor Hagenacker pointed out that stabilisation, naturally, will mean different things to different patients, depending on the status and severity of their condition – for a patient with SMA type 2, 'stable' disease may mean retaining finger function sufficient to operate a smartphone or control a wheelchair, whereas for an SMA type 3 patient it may mean maintaining the ability to walk.

> *"Patients will live longer and present with new care needs, not least in relation to the psychological burden of gradual disease progression and the prospect of loss of function and mobility."*

For healthcare professionals looking after SMA patients, being able to offer medical treatments means that patients will live longer and present with new care needs, not least in relation to the psychological burden of gradual disease progression and the prospect of loss of function and mobility. Professor Hagenacker anticipates that multidisciplinary teams looking after adult SMA patients will need to incorporate additional members from other specialties, and that this in itself will present challenges in terms of organisation and logistics and also with respect to training needs. As teenagers transition from the paediatric setting – where healthcare is largely caregiver-managed and focused on the patient and his/her family – to the more self-managed and individual patient-focused adult setting, a holistic approach will be important to facilitate shared decision-making and concordance with agreed management and rehabilitation plans. Professor Hagenacker stressed the importance of basing any decision to initiate treatment towards an agreed therapeutic goal in adult SMA – be it stabilising disease progression, improving motor function, reducing the need for ventilatory support, or simply improving patient and family quality of life – on a rationale that is clinically relevant and meaningful to the patient. For example, Professor Hagenacker suggested that a horizon of six months may not be sufficient for capturing significant loss of motor function in adult patients – instead, it may be necessary to go back as far as two or three years to probe for changes, and possibly also ask the patient's family or carer to obtain an adequate clinical picture.

In 2020 Professor Hagenacker led a group of paediatric and adult neurologists in a collaborative effort to make international recommendations for clinical assessment and monitoring of adult SMA patients.[5] One of the key proposals in this paper was that, given the changing phenotype of SMA, patients should be classified based on their current motor status, rather than SMA type. All patients should be monitored on an annual basis. For non-sitting patients, the group recommended annual evaluations using the CHOP-INTEND or CHOP-ATEND instrument (the latter being a modified version that is currently in development for use with adult patients, although it has yet to be fully validated for clinical use) and assessment of respiratory function based on nocturnal oximetry, need for ventilation, and the frequency of pulmonary infections and need for hospitalisation and/or antibiotics. For sitting patients, the Revised Upper

Limb Module (RULM) and Hammersmith Functional Motor Scale Expanded (HFMSE) instruments were recommended as suitable for annual evaluation, together with spirometric measurements of forced vital capacity (FVC) in the sitting and lying position and peak expiratory flow (PEF) for assessment of respiratory function. Practical challenges that need to be considered in this regard include the need for staff training on the use of the evaluation tools, equipment required for the RULM, and the fact that both procedures are relatively time-consuming. The same applies to the assessment of walking patients, where the group recommends the six-minute walking test as an additional tool to the RULM and HFSME and where factors such as the need for additional space to perform the test need to be considered. There may also be challenges for patients in terms of impact of any comorbidities such as pulmonary dysfunction, and in some countries lack of reimbursement may be an issue for adult SMA patients who are able to walk.

In Professor Hagenacker's view, it is clear that the availability of new and effective medical treatments for SMA will pose a range of new challenges for the multidisciplinary teams looking after SMA patients in the clinic. Understanding and managing patients' expectations and meeting their needs in a holistic way will be essential for utilising these new treatments to their full potential.

References:

1. Monani UR. Spinal Muscular Atrophy: A Deficiency in a Ubiquitous Protein; a Motor Neuron-Specific Disease. Neuron 2005;48:885–895. Available at: https://doi.org/10.1016/j.neuron.2005.12.001. **2.** Kaufmann P, McDermott MP, Darras BT, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology 2012;79:1889–1897. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23077013. **3.** Montes J, McDermott MP, Mirek E, et al. Ambulatory function in spinal muscular atrophy: Age-related patterns of progression. PLoS One 2018;13:e0199657. Available at: https://doi.org/10.1371/journal.pone.0199657. **4.** Rouault F, Christie-Brown V, Broekgaarden R, et al. Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients. Neuromuscul Disord 2017;27:428–438. Available at: https://doi.org/10.1016/j.nmd.2017.01.018. **5.** Sansone VA, Walter MC, Attarian S, et al. Measuring Outcomes in Adults with Spinal Muscular Atrophy – Challenges and Future Directions – Meeting Report. J Neuromuscul Dis 2020;7:523–534.

