Spinal Muscular Atrophy – Treatment Network

Monday 20th June 2022

Event will commence at 13:30

Information

- *All organisers and speakers declare no conflict of interest*

- *This meeting has been supported by Novartis Gene Therapies via provision of funding to cover use of a virtual event platform and logistical support. Novartis Gene Therapies had no involvement in the agenda or speaker selection.*

Agenda

Co-chairs: Drs Imelda Hughes and Gary McCullagh, Consultant Paediatric Neurologists, Royal Manchester Children's Hospital

Start	Duration	Topic	Learning objective	Speaker
13:30	1 min	**Welcome**		**Co-Chairs**
13:30	15 mins	**A new diagnosis & moving forwards**	Develop awareness of the diagnostic odyssey, the impact of diagnosis on family & parents' concerns at time of diagnosis	**A patient/family**
13:45	30 mins	**Care recommendations**	Develop awareness of the care considerations, the complications of SMA and all aspects of health which require attention	**Dr Gary McCullagh** Consultant Paediatric Neurologist, Royal Manchester Children's Hospital
14:15	45 mins	**Respiratory management**	Understand the importance of respiratory assessment and management, develop comprehensive awareness of respiratory management including prevention, secretion clearance, ventilatory support, management of acute exacerbations	**Dr Stuart Wilkinson** Lead for long term ventilation + paediatric respiratory medicine Paediatric respiratory consultant Royal Manchester Children's Hospital
14:15	30 mins	**New treatments**	Develop awareness of the new treatments available, mechanism of action, and evidence of effect	**Dr Gary McCullagh** Consultant Paediatric Neurologist, Royal Manchester Children's Hospital
15:00	30 mins	**Neuromuscular physiotherapy care**	Develop awareness of the changing phenotypes of treated children, postural management, stretching & splinting and enhancing function	**Miss E. Davies and Mrs S. Warner** Highly Specialised Paediatric Neuromuscular Physiotherapists, Royal Manchester Children's Hospital
15:30	15 mins	**Transitioning patient & parent**	Develop understanding of "living well" with spinal muscular atrophy and aspirations & considerations moving into adult life	**A patient/family**
16:00	15 mins	**Discussion**	Clarification and further elaboration of issues discussed	**Co-Chairs**

Housekeeping

- We ask for attendees to remain muted for the duration of the meeting to ensure good sound quality and clarity of the speakers
- Questions are very welcome – please use the chat function and these will be responded to at the end of each topic

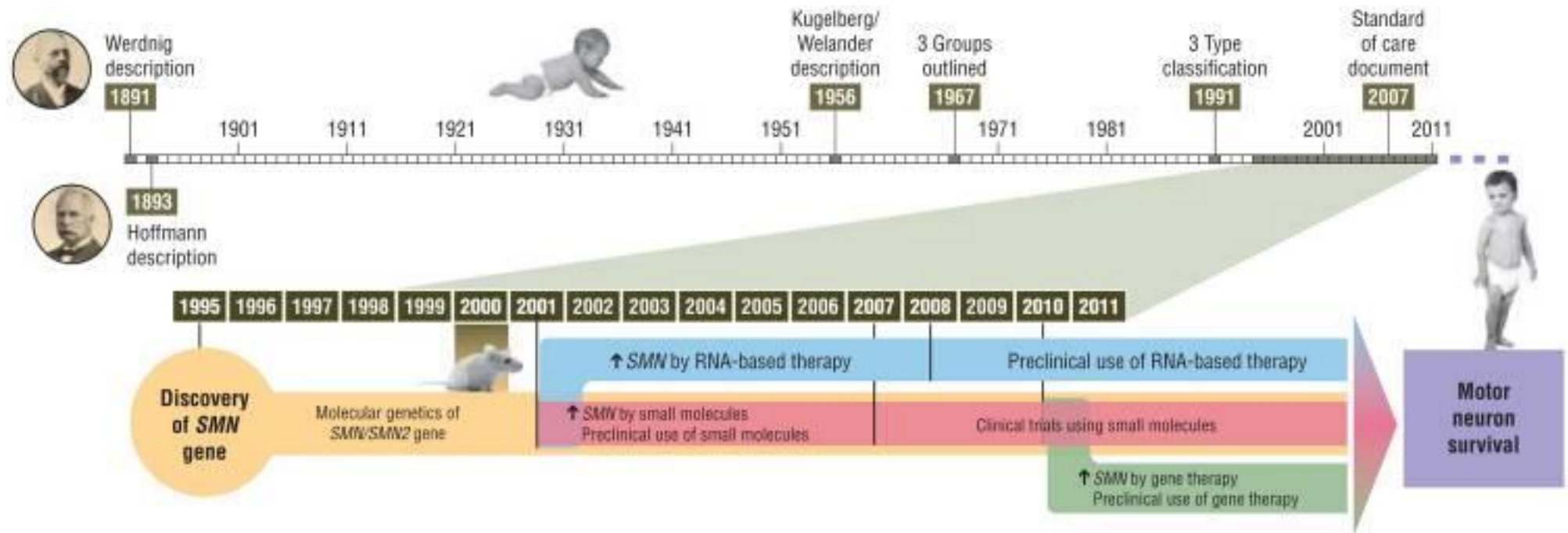
A new diagnosis & moving forwards

A family gave a short talk offering their experience of talking with health services about their child prior to, during and after diagnosis with SMA.

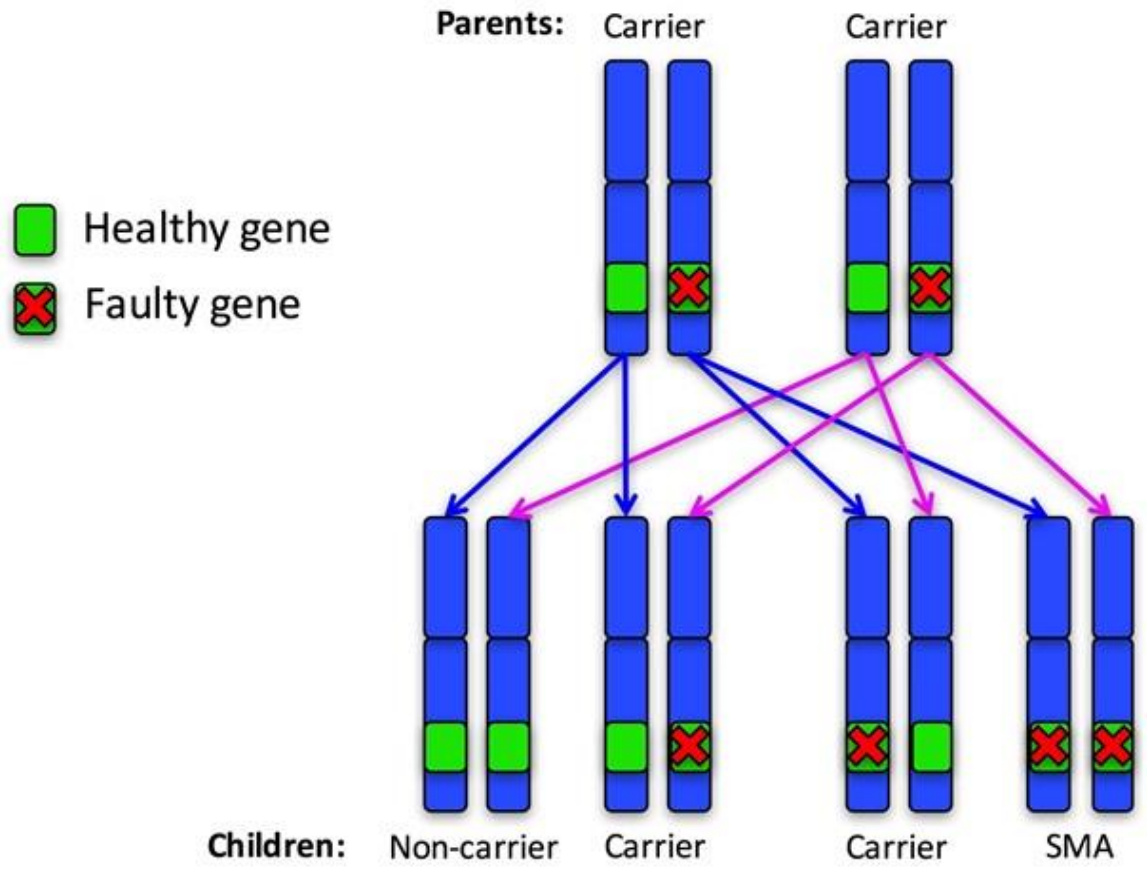
Care recommendations

Dr Gary McCullagh, Consultant Paediatric Neurologist,
Royal Manchester Children's Hospital

Setting the scene – what do we know about SMA?


Werdnig description
1891
1893
Hoffmann description
1901
1911
1921
1931
1941
1951
Kugelberg/ Welander description
1956
3 Groups outlined
1967
1971
1981
3 Type classification
1991
2001
Standard of care document
2007
2011
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
Discovery of SMN gene
Molecular genetics of SMN/SMN2 gene
↑ SMN by RNA-based therapy
Preclinical use of RNA-based therapy
↑ SMN by small molecules
Preclinical use of small molecules
Clinical trials using small molecules
↑ SMN by gene therapy
Preclinical use of gene therapy
Motor neuron survival

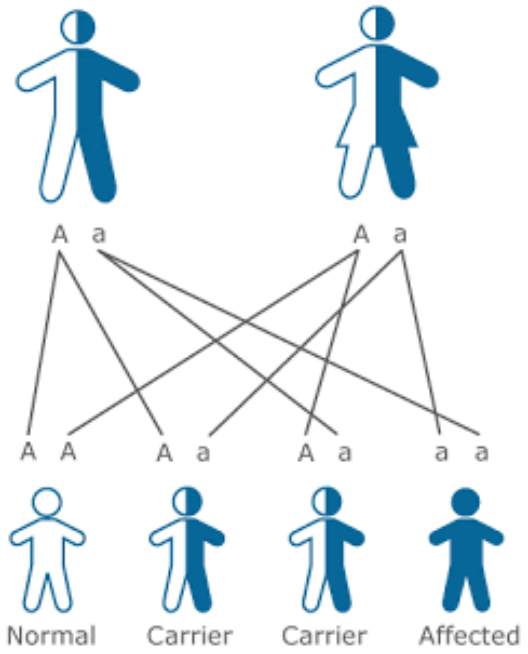
Autosomal Recessive

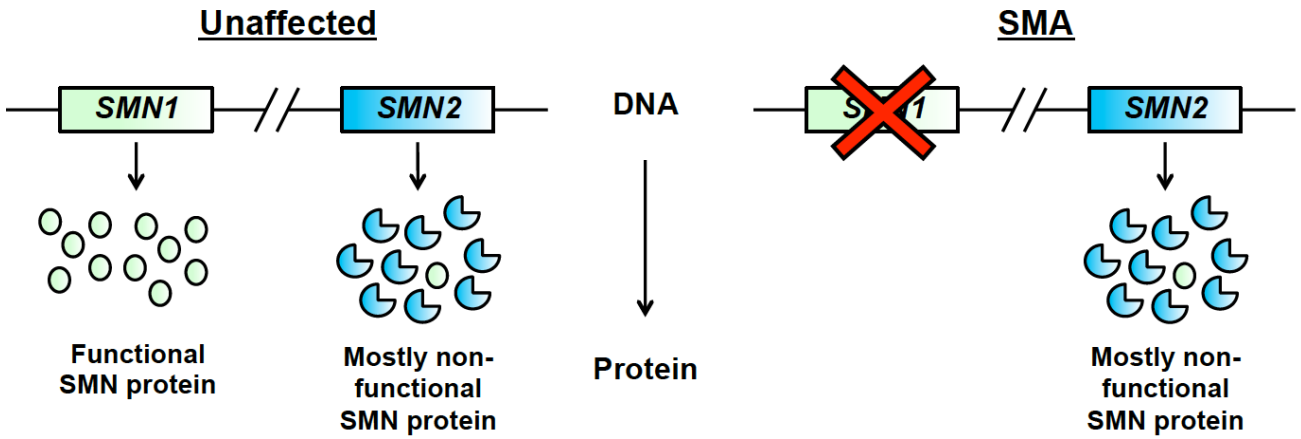


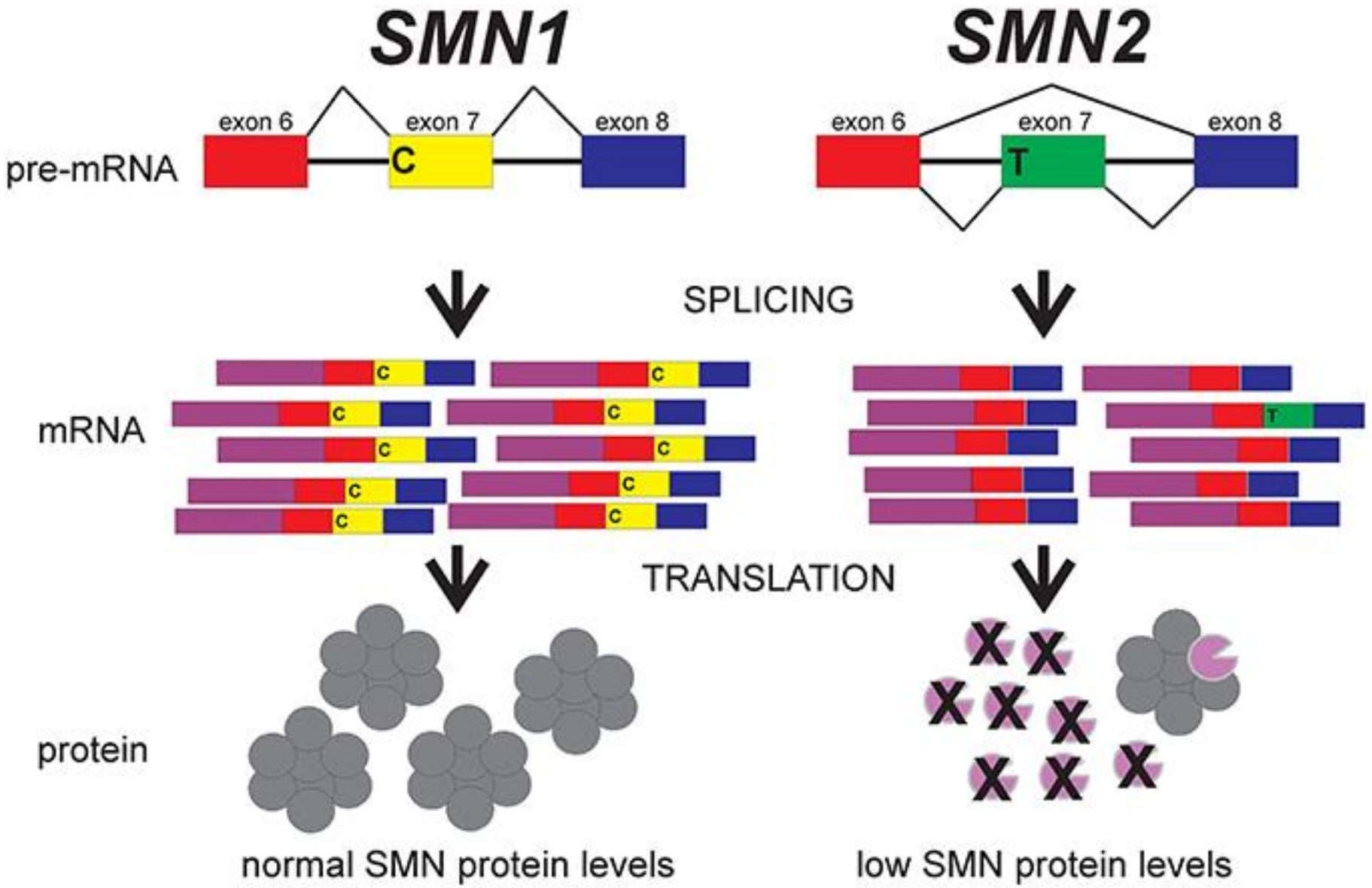
smauk.org.uk

Genetics

- Chromosome 5q
- Autosomal recessive inheritance
- Carrier status 1 in 50
- 1/14000 live births



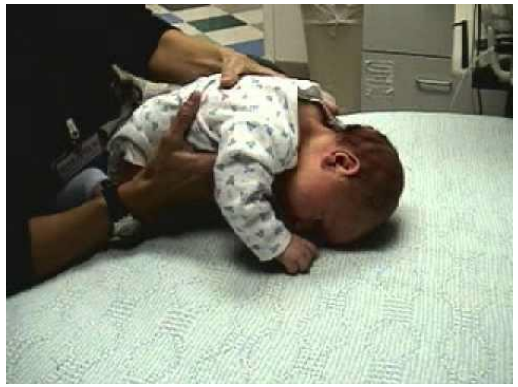




Butchbach, M. E. R., and Burghes, A. H. M. (2004). Perspectives on models of spinal muscular atrophy for drug discovery. *Drug Discover. Today Dis. Models* 1, 151–156. doi: 10.1016/j.ddmod.2004.07.001

SMA Types

SMA Type	Age of Onset	Motor Milestones	
0	prenatal	Nil	
I	<6 months	Never Sit	
II	<18 months	Sit, but don't walk	
III	>18 months	Walk	
IV	2nd/3rd decade	Walk in Adult life	



SMA 0

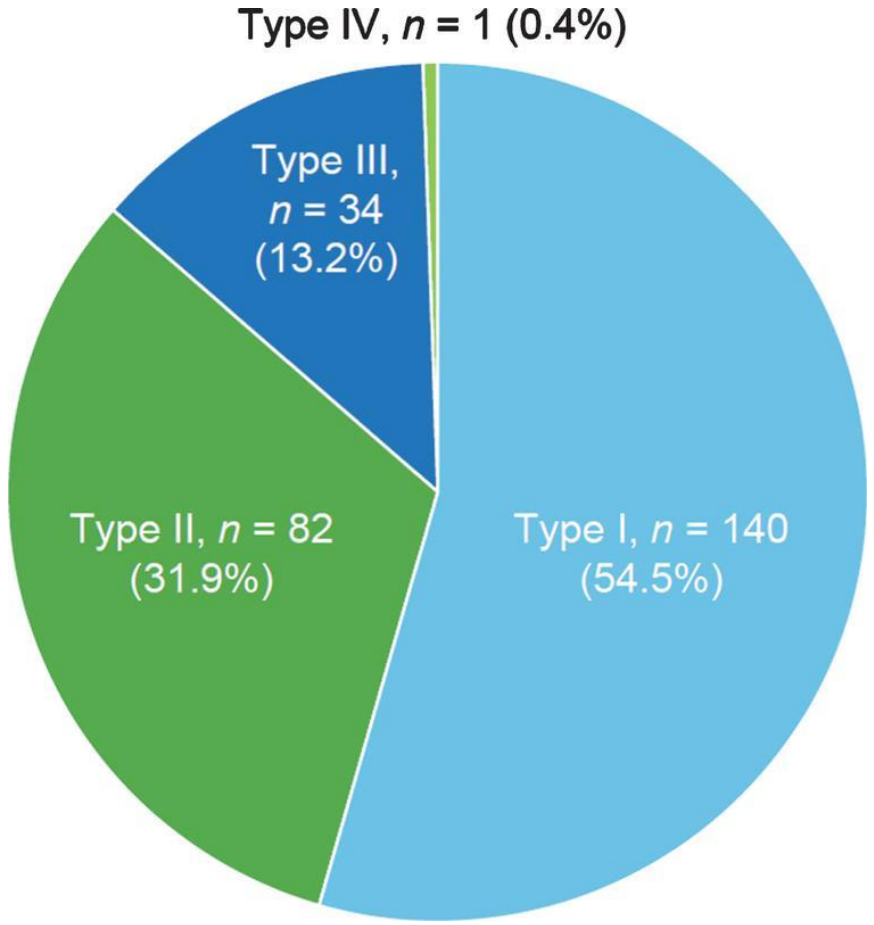
- Very severe
- Antenatal/early onset
- Reduced foetal movements
- Congenital contractures/ Arthrogryposis
- Respiratory failure at birth
- Survival rare beyond 6 months of life

SMA I – most common

- Profound hypotonia
- Severe muscle weakness
  - Never achieve sitting
- Respiratory weakness (diaphragm relatively spared)
  - Weak cry
  - Secretion difficulties
  - Bell shaped chest
  - Paradoxical breathing
- Bulbar denervation
  - Tongue fasciculation
- Swallowing and feeding difficulties

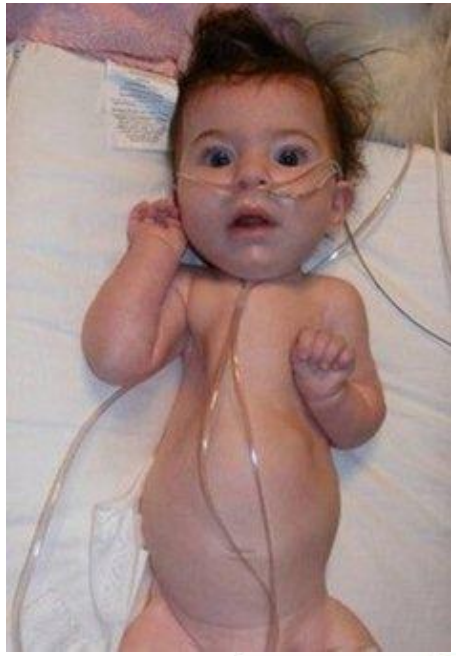
- Normal cognition
- Bright facies

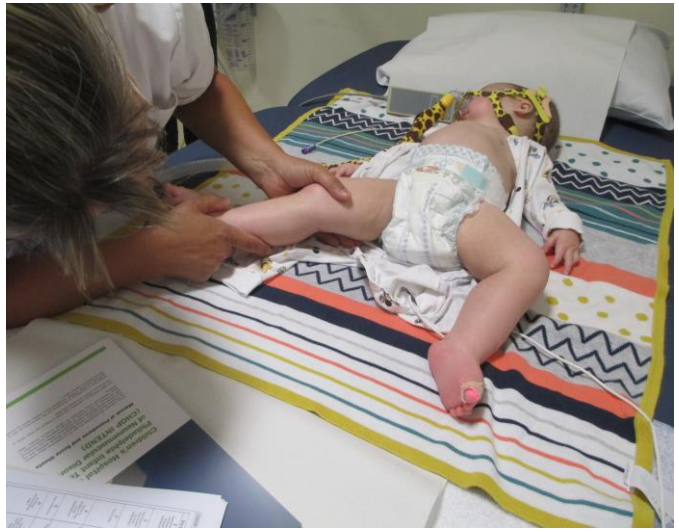
- Life expectancy <2 yrs*

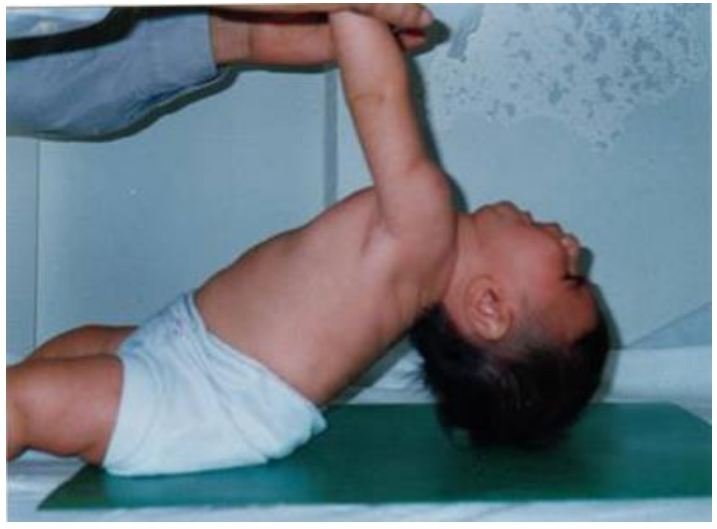


Jones, Cynthia C. et al. ‘Spinal Muscular Atrophy (SMA) Subtype Concordance in Siblings: Findings From the Cure SMA Cohort’. 1 Jan. 2020 : 33 – 40.

