BEST PRACTICES FOR PHYSICAL THERAPISTS & CLINICAL EVALUATORS IN SPINAL MUSCULAR ATROPHY (SMA)

RECOMMENDATIONS TO SUPPORT THE EFFECTIVE CONDUCT OF CLINICAL TRIALS IN SMA

cure SMA
Make today a breakthrough.

DISCLAIMER

The information in this document is provided for informational purposes only. It does not constitute advice on any medical, legal, or regulatory matters, and should not be used in place of consultation with appropriate medical, legal, or regulatory personnel. Receipt or use of this document does not create a relationship between the recipient or user and Cure SMA, the Cure SMA Industry Collaboration, or any other third party. The information included in this document is presented in a summary fashion and may not be exhaustive. The information is being provided as of August 2021 and may no longer be current. Consult guidance from regulatory authorities, study sponsors, and institutional review boards before taking action based on the information in this document.

This document was prepared by Cure SMA and funded by the Cure SMA Industry Collaboration. CURE SMA AND THE CURE SMA INDUSTRY COLLABORATION PROVIDE THIS DOCUMENT “AS IS, WHERE IS” AND WITHOUT WARRANTY OF ANY KIND, EITHER EXPRESS, IMPLIED, OR STATUTORY, INCLUDING BY NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PURPOSE, OR NONINFRINGEMENT. Cure SMA and the Cure SMA Industry Collaboration make no warranty that the document will meet your requirements or be error-free. The users and recipients of this document assume all risk as to the use of the information contained in the document.

The Cure SMA Industry Collaboration is a collaboration of pharmaceutical and biotech companies involved in the development of SMA therapeutics. The objectives of the Cure SMA Industry Collaboration include leveraging the experience, expertise, and resources of pharmaceutical and biotech companies to advance best practices, standards and approaches for development and clinical evaluation of therapeutics; enabling collaborative research; enhancing opportunities to engage health authorities in a patient-focused manner on topics related to drug development and review; sharing pertinent findings for the benefit of the broader scientific and regulatory community and the general public; and reducing patient fatigue through more streamlined and coordinated engagement of the patient and caregiver community.

Authorship & Acknowledgements

This document was prepared by Kristin J. Krosschell[ϕ], PT, DPT, MA, PCS,[1] Sally Dunaway Young, PT[ϕ], DPT,[2] Rosángel Cruz, MA,[3] BS, Allison Mazzella, BS,[3] Fatou Sarr, BA[4], Mary Curry, ND,[3] Ilse Peterson, MPH[4]. We wish to thank the Cure SMA Industry Collaboration for the funding that supported preparation of this document, and the clinical evaluators who contributed input to help ensure that this document would be useful to, and effectively help to support clinical evaluators at clinical trial sites interested in conducting clinical trials in SMA.

The Cure SMA Industry Collaboration (SMA-IC, https://www.curesma.org/sma-industry-collaboration/) was established in 2016 to leverage the experience, expertise, and resources of pharmaceutical and biotechnology companies, as well as other nonprofit organizations involved in the development of spinal muscular atrophy (SMA) therapeutics to more effectively address a range of scientific, clinical, and regulatory challenges. At the time that this was updated, the IC was comprised of our partners at Novartis Gene Therapies, Biogen, Genentech/Roche Pharmaceuticals, Scholar Rock, and SMA Europe. Funding for this work was provided by the 2018, 2019, and 2020 members of SMA-IC including Astellas, Biogen, Cytokinetics Inc., Genentech/ Roche Pharmaceuticals, Novartis Gene Therapies, Novartis, and Scholar Rock, Inc.

---

1 Northwestern University Feinberg School of Medicine

2 Stanford University School of Medicine

3 Cure SMA

4 Faegre Drinker Biddle & Reath LLP

ϕ These authors contributed equally to this work.

Table of Contents

List of Abbreviations

6MWT: Six-Minute Walk Test

9HPT: Nine Hole Peg Test

10MWRT: 10-Meter Walk/Run Test

30STS: 30 Second Sit to Stand

AAN: American Academy of Neurology

AANEM: American Association of Neuromuscular & Electrodiagnostic Medicine

ACEND: Assessment of Caregiver Experience with Neuromuscular Disease

ACTIVE: Ability Captured Through Interactive Video Evaluation

AIMS: Alberta Infant Motor Scale

ALCOA: Attributable, Legible, Contemporaneous, Original and Accurate

APPT: Academy of Pediatric PT

APTA: American Physical Therapy Association

ASO: Antisense Oligonucleotide

ATEND: Adult Test of Neuromuscular Disorders

BBT: Box and Blocks Test

BforSMA: Biomarkers for Spinal Muscular Atrophy

BSID-III: Bayley Scales of Infant Development III

Bayley-4: Bayley Scales of Infant Development 4

CE: Clinical Evaluator

CGI-S: Clinical Global Impression of Severity Score

CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

CHOP TOSS: CHOP Test of Strength in SMA

CNS: Child Neurology Society

CRF: Case Report Form

CRO: Contracting Research Organization

CV: Curriculum Vitae

EDX: Electrodiagnostic

EK2: Egen Klassification 2

ESBBT: Endurance Shuttle Box and Block Test

DUPLICATE: ESBBT: Endurance Shuttle Box and Block Test

ESNHPT: Endurance Shuttle Nine Hole Peg Test

ESWT: Endurance Shuttle Walk Test

FDA: U.S. Food and Drug Administration

FSS: Fatigue Severity Scale

FSTA: Fast Skeletal Muscle Troponin Activator

FVC: Forced Vital Capacity

GCP: Good Clinical Practice

GMFM: Gross Motor Function Measure

GRT: Gene-Replacement Therapy

HFMS: Hammersmith Functional Motor Scale

HFMSE: Hammersmith Functional Motor Scale Expanded

HHD: Hand Held Dynamometry

HINE: Hammersmith Infant Neurological Examination

HINE-2: Hammersmith Infant Neurological Exam-Section 2, Motor Milestone

HINT: Harris Infant Neuromotor Test

HIPAA: Health Insurance Portability and Accountability Act

HSP: Human Subjects Protection

ICC: Interclass Correlation Coefficient

ICF: International Classification of Functioning, Disability and Health Model

IM: investigator Meeting

IRB: Institutional Review Board

IT: Intrathecal

IV: Intravenous

MDA: Muscular Dystrophy Association

MEP: Maximal Expiratory Pressure

MFM: Motor Function Measure

MIP: Maximal Inspiratory Pressure

MMT: Manual Muscle Testing

MOP: Manuals of Procedures

MRC: Medical Research Council

MSG: Muscle Study Group

NBS: Newborn Screening

NHPT: Nine Hole Peg Test

NIH: National Institutes of Health

NINDS: National Institute of Neurological Disorders and Stroke

NM: Neuromuscular

NORD: National Organization for Rare Disorders

PCF: Peak Cough Flow

PDMS-2: Peabody Developmental Motor Scale II

PDMS-2: Peabody Developmental Motor Scales-2

PEDI-CAT: Pediatric Evaluation of Disability Inventory – Computer Adaptive Test

PedsQL™: Pediatric Quality of Life Inventory

PFDD: Patient-Focused Drug Development

PFT: Pulmonary Function Test

PI: Principal Investigator

PMS: Post Marketing Surveillance

PNCR: Pediatric Neuromuscular Clinical Research Netwrork

PRISM-SMA: Patient Reported Impact of Symptoms in Spinal Muscular Atrophy

PRO: Patient Reported Outcomes

PROM: Patient Reported Outcome Measure

PROMIS®: Patient-Reported Outcomes Measurement Information System

PT: Physical Therapist

QOL: Quality of Life

r9HPT: Repeated (5 times) Nine-hole peg test

RCT: Randomized Controlled Trial

RHS: Revised Hammersmith Scale

RIP: Respiratory Inductance Plethysmography

RULM: Revised Upper Limb Module

SMA: Spinal Muscular Atrophy

SMAFRS: SMA Functional Rating Scale

SMA-HI: SMA-Health Index

SNIP: Sniff Nasal Inspiratory Pressure

SOC: Standards of Care

TFT: Timed Function Tests

TIMP: Test of Infant Motor Performance

TIMPSI: Test of Infant Motor Performance Screening Items

Tlim: Time to Limitation

TTC: Time to Climb 4 Stairs

TTR: Timed Rise from Floor

TUG: Timed Up & Go

VoP: Voice of the Patient

VPA: Valproic Acid

WHO: World Health Organization

WMS: World Muscle Society

WSV: Workspace Volume

"How to Use" Toolkit Example Guide

The Best Practices for Physical Therapists & Clinical Evaluators in Spinal Muscular Atrophy document can be utilized as a toolkit for any experience level. Below are some example scenarios on how to apply and best use this toolkit.

Beginner CE Example: Scenarios & Recommended Sections of the Toolkit to Reference
A sponsor reaches out to your site for participating in a new clinical trial in SMA.

Your coordinator and PI ask you to complete regulatory trainings for the IRB.

A. Section 2: Steps to Take Before Participating in a Trial
   a. Clinical Evaluator Training and Development - For information about fundamental trainings see Table A1: Recommended Regulatory Training for Clinical Evaluators
      i. GCP certification through CITI Program
      ii. HIPPA training through CITI Program
      iii. If working with a pediatric population, please review, CFR 46 Subpart D—Additional Protections for Children Involved as Subjects in Research

You have an SMA patient who may be eligible for the study.

B. Section 2: Steps to Take Before Participating in a Trial
   a. Clinical Evaluator Training and Development – For those who want to further develop their skill set, many comprehensive manuscripts are available that can educate on SMA disease course, clinical presentation, recommended standards of care, etc. (see Table A2: SMA Seminal Paper Reference List for a comprehensive reference list on SMA Seminal Papers)
C. Table A2: SMA Seminal Paper Reference List
   a. Standard of Care articles to read
   b. Patient may have an orthopedic issue that could impact participation
      i. Articles on Orthopedic Issues (i.e. Contractures, Scoliosis, Hip dislocation)
D. Section 3A: Evaluation in the Clinical Setting
   a. Biomechanics of Movement in SMA – Given the prominent impairments of muscle weakness, contractures, and scoliosis, patients with SMA can develop compensatory mechanisms to maintain function and independence with movement. Common compensations and biomechanics are identified by position in Table 3

The protocol says the SMA type II sitter cohort will use the MFM and the RULM during the study.

E. Section 3B: Evaluation of Study Participants in Research Setting
   a. Available Motor Function Outcome Measures by Phenotype - Some of the most common outcome measures for SMA are listed in order of prioritization in Table 4: Commonly Used Outcomes by SMA Functional Level/ Phenotype
      i. MFM – Information about test and use in SMA
         1. Link provided to access to manual, proforma and relevant articles in Table A4: Outcome Measure and Evaluation Resources
      ii. RULM – Information about test and use in SMA
         1. Link provided to access to manual, proforma and relevant articles in Table A4: Outcome Measure and Evaluation Resources

F. Link for Table A6: RULM Kit Supply List to implement in clinic

Your coordinator approaches you with how much time you require as they are creating the budget.

Use Table of Contents to access each outcome measure in the study and estimated assessment times.

You have CME requirements and are interested in applying it to SMA education and training.

Table A5: Professional Development: Meetings for Continuing Education: See online e-learning modules and upcoming conferences.

Intermediate CE Example: Scenarios & Recommended Sections of the Toolkit to Reference
Newborn screening for SMA gets approved in your state.

You get a referral to your clinical from SMA newborn screening.