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International recommendations for assessment of adult SMA patients

Non-sitter

Frequency: As per routine clinical follow-up, at least once every 12 months

Measure	Practical challenges and considerations
CHOP INTEND *or* CHOP ATEND	• Some items in CHOP INTEND are not relevant for adult patients • Many NMD specialists are unfamiliar with CHOP ATEND
Respiratory function • Mandatory full work-up at baseline • Most universal: nocturnal oximetry • Need for NIV or IV • Changes in time required for NIV • Number of recurrent pulmonary infections • Hospitalizations (number of days) • Number of prescribed antibiotics	

Sitter

Frequency: As per routine clinical follow-up, at least once every 12 months

Measure	Practical challenges and considerations	
RULM	• Training • Equipment	• Time consuming
HFSME	• Training	• Time consuming

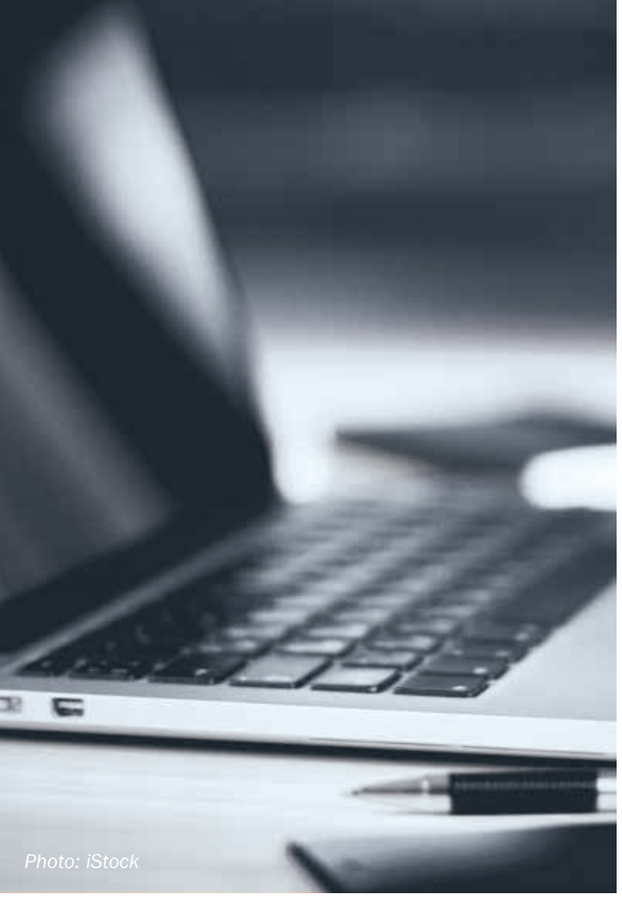
Respiratory function
• Mandatory full work-up at baseline
• Minimum requirement:
  • FVC sitting (mandatory)
  • FVC lying (recommended)
• PEF		

Walker

Frequency: As per routine clinical follow-up, at least once every 12 months

Measure	Practical challenges and considerations	
6MWT	• Time consuming • Space required • Training needed	• Impact of comorbidities, for instance pulmonary dysfunction • Reimbursement
HFSME	• Training	• Time consuming
RULM	• Training needed • Equipment	• Time consuming
Respiratory function		

Table adapted from Sansone V, et al. 2020



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ANNA-KARIN KROKSMARK

Physiotherapist, Queen Silvia Children's Hospital, Gothenburg, Sweden

Habilitation and rehabilitation in SMA

There is increasing consensus among healthcare professionals caring for SMA patients, that a proactive approach to rehabilitation and exercise can influence the clinical course of the disease and help to optimise function and mobility. The availability of effective medical treatments for SMA has brought this aspect of management even more into focus, as minimising impairment and restoring lost abilities have become achievable therapeutic goals.

The most recent set of evidence-based clinical guidelines for the diagnosis and management of SMA were published in 2017 and thus predate the introduction of the first approved medical treatment for SMA.[1] However, as Anna-Karin Kroksmark – who was one of the co-authors on the guidelines – highlighted in her workshop session on the topic of rehabilitation in SMA, concerted efforts were made to take into consideration the fact that new treatments were about to become part of clinical practice.