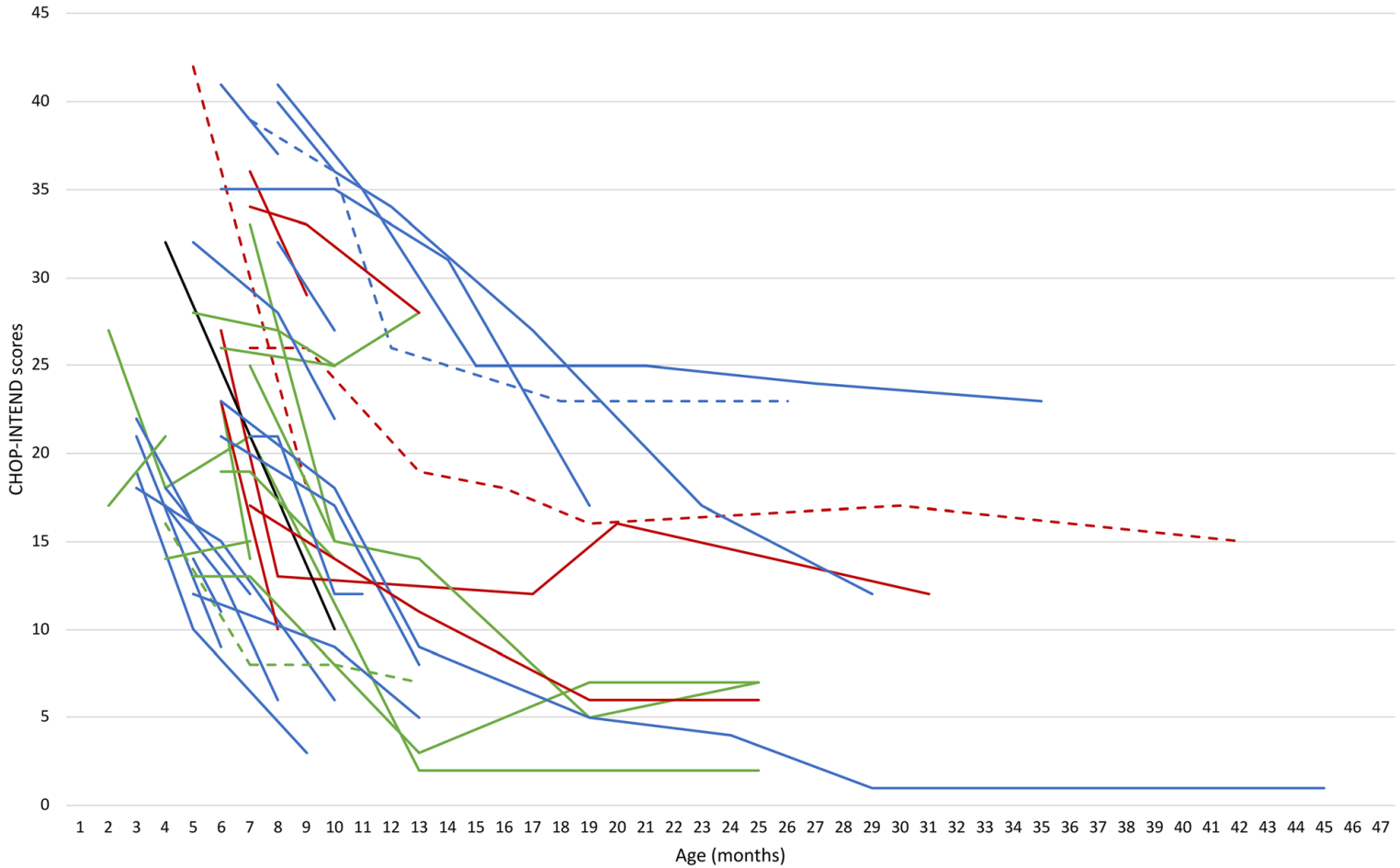
SMA I





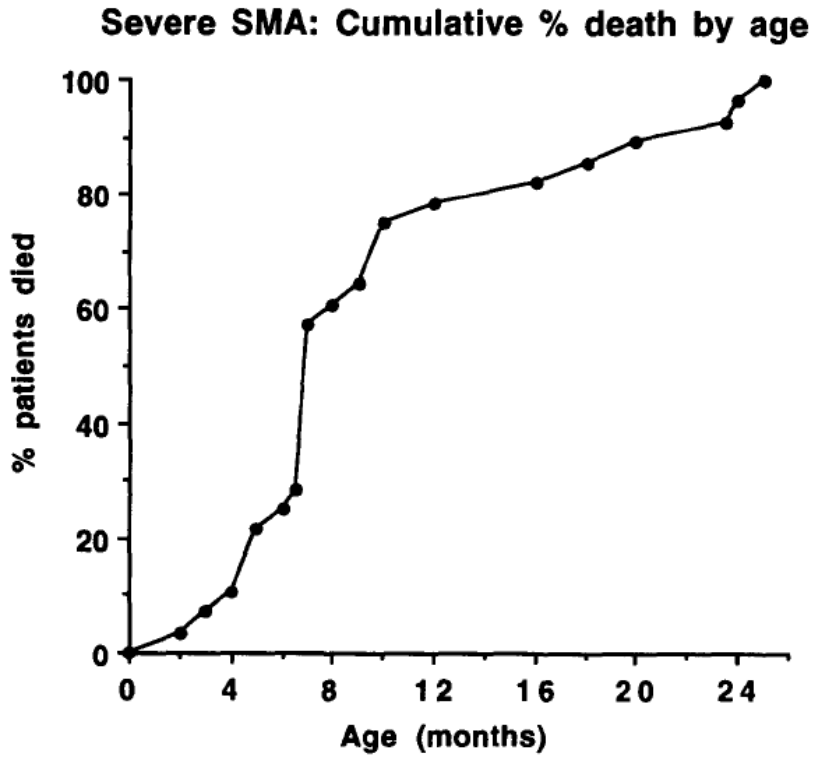


CHOP- INTEND scores



Mercuri et al 2020

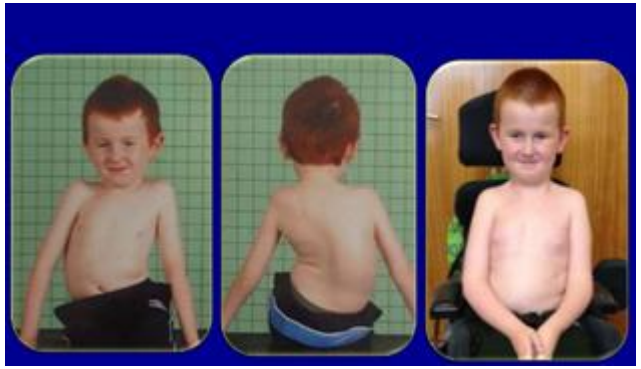
SMA I survival



Thomas N & Dubowitz V Neuromuscul Disord. 1994

SMA II

- Onset 6-18 months
- May stand – but with support
- Scoliosis
- Polyminimyoclonus
- Respiratory compromise



SMA III (Kugelberg-Welander Disease)

- Onset after acquisition of walking ability
- Widest range of ability
- Age of onset correlates with disease severity
  - 3a and 3b subtypes (age of onset before on after age 3 years)
  - 3a – high probability of loss of ambulation in childhood/ teenage years
- May develop scoliosis
- Diagnosis often delayed

- Normal life expectancy

SMA IV

- Onset of symptoms in adult age
- Milder course
- Normal life expectancy

SMA type	Number of *SMN2* copies carried by the majority of people with SMA
1	2
2	3
3a	3
3b	4
4	4-6

Why the spectrum of severity?

SMN2 gene copy number

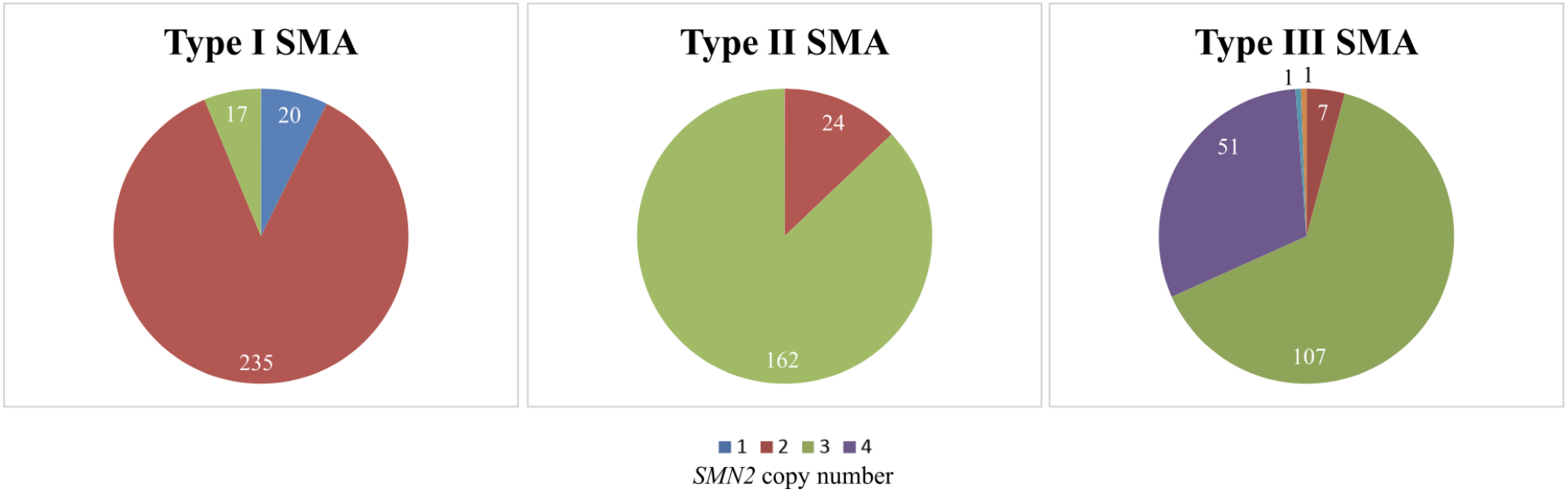


Fig. 1. Distribution of *SMN2* copy numbers according to SMA type. Number of Spanish SMA patients studied from our cohort of 625 index cases.

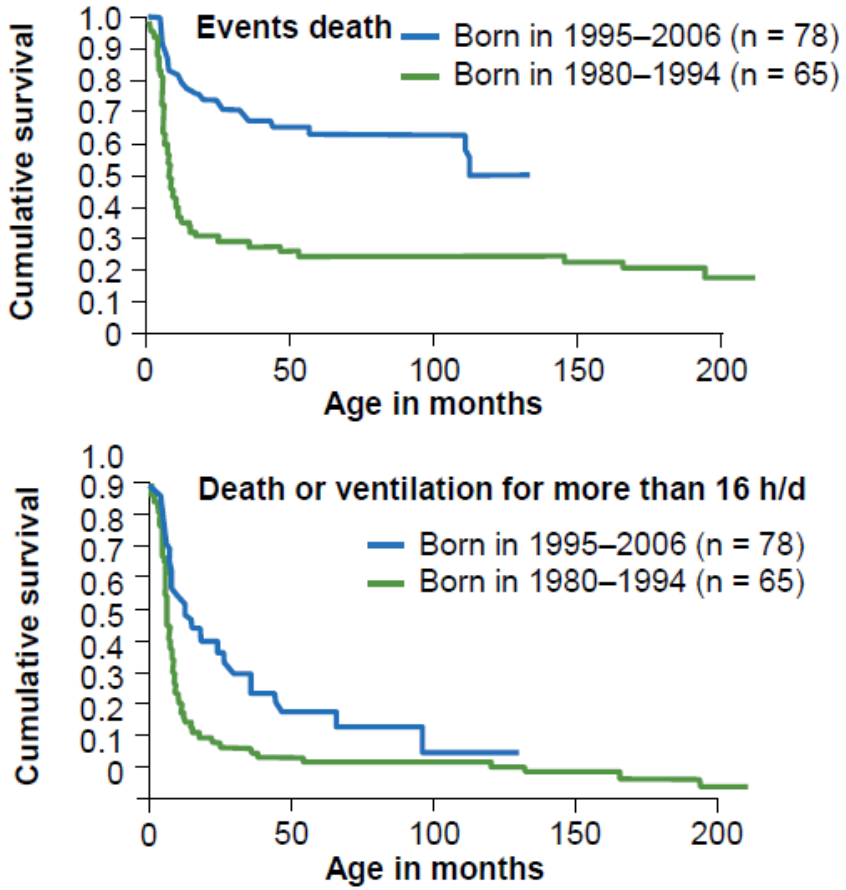
How do we care for patients with SMA?

Survival

Survival has increased in patients with SMA I

Change in survival:

- Cohort 1980–1994
  - 2 years old: 69.2% died
  - 4 years old: 73.8% died
- Cohort 1995–2006
  - with the presciption of nutritional support and respiratory support, mortality reduced
  - 2 years old: 26.1% died
  - 4 years old: 34.9% died



Hazard ratio [HR]: 0.3, 95% CI 0.2–0.5, p < 0.001.

Oskoui M, et al. Neurology. 2007;69:1931-6.

Special Issue Article

Journal of Child Neurology
Volume 22 Number 8
August 2007 1027-1049

10.1177/0883073807305788
http://jcn.sagepub.com
hosted at
http://online.sagepub.com

Consensus Statement for Standard of Care in Spinal Muscular Atrophy

Ching H. Wang, MD, PhD, Richard S. Finkel, MD, Enrico S. Bertini, MD, Mary Schroth, MD, Anita Simonds, MD, Brenda Wong, MD, Annie Aloysius, MRCSLT, HPC, Leslie Morrison, MD, Marion Main, MCSP, MA, Thomas O. Crawford, MD, Anthony Trela, BS, and Participants of the International Conference on SMA Standard of Care

Spinal muscular atrophy is a neurodegenerative disease that requires multidisciplinary medical care. Recent progress in the understanding of molecular pathogenesis of spinal muscular atrophy and advances in medical technology have not been matched by similar developments in the care for spinal muscular atrophy patients. Variations in medical practice coupled with differences in family resources and values have resulted in variable clinical outcomes that are likely to compromise valid measure of treatment effects during clinical trials. The International Standard of Care Committee for Spinal Muscular Atrophy was formed in 2005, with a goal of establishing practice guidelines for clinical care of these patients. The 12 core committee members worked with more than 60 spinal muscular atrophy experts in the field through conference calls, e-mail communications, a Delphi survey, and 2 in-person meetings to achieve consensus on 5 care areas: diagnostic/new interventions, pulmonary, gastrointestinal/nutrition, orthopedics/rehabilitation, and palliative care. Consensus was achieved on several topics related to common medical problems in spinal muscular atrophy, diagnostic strategies, recommendations for assessment and monitoring, and therapeutic interventions in each care area. A consensus statement was drafted to address the 5 care areas according to 3 functional levels of the patients: nonsitter, sitter, and walker. The committee also identified several medical practices lacking consensus and warranting further investigation. It is the authors' intention that this document be used as a guideline, not as a practice standard for their care. A practice standard for spinal muscular atrophy is urgently needed to help with the multidisciplinary care of these patients.

Keywords: spinal muscular atrophy; standard of care; consensus statement

Care Domains - 2007

- Diagnosis & Testing
- Family, Education & Counselling
- Pulmonary
- Gastro/Nutrition
- Orthopaedic
- Palliative care

Care Domains

- Diagnosis & Testing
  - Clinical diagnosis
  - Other types of SMA
  - Diagnostic procedures
- Family, Education & Counselling
- Pulmonary
  - Assessment and monitoring
  - Chronic management
  - Anticipatory management
  - Airway clearance
  - Respiratory support
  - Perioperative care
- Gastro/Nutrition
  - Feeding and swallowing problems
    - Assessment
    - Management
  - GI Dysfunction
    - Evaluation of GI dysfunction
  - Management of Gastroesophageal reflux
  - Growth & under/over nutrition problems
  - Management of Nutrition
- Orthopaedic
  - Orthotics
  - Orthopaedic surgery
  - Perioperative management in SMA
- Palliative care

Management of SMA - 2017

Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 28 (2018) 103–115
www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care

Eugenio Mercuri [a,b,l,*], Richard S. Finkel [c,l], Francesco Muntoni [d], Brunhilde Wirth [e], Jacqueline Montes [f], Marion Main [d], Elena S. Mazzone [a,b], Michael Vitale [g], Brian Snyder [h], Susana Quijano-Roy [i,j], Enrico Bertini [k], Rebecca Hurst Davis [l], Oscar H. Meyer [m], Anita K. Simonds [n], Mary K. Schroth [o], Robert J. Graham [p], Janbernd Kirschner [q], Susan T. Iannaccone [r], Thomas O. Crawford [s], Simon Woods [t], Ying Qian [u], Thomas Sejersen [v] for the SMA Care Group

Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 28 (2018) 197–207
www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics

Richard S. Finkel [a,l], Eugenio Mercuri [b,l,*], Oscar H. Meyer [c], Anita K. Simonds [d], Mary K. Schroth [e], Robert J. Graham [f], Janbernd Kirschner [g], Susan T. Iannaccone [h], Thomas O. Crawford [i], Simon Woods [j], Francesco Muntoni [k], Brunhilde Wirth [l], Jacqueline Montes [m], Marion Main [k], Elena S. Mazzone [b], Michael Vitale [n], Brian Snyder [o], Susana Quijano-Roy [p], Enrico Bertini [q], Rebecca Hurst Davis [r], Ying Qian [s], Thomas Sejersen [t] for the SMA Care group

Management of SMA

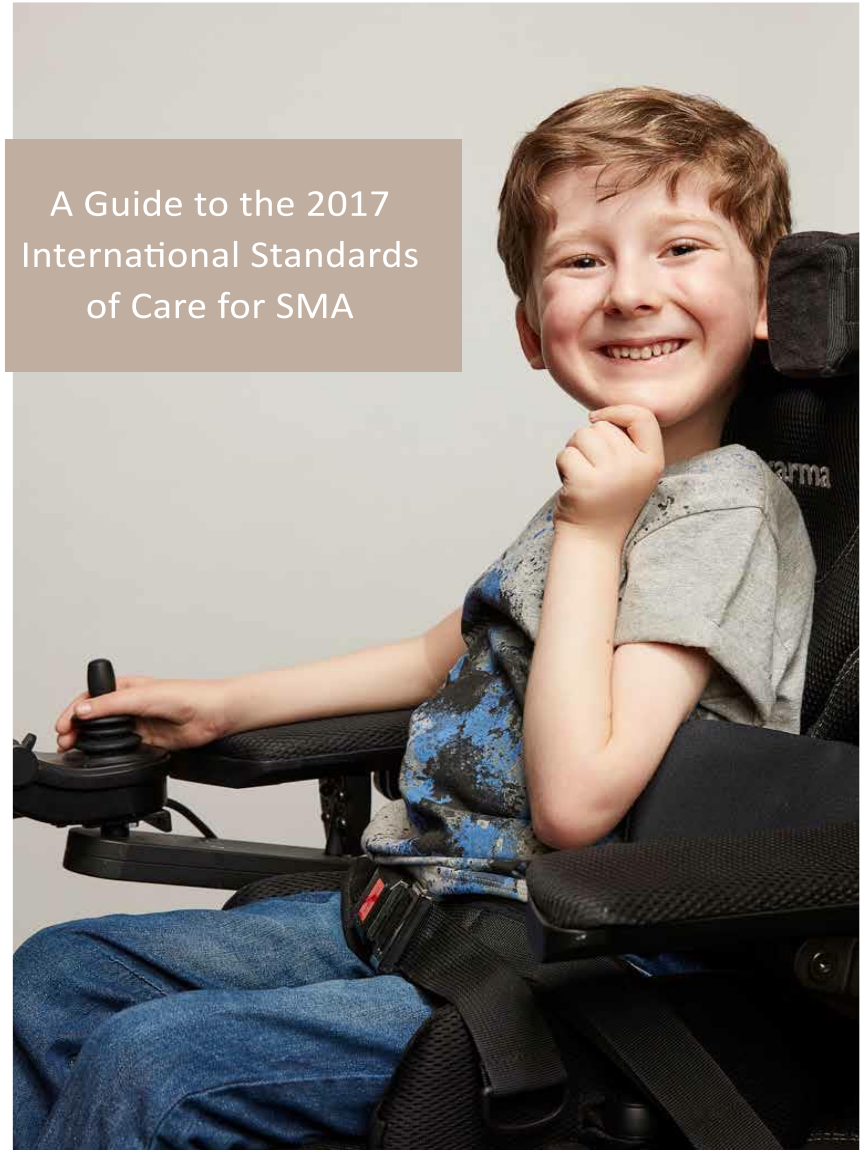
Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 28 (2018) 103–115
www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care

Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 28 (2018) 197–207
www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics

Richard S. Finkel [a,1], Eugenio Mercuri [b,1,*], Oscar H. Meyer [c], Anita K. Simonds [d], Mary K. Schroth [e], Robert J. Graham [f], Janbernd Kirschner [g], Susan T. Iannaccone [h], Thomas O. Crawford [i], Simon Woods [j], Francesco Muntoni [k], Brunhilde Wirth [l], Jacqueline Montes [m], Marion Main [k], Elena S. Mazzone [b], Michael Vitale [n], Brian Snyder [o], Susana Quijano-Roy [p], Enrico Bertini [q], Rebecca Hurst Davis [r], Ying Qian [s], Thomas Sejersen [t] for the SMA Care group



A Guide to the 2017 International Standards of Care for SMA

www.treat-nmd.org

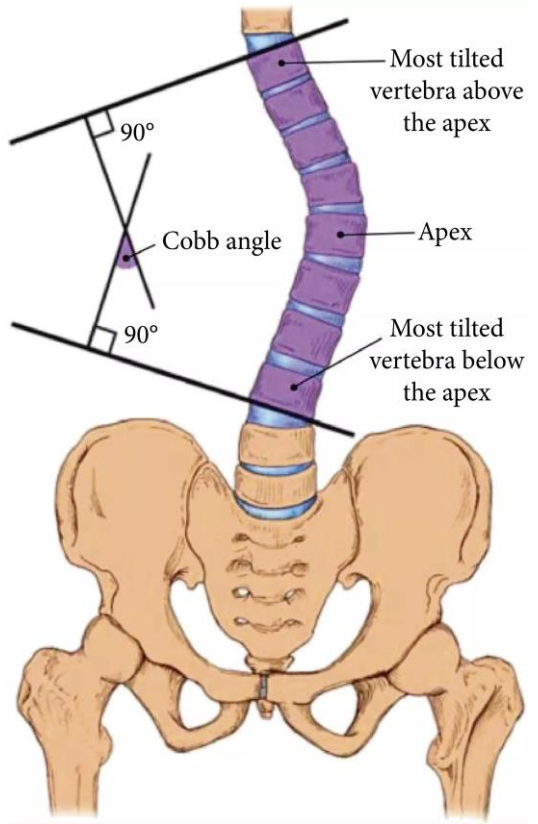
CONTENTS

CONTENTS

- Early recognition
- Early investigation & diagnosis
- Expedite genetic testing
- Awareness amongst colleagues

CONTENTS

- Specialist orthopaedic input &MDT clinics
- Hip instability
- Joint contractures
- Fractures – early mobilisation
- Anaesthetic expertise
- Spinal Surgery pathway
- DEXA scans
- Vitamin D



CONTENTS

- Swallowing
- Gastrostomy
- Minimise fasting
- Constipation
- Dietitian review

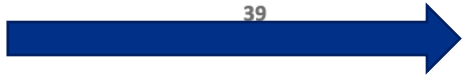
CONTENTS

- We are still learning…
- SMN protein expression is ubiquitous
- Non-neuronal manifestations
- Evolving phenotypes
- Cardiac, liver, autonomic system

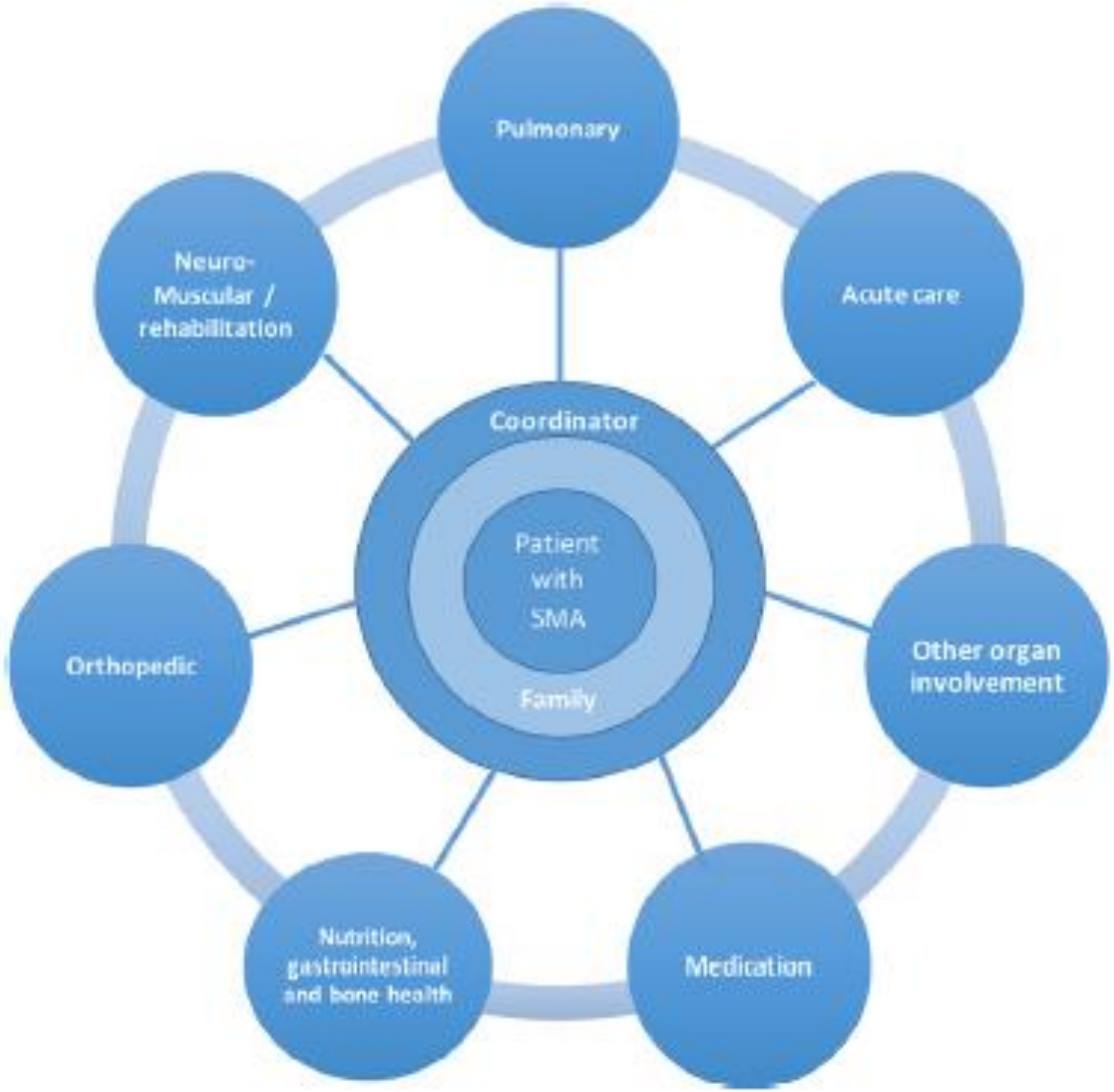
CONTENTS

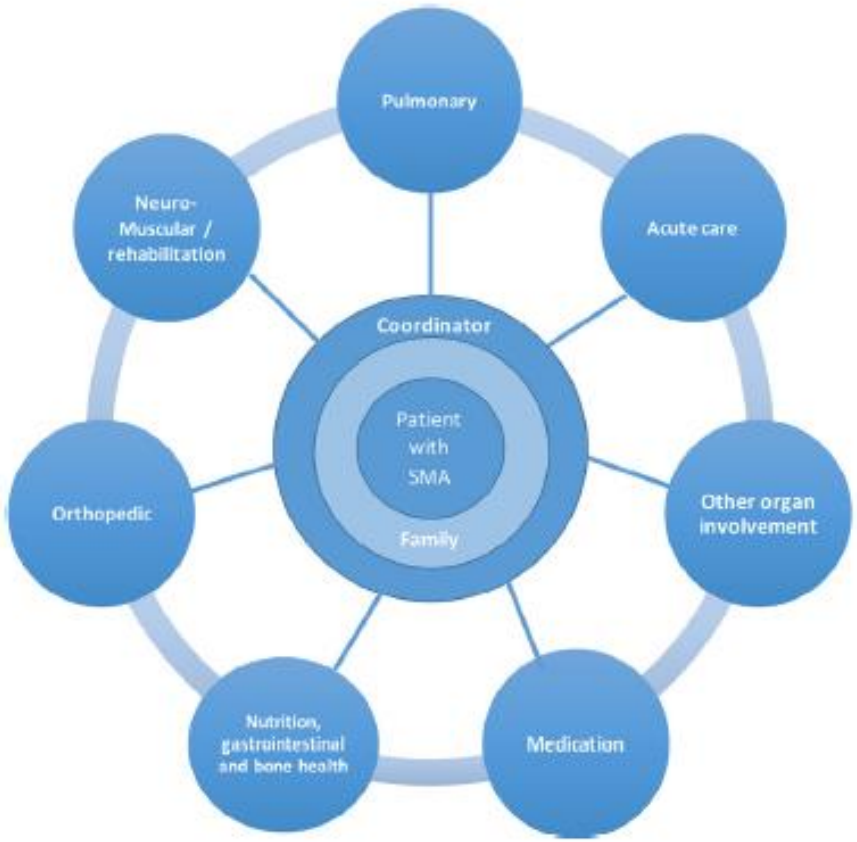
- The ‘SMA treatments’
- Vaccinations
- Vitamin D
- Supplementary feeds
- Antibiotics
- Laxatives