A. Section 3B: Evaluation of Study Participants in Research Setting
    a. Available Motor Function Outcome Measures by Phenotype – Some of the most common outcome measures for SMA are listed in order of prioritization in Table 4
    b. Can assess which pre-symptomatic measures are appropriate based on age
        i. CHOP INTEND – Biogen reported in an interim analysis of infants enrolled in the NURTURE pre-symptomatic study of Nusinersen that CHOP INTEND scores averaged 61 for infants with 2 copies of SMN2 and 62 for those with 3 copies of SMN2.
            1. Link provided to access to manual, proforma and relevant articles in Table A4: Outcome Measure and Evaluation Resources
        ii. WHO – Biogen reported in an interim analysis that WHO motor milestones were on target for infants enrolled in the NURTURE presymptomatic study of Nusinersen
            1. Link provided to access to manual, proforma and relevant articles in Table A4: Outcome Measure and Evaluation Resources
        iii. BSID-III – The BSID-III is currently being used in AveXis and Roche SMA clinical trials. To date no evidence is published on the BSID-III specific to SMA
            1. Link provided to access to order test kit in Table A4: Outcome Measure and Evaluation Resources

A patient asks you about a clinical trial they saw in a newsletter.

B. Table A3: External Resources for SMA Education and Training
    a. SMA Clinical Trials – Current List of SMA Clinical Trials for a comprehensive list of current clinical trials available for those with SMA on clinicaltrials.gov
    b. Pharmaceutical Related Resources – SMA Therapeutics: A Comparative Overview of Drugs Approved and in Development, a presentation outlining targets for therapeutic intervention in SMA

Your coordinator asks when is the best time to schedule the research patient for testing.

C. Section 4: Considerations Related to Assessments and Patient Evaluation: Standards of Care, Supportive Care, and Multidisciplinary Care
    a. Best Practices and Testing Considerations for Best Performance – to refer to for optimal testing and communication to patient

Advanced CE Example: Scenarios & Recommended Sections of the Toolkit to Reference
A sponsor contacts your center for participation in a new clinical trial in SMA.

You receive the protocol and see new fatigability testing you are unfamiliar with for their cohort of non-ambulatory SMA.

A. Section 3B: Evaluation of Study Participants in Research Setting
    a. Available Motor Function Outcome Measures by Phenotype – Some of the most common outcome measures for SMA are listed in order of prioritization in Table 4
        i. ESNHPT – read description of the test, read the evidence in SMA

1. Link provided to order test kit to practice in clinic, and related articles in SMA in Table A4: Outcome Measure and Evaluation Resources

ii. PROs for fatigue – read description of tests, read the evidence in SMA

1. FSS – read description of test, get access to resources and related articles in SMA, Table A4: Outcome Measure and Evaluation Resources

You are interested in networking and attending an upcoming conference that highlights SMA and neuromuscular diseases to learn about the late-breaking research

B. Table A5: Professional Development: Meetings for Continuing Education
   a. Organizations – World Muscle Society – sounds interesting and click to learn when is the next conference

Your coordinator asks when is the best time to schedule the research patient for testing.

C. Section 4: Considerations Related to Assessments and Patient Evaluation: Standards of Care, Supportive Care, and Multidisciplinary Care
   a. Best Practices and Testing Considerations for Best Performance – to refer to for optimal testing and communication to patient

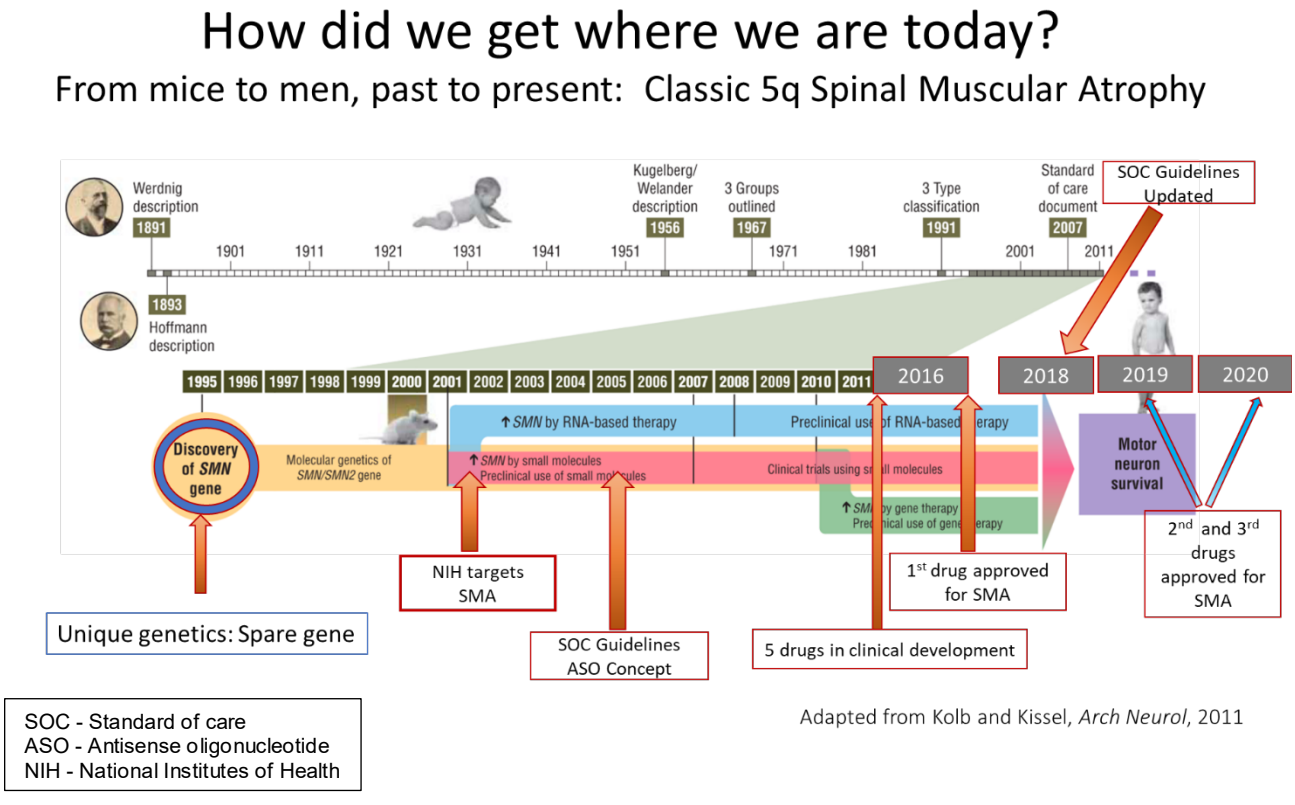
Introduction

Spinal Muscular Atrophy (SMA) is a genetic disorder characterized by degeneration of anterior horn cells with subsequent, progressive muscle atrophy and weakness. SMA has been classified into four primary clinical phenotypes, SMA type I-IV, based upon age of onset and highest motor function achieved.[1,2] The most common form of SMA is caused by mutations in the 5q13 survival motor neuron (*SMN1*) gene. The disorder affects 1 in 6-10,000 infants with a carrier frequency of 1 in 40.[3,4]

Individuals with untreated SMA often have difficulty performing the basic functions of life, such as walking, eating, breathing, and swallowing. As such, the recommended standard of care management of SMA is often complex and comprehensive, requiring the involvement of multi-disciplinary specialists, including neuromuscular specialists, pulmonologists, physical and occupational therapists, orthopedic doctors, among others.[5-7] The role of the physical therapist (PT) is, as such, vital in the optimal functioning and management of patients with SMA.

Over the past 10-20 years much progress has been made to better understand the pathophysiology and molecular genetics of SMA and such has provided the basis for pharmacologic and genetic therapy development leading to a new era of translational medicine for those with SMA. The convergence of basic science, preclinical, and clinical efforts has forged a solid path forward leading to treatments for SMA that were not previously available. Figure 1 provides a historical timeline highlighting important milestones toward development of SMA treatments. With the nature of the SMA clinical research landscape, evolving therapeutic pipeline, and three treatments that are now FDA-approved, with others on the horizon, supporting and expanding the existing clinical research infrastructure in SMA has never been more critical. To this end, Cure SMA is leading efforts to engage new clinical research centers and provide educational resources to research team members to support the effective conduct of clinical research in SMA (see Cure SMA Clinical Trial Readiness site for more details).

Figure 1: Historical perspective highlighting important milestones toward development of SMA treatments



To support CEs involved in SMA clinical trials, Cure SMA has developed recommended best practices to promote the most effective conduct in clinical trials. These best practices are intended to help CEs, especially those new to SMA clinical trials, understand challenges and issues they may encounter and find productive ways to navigate these challenges.* These recommendations were developed in collaboration with CEs who have significant experience in clinical trials in SMA and through an extensive literature review. Also included in this document is a set of Appendices with links to additional resources and articles for further reading, which delve more deeply into the issues discussed below.

More Information

- For a comprehensive list and description of the different therapeutic approaches to treat SMA, you may click here: Therapeutic Approaches in SMA.
- For a comprehensive list of current clinical trials available for those with SMA, you may search here: clinicaltrials.gov & SMA.
- Additional resources may also be found in Table A3: External Resources for SMA Education and Training, located within the Appendix.

* *This does not represent an exhaustive review of existing literature or resources but is offered as a starting place intended to increase awareness of the potential challenges that CEs may encounter in the course of SMA clinical trials.*

Section 1: The Role and Responsibilities of Physical Therapists and Clinical Evaluators in SMA Care and Research

Generally, physical therapists (PTs) are involved in diagnosis and management of children and adults affected with conditions that limit one's ability to move and function optimally when performing activities of daily living.[8] The role of PTs is multifaceted and includes injury prevention, restoring and maintaining physical function, and promoting wellness, fitness, and optimal quality of life as it relates to movement and health.[8] Physical therapists provide care across multiple settings, including hospitals/medical centers, private practices, outpatient clinics, schools, sports and fitness facilities, etc. When managing the care of children and adults with SMA, PTs focus on promoting function, mobility, positioning,bracing, and stretching. Physical therapists may also recommend equipment such as adaptive seating, strollers, wheelchairs, standers, and gait trainers. Physical therapists have emerged as leaders in Standard of Care Guideline development for SMA,[6,7] and as educators providing continuing medical education to address unmet needs for expertise to provide outstanding care for individuals with SMA.

Physical therapists also play a critical role in clinical research as clinical evaluators (CE), and a pivotal role in the successful execution of clinical trials in SMA. Clinical evaluators evaluate patients across multiple health dimensions using a variety of motor function scales and patient reported outcomes (PROs) and assess baseline function and potential changes with intervention in a research participant's motor function, respiratory function, and other developmental milestones that may be attributed to the effects of a potential therapeutic. Physical therapists have also undertaken critical roles as advisors, consultants, and CE trainers for trials. Figure 2 provides a timeline of key SMA clinical research and education milestones supported by PTs. See Table 1 for examples of SMA studies and research protocols where PTs and CEs have played a pivotal role.

Figure 2: Timeline of the most important SMA clinical research and education trial milestones.