In the rehabilitation module of the 2017 guidelines, SMA patients are classified according to their level of function rather than disease type. The three functional categories are non-sitters, sitters and walkers. The rationale for this classification was to ensure that the guidelines will remain relevant in cases where, for example, a patient with SMA type 3 has lost the ability to walk and thus requires rehabilitation suitable for SMA type 2 needs; or conversely, where a patient with SMA type 1 has acquired the ability to sit following medical treatment. In her outline of the rehabilitation module, Anna-Karin Kroksmark pointed out that the fact that the guidelines had been developed before the introduction of medical treatments has rendered the main objectives for rehabilitation in SMA no less relevant. They are, for non-sitters, to optimise function, minimise impairment, and optimise tolerance to various positions; for sitters, to prevent contractures and scoliosis and to maintain, restore and promote function and mobility; and for walkers, to restore or promote function, mobility and adequate joint range, as well as improve balance and endurance.

Non-sitters

Starting with the most severely affected group of SMA patients, the non-sitters, the 2017 guidelines make a number of recommendations regarding positioning and bracing, and on the use of stretching and orthoses. The former should include daily use of seating systems, as well as use of postural and positioning supports. Thoracic bracing and cervical bracing should be used for head support; static thoracic bracing should be done with appropriate modifications to provide adequate respiratory support, such as abdominal cut-outs. With respect to stretching and orthoses, the guidelines state that stretching and range of motion (ROM) exercises should be performed at least three to five times per week, and that orthoses should be applied for a minimum of 60 minutes. The guidelines also recommend the use of assistive technology and adaptive equipment to promote function, and highlight aquatic therapy as an option for selected non-sitting patients. The clinical experience at Queen Silvia Children's Hospital concurs with these recommendations. "As patients with SMA type 1 receive treatment and achieve the milestone of learning to sit, they tend to develop kyphosis or scoliosis quite early," said Anna-Karin Kroksmark. "To optimise the spinal position in these patients, it is important to begin early treatment with a well-fitting spinal brace of the so-called Boston brace type, as soon as asymmetries begin to appear." Anna-Karin Kroksmark also mentioned that as yet, there is no data on the extent to which surgical correction of scoliosis may be an option for very young SMA patients who have acquired the ability to sit following treatment.

Sitters

For SMA patients who are able to sit unaided, the recommendations regarding positioning and bracing include thoracic bracing at least five times a week, and supported standing for up to 60 minutes at least three to five times a week, ideally five to seven times. Stretching exercises should be performed a minimum of five to seven times a week, in areas that are known to be at risk of developing contractures such as hips, knees, ankles, wrists and hands. Orthoses should be used for more than 60 minutes, up to overnight. At Queen Silvia Children's Hospital, Anna-Karin Kroksmark and her colleagues often recommend supported standing for longer than 60 minutes for sitting patients, although not necessarily in one single session as this may be very tiring for the patient. Standing shells are frequently used, and some SMA patients at the centre have achieved good results by using a standing shell in combination with a swivel walker.

Main objectives for rehabilitation still relevant

Non-sitters	Optimization of function, minimization of impairment, and optimizing tolerance to various positions
Sitters	To prevent contractures and scoliosis, and maintain, restore or promote function and mobility
Walkers	To restore or promote function, mobility, and adequate joint range, and improve balance and endurance

Table adapted from Mercuri et al Neuromuscul Disord 2017

> *"As patients with SMA type 1 receive treatment and achieve the milestone of learning to sit, they tend to develop kyphosis or scoliosis quite early. To optimise the spinal position in these patients, it is important to begin early treatment with a well-fitting spinal brace, as soon as asymmetries begin to appear."*

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Night splints for the feet and hand orthoses are widely used, and Anna-Karin Kroksmark has also had a young patient who was able to successfully wear knee splints overnight, which is usually very difficult for patients.

Physical exercise such as swimming, hippotherapy and wheelchair sports can help to improve function, strength, ROM, endurance and balance for SMA patients who are able to sit unaided. This is especially important as with treatment, some sitting patients may be able to stand, and in some cases even walk short distances with support. The physiotherapy team at Queen Silvia Children's Hospital has used knee-ankle-foot orthoses (KAFOs) or long ankle-foot orthoses (AFOs) in such cases, with favourable outcomes.

Walkers

For the final and most mobile group of SMA patients, the walkers, the 2017 guidelines recommend (in addition to many of the elements recommended for sitters) implementing an individualised programme of aerobic and general conditioning exercise. The programme should be designed in consultation with a physiotherapist or occupational therapist, and could include activities such as swimming, walking, cycling or rowing. No specific recommendation is made regarding frequency, but for aerobic exercise the optimal duration should be at least 30 minutes. In addition, the guidelines recommend regular dynamic and static balance exercises to minimise the risk of falls. Active assisted stretching, using orthoses if needed, should be performed a minimum of two to three times a week, ideally three to five times a week, to maintain flexibility. Lower-limb orthoses can be used to improve posture and promote function of the ankles and knees, and thoracic bracing is useful for promoting sitting posture – however, Anna-Karin Kroksmark added a cautionary note that walking with a thoracic brace is difficult and restricts the patient's use of compensatory strategies.