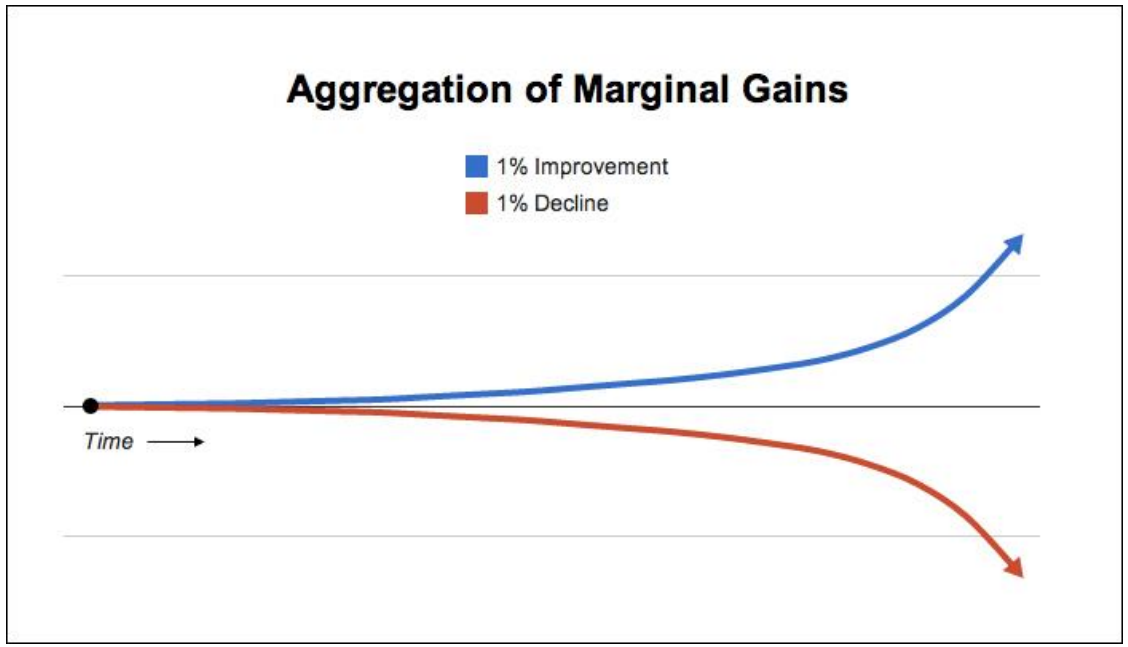
CONTENTS



- Alert cards
- Emergency care plans
  - Respiratory support
- Liaison with NM teams


Pulmonary
Neuro-
Muscular /
rehabilitation
Acute care
Coordinator
Patient
with
SMA
Family
Orthopedic
Other organ
involvement
Nutrition,
gastrointestinal
and bone health
Medication


Pulmonary
Neuro-
Muscular /
rehabilitation
Acute care
Coordinator
Patient
with
SMA
Family
Orthopedic
Other organ
involvement
Nutrition,
gastrointestinal
and bone health
Medication


Aggregation of Marginal Gains
1% Improvement
1% Decline
Time

New management issues…?

- “treated patients”
- Access to treatments
- New phenotypes

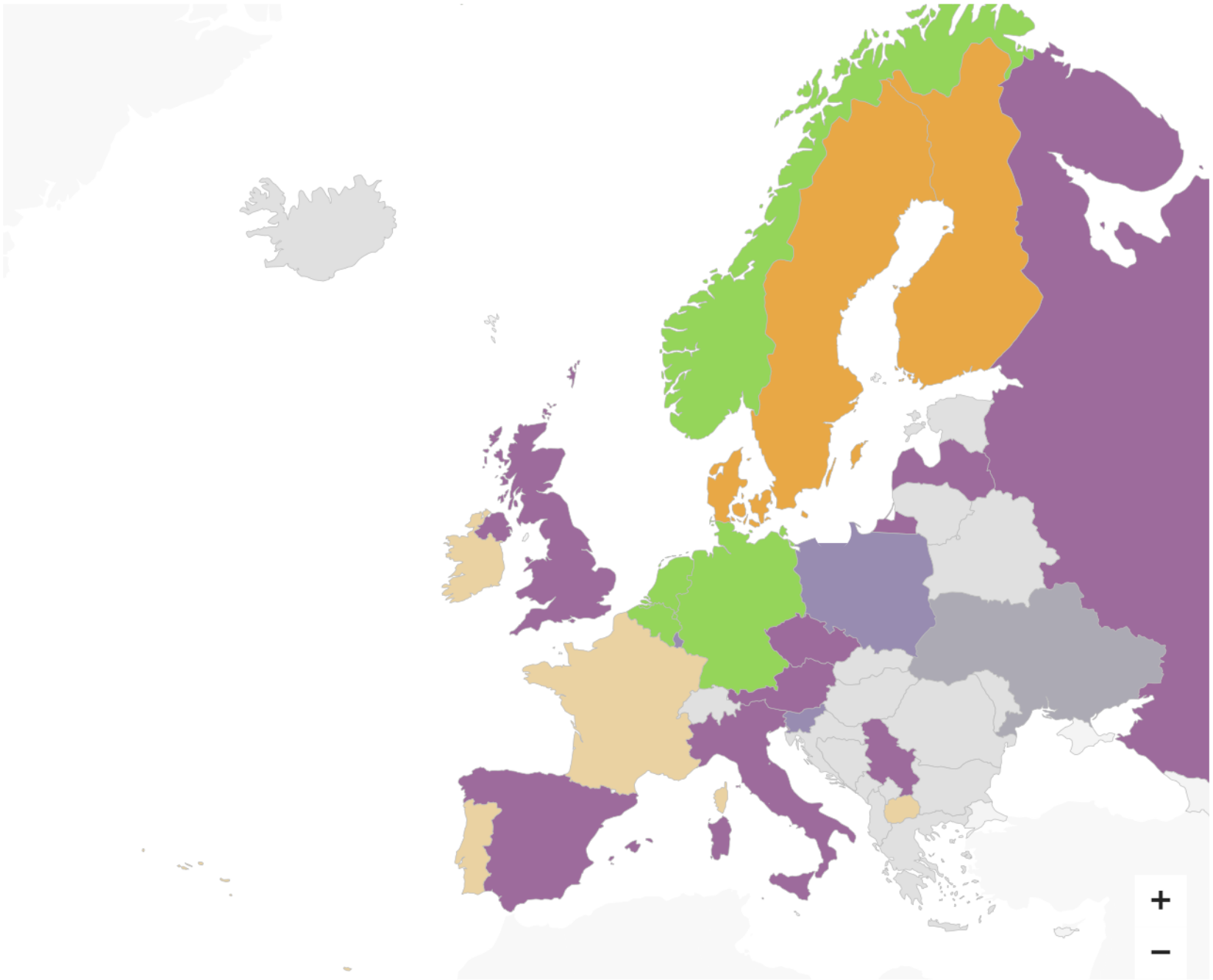
New Treatments – in context

Nusinersen/Spinraza

Onasemnogene
Abeparvovec/Zolgensma

Risdiplam/Evrysdi

What next?



Status of Newborn Screening for Spinal Muscular Atrophy

- National Program Active
- SMA approved for NBS panel, pending implementation
- Application for national program submitted
- Pilot planned
- Active Pilot
- No program

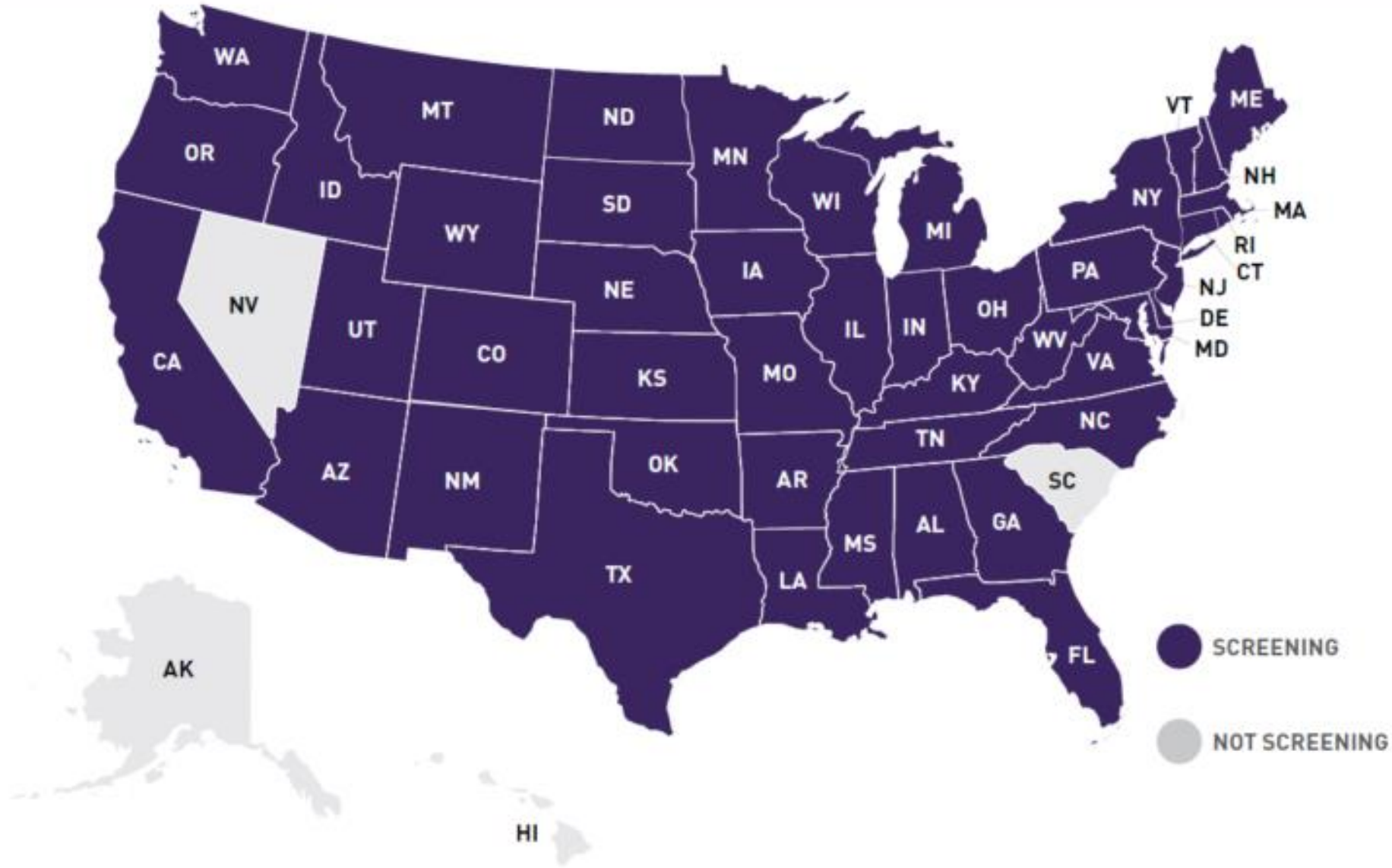
First UK pilot study of newborn screening for spinal muscular atrophy (SMA) launched in Oxford.

11 March 2022

In the UK, every 5 days a baby is born with SMA. Treatments are available now. If these treatments are delivered at birth, these newborns have the best chance of living long and healthy lives. If treated later, when they are identified because of the symptoms, they may survive, but with a severe disability. So, for every 5 days that a newborn screening is delayed, a baby in the UK loses the chance of a brighter future. Oxford University is initiating a population-based newborn screening study in the Thames Valley. This study aims to make it possible to detect SMA within days of birth, before symptoms develop, so that any affected newborn can receive diagnosis and treatment at the earliest possible opportunity. We hope that it will pave the way for a national newborn screening that will save about 70 babies/year in the UK from disability

STATES SCREENING & NOT SCREENING FOR SMA

46 States Currently Screen for SMA | **97%** of Newborn Babies in the U.S. are Screened



New Treatments – not a cure

Nusinersen/Spinraza

Onasemnogene
Abeparvovec/Zolgensma

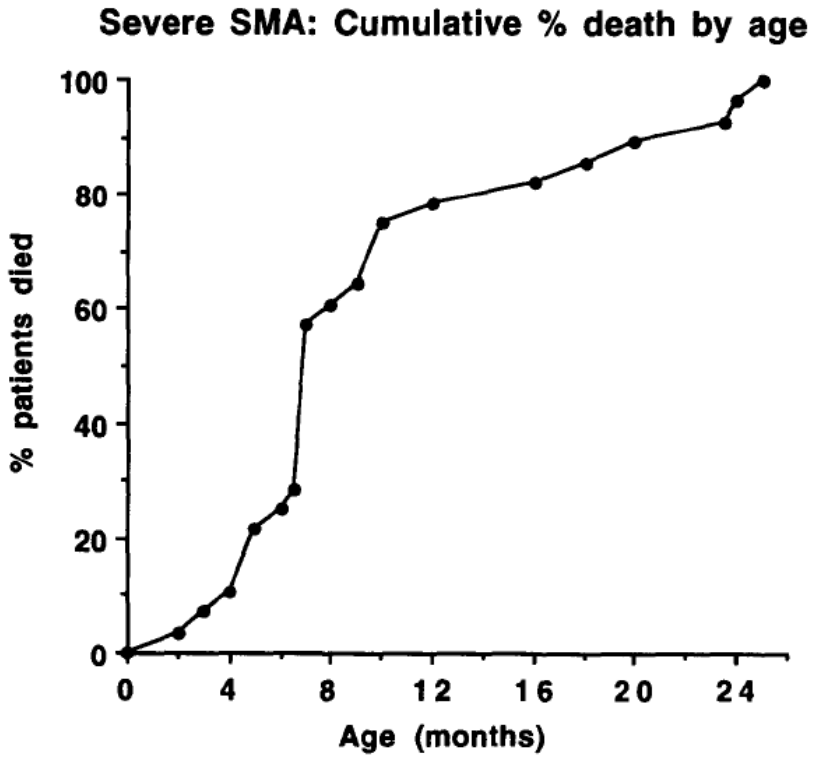
Risdiplam

Questions

New treatments

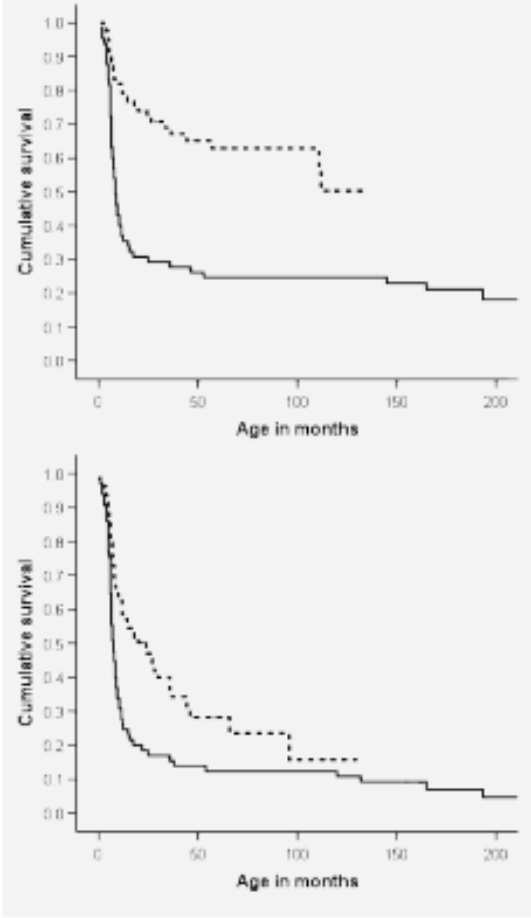
Dr Gary McCullagh, Consultant Paediatric Neurologist,
Royal Manchester Children’s Hospital

SMA I survival



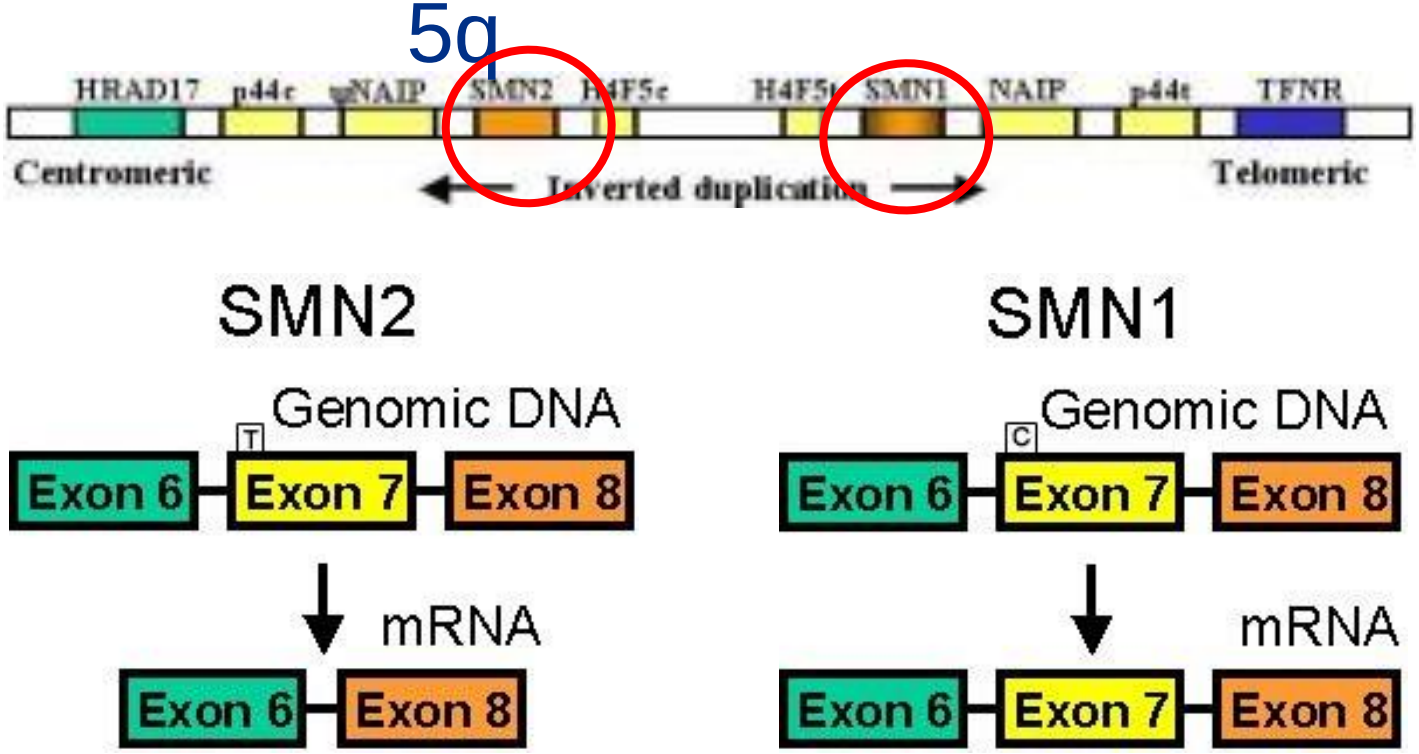
Thomas N & Dubowitz V Neuromuscul Disord. 1994

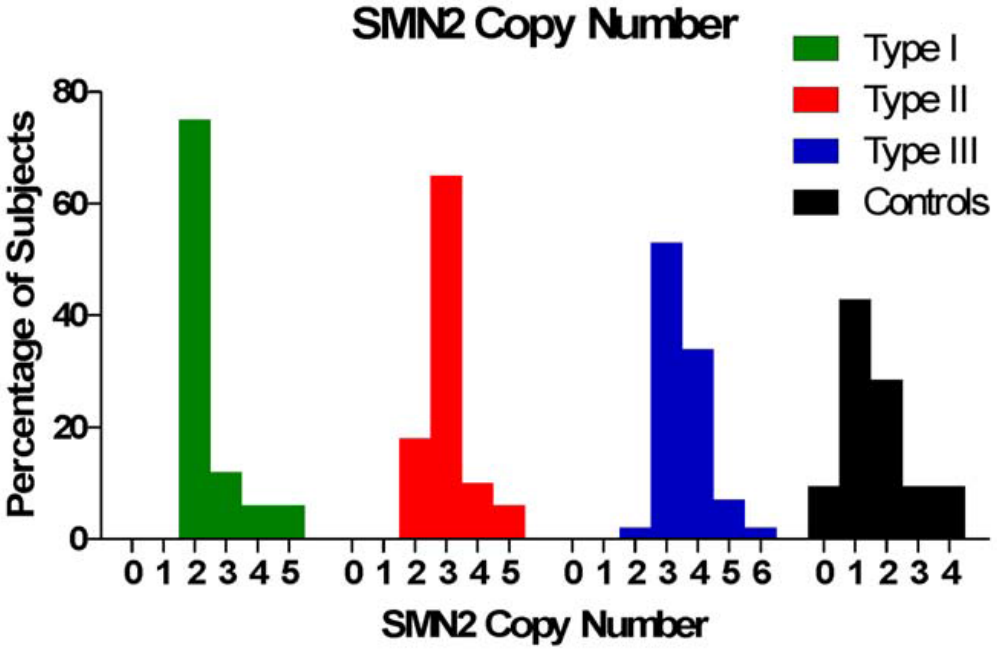
Figure Kaplan-Meier survival plots of spinal muscular atrophy type 1 patients born in 1995–2006 (dashed line) compared with those born in 1980–1994 (solid line), for events death (top panel) and death or ventilation for more than 16 h/d (bottom panel)



Oskoui M et al Neurology 2007;69

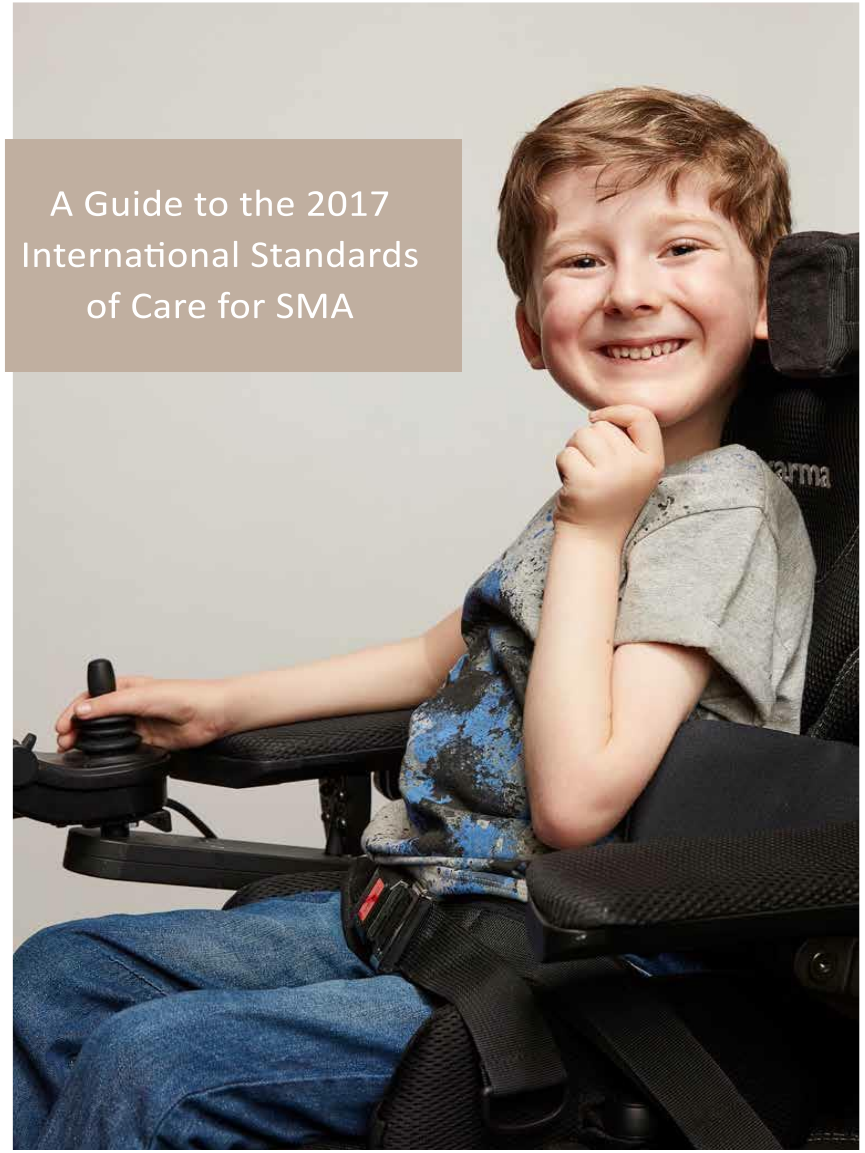
SMA Genetics





SMN2 mRNA
80% of pre-mRNA spliced to SMN protein with no exon 7, SMN without exon 7 is unstable & rapidly degraded