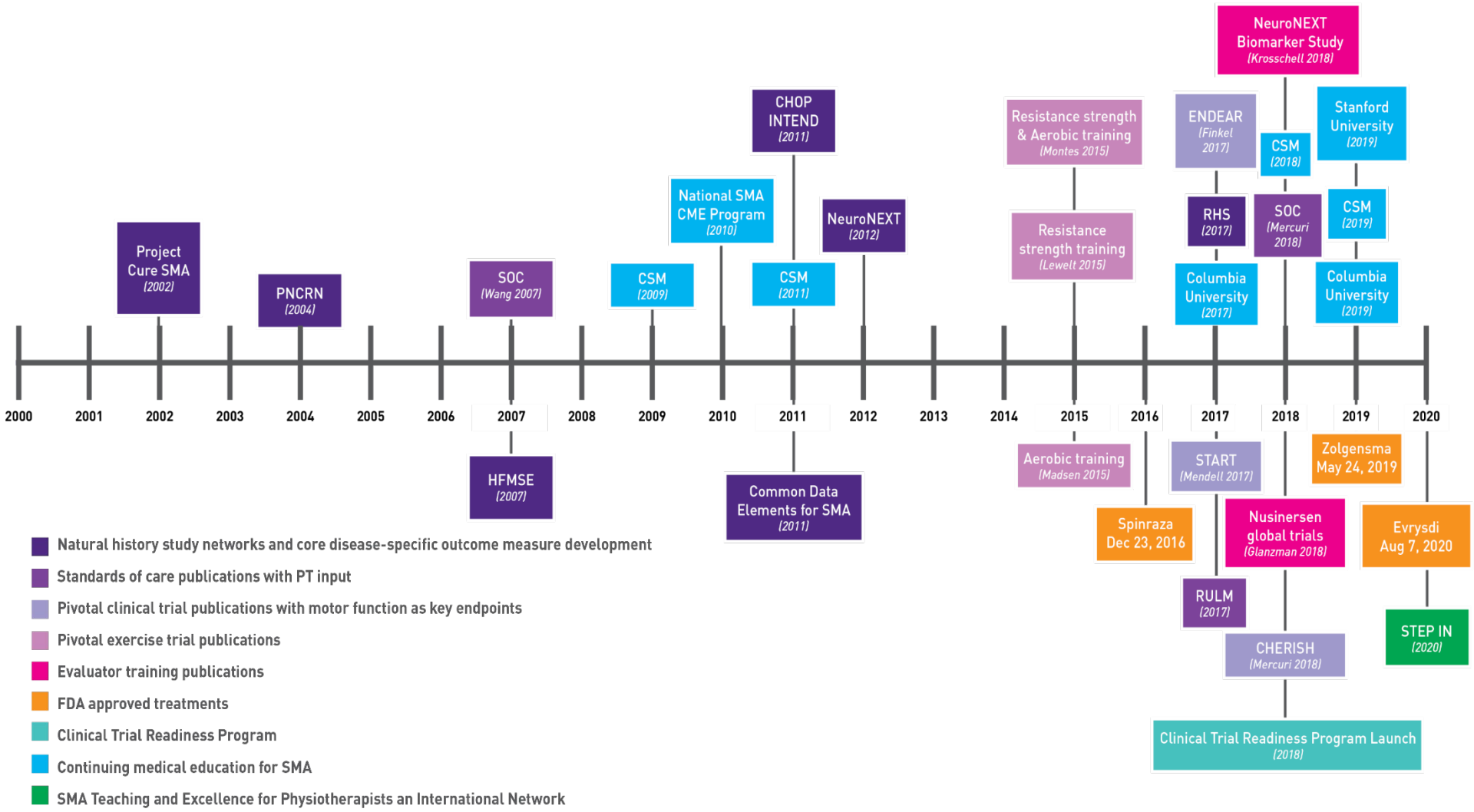


Table 1: The central roles of physical therapists in SMA research in the United States.

Natural History and Biomarker Studies			
Trial Network	**Study Type**	**Physical Therapist roles***	**Study status**
PNCR *Pediatric Neuromuscular Clinical Research Network*	Natural History study all types and ages of SMA in a US cohort	a, b, c, d, e, f, g	Ongoing[9]
NeuroNEXT *Spinal Muscular Atrophy (SMA) Biomarkers Study in the Immediate Postnatal Period of Development*	1st study supported by NeuroNEXT to assess natural history of infants with Type 1 SMA with control group of age related typically developing infants	a, b, c, d, e, f, g, h, o	Completed[3,10,11]
BforSMA *Biomarkers for SMA Study*	SMA Biomarker exploration study	a, b, c, d, e, h, i, j	Completed[12-14]
Therapeutic Trials: Phase I-VClinical Trials			
Sponsor	**Therapeutic agent**	**Physical Therapist roles***	**Study status**
Novartis Gene Therapies *STRIVE, STRIVE EU, STRONG, SPRINT, REACH*	Onasemnogene Abeparvovec-xioi/ Zolgensma *Single dose SMN1 gene replacement therapy, intravenous (IV)and intrathecal (IT) administration*	a, c, d, e, f, g, h, i	FDA approved May 2019[15,16]
Ionis/Biogen *CS1, CS2, CS10,CS12, CS3a, CS3b (ENDEAR), CS4 (CHERISH), CS11 (SHINE), NURTURE, EMBRACE, DEVOTE, RESPOND, ONWARD*	Nusinersen/Spinraza *Antisense Oligonucleotide, SMN2 splicing modulator/enhances SMN protein production centrally, via intrathecal (IT)administration*	a, c, d, e, f, g, h, i, k	FDA approved Dec 2016[17,18]
Genentech/Roche *SUNFISH, FIREFISH, JEWELFISH, RAINBOWFISH*	Risdiplam/Evrysdi *Orally administered liquid SMN-2 splicing modifier*	a, c, d, e, f, g, h, i	FDA approved August 2020[19,20]
Cytokinetics	Reldesemtiv *Fast skeletal muscle troponin activator (FSTA)*	a, c, d, h, i	Completed, awaiting results[21]
Scholar Rock *TOPAZ*	SRK-015/Apitegromab	a, c, d, h, i,	Ongoing, recruitment closed[22]
Project Cure SMA	Valproic acid (VPA) and Carnitor	a, c, d, e, f, g, h, i,	Completed[23-26]
Physical Therapist Intervention Studies			
PI	**Intervention**	**Physical therapist roles***	**Status**
Montes	Lower extremity strengthening and aerobic stationary bike exercise RCT for those with type III SMA	d, e, f, g, i, l, o, p, q	Completed[27,28]

Lewelt	Home-based, progressive resistance exercise in children with types II and III SMA	d, e, f, g, l, m, n, o, p, q	Completed[29]

**a. Clinical Evaluator, b. Outcomes development, c. Evaluator training, d. Protocol development, e. Manuscript development, f. Analyses, g. Publication, h. Advisory board, i. Outcomes selection, j. Consultant, k. Steering committee, l. Principal Investigator, m. Co-Investigator, n. Site PI, o. Grant submitted and awarded p. Recruitment, q. Interventionist*

Your Role as a Clinical Evaluator in a Clinical Trial

The fundamental role of CEs is to work with the research team under the principal investigator (PI), who takes ultimate responsibility for study conduct. All research team members, including CEs, ensure the effective conduct of clinical trials using good clinical practice (GCP). Clinical evaluators may participate in other clinical trial activities including study design, protocol development, data management and analysis, presentation, and manuscript preparation and publication.[30]

Clinical evaluators are responsible for promoting consistency across the course of a clinical study. Clinical evaluators must perform each assessment in a consistent, reliable, and standardized manner with all trial participants, such that the data collected is valid and reproducible and may be used to assess critical endpoints in a given clinical trial. This includes using standardized clinical outcome measures while following published manuals of procedures (MOP). Study protocols dictate the outcome measures used in trials.

- Physical therapists are trained to analyze movement and determine if the quality and/or quantity of movement meets test item criteria on motor function examinations.

- Typically, two trained CEs are assigned at each site as primary and back-up evaluators. It is very important for the same CE to administer assessments for each individual patient over the course of the clinical trial to reduce variability and maintain consistency. The back-up evaluator performs assessments only if the primary evaluator is unavailable. However, the primary and back-up evaluators are encouraged to work together in clinical and research settings to promote alignment in administration and scoring for future testing.

- Standardization of evaluations is critical to maintain consistency. This requires the CE to follow the manuals of procedures and instructions as written, including the:
    - Order of assessments
    - Specific order of test items
    - Demonstrations, etc.
    - Requirement to use the same equipment through the course of the study

- To reduce variability, the same CE (working with the back-up CE) should perform repeated evaluations within the same testing environment. Child cooperation, time of day, rest breaks, and parental involvement can be confounding factors that affect reliability and reproducibility of evaluations.

Becoming a Clinical Evaluator in a Clinical Trial: Education and Training

Primary CEs and back-up CEs for clinical trials need robust training (including didactic lecturing, hands-on training, and competency evaluations) to ensure consistency and quality assurance among all participating CEs and assessments. This promotes high-quality, reproducible data, essential for trial success.

- Formal sponsor-led CE trainings are required to ensure reliability and the standardization of administration and scoring of outcome measures. This training is designed to decrease variability across visit assessments and between CEs. It provides study-specific structure for the level of training and experience required as well as qualification to begin trial participation.

- Researchers and sponsors support the education and training of CEs to increase confidence in data robustness and accelerate study start-up.

Assuring Quality Control in the Clinical Trial: Whose Responsibility is it?

Quality assurance and control is the responsibility of the entire research team and the research sponsor. In a clinical research setting, the PI holds primary responsibility for proper study conduct and the protection of research participants. However, to ensure the validity of the trial results and to maintain uniformity, the industry sponsor is ultimately responsible for implementing uniform quality assurance measures and standards across all trial sites and ensuring that everyone involved in the conduct of research obtain the required regulatory, operational and role specific training prior to the conduct of research. Typically, an expert PT training team is involved to provide quality control for site evaluators' assessment of patients using functional outcomes. This may include requirements for videography to assure the trained CEs have maintained the proper testing environment, proper set-up of equipment, proper test administration of start positions, and any other conditions that could affect patient testing.

Regular refresher trainings (annual and/or bi-annual) typically occur to reduce drift (from administration and scoring) associated with time between training and test implementation. During these sessions, issues addressing quality control may be addressed, e.g., correct administration and/or scoring of test items. Additionally, these sessions allow evaluators to discuss new findings or testing issues that may come up with changes in function as the participants gain strength and skills. Refresher trainings help to maintain a high standard of reliability and reduce variability during the CE's assessments for the continuation of the trial.

KEY POINTS: ROLES AND RESPONSIBILITIES.

- Physical therapists/CEs are key members of the clinical research team who hold a wide variety of responsibilities. Clinical evaluators play a key role in the effective conduct of clinical trials and are involved in the assessment of patients with a wide range of diagnoses, including various neuromuscular and rare diseases such as SMA.
- Physical therapists/CEs may also participate in many aspects of research including study design, protocol development, data management and analysis, presentation, and manuscript preparation and publication.
- In SMA clinical trials, CEs are responsible for assessing patients across multiple health dimensions, using a variety of motor function scales and PROs, to assess baseline function and potential changes/improvements that may be captured over time, following the administration of a given therapeutic.
- Clinical evaluators must perform each assessment in a consistent, reliable, and standardized manner for all trial participants, to ensure collected data is valid and reproducible and may be used to assess critical endpoints.
- Becoming a CE for a clinical trial requires robust training to ensure consistency and quality among all participating CEs and assessments.

Section 2: Steps to Take Before Participating in a Trial

Clinical Evaluator Training and Development

Before CEs actively engage in clinical trials, they must complete training to ensure ethical research conduct. Additionally, as stated above, CEs must complete all training required per study protocol to ensure reliability/standardization of administration and scoring of all trial-related outcome measures. Individual sites may have site-specific evaluator training requirements as well. For information about fundamental trainings that CEs should complete as part of their professional training, see Table A1: Recommended Regulatory Training for Clinical Evaluators for an overview of recommended trainings.