The physiotherapy team at Queen Silvia Children's Hospital has had comprehensive experience of assisting SMA patients who have received medical treatment at different stages of their disease. There is increasing understanding among experienced centres that medical treatment should be combined with exercise and activation of the muscles to achieve the best possible clinical outcome. Exercise programmes and recommendations regarding physiotherapy should be individualised based on the patient's age, functional ability and interests.

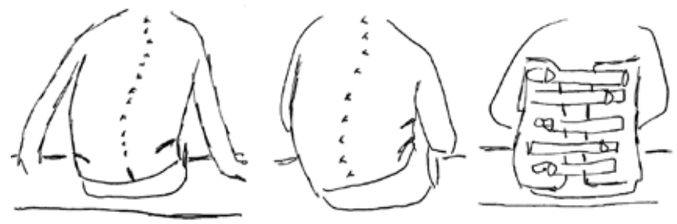
> *"Exercise must be fun to be sustainable over time – we recommend varying the exercise regime and equipment to keep the programme interesting and engaging."*

The latter is especially important, according to Anna-Karin Kroksmark. "As physiotherapists we know that exercise must be fun to be sustainable over time," she said. "We recommend varying the exercise regime and equipment to keep the programme interesting and engaging." For infants with SMA who receive medical treatment, the focus of the team is to educate the parents to be very active with the child to stimulate movement, to change positions often and pay attention to symmetry, and not be afraid of letting the child play on the floor to practice rolling. For treated infants who have reached the sitting stage and toddlers, sitting is important as it provides an opportunity to discover the world. The sitting should be restricted to short periods initially to minimise the risk of spinal deformities, but over time the sessions can be gradually extended. A spinal brace should be used in case of pronounced trunk weakness. Wheelchairs – manual or electric – should be introduced early, and adjusted carefully to ensure a symmetrical sitting position. For older children and teenagers who receive medical treatment, being given an exercise programme and instructions to go to the gym or perform it at school may be a challenge as they may not have had anything of this kind before; for this group, Anna-Karin Kroksmark stressed the importance of getting the patient interested and enthusiastic about the idea of exercise and explain the difference it can make. In Sweden, many older children and teenagers use equipment such as the MOTOmed ergometer or the Innowalk standing device, the latter often in combination with a standing frame. Anna-Karin Kroksmark and her colleagues at Queen Silvia Children's Hospital have been able to observe first-hand that having an exercise programme and sticking to it can make a real difference for SMA patients; however, clinical studies are needed to provide stringent scientific evidence on the effect.

The 'Together in SMA' app

Anna-Karin Kroksmark has recently been involved in the development of a smartphone app to help and encourage parents of children with SMA to use simple exercises to stimulate movement and activity. The app has been developed within the 'Together in SMA' support initiative which is sponsored by Biogen, and contains a total of 27 exercises – nine each for non-sitters, sitters and walkers. Each exercise is aimed at one of three different age groups: under three months, three months to one year, and older than one year; however, the exercises have all been designed to be suitable for patients of any age who has a need of a particular exercise. The app is currently being pilot-tested with a group of Swedish parents. Once finalised, the app is expected to be launched in Sweden, and translations and adaptations are planned for the other Nordic countries as well.

Development of scoliosis in SMA type 1



Development of kyfosis in SMA type 1

Illustrations: Anna-Karin Kroksmark

References:

1. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018;28:103–115.

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REIDUN FØRDE

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Start and stop criteria: Ethical considerations

National public-funded healthcare systems are under mounting pressure to allocate precious resources in the shape of new and innovative healthcare technologies in ways that are open, fair and transparent. In theory, any decision on who is given access to a treatment and who is denied should be based on the best available scientific evidence of efficacy and cost-effectiveness; however, in clinical practice the process may be a lot more complex.

The introduction of new medical treatments for rare and life-limiting conditions such as SMA raises complex questions about fairness and equity in the allocation of healthcare resources and access to treatment. One of the keynote speakers at this year's Lis-n & Ler-n was Professor Reidun Førde from the Centre for Medical Ethics at the University of Oslo, who has had a wealth of experience of addressing these questions in the context of clinical decision-making and resource allocation. In her presentation, Professor Førde posed the question whether a 'bedside' approach to decision-making regarding access to treatment is feasible, and acceptable from an ethical point of view, based on the example of new and effective medical treatments for SMA.