SMN1 mRNA
90% of pre-mRNA spliced to full length SMN protein



A Guide to the 2017 International Standards of Care for SMA

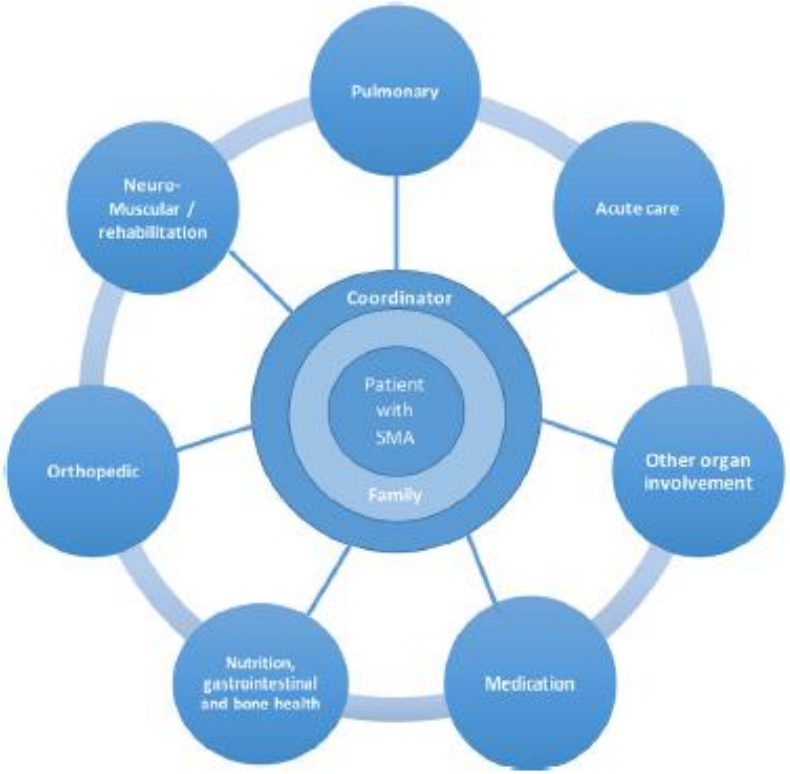
www.treat-nmd.org

CONTENTS

Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders ■■ (2017) ■■–■■
www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care

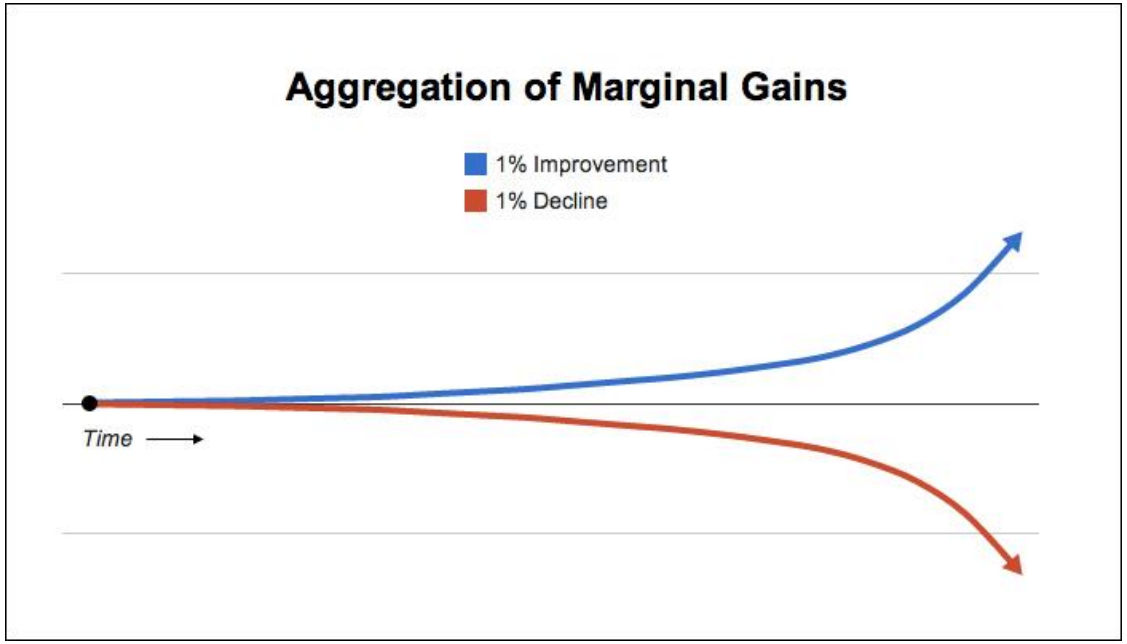
Eugenio Mercuri [a,b,l,*], Richard S. Finkel [c,l], Francesco Muntoni [d], Brunhilde Wirth [e], Jacqueline Montes [f], Marion Main [d], Elena S. Mazzone [a,b], Michael Vitale [g], Brian Snyder [h], Susana Quijano-Roy [i,j], Enrico Bertini [k], Rebecca Hurst Davis [l], Oscar H. Meyer [m], Anita K. Simonds [n], Mary K. Schroth [o], Robert J. Graham [p], Janbernd Kirschner [q], Susan T. Iannaccone [r], Thomas O. Crawford [s], Simon Woods [t], Ying Qian [u], Thomas Sejersen [v] for the SMA Care Group



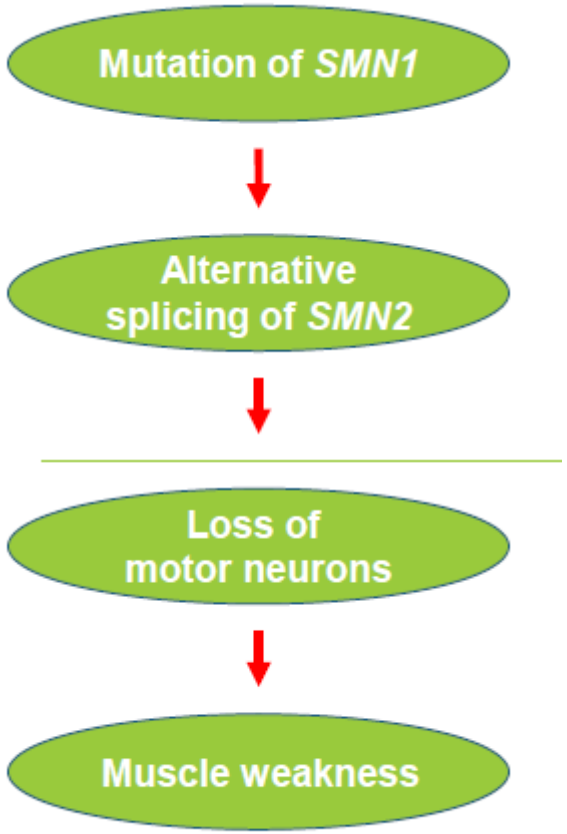
Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders ■■ (2017) ■■–■■
www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics

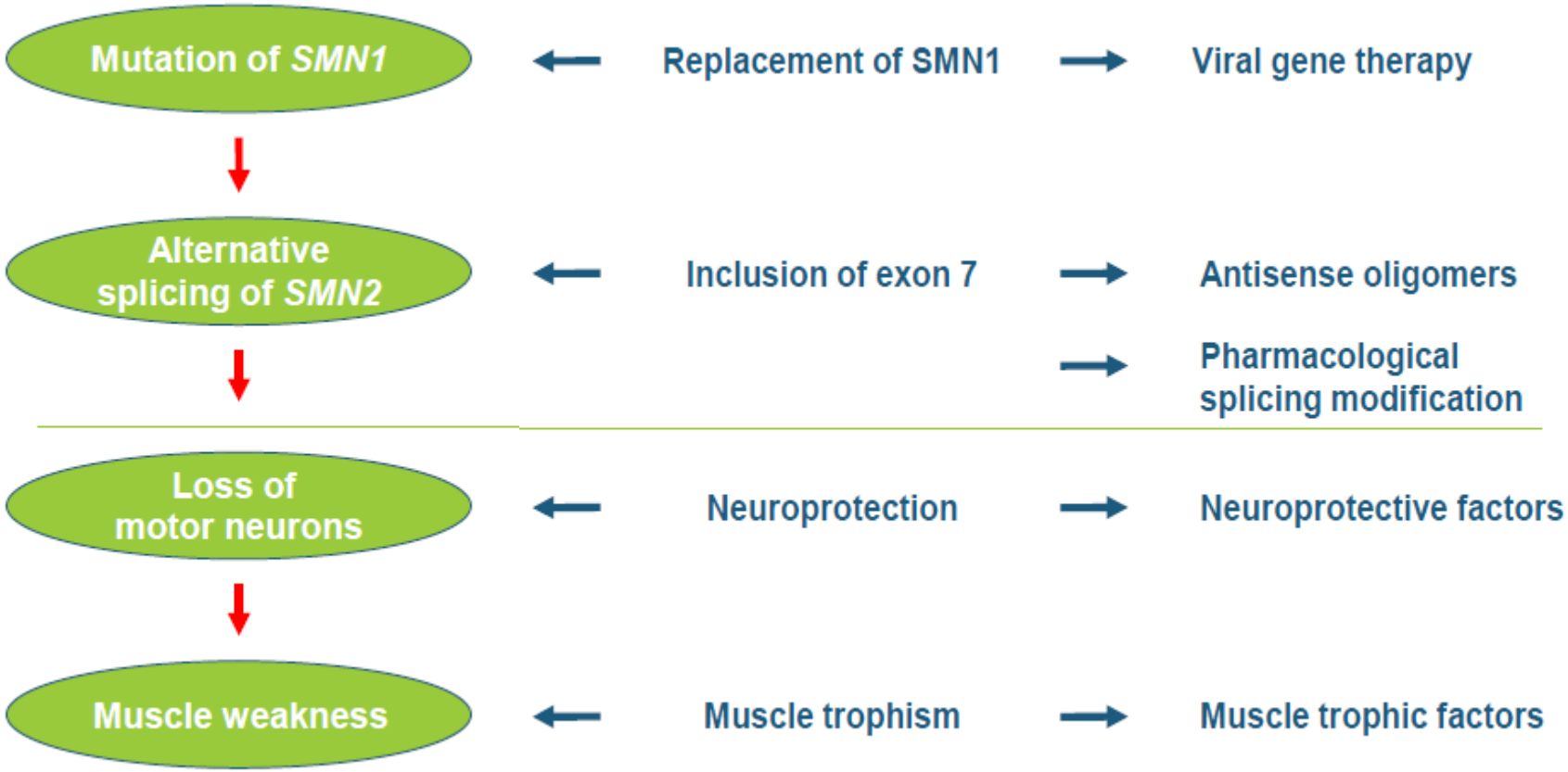
Richard S. Finkel [a,l], Eugenio Mercuri [b,l,*], Oscar H. Meyer [c], Anita K. Simonds [d], Mary K. Schroth [e], Robert J. Graham [f], Janbernd Kirschner [g], Susan T. Iannaccone [h], Thomas O. Crawford [i], Simon Woods [j], Francesco Muntoni [k], Brunhilde Wirth [l], Jacqueline Montes [m], Marion Main [k], Elena S. Mazzone [b], Michael Vitale [n], Brian Snyder [o], Susana Quijano-Roy [p], Enrico Bertini [q], Rebecca Hurst Davis [r], Ying Qian [s], Thomas Sejersen [t] for the SMA Care group



Treatment – where to start???



Treatment – where to start???



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 2, 2017 VOL. 377 NO. 18

Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Klapac, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Heitzer, A. Kaspar, S. Corcoran, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaspar

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group*

New Treatments

Nusinersen/Spinraza

Onasemnogene
Abeparvovec/Zolgensma

Risdiplam

	Mechanism of action	Administration	MHRA/NICE
Nusinersen	Anti-sense oligonucleotide Alters SMN2 splicing	Intrathecal loading & maintenance	July 2019 MAA
Onasemnogene abeparvovec	Gene replacement	IV infusion once	March 2021 NICE draft recommendation, July 2021 final +NHSE statement
Risdiplam	Small molecule Alters SMN2 splicing	Oral	Sept 2020 EAMS (type 1&2 unable to receive other treatment) May 2021 marketing authorisation MHRA 19/11/2021 NICE recommendation MAA

Nusinersen (Spinraza)

Anti-sense oligonucleotide - alters SMN2 splicing

Intrathecal loading & maintenance injections

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

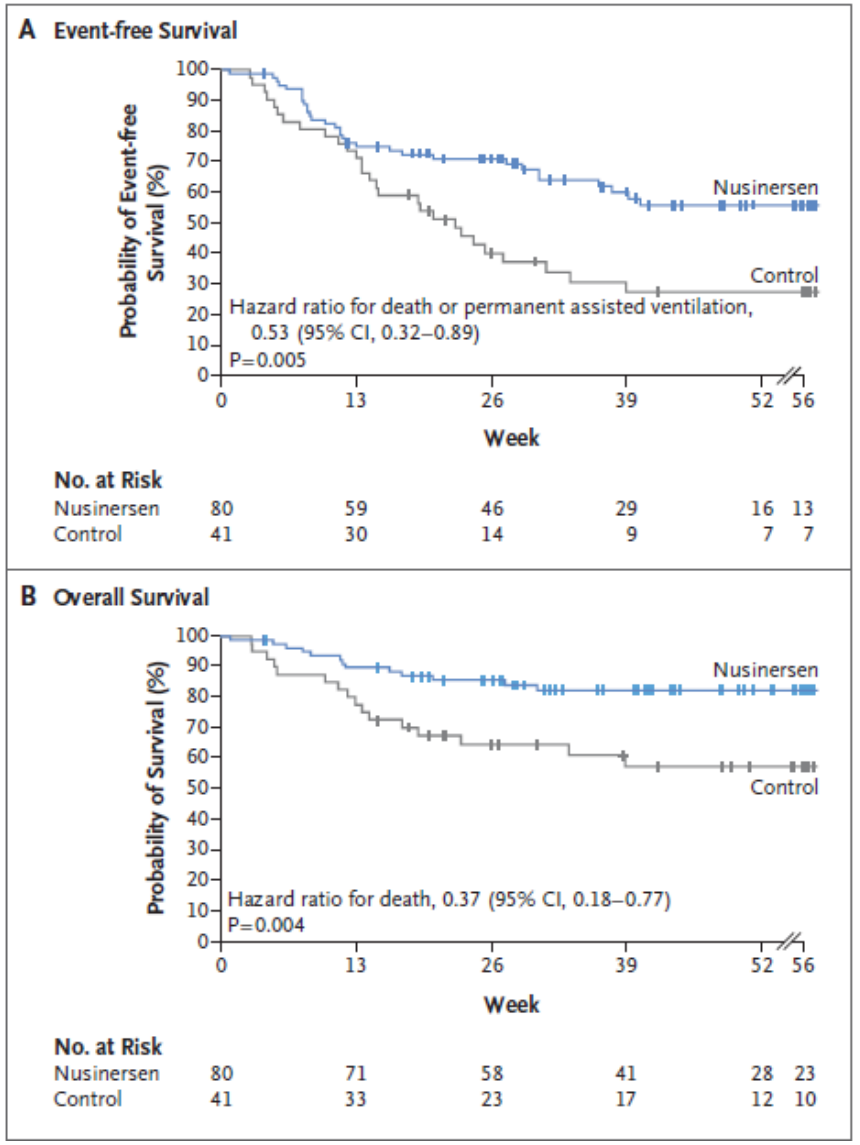
R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group*

2017

ENDEAR Trial

Table 2. Primary and Secondary End Points.*

End Point	Nusinersen Group	Control Group	Hazard Ratio (95% CI)	P Value
	no./total no. (%)			
Primary end points				
Motor-milestone response†				
Interim analysis	21/51 (41)	0/27	—	<0.001
Final analysis	37/73 (51)	0/37	—	—
No death or use of permanent assisted ventilation‡	49/80 (61)	13/41 (32)	0.53 (0.32–0.89)	0.005
Secondary end points§				
CHOP INTEND response¶	52/73 (71)	1/37 (3)	—	<0.001
No death	67/80 (84)	25/41 (61)	0.37 (0.18–0.77)	0.004
No use of permanent assisted ventilation‡	62/80 (78)	28/41 (68)	0.66 (0.32–1.37)	0.13
CMAP response‖	26/73 (36)	2/37 (5)	—	—
No death or use of permanent assisted ventilation among those with disease duration ≤13.1 wk at screening‡	30/39 (77)	7/21 (33)	0.24 (0.10–0.58)	—
No death or use of permanent assisted ventilation among those with disease duration >13.1 wk at screening‡	19/41 (46)	6/20 (30)	0.84 (0.43–1.67)	—



Finkel et al N Engl J Med. 2017 Nov 2;377(18):1723-1732

Nusinersen Managed Access Agreement

Entry criteria

Patient has a confirmed genetic diagnosis of 5q autosomal recessive SMA and meets one of the following criteria:
- Has SMA type1,2,or3.
- Pre-symptomatic of SMA and has one to four SMN2 copies.

•Nusinersen is used as a monotherapy.

•Must not have had successful treatment with onasemnogene abeparvovec. Non-successful treatment is defined in appendix F.

•No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline. Patients who do not meet this criterion but otherwise meet the eligibility criteria should be discussed with the NHS England Clinical Panel.

•Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated.

• Must not have received spinal fusion surgery following a diagnosis of scoliosis which, in the opinion of the treating clinician, prohibits safe administration of nusinersen.

Providing a patient meets the entry criteria as specified above, due to equity considerations there is no upper limit of age on treatment initiation.

Nusinersen Managed Access Agreement

Entry criteria

Patient has a confirmed genetic diagnosis of 5q autosomal recessive SMA and meets one of the following criteria:
- Has SMA type1,2,or3.
- Pre-symptomatic of SMA and has one to four SMN2 copies.

•Nusinersen is used as a monotherapy.

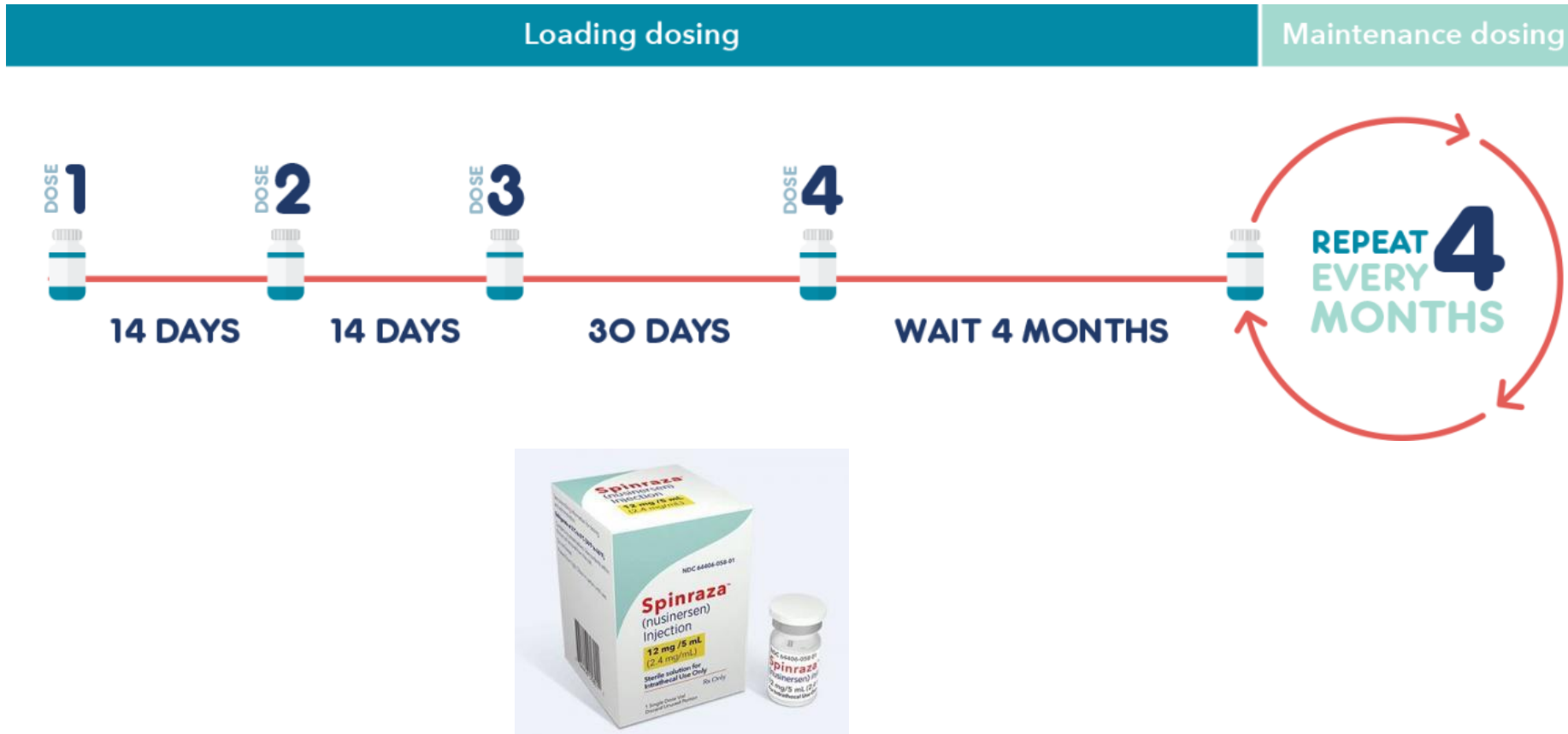
•Must not have had successful treatment with onasemnogene abeparvovec. Non-successful treatment is defined in appendix F.

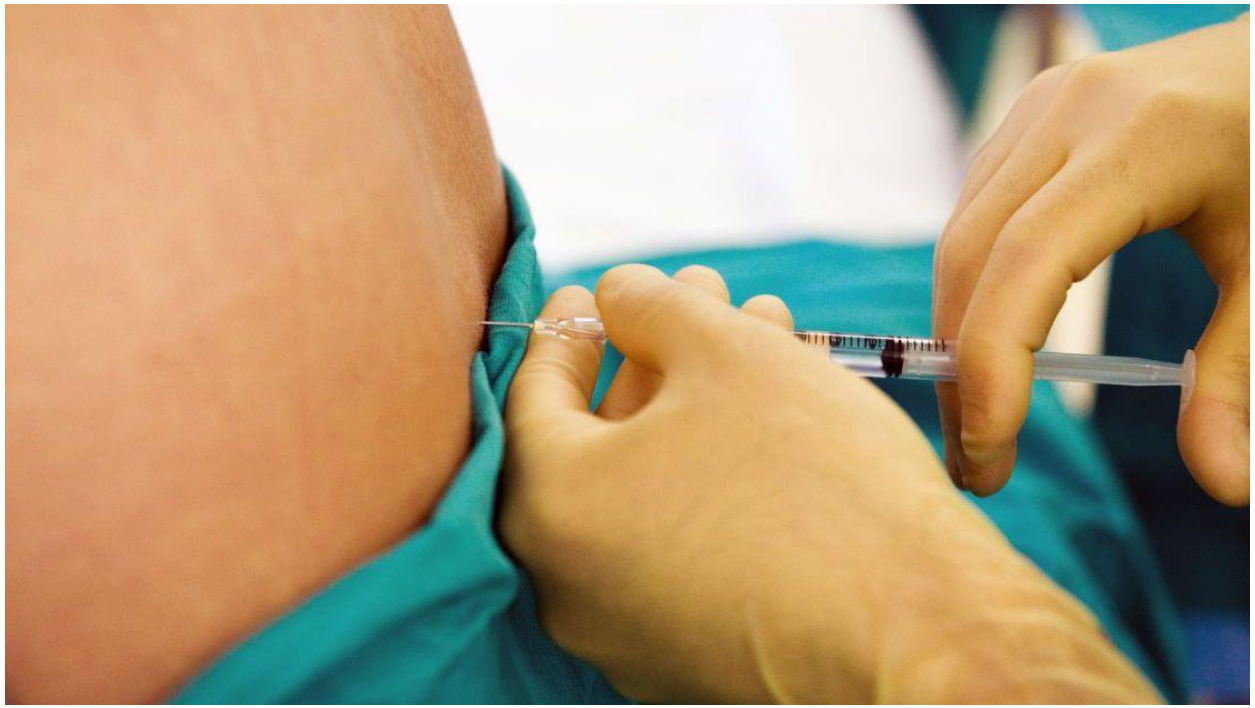
•No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline. Patients who do not meet this criterion but otherwise meet the eligibility criteria should be discussed with the NHS England Clinical Panel.

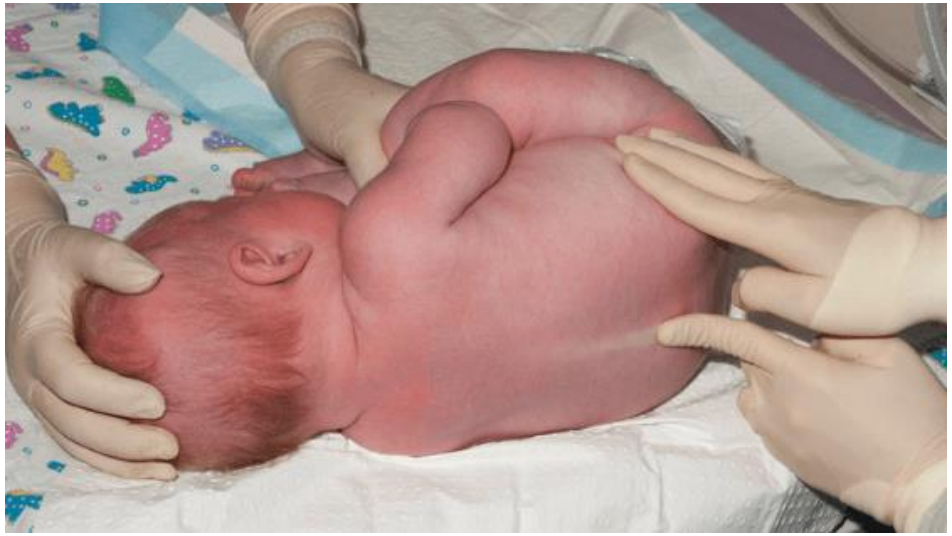
•Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated.