Clinical evaluators are encouraged to seek opportunities to further their professional development through continued learning. For CEs with little to no prior experience, or those who want to further develop their skill set, many comprehensive manuscripts are available that can educate on SMA disease course, clinical presentation, recommended standards of care, etc. (see Table A2: SMA Seminal Paper Reference List for a comprehensive reference list on SMA Seminal Papers); for other, more in depth, educational and training resources you may refer to Table A3: External Resources for SMA Education and Training. Importantly, these documents are a valuable resource to support the CE but do not supersede those that are required by a CEs institution or by the sponsor; they are simply suggested as additional resources.

Basic Clinical Research Practice: Regulatory Essentials for Clinical Trial Participation

Below, is a high-level overview of key regulatory training and certifications needed to conduct trials in SMA. Please note, this is not intended to be a comprehensive list. As mentioned in the previous section, these requirements are often dictated by your Institutional Review Board (IRB) and the specific study protocol in which you will participate. There should be adequate training for all staff participating in the conduct of a study, including any new staff members that start after the study has begun. For a more detailed description of the regulatory training required of the research team, including CEs, prior to the conduct of any clinical trial (see SMA Clinical Trial Readiness Toolkit - Part II: Key Elements of Trial Management).

Institutional Review Board (IRB) Requirements, Regulatory Certifications, and Training Recommendations

Several trainings and certifications on ethical and effective conduct of research are required of the research team prior to IRB approval and trial initiation. Certification that one has completed training in Human Subjects Protection (HSP) in research is required of all faculty, investigators, study coordinators, CEs, and other individuals directly involved in human subject research. This means anyone working directly with human research participants, data, or tissue that can link back to individual research participants.

Key types of training are presented in Table 2 below. While this list may provide a helpful starting point, it is not exhaustive. For a list of recommended regulatory training (including links to pertinent federal regulation), and required forms that the CE must complete, please refer to Table A1: Recommended Regulatory Training for Clinical Evaluators.

Table 2: Key Types of Training for Clinical Evaluators

Type of Training	Where to Find It
Research Ethics and Compliance Training	Ethics and compliance training (includes HSP training) provided by: • CITI Program (registration required) • IRBs at each academic institution
US FDA Regulated Research	FDA maintains a webpage called "Regulations: Good Clinical Practice and Clinical Trials" that contains links to regulations that govern clinical trial conduct and human subject protections. Key topics include FDA regulatory compliance; human subjects'

	protection (HSP) in research, including general requirements for the informed consent of human subjects / key elements of informed consent; responsible conduct of research; research with minors; and conflicts of interest.
Good Clinical Practice (GCP) Certification	CITI offers training on Good Clinical Practice
Information Privacy and Security	CITI offers training on the Health Insurance Portability and Accountability Act (HIPAA) specific for human subject research.

Good Clinical Practice (GCP) Requirements

The principles of GCP help assure the safety, integrity, and quality of clinical trials by addressing elements related to the ethics, design, conduct, and reporting of clinical trials. Adherence to GCP principles is universally required and critical to ethical human subjects' research. (For a review of the FDA consolidated guidance for GCP and HSP, see Integrated Addendum to ICH E6 (R1-R2.) A key aspect of GCP includes proper completion of study case report forms (CRFs). In clinical trials, recording of information must be **A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal and **A**ccurate (ALCOA):

- **Attributable**: Can you tell who completed the form(s)?
- **Legible**: Is it clear/readable?
- **Contemporaneous**: Is it dated?
- **Original**: Are all documents the original records (source) or certified copies of original records? Do they represent the *original* data, records or source where the data was initially recorded?
- **Accurate**: Does the content on the form reflect a consistent and real picture of what was captured on the evaluation?

For more on documentation, see Good documentation practice in clinical research[31] and refer to Table A1: Recommended Regulatory Training for Clinical Evaluators.

Required Documentation and Forms for CEs

The following are required per GCP and FDA regulations. For a comprehensive list of Essential Documents According to ICH E6(R2) guidelines, refer to the SMA Clinical Trials' Toolkit, v.2, Part II, section B2; also see, Table A1: Recommended Regulatory Training for Clinical Evaluators.

- **Updated Curriculum Vitae (CV)**, including affiliation, education, and responsibilities. This demonstrates that indeed, you have the qualifications required to perform the functions delegated to the CE, per protocol, as part of the research study. Guidance on CV requirements may be found within Table A1: Recommended Regulatory Training for Clinical Evaluators.
- **Professional state license** to demonstrate you are licensed to practice PT in your state of residence, per study protocol.
- **Professional certifications** to demonstrate you have the qualifications required to perform the functions delegated to the CE, per study protocol.
- **Form FDA 1572,** comprises the "Statement of Investigator." Specifically, it documents information requested regarding the investigator's qualifications and contact information. Every member of the

study team involved in data collection that will be used to assess any of the endpoints must be listed on this form (see Instructions for Filling out Form FDA 1572 for further instructions).

- **Financial Disclosure Form**, a study-specific financial disclosure form is required (59 FR 48708) from each study team member involved in the research study.[32,33] This includes any information concerning the compensation to, and financial interests of, any clinical investigator, including CEs, conducting any clinical research of a drug, biologic, or device. This information is collected to ensure that there are no existing conflicts of interest that may compromise the validity of the data. Financial interests and arrangements of the PI/research team that could affect reliability of data submitted to FDA in support of product marketing are identified and disclosed by the PI to the IRB and by the sponsor on a marketing application. For further information on this regulation, you may visit, the U.S. FDA site at Financial Disclosures by Clinical Investigators.

Review of Study Protocol

Clinical evaluators should have a solid understanding of the study protocol, including the study's purpose, methodology and design (e.g., single-arm, two-arm, open-label, placebo-controlled, blinded vs. double-blinded, etc.), the schedule of procedures, trial endpoints, attributes of the investigational product being evaluated, and other specific details, particularly pertaining to the CE's role and clinical evaluations (i.e., outcome measures). To learn more about clinical trial design, consider Clinical trial structures[34] by Evans (2010).

Investigator Meetings

Sponsors hold an investigator meeting (IM) prior to beginning study procedures to prepare study team members to conduct an effective trial. At the IM, the study team learns about the protocol and factors required to maintain compliance with the protocol, including inclusion/exclusion criteria, procedures performed at each study visit, adverse event reporting, lab procedures, regulatory issues, etc. PIs, study coordinators, and CEs from each clinical site are typically required to attend. Investigator meetings are designed to encourage interaction, provide education and training, and stimulate excitement for a successful clinical trial. Annual refresher meetings may occur after the IM to maintain compliance, consistency, and reliability for study procedures.

In addition to the initial IM, CEs may be asked to attend a separate study-specific training to meet requirements for certification and participation. This session may include didactic lecture series, video reviews, hands-on training, individual/group sessions, and competency testing including reliability of the outcome measures performed in the study.

The Need for and Benefits of a Collaborative, Patient-Focused Approach

When the patient is not at the heart of all research activities, the outcome and success of the clinical trials may be compromised.[35,36] A patient-focused approach emphasizes the needs of the patient and involves assessing trial design and operations from a patient's perspective; it may also include integrating patient community input into trial design. This type of approach can be particularly impactful in SMA, as clinical trials can be intensive, and require significant commitment on behalf of patients, families, and caregivers as well as the research team. These are on top of the daily challenges that these patients and families have in managing care and coping with the burden of/implications of an SMA diagnosis.[37,38] Families, caregivers, and the patients themselves (typically after 7 years of age children must provide assent regarding participation in a trial) may want to be very involved in care and in the trial process, and are likely to appreciate CEs who demonstrate empathy and understanding. Listening thoughtfully to patients, families, and caregivers can help them to feel heard, supported, and engaged. Clinical evaluators may also shadow families during clinical visits to gain perspective on their challenges and care needed. In general, patients and families are often open to questions and happy to help educate the research staff on matters pertaining to their care and that of their loved one. Patients and families may also request communication and outreach to their local rehabilitation team of

providers to promote continuity of care, discussion and advocacy, rehabilitation planning, and provision of resources with the CE acting as a community liaison.

KEY POINTS: BEFORE PARTICIPATING IN A TRIAL

- Before CEs become actively involved in clinical trials, it is important to ensure that they have completed basic SMA education and training to be effective and support the appropriate, ethical conduct of research. CEs are also encouraged to actively seek ongoing opportunities for professional development.
- Clinical evaluators must also complete all IRB requirements, and regulatory certifications related to the ethical and effective conduct of research, prior to IRB-review, approval, and conduct of any research procedures.
- In preparing for a trial, CEs must ensure that they attain a solid understanding of the study protocol, through participation in investigator meetings and self-review of all training materials pertinent to your role in the conduct of the study; this also includes participation at subsequent PT-related refresher trainings.
- Clinical evaluators are encouraged to adopt a collaborative, patient-focused approach. This will improve the participant's clinical trial experience and increase the likelihood that the participant remains engaged in the study.
- Study procedures should be coordinated, to ensure that the order of study procedures, as mandated by the protocol, are followed as to avoid any protocol deviations. Clinical evaluators can do this by maintaining an open dialogue with the PI, coordinator, and all key members of the team and by seeking to understand not only the disease but the current rehabilitation program and day-to-day experiences of the patients and families.

Section 3: Evaluating Patients with SMA

Overview of the Evolution and Use of Outcome Measures in SMA

In the past, muscle weakness in SMA was directly measured by assessments of strength which represent the level of impairment or disease severity, but not disease burden. More recently, outcome measures that relate to function in daily life have been shown to be more clinically relevant, meaningful, and essential to determine if a change in strength can impact a patient's performance. Functional scales have the advantage of capturing motor performance in a more comprehensive way while being able to reliably administer to many individuals.[39] As therapeutic approaches for SMA became more realistic, international and national networks of SMA experts worked hard on developing and validating old and new measures to identify surrogate endpoints for natural history data interpretation and for future treatment effects. This work has resulted in dramatic improvements in identifying appropriate and disease-specific tools to be applied in both clinical and research settings.[39]

Disease-specific assessments are recommended as they have been designed to target the functionally relevant issues in SMA. These disease-specific scales were designed to capture the broad phenotypic spectrum of SMA including the severely weak infants (typical in the untreated, type I presentation) to the mildly impaired adults (typical in untreated, ambulatory strong type III/IV presentation). Many of the scales developed hierarchical tasks according to frequency distribution and the number of patients being able to achieve them, to allow us to anticipate the next developmental gain or milestone. A classification system based on age of symptom onset and highest ever motor function achieved has been widely adopted to describe SMA types I-IV.[7] More recently, the updates to the standards of care have classified phenotypes by their current motor function status (non-sitters, sitters, and walkers) to provide guidelines on evaluation and rehabilitation.[6,39]

Section 3A: Evaluation in the Clinical Setting

Standards of care for SMA support regular multidisciplinary visits including physical therapy evaluations using standardized disease-specific outcome measures to monitor disease progression and support rehabilitation management and clinical decision making.[5-7] A rehabilitation standard of care consensus statement for SMA was originally published in 2007 and was revised in 2018.[6] These guidelines include a review of evidence and expert consensus that have been widely adopted by clinicians all over the world. Increasing evidence of improvements in the natural history as well as with disease modifying therapies have promoted a more proactive, anticipatory approach to rehabilitation management and it has been observed that regular physical therapy sessions may influence trajectories of progression.[6,7] The rehabilitation section of this manuscript describes rehabilitation goals for the 3 different functional classifications: Non-Sitter, Sitters, and Walkers. Each functional group has intervention recommendations for stretching, positioning, mobility, and exercise as well as care considerations and assessment options that have been thoroughly reviewed.[6] Please see Table A3: External Resources for SMA Education and Training for additional information regarding SMA standard of care.