Norway has been a pioneer in the Nordic region when it comes to efforts to promote equity in healthcare resource allocation and access to treatment. The first government commission on this topic was formed in 1985; since then, there have been a further three commissions, two of which with Professor Førde as a serving member. The primary outcome of the first commission has remained largely unchanged throughout this process: that access to healthcare technologies should be based on the severity of the condition they are intended to treat (defined as measures such as life-years lost, morbidity, loss of function and pain), the efficacy of treatment (assessed using scientific and evidence-based methods), and the use of resources. The guiding principle has been that there should be a reasonable correlation between the cost of a new technology and its effect.

While there is almost universal support for the idea that resource allocation decisions in healthcare should be made in a spirit of fairness, transparency and solidarity, a key finding of the last government commission was that these lofty ideals do not fully permeate into clinical practice. Instead, a number of open and hidden factors influence resource use in healthcare, such as media coverage and pressure from patient organisations, or lobbying by the pharmaceutical industry. "We know that resource allocation takes place at a clinical level," said Professor Førde. "The question is, how can it be made more fair?" Research in this field is scarce, but the Norwegian department has developed systematic resource allocation processes to facilitate fair

> *"We know that resource allocation takes place at a clinical level. The question is, how can it be made more fair?"*

and open access to new healthcare technologies. These include the 'Procurement Forum' (Norwegian: *Bestillerforum*) and 'Decision Forum' (Norwegian: *Beslutningsforum*) which are mandated to approve new and expensive medical treatments for public reimbursement, based on evidence-based review of efficacy and cost. In Norway, physicians have a duty to act responsibly when providing access to new healthcare technologies in clinical practice. Ethical guidelines published by the Norwegian Medical Association (NMA) state that physicians must have "due regard for the national economy" and must "contribute to the distribution of medical resources in accordance with generally accepted ethical norms." In addition, the guidelines also state that physicians must in no way "seek to provide individual patients or groups with unjustified advantages."[1] This position has been and is being challenged by physicians who argue that tasking physicians with decision-making that restricts patients' access to treatment effectively amounts to rationing, and is potentially harmful to the ethos of medical care.[2]

The introduction of new and effective treatments for SMA provided a textbook case for Professor Førde and her colleagues to study the practical implementation of ethical resource allocation in the Norwegian healthcare system. "As an extremely serious condition affecting infants and children, with no other treatment options available and with a very strong parent organisation, SMA 'ticked all the boxes' for a condition where the pressure to make new treatments widely available would be immense," said Professor Førde. Given the limited evidence available at the point of approval of the first treatment, a national expert group, consisting of paediatric specialists from all regional healthcare trusts in Norway, was appointed and tasked with implementing annual evaluations of treatment efficacy and developing 'start and stop' criteria for continued treatment. The initial criterion was a basic age restriction – treatment could only be initiated for patients up to the age of 18 years. The experience of the first two years of access shows that the age criterion had been respected, and the consensus view is that the work of the SMA expert group has promoted national equity in access to treatment; however, no patient was actually denied treatment or had treatment withdrawn during this time, indicating that a 'bedside' approach with 'start and stop' criteria may not be optimal in clinical practice. Professor Førde cautioned that making individual physicians responsible for decisions regarding access to treatment will inevitably undermine the trust in their relationship with patients and families, and in the longer term the moral stress of such decision-making

> *"As an extremely serious condition affecting infants and children, with no other treatment options available and with a very strong parent organisation, SMA 'ticked all the boxes' for a condition where the pressure to make new treatments widely available would be immense."*

may blunt their ethical sensitivity. On the other hand, removing resource allocation decisions from the bedside and placing it with faceless officials in a higher bureaucracy risks undermining public trust in the healthcare system as a whole, and there is also a risk that the criteria for decision-making may become cruder and less based on expert knowledge. Professor Førde suggested that closer dialogue between clinical experts and healthcare decision makers could improve the decision-making process by promoting greater understanding and knowledge on both sides. In her view, the pharmaceutical industry is a powerful stakeholder that shares a moral responsibility to contribute to a fair distribution of resources in healthcare.