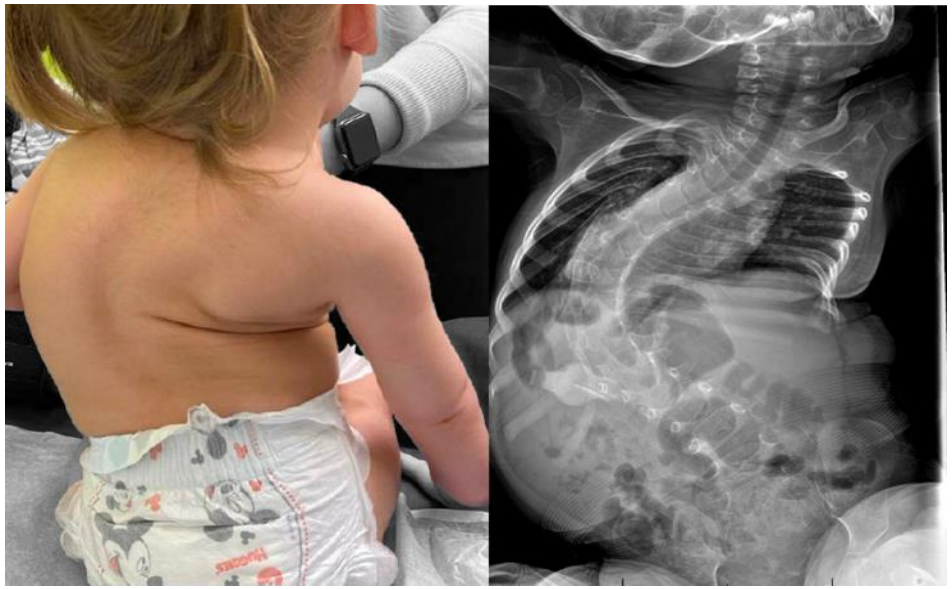
• Must not have received spinal fusion surgery following a diagnosis of scoliosis which, in the opinion of the treating clinician, prohibits safe administration of nusinersen.

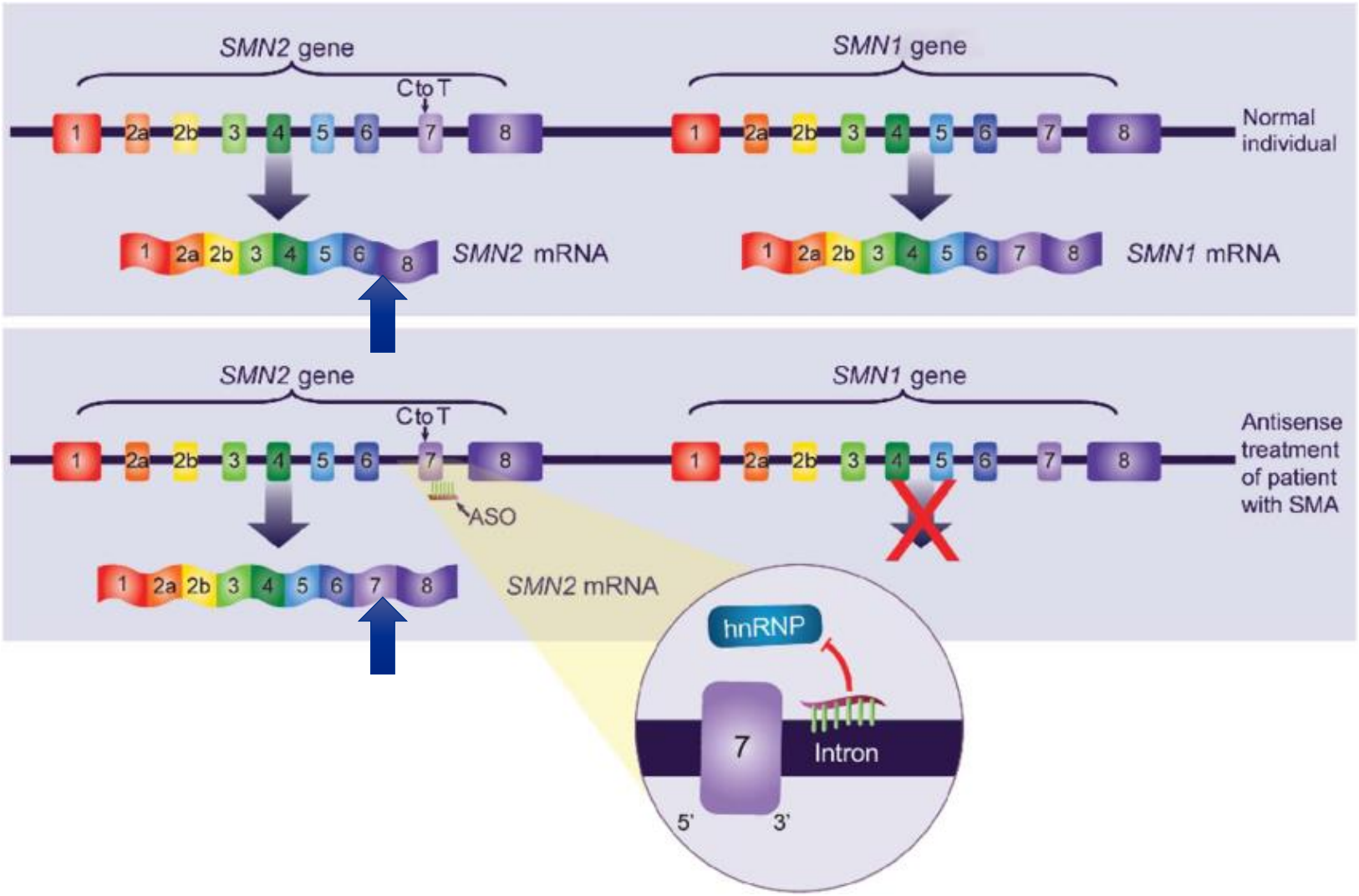
Providing a patient meets the entry criteria as specified above, due to equity considerations there is no upper limit of age on treatment initiation.


Loading dosing
Maintenance dosing
DOSE 1
DOSE 2
DOSE 3
DOSE 4
14 DAYS
14 DAYS
30 DAYS
WAIT 4 MONTHS
REPEAT EVERY 4 MONTHS
Spinraza
(nusinersen)
Injection
12 mg /5 mL
(2.4 mg/mL)
Sterile solution for Intrathecal Use Only
Rx Only









A Chiriboga, et al. (2016). Results from a phase 1 study of nusinersen (ISIS-SMNRx) in children with spinal muscular atrophy. Neurology. 86. 10.1212

SPINRAZA Continues to Demonstrate Benefit Across a Broad Range of Patients with SMA[1]

- All infants in study were alive and none required permanent ventilation
- Most infants achieved motor milestones at the age expected for healthy infants

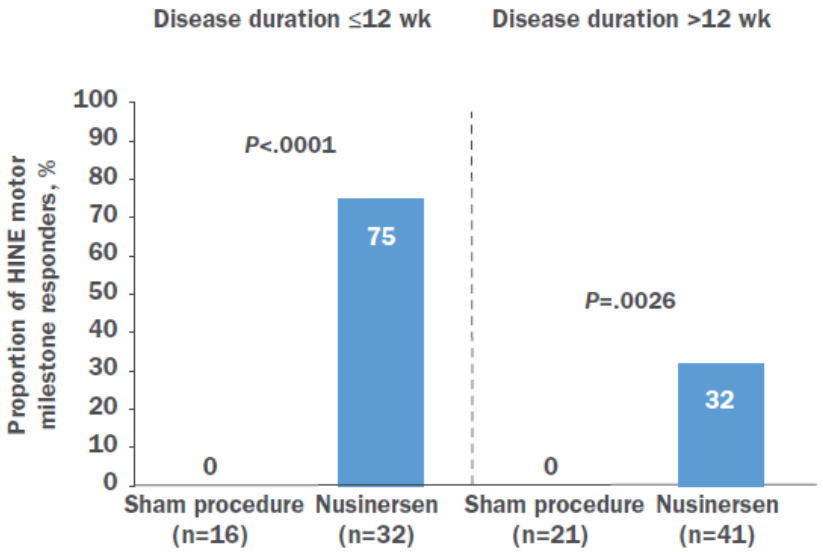
- Increased event-free survival vs. placebo
- Continued improvements in strength and function

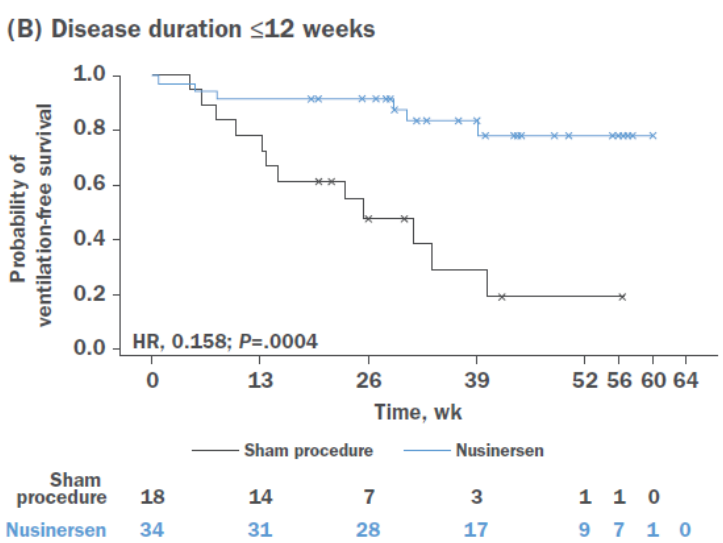
- Stability or continued improvement in strength and function
- Some children gained or regained the ability to walk[2]

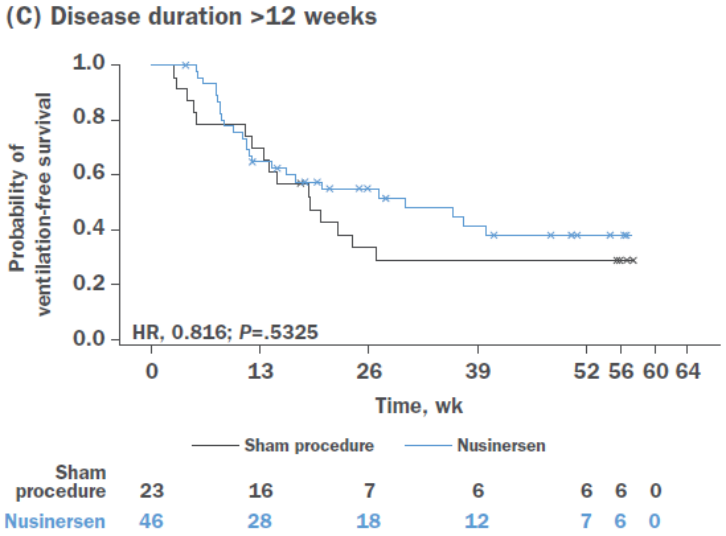
1. *Results from Phase 2 open-label studies in infantile-onset and later-onset SMA, Phase 3 ENDEAR study, Phase 3 CHERISH study, Phase 2 NURTURE study (NURTURE data cut-off date: October 31, 2016)*
2. *Results from CS2-CS12 analysis*

Effect of disease duration

Finkel et al N Engl J Med. 2017 Nov 2;377(18):1723-1732





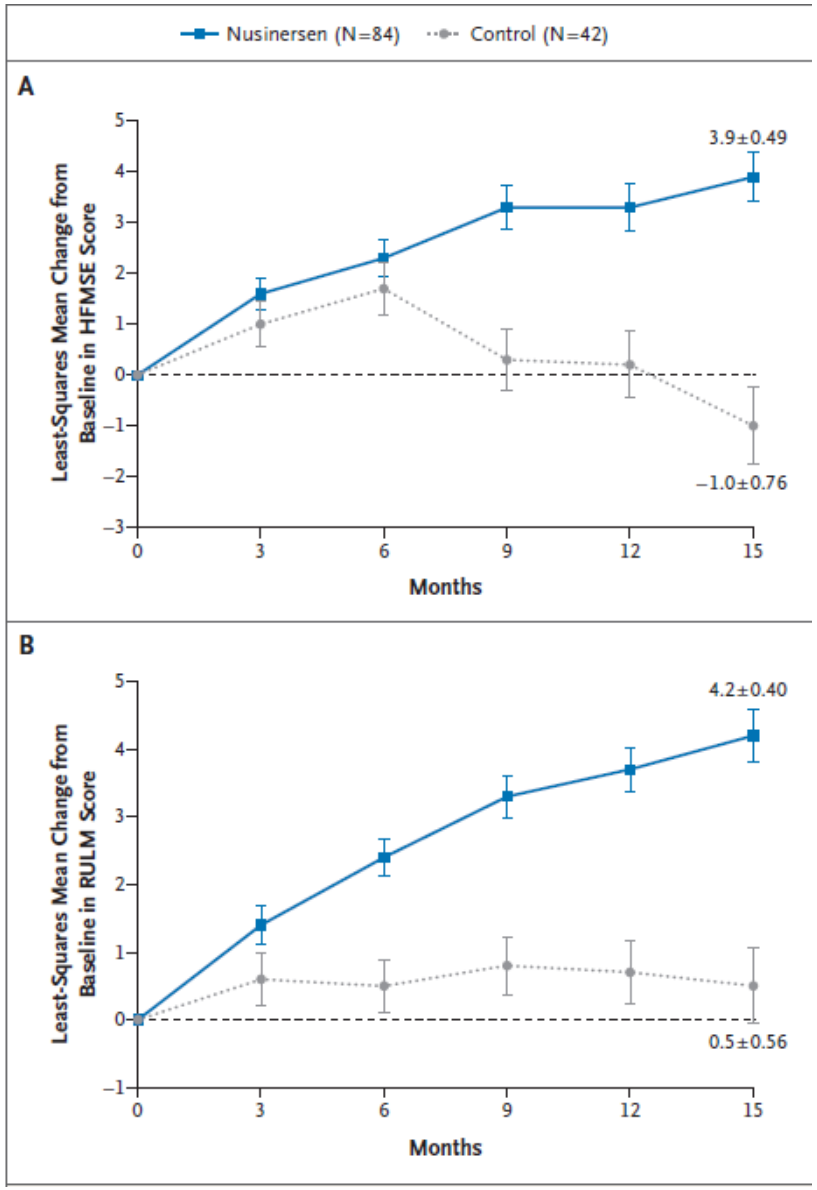


Cherish-SMA 2&3

Table 2. Primary and Secondary End Points Assessed at Month 15.*

End Point	Nusinersen (N=84)	Control (N=42)	Difference	P Value
Interim analysis†				
Primary end point: change from baseline in HFMSE score — least-squares mean (95% CI)‡	4.0 (2.9 to 5.1)	−1.9 (−3.8 to 0)	5.9 (3.7 to 8.1)	<0.001
Final analysis§				
Primary end point: change from baseline in HFMSE score — least-squares mean (95% CI)‡	3.9 (3.0 to 4.9)	−1.0 (−2.5 to 0.5)	4.9 (3.1 to 6.7)	—
Secondary end points				
Children with change in HFMSE score of ≥3 points				
% (95% CI)¶	57 (46 to 68)	26 (12 to 40)	30.5 (12.7 to 48.3)	
Odds ratio (95% CI)	—	—	6 (2 to 15)‖	<0.001
Children who achieved ≥1 new WHO motor milestone				
No.	13	2	—	—
% (95% CI)**	20 (11 to 31)	6 (1 to 20)	14 (−7 to 34)	0.08
Change from baseline in number of WHO motor milestones achieved — least-squares mean (95% CI)‡	0.2 (0.1 to 0.3)	−0.2 (−0.4 to 0)	0.4 (0.2 to 0.7)	—
Change from baseline in RULM score — least-squares mean (95% CI)‡	4.2 (3.4 to 5.0)	0.5 (−0.6 to 1.6)	3.7 (2.3 to 5.0)	—
Children who achieved ability to stand alone				
No.	1	1	—	—
% (95% CI)**	2 (0 to 8)	3 (0 to 15)	−1 (−22 to 19)	—
Children who achieved ability to walk with assistance				
No.	1	0	—	—
% (95% CI)**	2 (0 to 8)	0 (0 to 10)	2 (−19 to 22)	—

Mercuri et al N Engl J Med. 2018 Feb 15;378(7):625-635.



Nurture pre-symptomatic

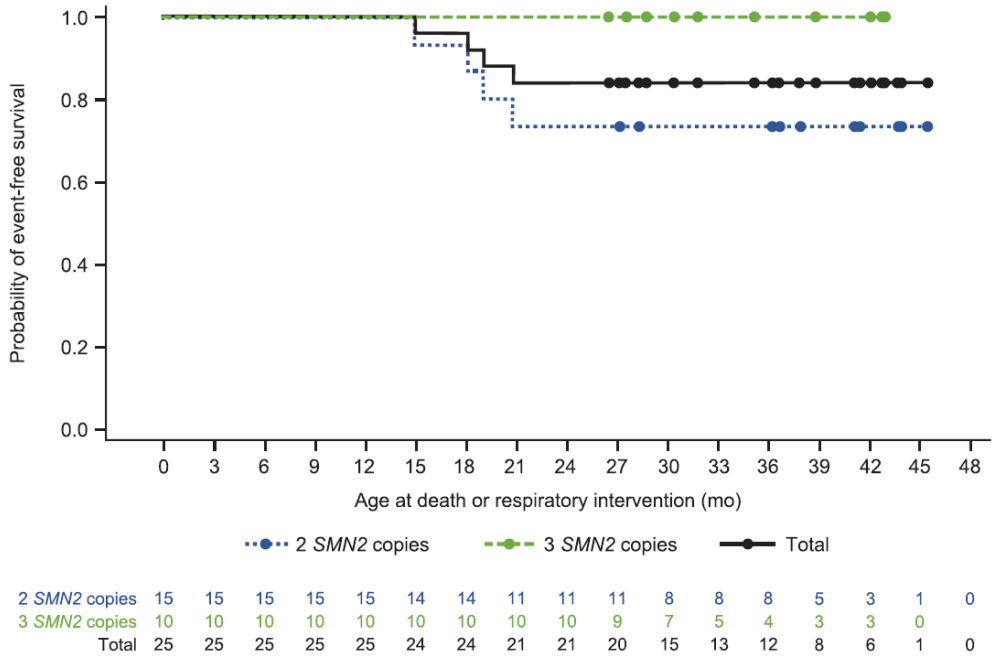
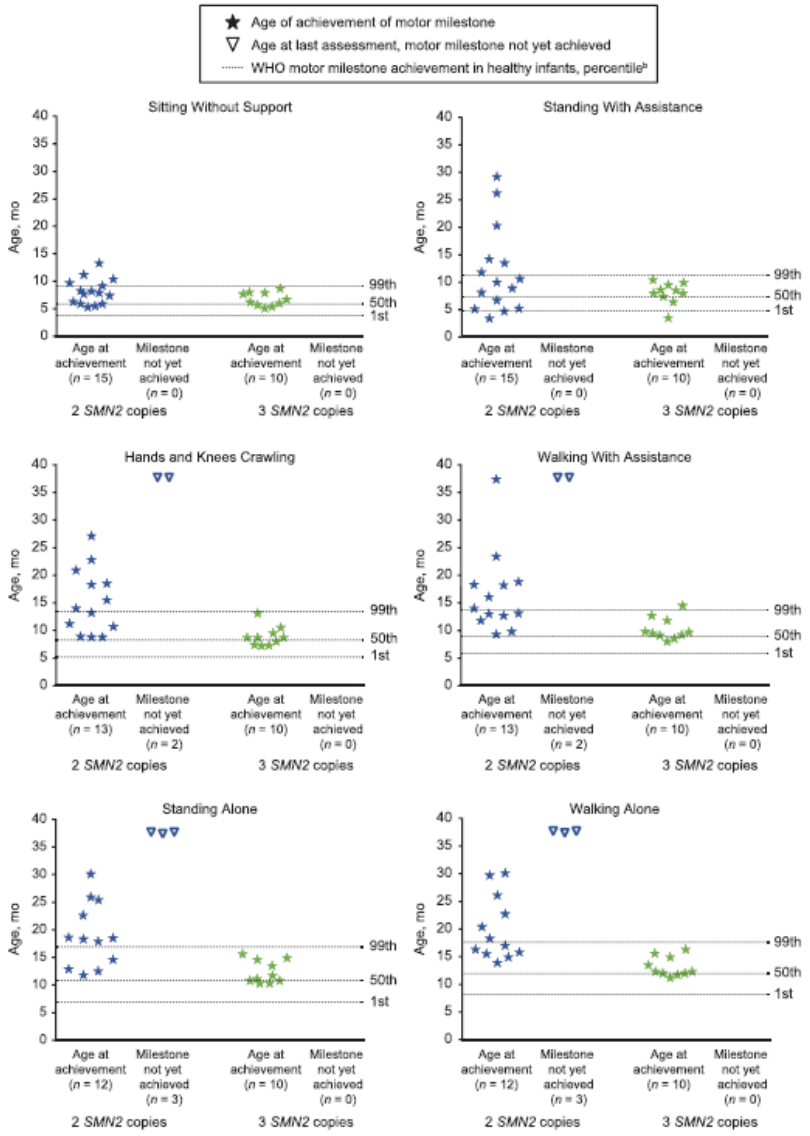


Fig. 2. Kaplan–Meier plot for age at death or respiratory intervention.[a]
SMN2, survival motor neuron 2.
No participants have died or required tracheostomy or permanent ventilation (defined as ≥16 h/day continuously for >21 days in the absence of an acute reversible event or tracheostomy).
[a]Respiratory intervention was defined as ventilator use for ≥6 h per day for ≥7 days or tracheostomy.



De Vivo et al Neuromuscul Disord. 2019 Sep 12.

Nurture pre-symptomatic

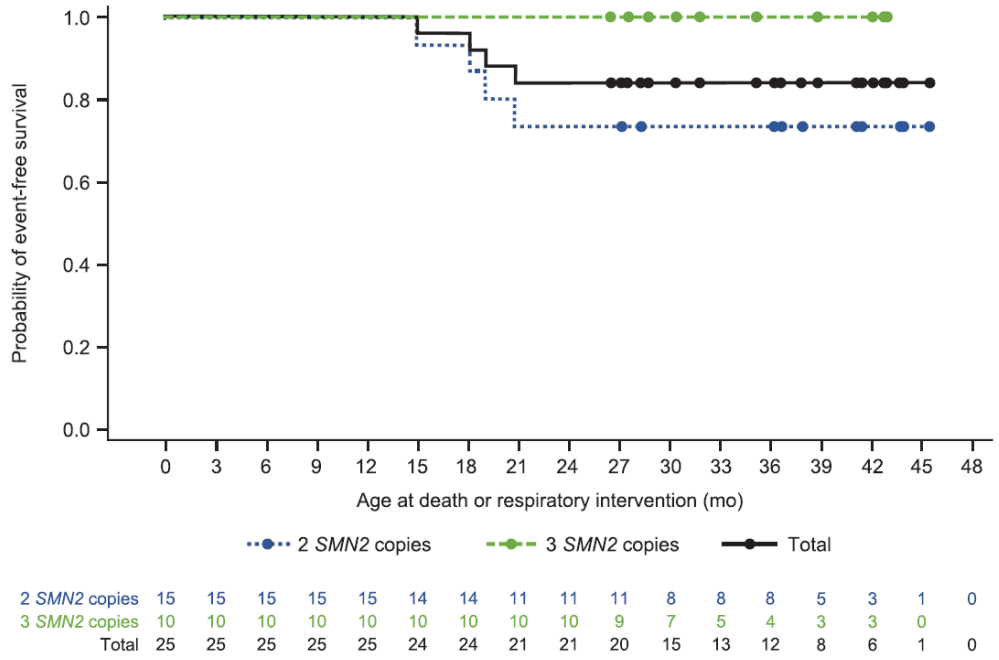


Fig. 2. Kaplan–Meier plot for age at death or respiratory intervention.[a]
SMN2, survival motor neuron 2.
No participants have died or required tracheostomy or permanent ventilation (defined as ≥16 h/day continuously for >21 days in the absence of an acute reversible event or tracheostomy).
[a]Respiratory intervention was defined as ventilator use for ≥6 h per day for ≥7 days or tracheostomy.

- Dosing onset <6 weeks
- 100% sitting
- 92% walking with assistance
- 88% walking independently
- No permanent ventilation

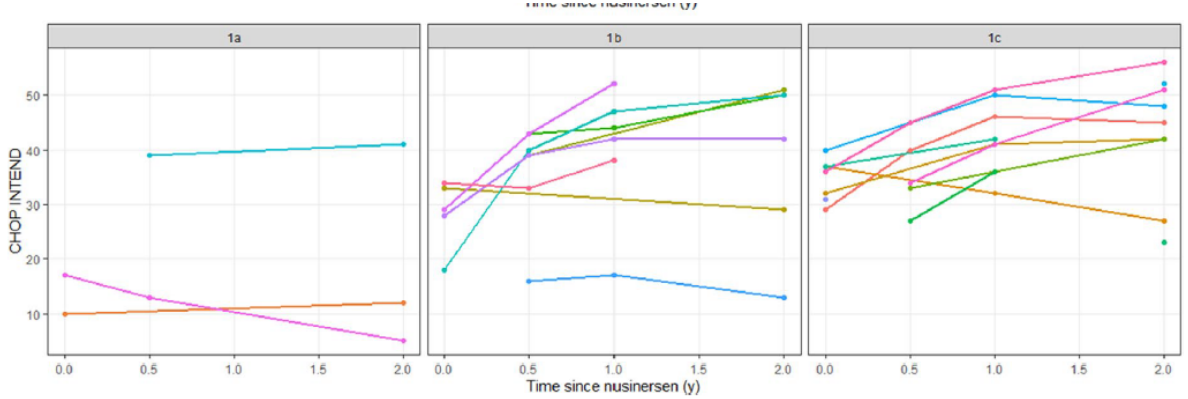
De Vivo et al Neuromuscul Disord. 2019 Sep 12.