Evaluation using these evidence-based assessments, whether used in the clinic setting or as part of a research/clinical trial, can help determine treatment response and the impact on the natural history of SMA. Good clinical practice includes use in the clinic to allow documentation of change over time for your clinic patients and help you, as a clinician and researcher, better understand trajectories and change across the population of patients with SMA over time. As selected measures have been developed for and/or used in SMA clinical trials for many years, many of these measures have established statistical reliability, validity and sensitivity to change to support their application and use in a clinic setting when evaluating patients with SMA.

To establish best practice, it is important to be consistent and thorough in your assessment of patients with SMA in both the clinic and research setting. In addition to evaluations using standardized outcome measures it is important to take a clear history at each visit and document change in compensatory movements, see Table 3, and/or movement limitations as well as decline or improvement in function using your clinical observation skills.

Standard Evaluation Questions to Ask Patients and/or Families

The CE may ask questions to gain a better understanding of the patients SMA history and current presentation and abilities. Standard SMA evaluation questions to ask patients and families include, but are not limited to:

- What is your current level of functional mobility?
- What is your primary means of mobility?
- What age did symptom onset begin?
- What was the highest level of function achieved?
- What is your current therapy/exercise program?
    - Frequency: sessions per week?
    - Intensity level: Rate of Perceived Exertion (OMNI scale)?
    - Time: session duration?
    - Type: PT, OT, ST, DT, other alternative therapies (aquatic, hippo, whole-body vibration, etc.)?
    - Location: home, EI, school, hospital, outpatient clinic, etc.?
- What is your preferred positioning and mobility?
    - Are there positions that cause pain or discomfort?
    - Positions that are not used?
- What is your equipment and or bracing use?
- Any recent changes in mobility and/or function?
- Any changes since last visit including?
    - Any illnesses or surgeries?
    - Any change in bracing, equipment, etc.?
    - Any changes in therapy/intervention?

Biomechanics of Movement in SMA

Given the prominent impairments of muscle weakness, contractures, and scoliosis, patients with SMA can develop compensatory mechanisms to maintain function and independence with movement. Common compensations and biomechanics are identified by position in Table 3.

Table 3: Common Compensations and Biomechanics

Sitting
Children and adults can display fixation or bracing techniques using their arms to support their weak trunk muscles in an upright sitting posture.
Scoliosis may impact the ability to sit, creating an asymmetrical sitting posture with shoulders slanting and trunk leaning (in lateral or forward direction); impacting head alignment and creating difficulty in maintaining head control. Postural compensatory maneuvers can be limited post spinal surgery due to spinal rigidity.
Severely weak patients may have to “stack” in order to maintain head control and find the right balance in their trunk in supported sitting. The head can drop quickly and when flexed forward, it can be very difficult to lift the head back up. An inability to quickly recover and lift the head back up can also lead to airway blockage.
Excessive lateral trunk lean can occur when trying to use or lift the arm.
Active knee extension may be observed but it should be determined if it is recoil from active knee flexion only.
Lower extremity contractures can limit their ability to tolerate certain sitting positions (crossed leg, long sitting, etc.). This may be exacerbated post spinal surgery.
Sitting balance and weight shifts are often difficult due to diminished protective and righting reactions secondary to weakness.
Transitions from sitting to lying can be difficult and many are at risk of falling from a lack of control. Some will exhibit a controlled flopping forward or will turn to prone in order to transition from sitting to lying.
In transitions from lying to sitting, a patient may also have to move into prone or quadruped to push up. Some patients state they are unable to sit up without being able to move their legs off the edge of their bed for momentum to assist.
Lying
Lifting the head off the bed (from either prone or supine) is often difficult and you may see neck protraction or side flexion to accomplish this as well as excessive arm or trunk movements.
Arms and legs may be used to try to roll independently. Patients may also need to grab the edge of the bed or a bed rail to perform.
When in supine and lifting their leg(s) or bringing knee(s) to chest, patients may use their arms to help, externally rotate, roll to their side to create momentum, or use two legs to brace and support movement.
Lower extremity contractures of the knees and hips can impact the ability to straighten the legs out, externally rotate or tolerate the prone position. This may be exacerbated post spinal surgery.
When in prone, patients may require the use of their arms to support their head upright when propped.
When in prone prop on extended elbows patients may internally rotate and hyperextend their elbows due to weakness and poor stability. Scapular winging, as well as hands turning in may be observed.
Severely weak patients may require external support of the arms or legs to promote any active movement and eliminate friction from the surface
Neck contractures may also limit the ability to rotate their head in either direction or maintain midline.
Kneeling & Crawling
Patients may have difficulty holding their head up when on their hands and knees and when attempting to crawl. Proximal weakness creates great difficulty when pulling the leg forward to crawl and may require an alternative crawling pattern to accomplish any locomotion.

Transitions from kneeling to standing may require the use of their arms on their body (Gowers maneuver), furniture, or external support. The patient may have to lean their trunk on the support surface as well to help with this transition.

Standing

If a patient has difficulty standing unsupported, you may see them leaning their trunk on a support surface to stand.

Squatting can be very difficult and may require the use of arm support or furniture to accomplish. Some may only be able to unlock their knees minimally or flex their trunk/hips forward to attempt a squat.

Transitions from standing to sitting can be unsafe. Many may lose control and “crash” part of the way down. Hand support on either the ground or thighs may be required.

Standing posture may include a wide-base of support, knee hyperextension, increased lumbar lordosis, and/or Achilles tendon tightness. If using an assistive device, elbow hyperextension may be noted.

Walking

A waddling, Trendelenburg gait pattern may be exhibited with a wide-base, increased external rotation, knee hyperextension, minimal heel strike, and increased foot pronation.

Lumbar lordosis may be prominent due to weak hip flexors.

Jumping

Jumping can be unsafe and put a patient at risk of falling. Jumping with both feet simultaneously can be challenging as well as landing safely without falling.

Stair Climbing

Patients may require assistance or use one or two railings to ascend/descend stairs. They may use their hands on their bodies (hand on thigh) to help as well. Different patterns may include side-stepping facing the railing, step-to, or alternating steps.

Arm Function

In order to increase upper extremity function, patients may use their fingers to climb up their body, or may flex their body to bring it closer to their hands. Patients may use two hands to support or accomplish a task.

When writing, patients may need to move and adjust the position of their hand or the paper to maintain this ability.

Patients may slide items off of a table in order to make it easier to pick up.

When moving or picking up items, the patient may need to pivot on their elbow or use their forearm for support. Pauses in motion may occur due to weakness or contractures.

Excessive trunk leaning (laterally or forward) may occur when using arms, lifting, or pushing buttons.

Hyperextension of the elbows and fingers is common and should not be discouraged if it impacts function.

Shoulder abduction motion may be seen as a compensation for pure shoulder flexion.

The severely weak patient may have difficulty gripping and exhibit only distal finger flexion to hold onto an item. Weakness and contractures can impact the ability to hold, grasp, or lift a toy.

Selection of Outcome Measures

When choosing an outcome measure, one needs to consider whether a disease-specific or norm-referenced tool is the best for the assessment of a specific child. A norm-referenced tool follows a developmental trajectory based on typical development. Tools that are norm-referenced provide variability of the population on a typical progression across time and over the age range. These may be limited by floor effects and/or lack gradation for sensitivity. Disease-specific outcomes are developed specifically for those with SMA and often make the most sense and are best supported by current evidence for historical phenotype progression and trajectories.

There are various areas of concern for those with SMA that should be evaluated and monitored on a regular basis. Primary areas for assessment are outlined and categorized using the domains of the International Classification of Functioning, Disability and Health Model (ICF) below (Figure 3).

Consideration of goals, patient concerns, and needs should guide your selection of outcome measures for those with SMA across the various levels of the ICF. There are a set of core outcome measures currently recommended for SMA. At the levels of body structure and function, activities, and participation, Figure 3 depicts where many commonly used SMA assessments would fall within the ICF framework. Selection and use of outcome measures in a clinical setting may also be dependent on SMA type, current functional level (Non-Sitter, Sitter, Walker) and/or the patient's presenting symptoms, complaints and desired goals (Figure 4). Details on specific, commonly used outcome measures in order or prioritization can be found in Table 4.