References:

1. NMA. Etiske regler for leger. https://www.legeforeningen.no/om-oss/Styrende-dokumenter/legeforeningens-lover-og-andre-organisatoriske-regler/etiske-regler-for-leger/. **2.** Wyller VB. Give to the doctor what is due to the doctor! In: Fair Resource Allocation and Rationing at the Bedside.; 2014.

Take-home summaries

Outcome measures: current use and future needs
Anna-Karin Kroksmark, Physiotherapist, Queen Silvia Children's Hospital, Gothenburg, Sweden

Current tools for evaluating motor function and muscle strength in SMA, such as CHOP INTEND and HFMSE, have to a large extent been developed for use with infants and children, and may be less suitable for use with very weak teenagers and adults, or with patients with severe contractures. However, other tools that have been developed for different neuromuscular disorders, such as the EK scale and MFM, have also been validated for adult patients with SMA. There is also a need for tools for assessing fatigue in SMA.

Paediatric-adult transition: Experiences from Gothenburg
Már Tulinius, Neuropediatrician, Queen Silvia Children's Hospital, Gothenburg, Sweden
Christopher Lindberg, Neurologist, Sahlgrenska University Hospital, Gothenburg, Sweden

Sahlgrenska University Hospital, with Queen Silvia Children's Hospital, is one of the foremost centres of excellence in the Nordic region for the treatment and follow-up of patients with SMA. The paediatric and adult neurology departments are working in increasingly close collaboration to support children with SMA and their families during the transition from paediatric into adult care. All care is delivered in multidisciplinary teams and in close cooperation with the patient's local caregiver.

Adult SMA: natural history
Tim Hagenacker, Neurologist, University Hospital Essen, Germany

As effective medical therapies for SMA become more widely available, multidisciplinary teams looking after SMA patients will face several new challenges in relation to new SMA phenotypes as well as organisational and training requirements. Understanding and managing patients' expectations and meeting their needs in a holistic way will be essential for utilising these new treatments to their full potential.

Habilitation and rehabilitation in SMA
Anna-Karin Kroksmark, Physiotherapist, Queen Silvia Children's Hospital, Gothenburg, Sweden

The main therapeutic objectives for rehabilitation in SMA, to optimise function and mobility and minimise long-term complications, remain relevant as new and effective medical treatments are entering clinical practice. There is increasing understanding among experienced centres that medical treatment should be combined with exercise and activation of the muscles to achieve the best possible clinical outcome. A team of experts have developed a smartphone app, which aims to help and encourage parents to stimulate children with SMA to movement and activity using simple exercises.

Start and stop criteria: Ethical considerations
Reidun Førde, Medical ethicist, University of Oslo, Norway

The idea that resource allocation decisions in healthcare should be made in a spirit of fairness, transparency and solidarity is widely embraced; however, in real-life clinical practice, a number of open and hidden factors influence resource use. Making individual physicians gatekeepers of new medical treatments for rare and life-limiting conditions such as SMA, may compromise patient and family relationships and cause moral stress. On the other hand, removing resource allocation decisions from the bedside risks undermining public trust in the healthcare system as a whole. The dialogue between the agencies making the resource allocation decisions and the clinicians experiencing the outcomes of such decisions needs to be strengthened.

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Anna-Karin Kroksmark is a physiotherapist specialised in neuromuscular disorders at Queen Silvia Children's Hospital within Sahlgrenska University Hospital, and Assistant Professor of Physiotherapy at the University of Gothenburg. Dr Kroksmark has many years of experience from caring for children with spinal muscular atrophy, with a research focus on muscle strength and motor function. Dr Kroksmark was also a clinical evaluator on the ENDEAR and CHERISH studies from 2015 onwards.

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TIM HAGENACKER

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Tim Hagenacker is Professor of Neurology and senior physician at the Department of Neurology at the University Hospital in Essen in Germany, where he is head of the neuromuscular section and supervises the outpatient clinic for patients with neuromuscular disorders. Dr Hagenacker is also in charge of a basic research group for diseases of the peripheral nervous system and neuropathic pain. The main areas of Dr Hagenacker's clinical expertise include neuromuscular junction disorders, spinal muscular atrophy and clinical neurophysiology.

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Professor Reidun Førde has obtained comprehensive knowledge of the Norwegian healthcare system during ten years of research within the Research Institute of The Norwegian Medical Association and 12 years of service on its Ethics Council, in addition to membership of a broad variety of public committees. Since 2000 she has been in charge of implementing clinical ethics committees in Norwegian hospitals; from 2007 also in community healthcare. In 2019, Professor Førde was appointed "Commander of the Order of St Olav" for her work in medical ethics.

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