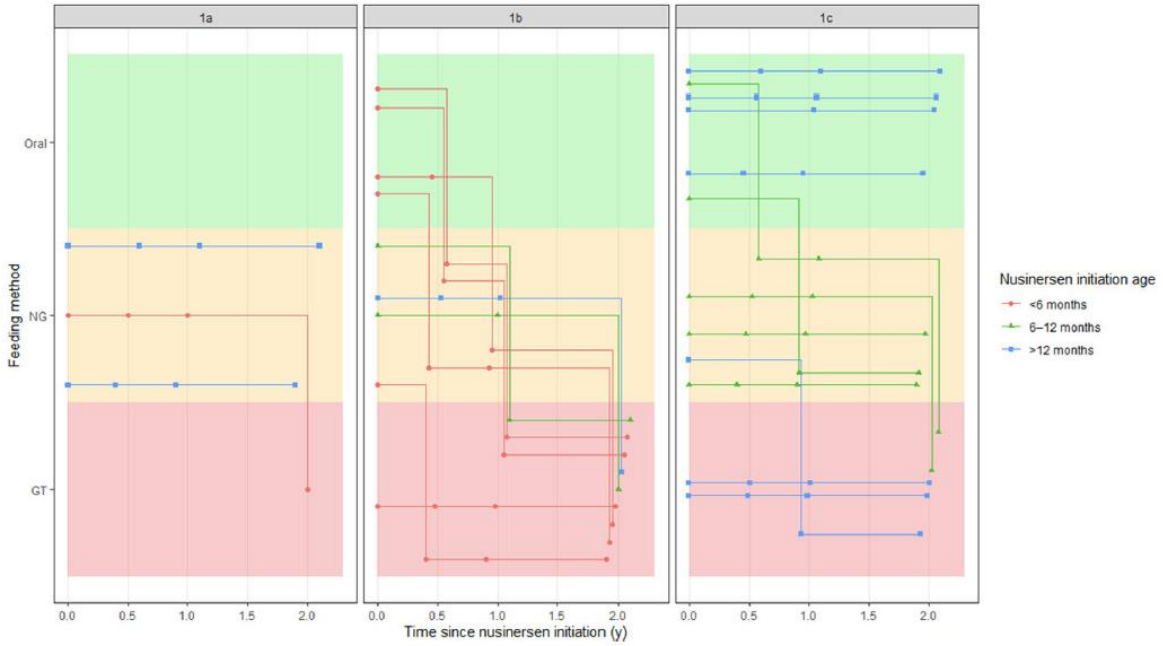
ORIGINAL ARTICLE **Open Access 2022**

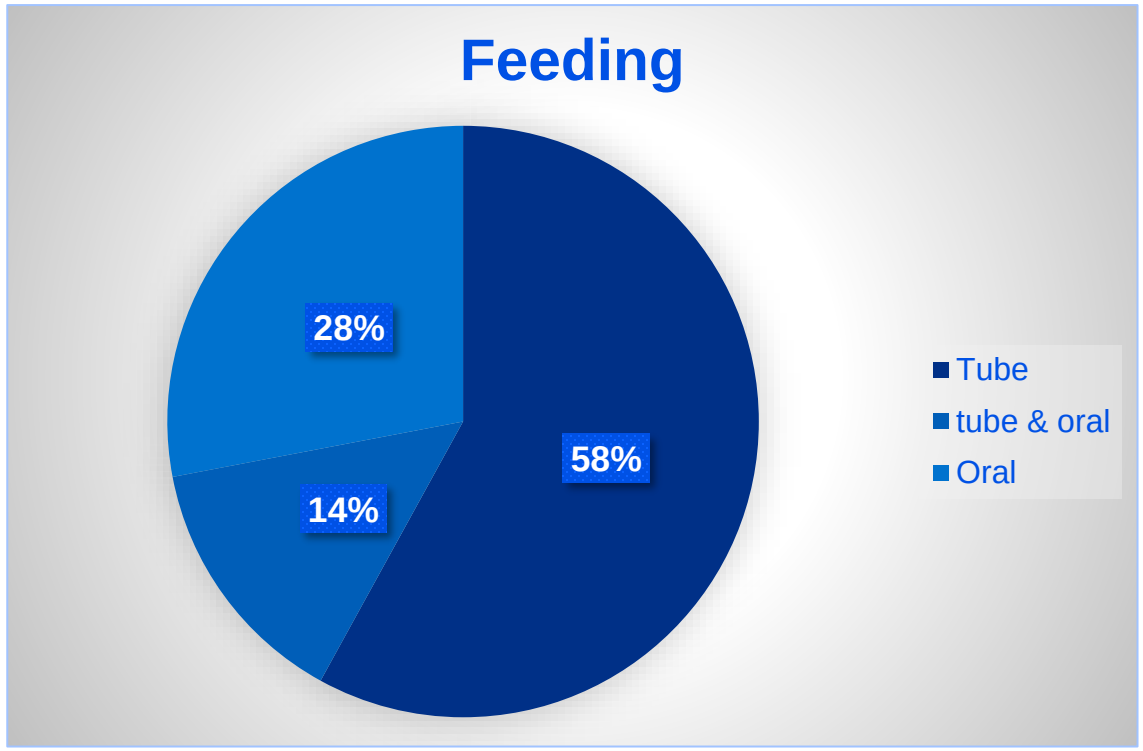
Evolution of bulbar function in spinal muscular atrophy type 1 treated with nusinersen

Harriet Weststrate, Georgia Stimpson, Lily Thomas, Mariacristina Scoto, Emily Johnson, Alexandra Stewart, Francesco Muntoni, Giovanni Baranello, Eleanor Conway, SMA p-FOIS Working Group*

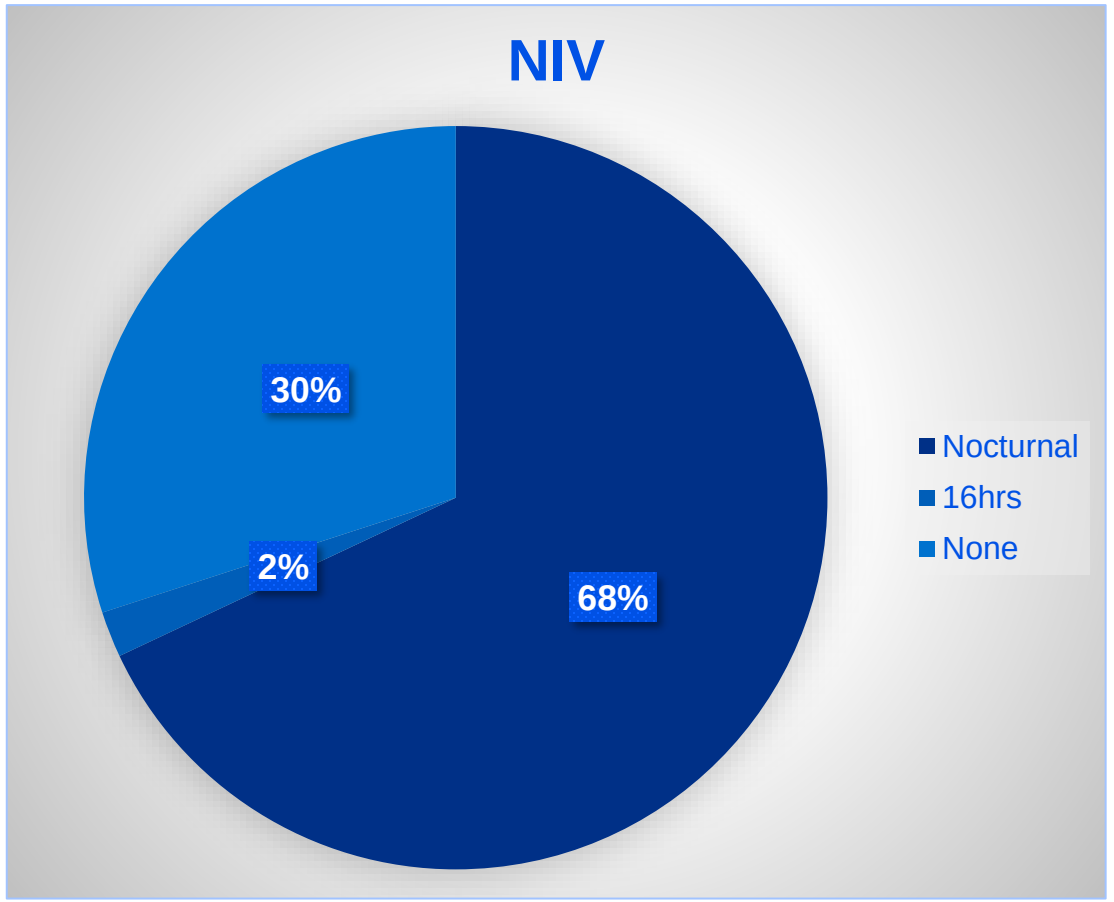
24 months after initiation, *n*	24
NIV use[a]	21 (88)
None[a]	3 (13)
As needed[a]	2 (8)
Nocturnal use[a]	14 (58)
>16 hours/day[a]	5 (21)







Feeding & NIV in 50 nusinersen treated SMA1 patients referred to NMDT
Age: 3m-6y5m
Nusinersen injections: 2-19



Nusinersen – reported side effects

- Low platelets
- Renal impairment
- **Risk of Hydrocephalus**
  - A small number of cases of hydrocephalus were picked up via the ‘reporting side effects’ systems in place; most cases developed after 2 to 4 loading doses.
  - discuss this risk with parents considering the treatment.
- LP side effects

Risdiplam

Oral administered

Small molecule, modifies SMN2 pre-mRNA splicing

Risdiplam

- Firefish
  - SMA 1
  - Aged 1-7 months
- Sunfish
  - SMA 2 & 3
- Jewelfish
  - SMA 1, 2 & 3
  - Some previously treated with nusinersen or zolgensma
- Rainbowfish
  - Presymptomatic
  - Up to 6 weeks

Risdiplam

- Firefish
  - SMA 1
  - Aged 1-7 months

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risdiplam in Type 1 Spinal Muscular Atrophy

Giovanni Baranello, M.D., Ph.D., Basil T. Darras, M.D., John W. Day, M.D., Ph.D., Nicolas Deconinck, M.D., Ph.D., Andrea Klein, M.D., Riccardo Masson, M.D., Eugenio Mercuri, M.D., Ph.D., Kristy Rose, Ph.D., Muna El-Khairi, Ph.D., Marianne Gerber, Ph.D., Ksenija Gorni, M.D., Ph.D., Omar Khwaja, M.D., Ph.D., Heidemarie Kletzl, Ph.D., Renata S. Scalco, M.D., Ph.D., Timothy Seabrook, Ph.D., Paulo Fontoura, M.D., Ph.D., and Laurent Servais, M.D., Ph.D., for the FIREFISH Working Group*

- 7 out of 17 (41%) able to sit without support for at least five seconds, compared to 0% of untreated infants (natural history data).
- 11 (65%) able to sit (with or without support),
- 9 (53%) achieved upright head control (assessed by HINE-2)
- 1 (6%) achieved the milestone of standing (supporting own weight).
- 10 out of 17 (59%) achieved a CHOP-INTEND total score of 40 points or more.

- After 16 months of treatment, no infant required tracheostomy or reached permanent ventilation
- 86% (18/21) of all infants were event-free after receiving risdiplam for 16 months.

Risdiplam

- Firefish
  - SMA 1
  - Aged 1-7 months

- Sunfish
  - SMA 2 & 3

51 SMA II or III,
43 completed motor assessments to 12 m
58% improvement of at least 3 points
2-11 y 71%,
12-25 y 42%

At least stabilization of motor function
Ongoing

- Jewelfish
  - SMA 1, 2 & 3
  - Some previously treated with nusinersen or zolgensma

- Rainbowfish
  - Presymptomatic
  - Up to 6 weeks

12 enrolled, 5 completed 12 mo FU

All 5 feeding orally, 4 walking independently

Reported side effects

- **Common or very common**
  - Arthralgia; cystitis; diarrhoea; fever; headache; hyperpyrexia; increased risk of infection; nausea; oral ulceration; skin reactions

- **Conception and contraception**
  - Females of childbearing potential should use highly effective contraception during treatment and for at least 1 month after last treatment; male patients should use highly effective contraception during treatment and for at least 4 months after last treatment if their partner is of childbearing potential.
  - Male fertility may be impaired during treatment; sperm degeneration and reduced sperm numbers in *animal* studies.

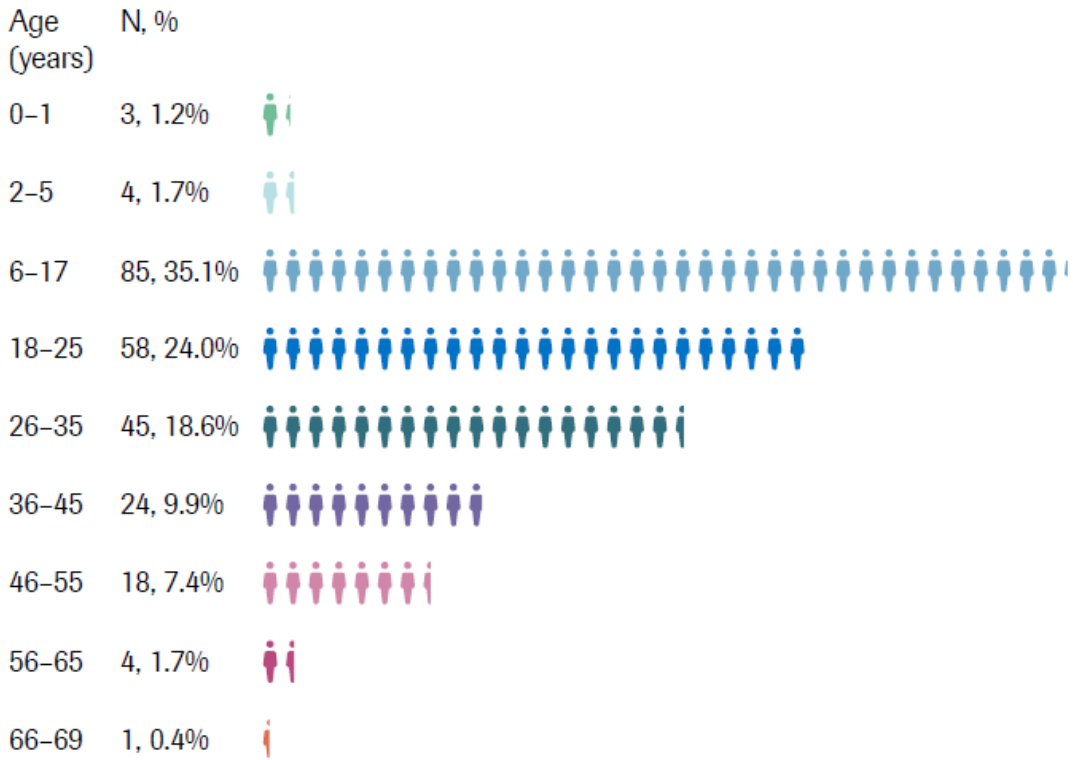
Risdiplam EAMS

- Clinical diagnosis of SMA type 1, 2, or 3
- Pre-symptomatic of SMA and has been confirmed to have SMA via genetic testing and has one to four SMN2 copies
- Risdiplam is used as a monotherapy
- Must not have had successful treatment with onasemnogene abeparvovec.
- No permanent ventilation
- Mandated data items have been collected prior to starting treatment within this MAA
- Patient/carer has signed the ‘Managed Access Patient Agreement’ and agreed to the associated monitoring, clinical assessments and sharing of data for the purpose of the MAA

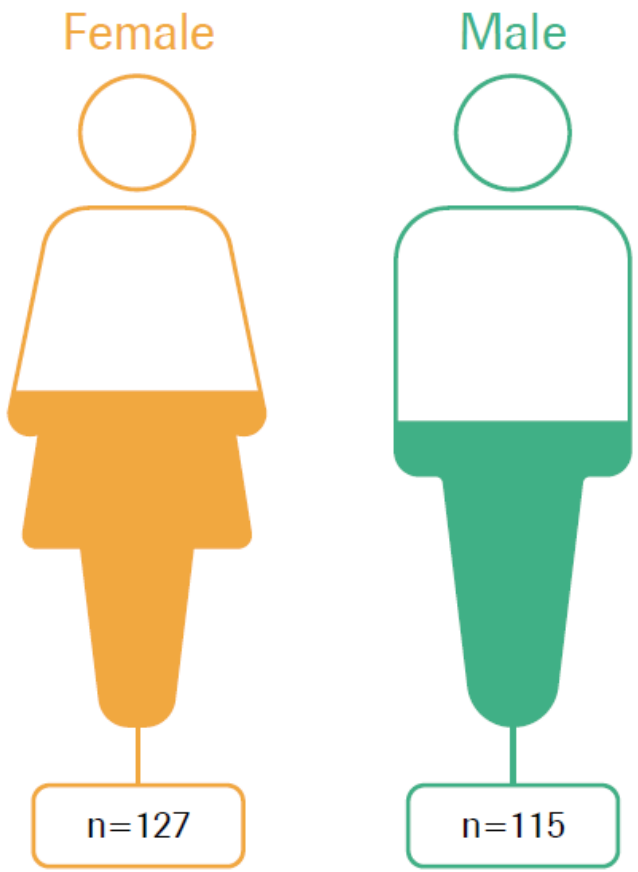
Patient Demographics – Age and Gender Distribution

At the time of analysis in December 2021:

- 4 (1.7%) patients were <3 years old
- 88 (36.4%) patients were 3–17 years old
- 150 (62.0%) patients were 18–69 years old



The proportion of male (47.5%) and female (52.5%) patients was well-balanced.



Roche

Onasemnogene abeparvovec

IV administration

One dose

Onasemnogene abeparvovec

- non-replicating recombinant adeno-associated virus serotype 9 (AAV9) based vector containing the cDNA of the human SMN gene under the control of the cytomegalovirus enhancer/chicken-β-actin-hybrid promoter.
- Single IV infusion
- Therapeutic indication
  - patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or
  - patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene
- Dose 1.1×10^{14} vg/kg

Pre-infusion

- AAV9ab (<1:50)
- FBC, LFTs, Creatinine, Troponin I
- Start prednisolone 24hrs before infusion

Post-infusion monitoring

- FBC, LFTs, Troponin, creatinine
- Weekly 1 month, 2 weekly months 2-3
- Prednisolone 1mg/kg 1 month, weaned if bloods normal

Adverse Effects

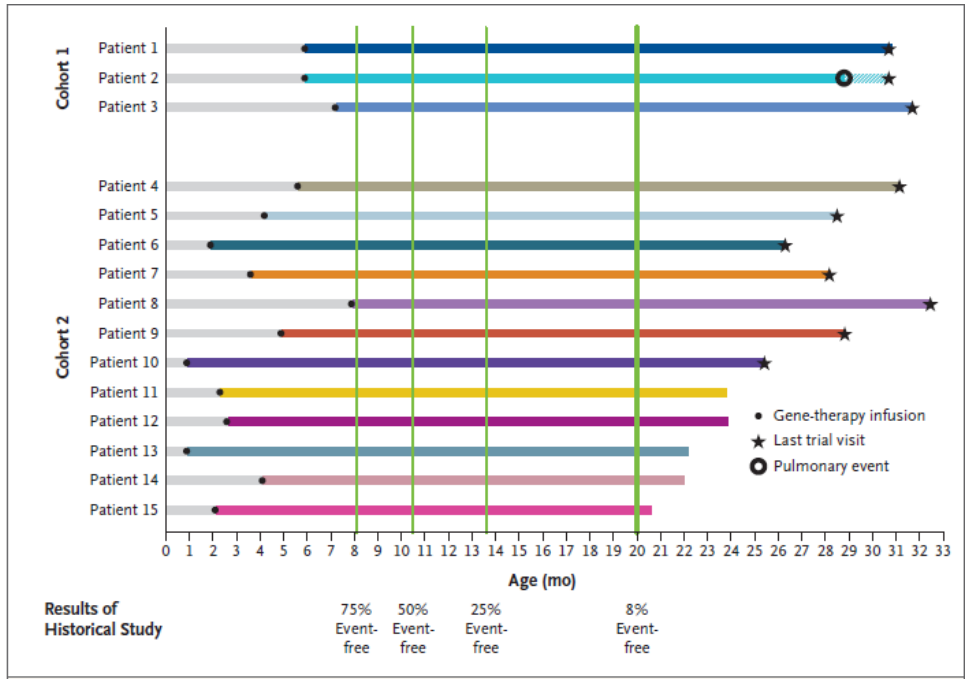
- Pyrexia, vomiting
- Thrombocytopenia 1st week
- Transaminitis

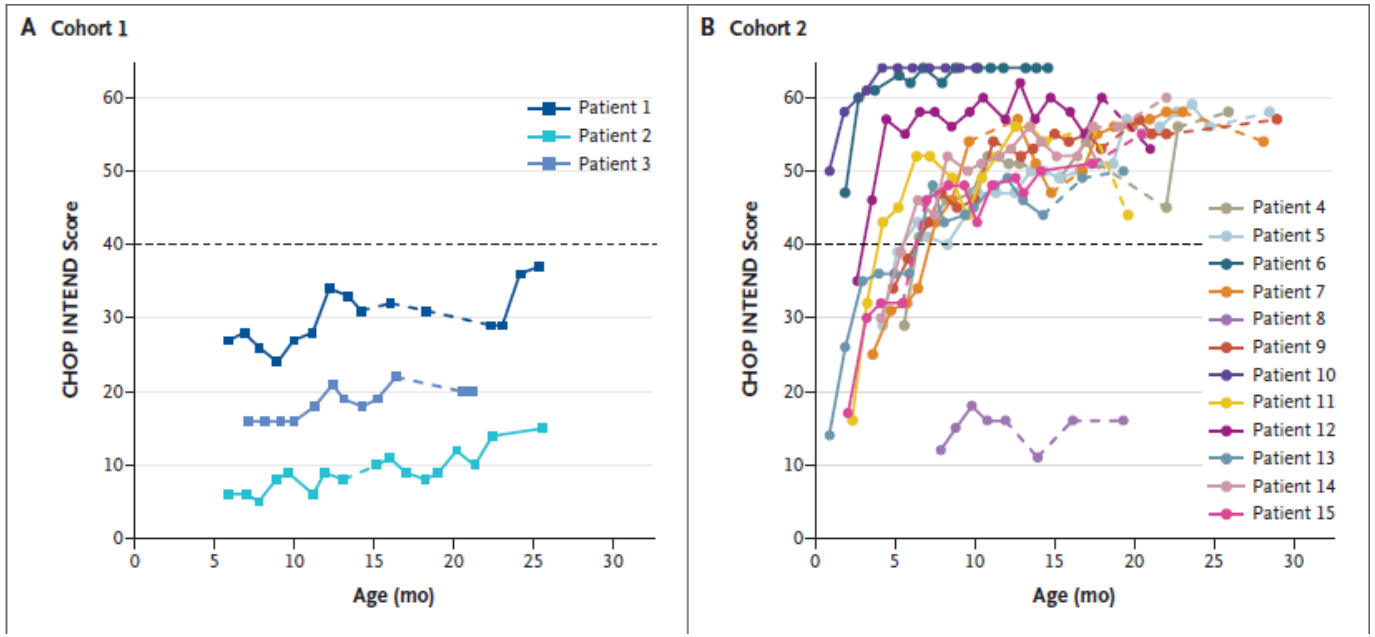
Thrombotic Microangiopathy Following Onasemnogene Abeparvovec for Spinal Muscular Atrophy: A Case Series

Deepa H. Chand, MD[1,2], Craig Zaidman, MD[2], Kapil Arya, MD[3], Rachel Millner, MD[3], Michelle A. Farrar, MBBS[4], Fiona E. Mackie, MBBS[4], Natalie L. Goedeker, CPNP[2], Vikas R. Dharnidharka, MD[2], Raja Dandamudi, MD[2], and Sandra P. Reyna, MD[1]

Spinal muscular atrophy is treated with onasemnogene abeparvovec, which replaces the missing *survival motor neuron 1* gene via an adeno-associated virus vector. As of July 1, 2020, we had identified 3 infants who developed thrombotic microangiopathy following onasemnogene abeparvovec. Early recognition and treatment of drug-induced thrombotic microangiopathy may lessen mortality and morbidity. *(J Pediatr 2020; ■:1-4).*

START open label – 2014-2017





- Primary outcome : safety
- Secondary outcome time to death/permanent ventilation
- Exploratory outcomes motor milestones, CHOP-INTEND

- 56 SAEs
- 2 treatment related, abnormal LFTs

Table 2. Event-free Survival and Motor and Other Milestones among the 12 Patients in Cohort 2.*

Variable	Age at Study Entry	Event-free Survival†	Motor Milestones							Other Achievements			
			Brings Hand to Mouth	Controls Head	Rolls Over‡	Sits with Assistance	Sits Unassisted§			Speaks	Swallows	No NIV Use	No Nutritional Support¶
	mo						*≥5 sec*	*≥10 sec*	*≥30 sec*				
Patient no.													
4	5.6	31.1	+	+	+	+	+			+	+		
5	4.2	28.5	+	+	+	+	+	+	+	+	+	+	+
6	1.9	26.1	+	+	+	+	+	+	+	+	+	+	+
7	3.6	28.1	+	+	+	+	+	+		+	+	+	
8	7.9	32.4	+										
9	4.9	28.9	+	+	+	+	+	+	+	+	+	+	+
10	0.9	25.3	+	+	+	+	+	+	+	+	+	+	+
11	2.3	23.8	+	+	+	+	+	+	+	+	+		
12	2.6	23.9	+	+	+	+	+	+	+	+	+	+	+
13	0.9	22.1	+	+		+	+	+	+	+	+		
14	4.1	22.0	+	+	+	+	+	+	+	+	+	+	+
15	2.1	20.6	+	+		+	+	+	+	+	+		
Patients with outcome (%)													
This study		100	100	92	75	92	92	83	75	92	92	58	50
Natural-history studies		8 by 20 mo‖	NA	0	0**	0**	0**	0**	0**	NA	NA	NA	8 by 20 mo‖

5 year outcome

JAMA Neurology | Original Investigation

Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy

Jerry R. Mendell, MD; Samiah A. Al-Zaidy, MD; Kelly J. Lehman, MSN; Markus McColly, BA; Linda P. Lowes, PT, PhD; Lindsay N. Alfano, PT, DPT; Natalie F. Reash, PT, DPT; Megan A. Iammarino, PT, DPT; Kathleen R. Church, MSW; Aaron Kleyn, PhD; Matthew N. Meriggioli, MD; Richard Shell, MD

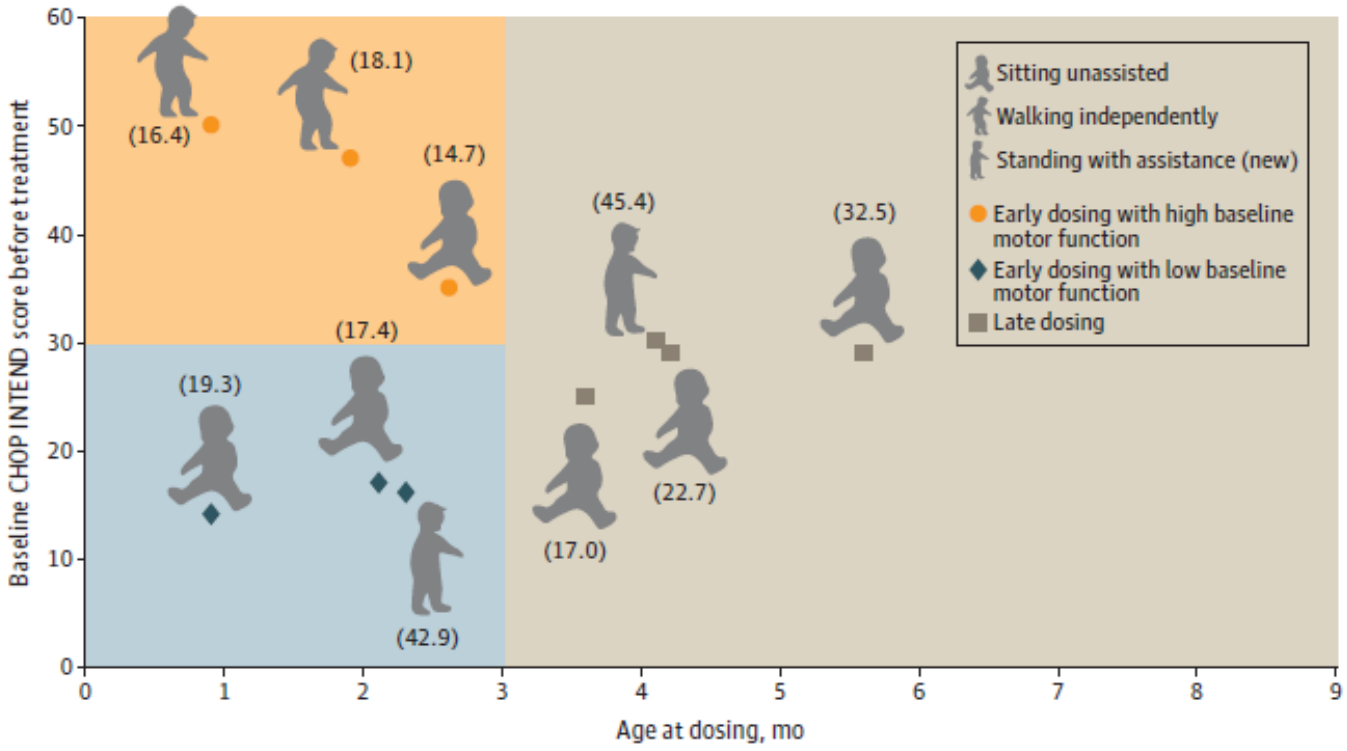
JAMA Neurol. doi:10.1001/jamaneurol.2021.1272
Published online May 17, 2021.