Figure 3: Primary Areas and Commonly Used Assessments across Domains of ICF

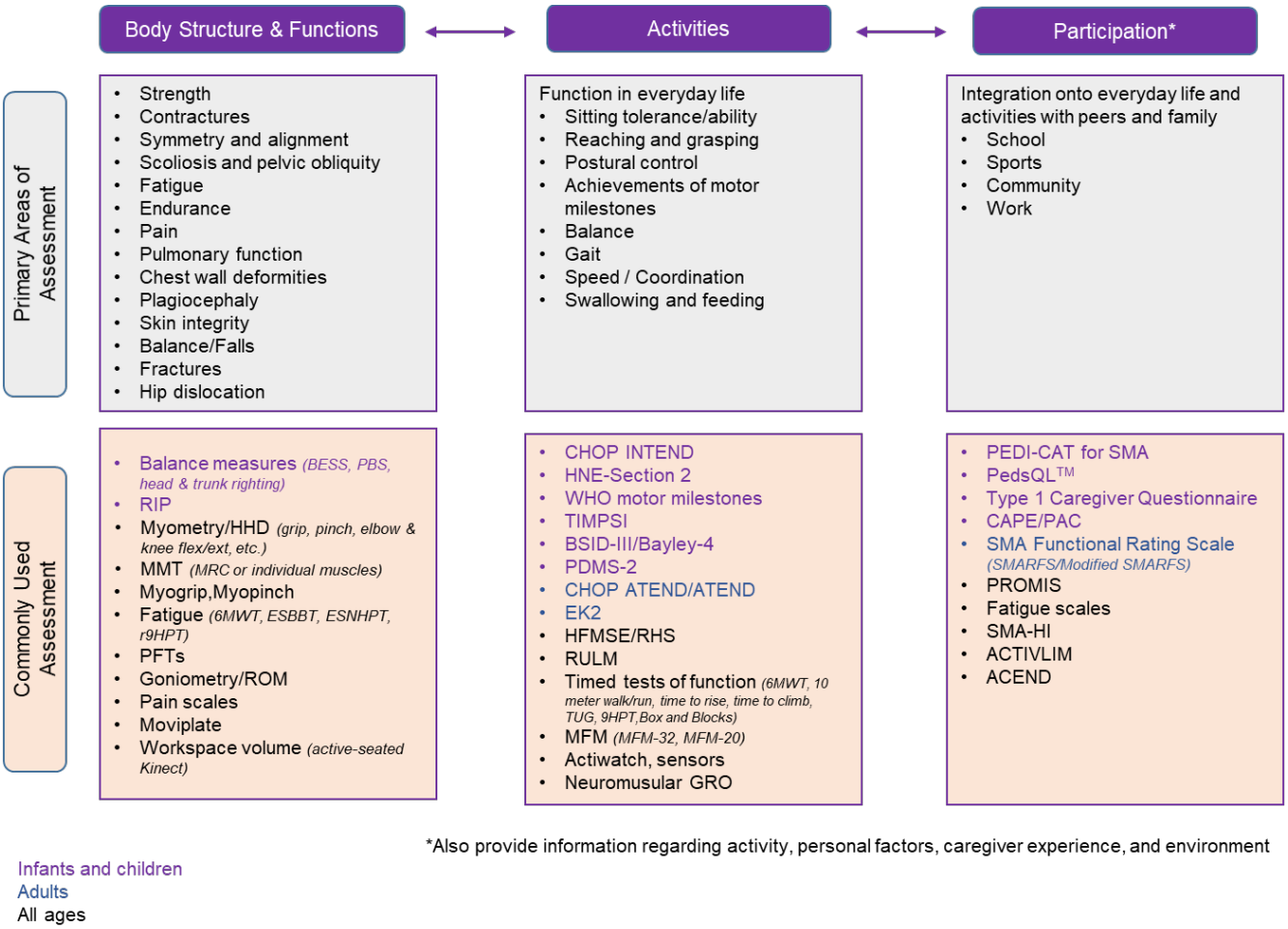
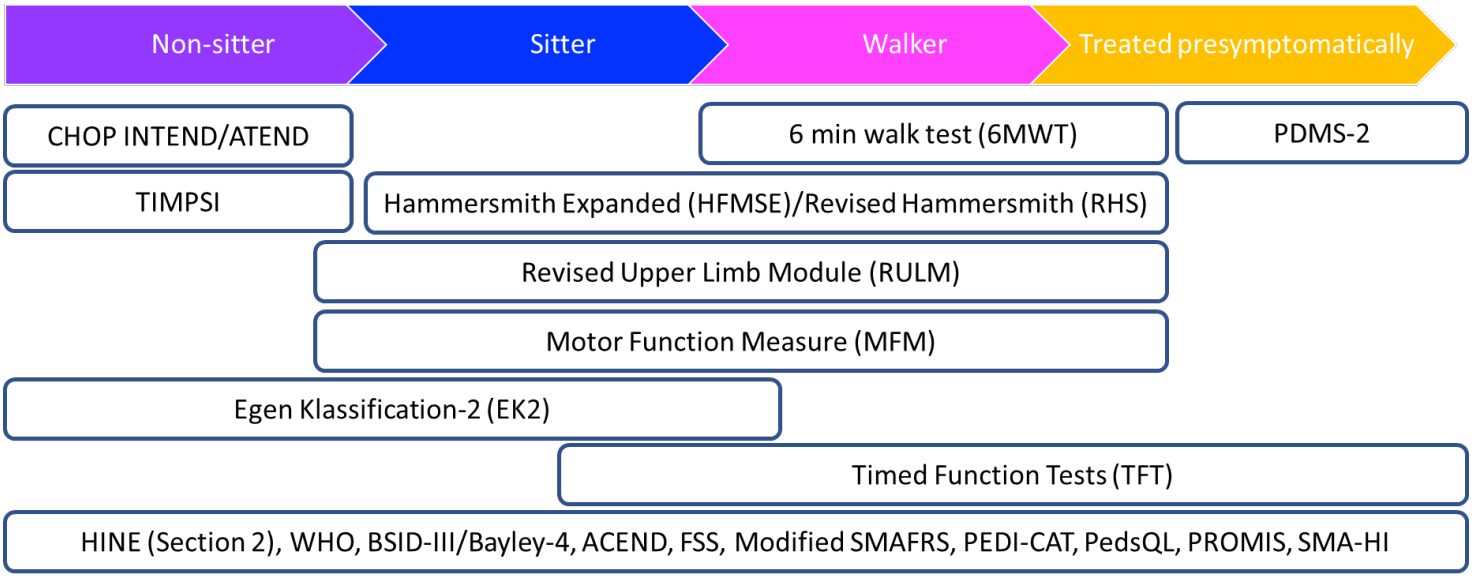


Figure 4: Commonly Used Activity and Participation Functional Outcome Measures across Functional Categories of SMA



KEY POINTS: EVALUATION IN THE CLINICAL SETTING

- Understanding areas of concern across the ICF model for those with SMA as well as commonly used assessment tools for each type of SMA should guide both clinical and research practice.
- Evaluation using evidence-based assessments, whether in the clinic setting or as part of a research/clinical trial, can help determine treatment response and the impact on the natural history of SMA.
- An awareness of common compensatory movements seen in those with SMA can be invaluable in evaluation and assessment in both the clinic and research setting.
- While the best understood and most commonly used assessment tools for this population are disease-specific, infants and children treated early in the pre-symptomatic phase of their disease may also benefit from assessment using norm-referenced tools.

Section 3B: Evaluation of Study Participants in Research Settings

For clinical trials, it is important to not only be familiar with the considerations above, but to understand the role of natural history studies and be deeply familiar with and able to reliably administer relevant outcome measures.

The Role of Natural History Studies and Factors Involved in Outcome Measure Selection

Longitudinal natural history studies are essential to: 1) determine treatment effectiveness, 2) identify any changes from expected progression, and 3) design and power a clinical trial. The rates of disease progression can be different at varying ages and disease durations and must be well understood to interpret clinical benefit for a therapeutic intervention.[40] This highlights the challenge of having one scale that can be used for all SMA populations. Therefore, outcome measures have been selected in clinical trials based on age of the population, functional status, duration of the study, and possible effect of treatment. Natural history study data collection for a large collaborative network including US and Europe have published data identifying different trajectories of progression among patient subgroups. Generally, younger children (<5 years old) can continue to gain skills or show less deterioration than those assessed from 5 years old throughout puberty. During this period, many changes occur including the enhancement of co-morbidities including contracture development, scoliosis, and weight gain impacting a rapid progression of deterioration. Older children beyond adolescents have shown stability and/or gradual declines after this rapid progression.[39]

The National Institutes of Health (NIH) encourages the use of common data elements in clinical research and patient registries to improve data quality and opportunities for combination and comparison of electronic health records across multiple studies and centers.[41] The National Institute of Neurological Disorders and Stroke (NINDS) developed the first comprehensive set of common data elements for use across multiple types of SMA clinical research studies, allowing investigators to systematically collect, analyze, and share data across the research community.

Available Motor Function Outcome Measures by Phenotype

Clinical trials to date have included patients with SMA at varying levels of disease severity and progression. Finding the appropriate outcome measure that is sensitive and reliable to quantify change across the disease spectrum is challenging. Outcome measures have been applied based on phenotypes by age at symptom onset. However, with the evolution in the phenotypic spectrum, new outcomes that reflect skill acquisition for high-risk or typically developing infants and children have been added, particularly to assess infants treated pre-symptomatically and/or those gaining skills at a more rapid pace. Likewise, some newer outcomes have been added to assess patients with a more chronic progression including the SMA adult population. Some of the most common outcome measures for SMA are listed below in order of prioritization in Table 4 with additional details in the next section and in Table A4: Outcome Measure and Evaluation Resources.

It is important to include the patient perspective in assessments performed clinically and in research trials. Patient-reported outcomes establish what is meaningful to those affected by SMA and are intended to complement, not replace, clinician-reported measures. Psychometrically sound, validated, flexible, and comprehensive assessments which are feasible in children and sensitive to change (e.g., PROMIS®) should be used as frameworks to generate these patient-reported outcomes. A recent systematic review of quality of life in children with SMA noted that the PedsQL™ is the most commonly used in SMA studies, both the generic and neuromuscular modules. While there is a wide selection of measurement tools available in QOL literature, these are not disease-specific and there is not yet consensus on which tool is best for those with SMA.[42] SMA specific modules or tools may be most sensitive to capture change across studies.

Table 4: Commonly Used Outcomes by SMA Functional Level/ Phenotype

Non-Sitters	CHOP INTEND	HINE-2 Motor	WHO – Motor Milestones	BSID-III/ Bayley-4	TIMPSI				
Sitters	HFMSE/ RHS	RULM	WHO	MFM	HHD (grip/ pinch, elbow flex/ext, knee flex/ext, etc)	TFT (9HPT, r9HPT, ESNHPT, BBT, ESBBT)	BSID-III, Bayley-4	ACTIVE	
Walkers	HFMSE/ RHS	6MWT	Other TFT (10MWRT, TTR, TTC, TUG, 30STS, ESWT, 9HPT, r9HPT, ESNHPT, BBT, ESBBT)	MFM	HHD (grip/ pinch, elbow flex/ext, knee flex/ext, etc)	RULM			
Presymptomatic and/or identified by Newborn Screening (NBS)	CHOP INTEND	HFMSE/ RHS	HINE-2 Motor	WHO	6MWT	PDMS-2 BSID-III, Bayley-4	TIMP/ TIMPSI HINT AIMS	Other TFT (10MWRT, TTR, TTC, TUG, 9HPT, r9HPT, ESNHPT, BBT, ESBBT)	
Chronic Adult [2]	CHOP ATEND/ ATEND	HHD (grip/ pinch)	Modified SMAFRS	EK2	TFT (9HPT, r9HPT, ESNHPT)				
Pulmonary Outcomes	PFT	RIP							
Patient Reported Outcomes (PROs) [3]	ACEND	EK2	Fatigue (FSS, PedsQL™, PROMIS®)	Modified SMAFRS	PEDI-CAT	PedsQL™	PROMIS®	SMA-HI	ACTIVLIM

[2] *In addition to functional level above if appropriate*
[3] *Test in alphabetical order (can be administered to all types of SMA)*

Most Commonly Used Outcomes Tests

For additional details on each outcome test listed below see Table A4: Outcome Measure and Evaluation Resources.

Test Most Commonly Used for Non-Sitters

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

Click here for test manual, proforma, and references

The CHOP INTEND was developed as a disease-specific measure to assess weak patients with neuromuscular disease, including those with SMA type I. Development of the tool was based on the natural history progression of motor function for infants with type I. Items chosen include spontaneous goal-directed movements as well as reflexive movements and were derived in part from items that were from the CHOP Test of Strength in SMA (CHOP TOSS) and the Test of Infant Motor Performance (TIMP). The test includes 16 items that provide information about strength and function, including gravity-eliminated and gravity-assisted (lower scores) to antigravity movements (higher scores).

The items are ordered to minimize position changes and prone positioning secondary to limited tolerance and also ordered such that least tolerated items are tested last.[43]

The test is valid and reliable and sensitive to change in SMA type I.[43,44] This tool has been utilized in multiple natural history studies of SMA type I, as well as in multiple SMA clinical trials. The test is best for younger, very weak or fragile infants, but may be used across a range of ages. A new version adapted for adults in a wheelchair (ATEND) is under development.