Table 3. Follow-up Times Since Dosing, Ages at Dosing, and Current Patient Ages

Variable	Low-dose cohort (n = 3)	Therapeutic-dose cohort (n = 10)	All (N = 13)
Age at dosing, y			
Mean (SD)	0.5 (0.1)	0.3 (0.1)	0.3 (0.2)
Median (range)	0.5 (0.5-0.6)	0.2 (0.1-0.5)	0.3 (0.1-0.6)
Age on June 11, 2020, y			
Mean (SD)	6.5 (0.2)	5.2 (0.5)	5.5 (0.7)
Median (range)	6.4 (6.4-6.7)	5.0 (4.7-6.1)	5.5 (4.7-6.7)
Time since dosing as of June 11, 2020, y			
Mean (SD)	6.0 (0.2)	5.0 (0.4)	5.2 (0.6)
Median (range)	5.9 (5.8-6.2)	4.8 (4.6-5.6)	5.2 (4.6-6.2)

5 year outcome

Figure 2. Greatest Development Milestones Achieved During the START Long-term Follow-up Study



SAEs
8 patients : 1 cohort 1, 7 cohort 2
Most common acute respiratory failure, pneumonia, respiratory distress, bronchiolitis

STR1VE US/EU <6 months, 1-2 SMN2

Lancet Neurol 2021;20:284-293. Day et al
Lancet Neurol 2021;20:832-841. Mercuri et al

STR1VE US	N=22	PNCR n=23
Sitting ≥30sec by 18 months	13	0
Survival without permanent ventilation	20	6
22 @least 1 AE, 3SAEs 2 transaminitis, 1 hydrocephalus		

STR1VE EU	N=33 ITT=32	PNCR n=23
Sitting ≥10 sec by 18 months	14	0
Survival without permanent ventilation	31	6
32 @least 1AE, 9 transaminitis, 1 death HIE secondary to RTI		

SPR1NT
Pre-symptomatic 2 SMN2 n=14

Skill achieved	Number	Within normal dev window
Sitting ≥30sec	14	11
Standing ≥3sec	11	7
Walking independently	9	5
No patient required ventilation support at any point		

SMART
8.5-21kg
STRONG
Type 2, intrathecal
STEER
Type 2, intrathecal
2-18 yrs

Strauss KA, *et al.* Oral presentation. Presented at EAN 2021, 19–22 June 2021. 2. Strauss KA, *et al.* Abstract. Presented at EAN 2021, 19–22 June 2021.

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01866-4

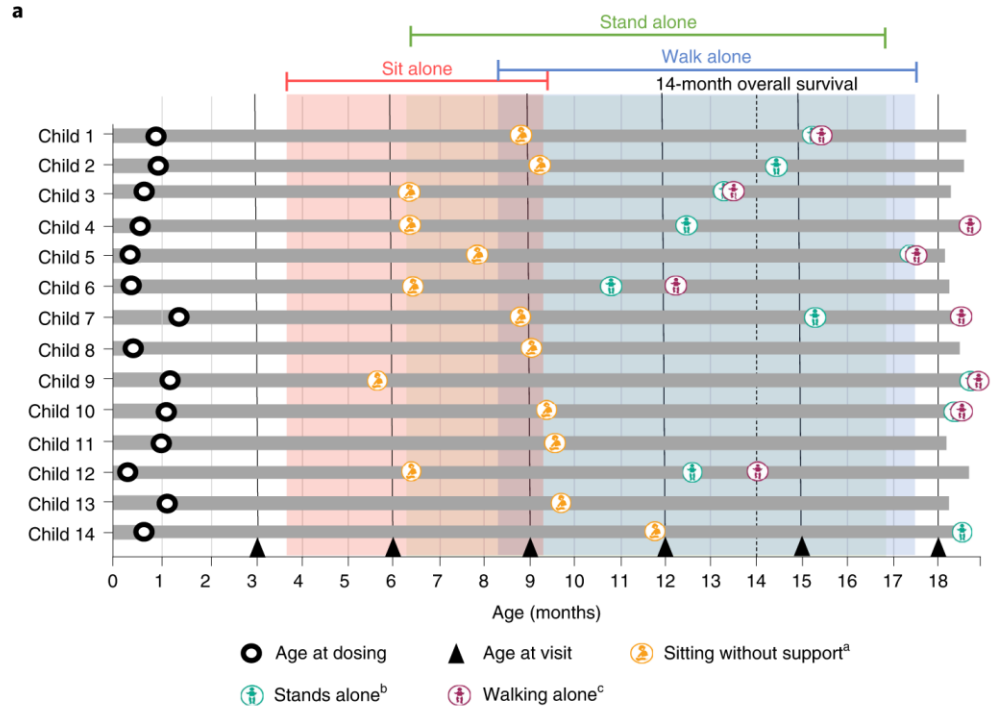
Check for updates

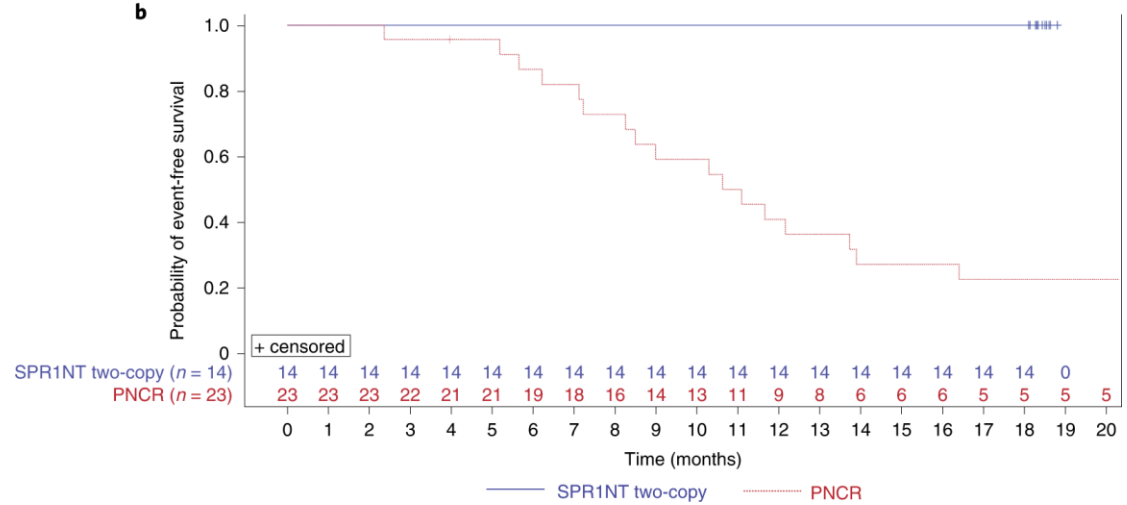
OPEN

Onasemnogene abeparvovec for presymptomatic infants with two copies of *SMN2* at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial

Kevin A. Strauss[1,2,3]✉, Michelle A. Farrar[4,5], Francesco Muntoni[6,7], Kayoko Saito[8], Jerry R. Mendell[9,10], Laurent Servais[11,12], Hugh J. McMillan[13], Richard S. Finkel[14,15], Kathryn J. Swoboda[16], Jennifer M. Kwon[17], Craig M. Zaidman[18], Claudia A. Chiriboga[19], Susan T. Iannaccone[20], Jena M. Krueger[21], Julie A. Parsons[22], Perry B. Shieh[23], Sarah Kavanagh[24], Sitra Tauscher-Wisniewski[24], Bryan E. McGill[25] and Thomas A. Macek[24]

SPR1NT (NCT03505099) was a Phase III, multicenter, single-arm study to investigate the efficacy and safety of onasemnogene abeparvovec for presymptomatic children with biallelic *SMN1* mutations treated at ≤6 weeks of life. Here, we report final results for 14 children with two copies of *SMN2*, expected to develop spinal muscular atrophy (SMA) type 1. Efficacy was compared with a matched Pediatric Neuromuscular Clinical Research natural-history cohort ($n = 23$). All 14 enrolled infants sat independently for ≥30 seconds at any visit ≤18 months (Bayley-III item #26; $P < 0.001$; 11 within the normal developmental window). All survived without permanent ventilation at 14 months as per protocol; 13 maintained body weight (≥3rd WHO percentile) through 18 months. No child used nutritional or respiratory support. No serious adverse events were considered related to treatment by the investigator. Onasemnogene abeparvovec was effective and well-tolerated for children expected to develop SMA type 1, highlighting the urgency for universal newborn screening.





Which is best?

Systematic Review

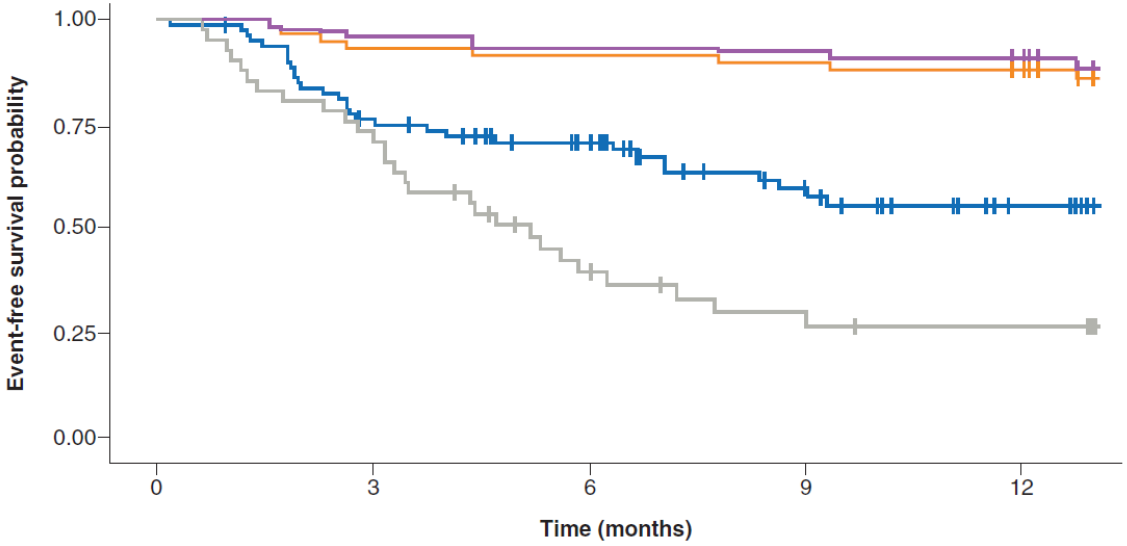
For reprint orders, please contact: reprints@futuremedicine.com

How does risdiplam compare with other treatments for Types 1–3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison

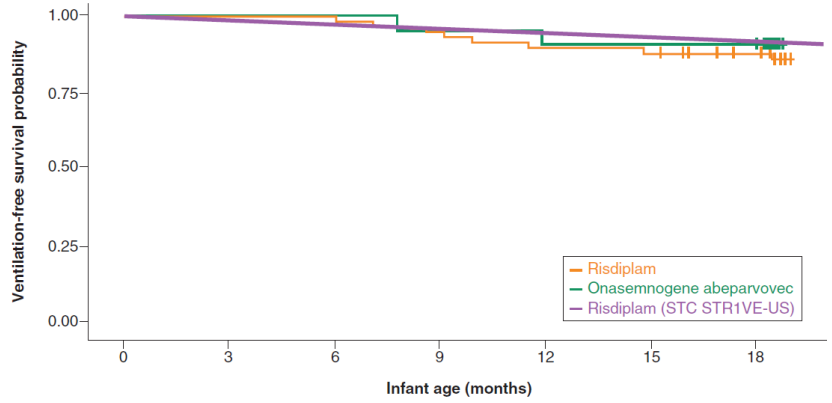
Journal of Comparative Effectiveness Research

Valerie Aponte Ribero*,[1], Monica Daigl[1], Yasmina Marti[1], Ksenija Gorni[2], Rachel Evans[3], David Alexander Scott[3], Anadi Mahajan[4], Keith R Abrams[1,3] & Neil Hawkins[1,3]

[1]Global Access, F. Hoffmann-La Roche Ltd, 4070, Basel, Switzerland
[2]PDMA Neuroscience and Rare Disease, F. Hoffmann-La Roche Ltd, 4070, Basel, Switzerland
[3]Visible Analytics, Oxford, OX2 0DP, UK
[4]Bridge Medical Consulting Ltd., Richmond, London, TW9 2SS, UK
*Author for correspondence: valerie.aponte_ribero@roche.com
‡Authors contributed equally



Treatment (study)	Number at risk				
Risdiplam	58	54	53	52	50
Risdiplam re-weighted	44	43	41	41	40
Nusinersen	80	59	46	29	16
BSC	41	30	14	9	7



Treatment (study)	Number at risk						
Risdiplam	58	58	58	55	52	51	45
Onasemnogene abeparvovec	22	22	22	21	20	20	20

Conclusion

SMA1 MAIC showed significant improvement in survival & motor function & reduced likelihood SAEs with risdiplam v nusinersen

Due to differences in study population no conclusion for risdiplam v OA in SMA1 or risdiplam v nusinersen in SMA2&3

Onasemnogene abeparvovec in UK

Onasemnogene abeparvovec in UK

1 Recommendations

1.1 Onasemnogene abeparvovec is recommended as an option for treating 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of type 1 SMA in babies, only if:

- they are 6 months or younger, or
- they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team.

It is only recommended for these groups if:

- permanent ventilation for more than 16 hours per day or tracheostomy is not needed
- the company provides it according to the commercial arrangement (see section 3).

1.2 For babies aged 7 to 12 months, the national multidisciplinary team should develop auditable criteria to enable onasemnogene abeparvovec to be allocated to babies in whom treatment will give them at least a 70% chance of being able to sit independently.

1.3 Onasemnogene abeparvovec is recommended as an option for treating presymptomatic 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies, only if the conditions in the managed access agreement are followed.

- The terms of the deal mean that some young children that currently fall outside the NICE recommendation criteria will also be eligible to be considered for treatment by a national multidisciplinary clinical team (MDT) made up of the country's leading experts in the treatment of SMA.

Zolgensma NMDT

- 3 members from each centre
  - 1 consultant neuromuscular specialist
  - 1 specialist neuromuscular paediatric physiotherapist
  - one other member of the clinical MDT
- ATMP pharmacist
- RNMC representative
- SMA expert
- Centres Chair for 12 months in turn
- Weekly meetings since 18/05/2021
- Referral portal

NMDT tasks

- Clarification of wording of NICE recommendation
- Establish group, ToR, meetings
- Referral system - work on portal & establish interim system
- Establish database for recording referrals, decisions, centre allocation, dates of treatment
- Policies – vaccination, RSV prophylaxis
- Communication with RNMCs
- Regular communication with SMAUK
- Census

How many patients – Survey 1

Category	Number
Pre-symptomatic	1
< 7 mo treatment naïve	2
<7 mo treated	6
7-12 mo treatment naïve	1
7-12 mo treated	10
>13 mo <13.5kg treated	32
>13 mo >13.5 kg treated	41
>13 mo treatment naïve	1
Total	94

NMDT tasks

- Clarification of wording of NICE recommendation
- Establish group, ToR, meetings
- Referral system - work on portal & establish interim system
- Establish database for recording referrals, decisions, centre allocation, dates of treatment
- Communication with RNMCs
- Regular communication with SMAUK
- Census
- Prioritisation of cases

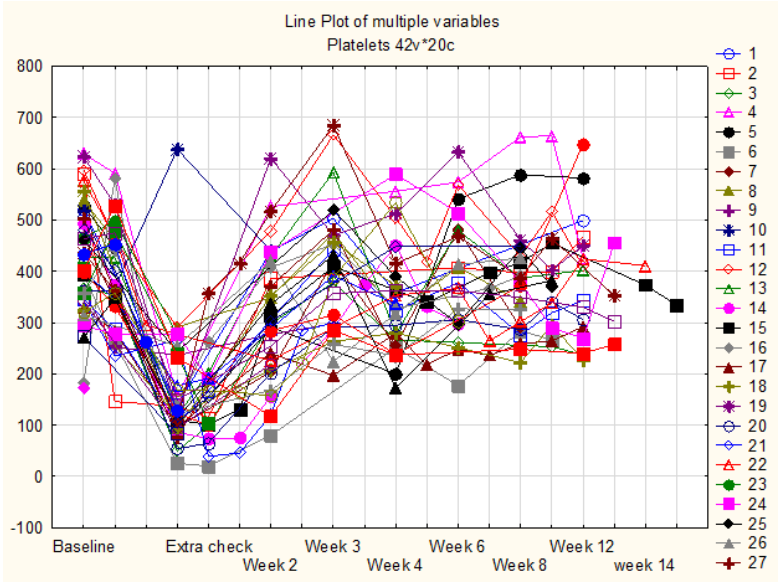
Invitations for referral

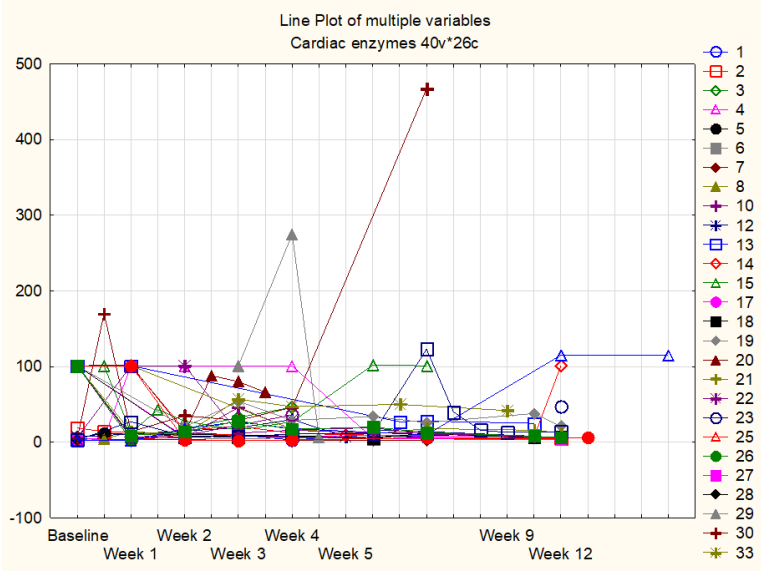
Group	Date
Incident cases	
≥6 mo <7mo, ≥12 mo <13mo	09/06/2021
< 7 mo	15/06/2021
≥ 7 mo <13 mo	22/06/2021
≥13 mo <18mo <13.5kg	05/08/2021
≥18 mo <24 mo <13.5kg	31/08/2021
<30 mo <13.5kg	14/09/2021
Any age <13.5kg	21/09/2021
Any age <15kg	16/11/2021
≥15kg <18kg	19/01/2022

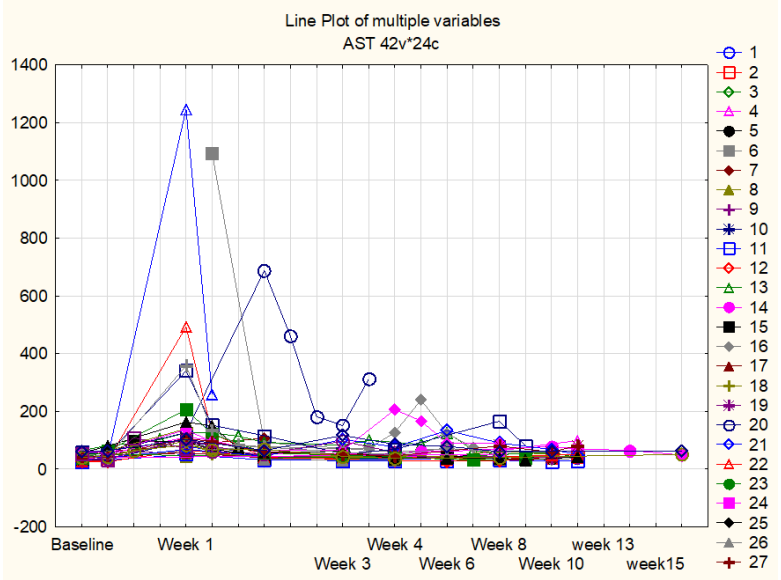
Recurring themes

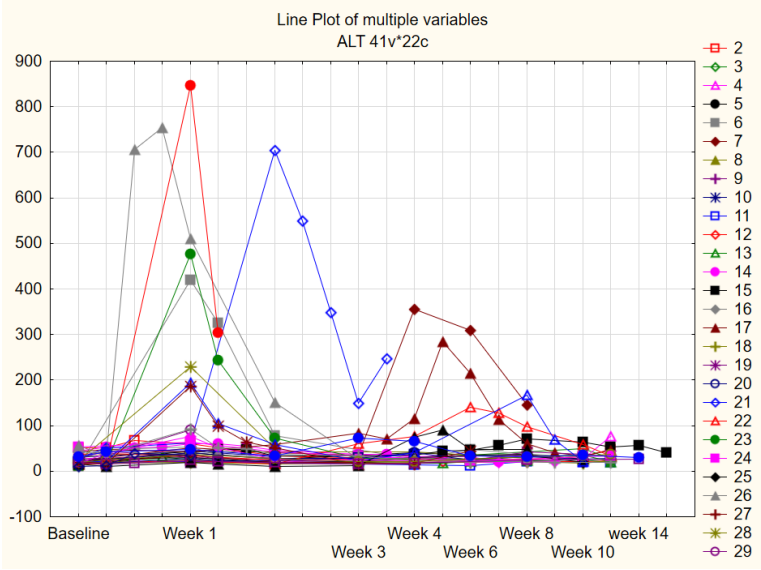
- Practical problems
  - Venous access
  - Delays because of illness

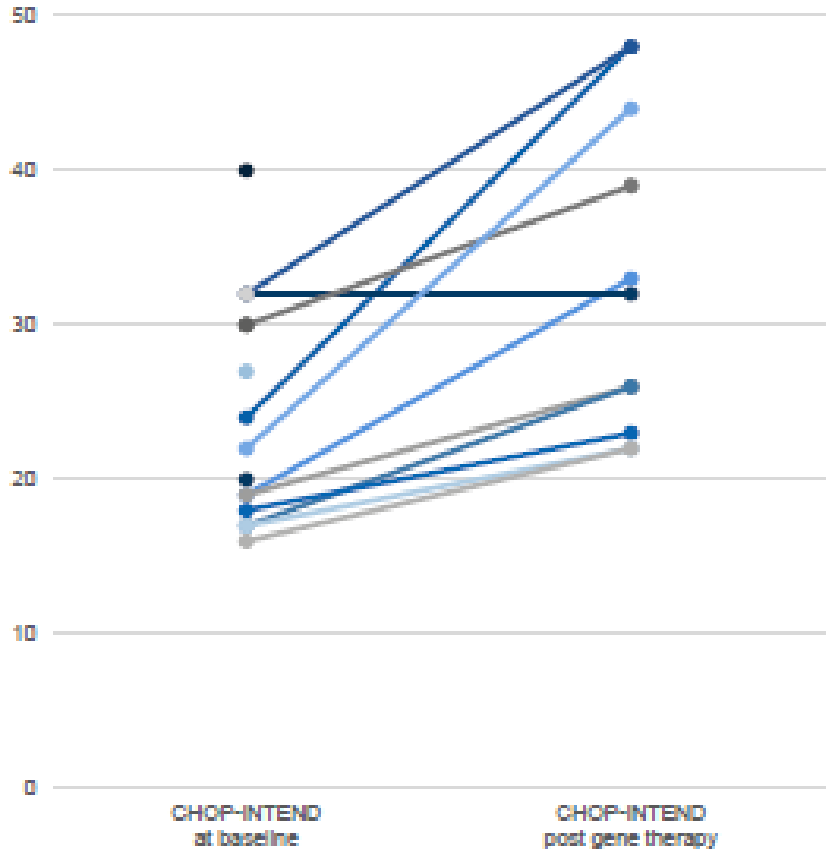
- Adverse events
  - Pyrexia, vomiting 48-72 hrs
  - Thrombocytopenia
  - Transaminitis
  - Hydrocephalus (1)

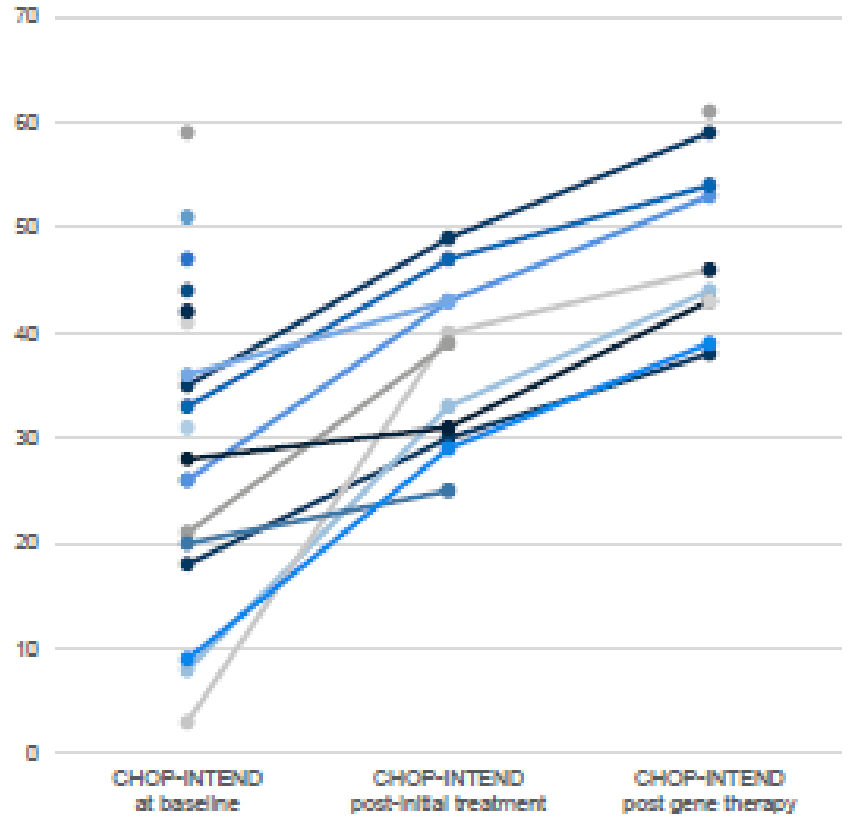

Line Plot of multiple variables
Platelets 42v*20c
800
700
600
500
400
300
200
100
0
-100
Baseline
Extra check
Week 2
Week 3
Week 4
Week 6
Week 8
Week 12
week 14
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27


Line Plot of multiple variables
Cardiac enzymes 40v*26c
500
400
300
200
100
0
-100
Baseline
Week 1
Week 2
Week 3
Week 4
Week 5
Week 9
Week 12
1
2
3
4
5
6
7
8
10
12
13
14
15
17
18
19
20
21
22
23
25
26
27
28
29
30
33


Line Plot of multiple variables
AST 42v*24c
1400
1200
1000
800
600
400
200
0
-200
Baseline
Week 1
Week 3
Week 4
Week 6
Week 8
Week 10
week 13
week15
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27


Line Plot of multiple variables
ALT 41v*22c
900
800
700
600
500
400
300
200
100
0
-100
Baseline
Week 1
Week 3
Week 4
Week 6
Week 8
Week 10
week 14
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29


50
40
30
20
10
0
CHOP-INTEND
at baseline
CHOP-INTEND
post gene therapy


70
60
50
40
30
20
10
0
CHOP-INTEND
at baseline
CHOP-INTEND
post-initial treatment
CHOP-INTEND
post gene therapy

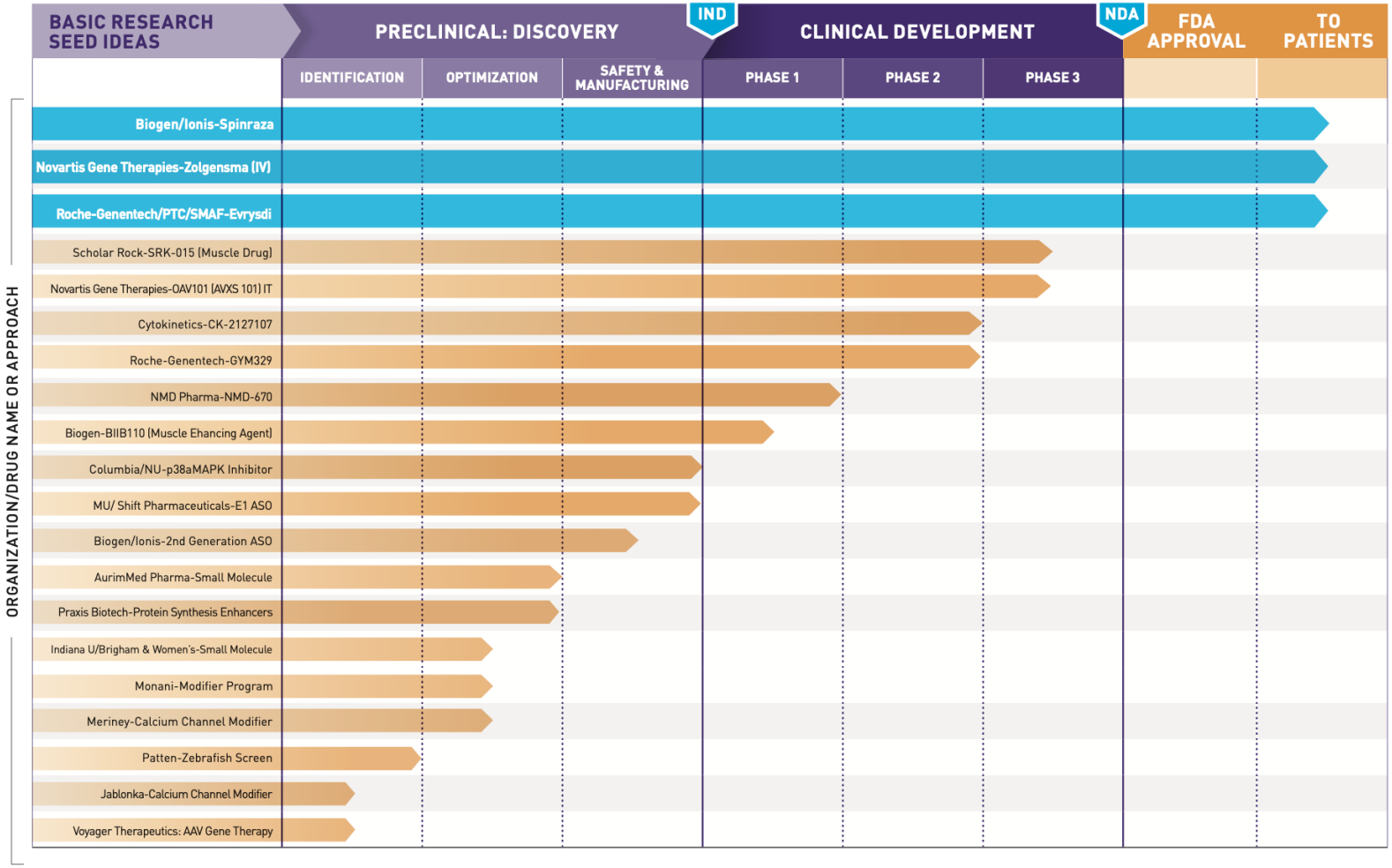
Other Therapeutic Strategies….

- Neuroprotection
  - protect neurons from damage or degradation
- Neural Transmission
  - calcium channel agonists
- Regenerative targets
  - promote axonal growth
  - promote muscle regenerations
- Muscle enhancement
- Genetic modifiers

New treatments

SMA DRUG PIPELINE

We're funding and directing research with more breadth and depth than ever before. We know what we need to do to develop and deliver new therapies, which could also work in combination, to reach our goal of treatments for all ages and types. And we're on the verge of further breakthroughs that will continue to change the course of SMA, and eventually lead to a cure.



Summary

- New treatments have demonstrated efficacy in SMA
- Time to treatment from symptom onset impacts efficacy of treatment in all of these
- A programme for gene replacement therapy for SMA has been successfully implemented in England
- So far no new safety signals have been identified with onasemnogene abeparvovec
- Remaining challenges are delays in diagnosis, changing phenotype and increasing number of patients surviving, at present, with high care requirements

Questions?

Non-success of onasemnogene abeparvovec

(a) **A reduction in motor ability**, defined as:

- Total worsening in scale score corroborated by two consecutive measurements from any two of the following three scales:
- >2 points on horizontal kick or 1 point on other HINE scores excluding voluntary grasp
- >4 points on the CHOP INTEND scale
- >3 points on the RHS scale
- A scaled equivalent of these losses would apply if a domain was unmeasurable / not suitable. These scores are derived from the minimal clinical indicators of difference. For example, if a patient deteriorates on one scale (e.g. loses >3 points on the RHS scale) but maintains stability or demonstrates improvement on another scale that has been measured since baseline (e.g. RULM), the patient's treatment with onasemnogene abeparvovec would be considered to be successful. A treating clinician must refer any case to the NHS England Clinical Panel for advice on non- success in respect of deterioration in scale scores.
- AND/OR
- (b) **A deterioration in respiratory function**, defined as an increasing requirement for respiratory support overnight and/or, for that patient, an uncharacteristic increase in respiratory infections requiring hospital treatment that cannot be accounted for by aspiration or intrinsic lung disease.

Neuromuscular physiotherapy care
Spinal Muscular Atrophy – Changing Phenotypes
Postural management and enhancing function

Mrs S. Warner and Miss E. Davies

Highly Specialised Neuromuscular Physiotherapists

RMCH

Nusinersen: 11 patients

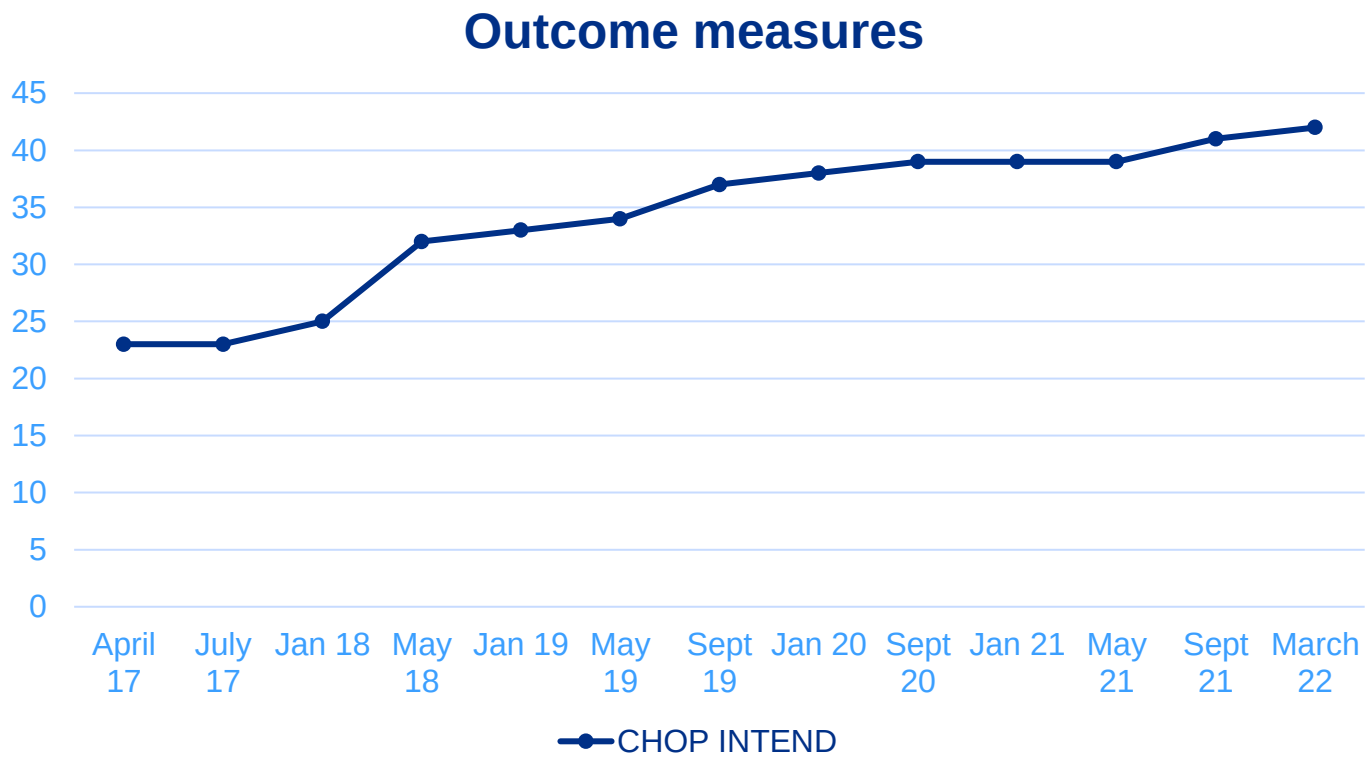
Risdiplam: 8 patients

Zolgensma: >10 patient referrals since July 2021

- All SMA patients receive 6 monthly review minimum
- Increase demand on assessments due to MAA's
- Gene therapy patients – including those out of area
- Supporting community teams
- Airway clearance support
- Considering Rx options to maximise gains from Rx and enable Rx
- Standards of care (2017) advocate a proactive approach to Physiotherapy input

Patient 1
Summary

- SMA Type 1 (with homozygous deletion of exon 7 and 8 of the SMN1 gene and 2 copies of SMN2)
- Current age: 5 years 9 months
- Age at symptom onset: <7 months
- Treatment: Nusinursen – Intrathecal Treatment
- Age at initial treatment: 11 months
- Date of 1st dose of nusinersen: 20/07/2017



Patient 1
Physio input

Initial Physiotherapy assessment observations:

- Antigravity elbow movement
- Could grip items
- Antigravity hip add
- No head control
- Not weight bearing through LL's when supported in standing

Initial Physiotherapy management:

- Stretching
- Referral to orthotics
- Referral for car seat assessments
- Community therapy referral

Patient 1
Ongoing Management

- Standing frame
- Home Seating
- Wheelchair – Manual chair and Wizzybug
- Airway Clearance plan
- Assessment for arm supports
- Spinal Jacket
- Sleep system
- Planning for school

Patient 1
Current Presentation

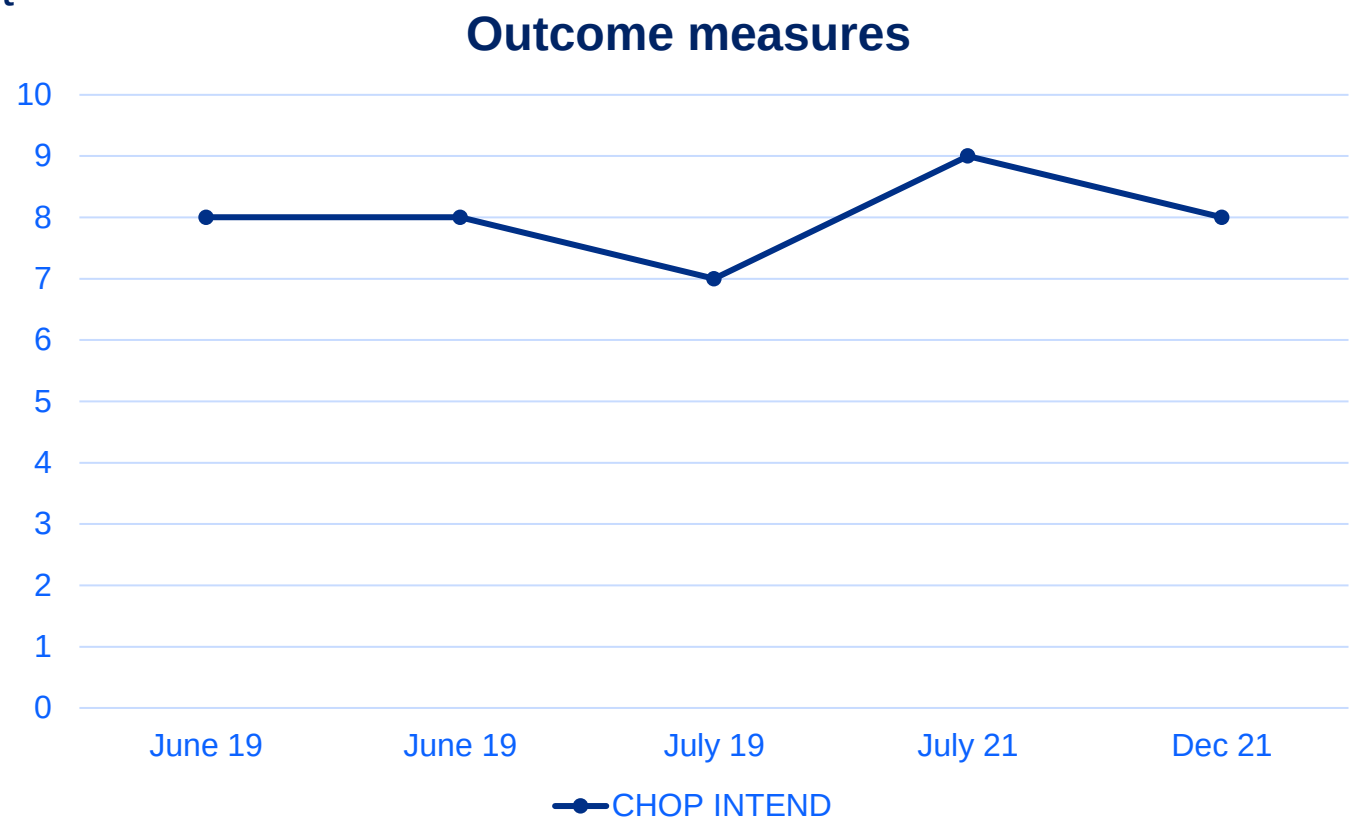
- Gained some head control
- Independent sitting for 3 secs with arms free
- Antigravity hip and knee flexion
- Rolls independently into side lying
- Change of outcome measure due to age and ability/independence – RHS
- Daily prophylactic use of cough assist

Patient 1
Key Learning Points

- Continuing to make improvements with head control and sitting balance
- Postural management - seating, orthotics, standing frame, night time
- Planning with parents - long term goals and managing expectations
- Early planning of home and school environments for future needs
- Consideration of aids to increase participation and independence
    - Wheelchairs
    - Arm supports
    - Use of technology

Patient 2
Summary

- SMA Type 1 (with homozygous deletion of exon 7 and 8 of the SMN1 gene)
- Current age: 3 years 8 months
- Age at symptom onset: by 6/52 health check
- Treatment: Nusinursen – Intrathecal Treatment
- Age at initial treatment: 1 year 3 months
- Date of 1st dose of nusinersen: 05/11/2019



Patient 2
Physio Input

Initial Physiotherapy assessment observations:

- Minimal active movement
- Ankle contractures
- Only able to lie flat
- Dependant on suction for secretion management
- Unable to tolerate cough assist device
- Hypotonic ++, frog legged posture with head preference to R)

Initial Physiotherapy management:

- Stretches
- Orthotics
- Arranged Respiratory Physio assessment as IP with medical support
- OT referral – UL splints
- Community Physiotherapy referral
- Buggy referral

Patient 2
Current Presentation

CHOP-INTEND score stable… However parents and NM team have noticed some positive changes including:

- Tolerating Prophylactic airway clearance plan – cough assist, percussion, suction, nebs
- Improved tolerance of positional changes – side lying, some elevation
- Introduction of some equipment at home – chair, standing frame for short periods
- Increased vocalisation
- Increased peripheral movements

Patient 2
Key learning points

- Challenges in handling, positioning and equipment due to severe weakness
- Globally there are limited experiences with this patient group for all therapists
- Small changes can have a big impact on quality of life
- Empowering parents is key to good outcomes - parents have managed joint range, prophylactic management

Patient 3
Summary

- SMA Type 2 (with homozygous deletion of exon 7 and 8 of the SMN1 gene)
- Current age: 17 years
- Age at diagnosis: 7 months (Older brother known to have SMA)
- Treatment: Risdiplam – Oral treatment
- Treatment commenced: Feb 2021
- Age commencing treatment: 15 years 10 months

Patient 3

Current Presentation

Benefits reported by patient:

- Easier to use mouse and keyboard
- Improved strength when swimming
- Improved trunk movement in sitting

Current Physiotherapy management:

- Liaison with wheelchair services – moulded seat becoming uncomfortable / restrictive with improvements in trunk mobility
- Airway Clearance Plan – cough assist set up
- Advice re: stretching / activity programme to complete with carers

Patient 3
Key Learning Points

- Older patients very good at reporting small changes and benefits of these
- Important to regularly reassess equipment needs
- Consider upcoming transition to adult services and need for ongoing support
- Supporting aspirations for the future

Patient 4
Summary

- SMA Type 1 (with homozygous deletion of exon 7 and 8 of the SMN1 gene and two copies of SMN2)
- Age at symptom onset: By one month of age
- Current age: 30 weeks old
- Treatment : Zolgensma – Gene Therapy
- Age at time of infusion: 10 weeks old
- Date of infusion: 11/02/2022
- Outcome measure: CHOP INTEND

Date completed	10/02/2022 Baseline	18/05/2022 3 months post infusion
Score	30	35

Patient 4
Physio Input

Initial Physiotherapy assessment/observations:

- Knee flexion contractures
- Pattern of movements in UL's
- Trigger finger R)
- Head preference to R)
- NG fed
- Difficulty managing secretions

Initial Physiotherapy management:

- Positioning advice
- Stretching programme
- Early test tape application
- OT referral – UL splinting
- Referral to community services

Patient 4
Upper Limb Elastic Therapeutic Taping

Goals of Taping:

- Influence direction of movement
- To facilitate muscle strength and function
- Promote UL independence

Taping in Paediatrics:

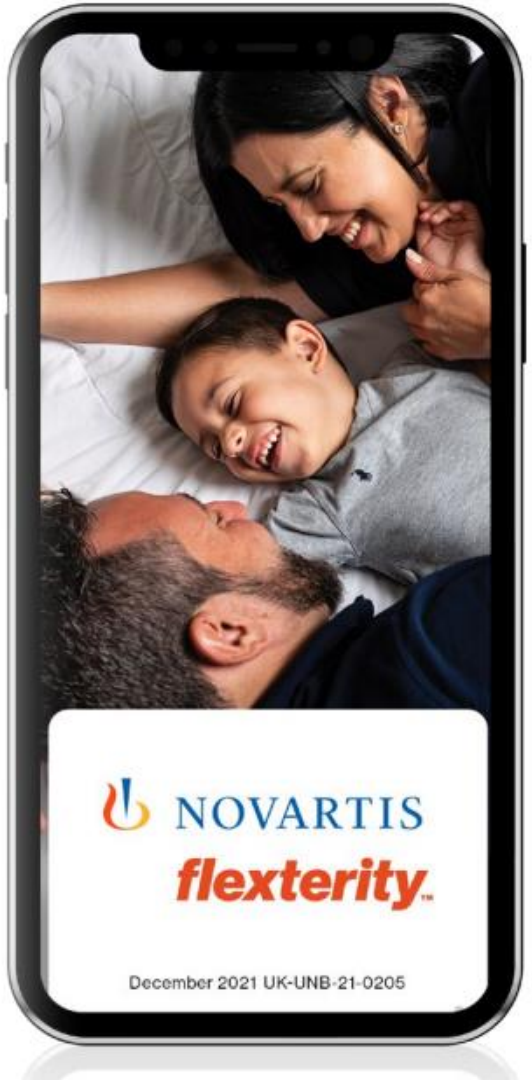
- Complete with caution
- Apply small patch of test tape 48 hrs prior – regular skin checks
- Educate parents re. potential adverse effects
- Skin continues to develop for the first 2 years of life
- Limited evidence in Paediatrics

Patient 4
Upper Limb Elastic Therapeutic Taping

How it works:

- Kinesio tape is made of elastic cotton
- Targeting receptors within the somatosensory system
- Stimulates sensory neurones of the peripheral nervous system
- Provides visual and proprioceptive feedback
- Direction of stretch is key - not amount of stretch (15-25% stretch)
- Tape is rarely the only therapy

Patient 4
Programmes



Download the Flexterity app via Google Play and the App Store

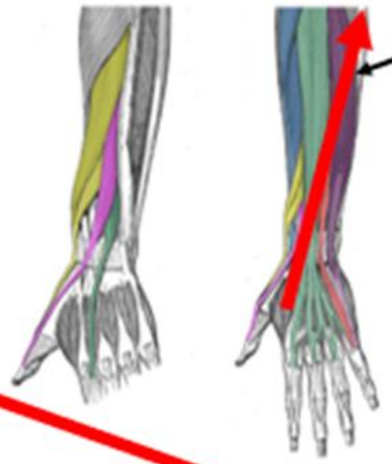
Download on the App Store

GET IT ON Google Play

Taping Instructions for Upper Limbs

Select a piece of tape.

Rip through the paper on the back of the tape, a finger width from the edge. This is going to form your 'anchor'.



The red arrow indicates the direction the tape should be applied.

1.) Starting at the base of the thumb, stick the anchor to the skin.
2.) Peel back the paper and apply tension to the tape, stretching it and sticking it to the skin, up to the elbow. You want to leave a finger width of tape at the end. This is going to be your finish point.
3.) Release the tension and stick the final piece of tape directly to the skin.

NOTE:

You will need two people to complete this. One to apply the tape and one to hold the wrist in a midline/neutral position.

When you have finished, it should look like this.

Patient 4
Key learning points

- Head control – educate parents re: sitting and normal development
- Parents report improved UL movements with taping and splinting
- Empowering parents with stretching / taping programmes that parents can implement at home
- Seating – variable tolerance due to secretions (car seat / buggy)
- Early community input and joint working

Summary

- Changing phenotypes in SMA
- With available treatments, presentation of children and progression of condition is changing
- All children are different and respond differently
- Challenges for Physiotherapy management
- Ongoing learning
- Importance of working together and learning from experiences

Transitioning patient & parent

A young person with SMA gave a short talk discussing their life experience

Discussion

Mrs Sinead Warner

Ms Emily Davies

Dr Gary McCullagh

Close

Dr Gary McCullagh, Consultant Paediatric Neurologist,
Royal Manchester Children’s Hospital