- **Scoring:** Gradated scoring from 0 (no response) to 4 (full response). The best side score for all items are summed for a total test score of 64.
- **Time to complete:** The test can be completed in 15-40 minutes with a cooperative infant/child and is typically well-tolerated.
- **Equipment:** mat, rattle, Sophie the giraffe, toy phone
- **Supportive evidence in SMA research:** The CHOP INTEND scores in untreated children with SMA decline over time. A prospective, longitudinal natural history study[3,45] demonstrated that infants with genetically confirmed SMA have significantly lower CHOP INTEND scores than age-matched typically developing infants over the same period. Infants with SMA type I with two copies of SMN2 diverge from typical progression very early and on average score 20.2, never scoring >36, while typically developing children easily score 40 or above. Longitudinal data shows a mean change in moderate to severe phenotypes with a loss of -0.31 points/mo., with mild phenotypes averaging a loss of -0.04 points/month[46,47] and a mean loss of -12.67 points was demonstrated over 2 years[45]. A review of 3 longitudinal natural history studies using the CHOP INTEND for infants with type I SMA clearly indicates that infants first assessed prior to 7 months of age and without treatment do not demonstrate improvement on the CHOP INTEND over time.[48] Infants enrolled in the NURTURE presymptomatic study of Nusinersen reported mean scores rose steadily from baseline to day 183 and then stabilized. At the last reported visit mean (range) CHOP INTEND score was 62.1 (48-64) for those with 2 copies of SMN2 and 63.4 (58-64) in those with 3 SMN2 copies.[49] In the ENDEAR study, a randomized controlled trial (RCT) of symptomatic type I infants, the CHOP INTEND response in the treated group was 71% vs 3% in the sham group.[50,51] In the AveXis Phase 1 gene therapy study the CHOP INTEND has also

shown promising changes with enrolled infants reaching an average total score of 54 points by 30 months of age.[52,53] In the FIREFISH study infants with type I SMA showed a median change from baseline of 16 points at 2 years of age.[54] Participants enrolled in the FIREFISH phase II/III open label study have demonstrated positive improvements on the CHOP INTEND.[55]

Hammersmith Infant Neurological Exam-Section 2, Motor Milestone (HINE-2)

Click here for test manual, proforma, and references

The complete HINE assesses different aspects of neurologic development (cranial nerves, motor milestones, posture, tone, reflexes and reactions, and behavior). The HINE Motor Milestones Part 2 or HINE-2 is a brief, standardized assessment designed for assessment of 8 motor skills and their progression in healthy or high-risk infants up to 24 months of age.[56-58] The tool is based on normal motor development (norm-referenced) and has been validated on typically developing children and demonstrates good inter-observer reliability, even with less experienced assessors.[57] The test allows age at which milestones are achieved to be recorded and is a more granular assessment than World Health Organization (WHO) motor milestones. The HINE-2 assesses intermediate gradations for each milestone that lead to full achievement of each milestone. While it was not specifically designed for those with SMA type I, it has been used in several SMA clinical trials. Testing in SMA clinical trials has demonstrated excellent test-retest reliability and has demonstrated feasibility and sensitivity when utilized in an SMA phase 2 clinical trial of Nusinersen.[59]

- **Scoring**: Items are checked when completed on the proforma and each item has gradations from 0-3 to 0-5.
- **Time to complete:** 5-15 minutes
- **Equipment:** Does not require any specific equipment
- **Supportive evidence in SMA research**: The HINE-2 is reliable and sensitive to change and demonstrated the ability to detect change over time in 16/19 infants with SMA in each of the 8 motor skill domains. Hammersmith Infant Neurological Exam-Section 2, Motor Milestone improvements were also correlated with changes in other neuromuscular outcome measures.[59] In recent SMA studies there are documented changes from baseline in the HINE motor milestones in the Nusinersen ENDEAR phase 3 RCT study where a significantly higher percentage of infants in the Nusinersen group than in the control group had a motor-milestone response (37 of 73 infants [51%] vs. 0 of 37 [0%]).[51] In the NURTURE study of presymptomatic infants receiving Nusinersen, mean scores on the HINE-2 motor milestones, for infants with SMA with two or three SMN2 copies, approached the scale maximum of 26 points, with three copy participants reaching the maximum earlier than those with two copies.[49] Participants enrolled in the FIREFISH phase II/III open label study of those with SMA type I have demonstrated positive improvements on the HINE-Section 2.[55]

World Health Organization Motor Milestones (WHO)

Click here for test manual, proforma, and references

The WHO motor milestones were developed by the World Health Organization to assess acquisition of 6 key gross motor milestones. The WHO is a norm-referenced tool developed as a part of the World Health Organization multi-center growth reference study. Longitudinal data were collected to describe the attainment

of 6 gross motor milestones by children between 4 and 24 months of age in the US, Ghana, India, Norway, and Omen.[60] The milestones described are reflective of typical development across the first 18 months of life. The windows represent normal variation in ages of milestone achievement among healthy children and are recommended for descriptive comparisons among populations. The comparisons can signal the need for appropriate screening in individual children who appear to be late in achieving the milestones, and to raise awareness about the importance of overall development in child health.

WHO motor milestones have been utilized in multiple SMA clinical trials to longitudinally assess attainment of motor milestones either by the parent and/or the CE. The advantage of the WHO is that it includes easy to assess clinically meaningful items that are discrete. There is broad variability of time within which they may be achieved. Limitations of the assessment include large milestone increments without scalar scoring.

- **Scoring:** Items are scored as able or unable.
- **Time to complete:** 5-15 minutes
- **Equipment:** Requires a floor mat and table or bench at an appropriate height that the child can cruise along
- **Supportive evidence in SMA research**: The WHO motor milestones are currently used in clinical trials for those with SMA including Biogen and Roche studies. All infants enrolled in the NURTURE presymptomatic study of Nusinersen (25/25) had achieved the WHO motor milestone of sitting without support. Walking with assistance was achieved by 23/25, and 22/25 achieved walking alone. Most participants achieved these milestones within the window for healthy children established by the WHO.[49]

Bayley Scales of Infant Development III (BSID-III)/Bayley-4

Click here for test manual, proforma, and references

The BSID-III/Bayley-4 measures both cognitive and motor development and tests the behavior of infants from 1 to 42 months of age. The BSID-III is used to describe the current developmental functioning of infants and toddlers and to assist in diagnosis and treatment planning for those with developmental delays or disabilities. Both tests are intended to measure a child's level of development in 5 domains: cognitive, language, motor, social-emotional and adaptive behavior. This measure consists of a series of developmental skills and derives a developmental quotient. Raw scores of successfully completed items are converted to scaled scores and composite scores.[61,62] The scores are used to determine the child's performance compared with norms taken from typically developing children of their age. The BSID-III has 3 main subtests: the Cognitive Scale which includes items such as attention to familiar and unfamiliar objects, looking for a falling object and pretend play; the Language Scale, which taps into understanding receptive and expressive language such as recognition of objects and people, following directions, and naming objects and pictures; and the Motor Scale, which assesses fine and gross motor skills such as grasping, stacking blocks, sitting and climbing stairs.[61,62]

- **Scoring:** BSID-III: Items are scored as not able (0) or able (1). Bayley-4: Items are scored as not present (0), emerging (1), or mastery (2),
- **Time to complete:** 45-120 minutes
- **Equipment:** Bayley kit, large room with minimal distractions, floor mat and table or bench at an appropriate height chair and table

- **Supportive evidence in SMA research:** The BSID-III is currently being used in AveXis and Roche SMA clinical trials. To date no evidence is published on the BSID-III specific to SMA.

Test of Infant Motor Performance Screening Items (TIMPSI)

Click here for test manual, proforma, and references

The Test of Infant Motor Performance (TIMP) is a psychometrically valid, well-constructed scale that is useful as an evaluative and predictive tool to assess motor performance in infants born preterm through 4 months of age. It is used to assess the postural and selective control of movement typically used by infants younger than 5 months.[63] It has demonstrated excellent reliability, sensitivity and validity when used in infants born prematurely and at high risk for poor motor performance.[64,65] The TIMPSI is a shorter, screening version of the TIMP[63] which estimates concurrent performance on the TIMP. The test items and item scoring seemed well suited to assess strength, endurance, and antigravity movement in all body segments in various planes and directions, which are significant impairments for infants with type I SMA. The TIMPSI is based on extensive psychometrics, including Rasch analysis. The TIMPSI is shorter and thus can be administered quickly and with less stress. The TIMPSI has demonstrated reliability and validity in infants with SMA.[3,11,45,66] The construct of the TIMPSI and its reliability in infants with SMA type I facilitate its use as a secondary outcome measure for use in assessing potential change in a clinical trial or study to assess an intervention specifically intended to improve motor function. The TIMPSI is a valuable assessment for infants clinically post newborn screening (NBS) due to its' ability to capture changes in postural and selective control in young infants at high risk.

There are 3 item sets: Screening, Easy and Hard. Each set takes 10-20 minutes to complete. Items assessed include strength, head control, rolling, righting, reaching, weight bearing, etc.

- **Scoring:** 0-6, varies by item. The maximum achievable score is 99.
- **Time to complete:** 15-40 minutes
- **Equipment:** mat, small red ball and rattle
- **Supportive evidence in SMA research:** The TIMPSI has been utilized in the Carni-VAL trial of infants with type I SMA,[11] in the NeuroNEXT Infant Study of Biomarkers for SMA[3,11,45] and in several natural history studies. While the TIMPSI score increases with age in typically developing infants, there is no change with age in those with SMA with controls averaging 73/99 at 4 months of age and those with SMA averaging only 38/99 points at 6.7 months of age.[67] Further correlation of TIMPSI total scores of SMA infants with mean values of a normative population of low-high risk infants demonstrated a progressive deviation, with SMA infants scoring > 2 standard deviations below the normative population mean by 4-5 weeks of age.[67] In the Carni-Val valproic acid (VPA) study for infants with type I SMA, the TIMPSI was correlated with the Parent Caregiver Functional Rating Scale and with the ability to reach from supported sit and supine.[11,66] In the NeuroNEXT study the TIMPSI demonstrated excellent reliability during a multisite clinical trial and established baseline motor function over a two-year period for infants with type I SMA. Test of Infant Motor Performance Screening Items scores diverged early for infants with type I SMA vs healthy controls and decline was similar to the decline noted in the CHOP INTEND over a similar time period.[45,47] The TIMPSI scores were correlated with risk of survival or need for permanent invasive ventilation in infants with SMA.[45]

Tests Most Commonly Used for Sitters

Hammersmith Functional Motor Scale Expanded (HFMSE)

Click here for test manual, proforma, and references

The HFMSE assesses motor function of those with both type II and type III SMA.[68] The HFMSE originated from the Hammersmith Functional Motor Scale (HFMS), a 20-item test of motor function developed for those with SMA type II and based on the natural history of the disorder. Thirteen items from the Gross Motor Function Measure (GMFM), were added to the original scale to allow its use in both ambulant and non-ambulant patients with SMA type II and III (33 items). The HFMSE should be performed by individuals who have experience in the handling of children and adults with SMA, such as physical or occupational therapists. Use of the scale should be predicated by the understanding of the skills' starting positions, operational definitions, and scoring criteria.

- **Scoring:** Items are graded on a scale of 0, 1, 2, where 0 indicates unable, 1 indicates the item is performed with modification, adaptation or compensation, and a 2 indicates the item was performed without modification, adaptation or compensation. The maximum achievable score is 66.
- **Time to complete:** 10-30 minutes
- **Equipment:** mat, adjustable bench, stairs, tape and ruler
- **Supportive evidence in SMA research:** Evidence demonstrates that the HFMSE differentiates ambulant patients not captured on the original HFMS.[68] The HFMSE is highly correlated with the GMFM and discriminates between SMA type, ambulatory function, and respiratory function (BiPAP use).[69] Excellent inter and intra-rater reliability has been demonstrated across multiple multisite clinical trials.[70] Expected change in HFMSE scores with age and type of SMA has been established.[9,71] A recent longitudinal HFMSE analysis demonstrated some improvement in scores through age 5, with stabilization or slow loss of function (about 2 points per year) from 5-13 years of age.[72] In the Biogen CHERISH Phase 3 RCT study of Nusinersen, 57% of the children in the Nusinersen group as compared with 26% in the control group had a significant increase from baseline to month 15 in the HFMSE score of at least 3 points.[73] Content validity and clinical meaningfulness of the HFMSE has been established.[74]

Revised Hammersmith Scale (RHS)

Click here for test manual, proforma, and references

The RHS is a 36-item assessment of motor/functional ability for those with non-ambulatory (type II and III) and ambulatory (type III) SMA. The RHS includes items adapted from the HFMSE and includes higher functioning items adapted from the North Star Ambulatory Assessment including timed rise from floor and 10-meter walk/run tests.[75] Rasch analysis demonstrated very good fit of all 36 items to the construct of motor performance, good reliability with a high Person Separation Index PSI 0.98, logical and hierarchical scoring in 27/36 items and excellent targeting with minimal ceiling. Validity is demonstrated as RHS scores discriminate for SMA types, ambulatory status, and correlates strongly with the WHO motor milestones confirming the scale's ability to measure progressively more difficult motor abilities.[75]

- **Scoring:** Thirty-three items are graded on a scale of 0, 1, 2, where 0 denotes the lowest level of ability/function and 2 denotes the highest level of ability. An additional three items are scored 0, 1, where 0 denotes an inability and 1 denotes an ability to achieve. The maximum achievable score is 69.
- **Time to complete:** 15-40 minutes
- **Equipment:** chair, bench, mat, box step, stairs, stop watch, tape and ruler
- **Supportive evidence in SMA research:** The RHS has not been used in past clinical trials but is currently being utilized in the Scholar Rock Study of SKR-015, a latent myostatin inhibitor.

Revised Upper Limb Module (RULM)

Click here for test manual, proforma, and references

The RULM is a 20-item evaluation of upper limb function primarily used for those with SMA who are non-ambulatory (young children through adults). The 19 items test upper extremity and ADL functions that relate to everyday life, such as placing hands on lap, pressing a button, and picking up a token.[76,77] The RULM has demonstrated reliability and validity.[76,78,79]

- **Scoring:** Items are scored 0, 1, 2, where 0 denotes unable, 1 denotes able to with modification, and 2 denotes able with no difficulty. One item is scored 0 (unable) or 1 (able). The maximum score achievable for each extremity is 37.
- **Time to complete:** 10-15 minutes
- **Equipment:** plastic cup, soft touch light, small kitchen weights, hand cuff weight, pencil, adjustable seating and table, Ziploc container, paper (A-14 size), activity mat for use with weight, coins (see Table A6: RULM Kit Supply List)
- **Supportive evidence in SMA research:** A recent longitudinal natural history study reported a mean change in RULM score of -0.23 to -0.45 points over 12 months in 114 patients with type II and type III SMA (Pera et al., 2019). The RULM was previously used in the Biogen CHERISH Phase 3 RCT study where the least-squares mean increased from baseline in the RULM score in the Nusinersen group and in the control group (by 4.2 points and 0.5 points, respectively). It is currently being used in the Biogen, Roche, and Scholar Rock clinical trials.

World Health Organization Motor Milestones (WHO)

See above under Non-Sitters

Motor Function Measure (MFM-32, MFM-20)

Click here for test manual, proforma, and references

The Motor Function Measure (MFM) was designed to evaluate both ambulatory and non-ambulatory patients aged between 6 and 60 years with neuromuscular diseases of all degrees of disease severity. The MFM measures motor function in three functional dimensions: standing position and transfers (13 items), axial and proximal motor function (12 items) and distal motor function (7 items). The 3 subsets of items can be completed together or individually. It has been validated in terms of reliability, construct validity, concurrent validity and sensitivity to change over one year.[80] The MFM-32 has demonstrated reliability in non-ambulatory types II- and III SMA and MFM-32 scores correlated with the Vignos Scale, Clinical Global Impression of Severity Score (CGI-S), FVC and Hammersmith Functional Motor Scale (HFMS).[81,82] Psychometric properties of the MFM-20 include principal component analysis which confirmed the 3 functional domains. Inter- and intra-rater reliability of the 3 sub-scores and total score were high, and discriminant validity was good.[83] Training is required to learn how to administer and score the test correctly. While onsite training is preferred, a self-study DVD is available in English.

- **Scoring:** Scoring is on a 4-point Likert scale based on the subject's best abilities without assistance: 0 (does not initiate movements or starting position cannot be maintained); 1 (partially completes the exercise); 2 (completes the exercise with compensation, slowly, or with obvious clumsiness); and 3 (completes the exercise in the standard pattern). The total score ranges from 0 to 60 when summing the 20 items. The total score and sub-scores are expressed as a percentage of the maximum possible score.

- **Time to complete:** MFM-32: 30-50 minutes, MFM-20: 12-50 minutes

- **Equipment:** tennis ball, coins, CD, pencil, paper, stop watch, and other items found in therapy settings

- **Supportive evidence in SMA research:** The MFM was utilized in the Olesoxime clinical trial for SMA. The primary study outcome for the Olesoxime study was the MFM-32 (D1 and D2). Patients younger than 6 were assessed using the shorter version, the MFM-20. Mean change from baseline to month 24 was not significant in treated vs placebo groups.[84] The MFM-32 has been used in SMA natural history studies of those with types 2 and 3[85] and is currently being utilized in the Roche clinical trials.

Hand Held Dynamometry (HHD)

Click here for test manual, proforma, and references

Strength measurement with a dynamometer is more quantifiable and reliable than using manual muscle testing (MMT) or grading using the Medical Research Council (MRC) scale. Myometry provides quantitative measurement of strength over a continuous range and allows us to monitor change in strength over time.[86-88] Inter-rater reliability is excellent in the upper limbs with interclass correlation coefficients (ICCs) of 0.98 for elbow flexion and grip, and 0.92 for 3-point pinch. In lower limbs inter-rater reliability is good (ICC>0.85) in all muscles except foot dorsiflexion. Test-retest in SMA is excellent with all ICC >0.92.[89] A clear understanding of muscle action, standardized testing positioning, as well as the placement of the dynamometer and type of test protocol (make vs break test) is required to get consistent, repeatable measurement from session to session. Isometric torque reference values for children and adolescents (influenced by age, weight, and height) are available to allow for identification of muscle strength impairments and deviation from typical patterns of strength progression.[86,90,91] Hand held dynamometry discriminates between walkers and non-walkers and correlates with TFTs.[92]

- **Scoring:** Quantitative measurement in kilograms, pounds, or newtons of force using a make or break test

- **Time to complete:** < 5 minutes per muscle group
- **Equipment:** Hand-held dynamometer
- **Supportive evidence in SMA research:** Elbow flexion/extension and knee flexion/extension HHD were collected in the Carni-VAL clinical trial of VPA in those with type II and III SMA ≥5 years of age.[24] There was no statistical difference in myometry from baseline to 6 or 12 months. Hand held dynamometry was also used to assess changes in strength in a resistive exercise training protocol with no change noted over 12 weeks despite an increase in the amount of weight lifted.[29] Both studies reported high reliability (≥ 0.95), however, included small participant samples (n<20).

Timed Function Tests (TFT)

The TFTs can be used to assess time to complete a task. They can also be incorporated as part of another test (e.g. the 10-meter walk/run and the timed rise from the floor are also included as part of the RHS).

Nine Hole Peg Test (9HPT)

Click here for test manual, proforma, and references

The originally validated and reliable 9HPT assessed fine motor dexterity in the distal upper extremity.[93] The patient is instructed to pick up the 9 pegs one at a time, put them in the 9 holes of the pegboard as quickly as possible, and once they are in the holes, remove them again as quickly as possible one at a time, placing them into the shallow well opposite the pegboard.

- **Scoring:** The time to complete the task is recorded for placing pegs in and then moving pegs out in seconds and the two times are added together for the 'total score'.
- **Time to complete:** 1-3 minutes
- **Equipment:** Nine hole peg test, adjustable chair and table, stop watch
- **Supportive evidence in SMA research:** Use of the 9HPT has not been reported in SMA clinical trials to date. The test was used as a secondary measure in the type II/III Carni-VAL trial and there was no reported change in time from baseline to 6 months or 12 months for the 9HPT.[24]

Repeated (5 times) Nine-hole peg test (r9HPT)

Click here for test manual, proforma, and references

The r9HPT is a modified version of original 9HPT which is targeted to examine endurance versus fine motor function. The patient is instructed to pick up the 9 pegs one at a time, put them in the 9 holes of the pegboard as quickly as possible, and once they are in the holes, remove them again as quickly as possible one at a time,

placing them into the shallow well opposite the pegboard. Participants perform 5 consecutive rounds with the same hand of choice. The time to complete the task is recorded for each round. The score for the r9HPT is an average of the five rounds. The change in scores from one round to the next is also examined to determine if increasing time is needed to perform as a result of muscle fatigability.[94]

- **Scoring:** The time to complete the task is recorded for each round. The score for the r9HPT is an average of the five rounds.
- **Time to complete:** ~20 minutes
- **Equipment:** Nine hole peg test, adjustable chair and table, stop watch
- **Supportive evidence in SMA research:** The r9HPT was feasible and sensitive to detect fatigability in patients with SMA type II. A recent study included patients with SMA type II, IIIa, IIIb and IV as well as healthy and disease controls and demonstrated that those with type II SMA perform slower than all other groups. Time needed to complete each round increased in 65% of patients with SMA type II, 36% of type IIIa, 22% of type IIIb/IV, 31% of disease controls and 6% of healthy controls. Patients with SMA type II performed the test significantly more slowly than all other groups ($p<0.005$) specifically performing round five 27% slower overall as compared to healthy controls who performed round five 14% faster than round 1. Those with types IIIa, IIIb, IV and disease controls performed similarly to healthy controls. The probability of continuing the test also decreased for those with type II as compared to other groups.[94]

Endurance Shuttle Nine Hole Peg Test (ESNHPT)

Click here for test manual, proforma, and references

The ESNHPT was developed for neuromuscular patients with upper extremity weakness to provide a measure of upper limb endurance for those who cannot participate in other endurance tests (six-minute walk test). This test, along with the Endurance Shuttle Box and Block Test (ESBBT) assesses fatigability of both distal and proximal upper extremity musculature using a submaximal repetitive test protocol while pace is externally regulated. Participants are instructed to continuously perform the original 9HPT moving 9 pegs into and out of the peg board as fast as possible at 75% of their individual maximum speed. Auditory cuing by set-speed metronome is used to maintain 75% max speed. They are encouraged to continue as long as possible. The test ends when the patient misses 2 consecutive beeps. Primary outcome parameter is time to limitation (Tlim), the time a task can be maintained at the pre-set intensity. In a small study including 13 patients with SMA 31% of patients demonstrated fatigability at the end of the ESNHPT reflected by decrease in coordination, compensatory movements and changes in perceived exertion.[95] Construct, convergent and discriminant validity and reliability of the ESNHPT has been demonstrated and supports use of the ESNHPT to assess fatigability in patients with types II, III & IV SMA older than 10 years of age.[96]

- **Scoring:** Time to limitation in seconds when task continued at a preset speed
- **Time to complete:** Maximum test duration is 20 minutes. Test discontinued when T-lim is met.
- **Equipment:** 9HPT, adjustable chair and table, metronome, stop watch
- **Supportive evidence in SMA research**: The ESNHPT has not been used in past clinical trials. It is currently being utilized in a phase 2 study of pyridostigmine in SMA and the Scholar Rock Study of SKR-015, a latent myostatin inhibitor.

Box and Blocks Test (BBT)

Click here for test manual, proforma, and references

The BBT is a test of gross manual dexterity of the upper limb. When testing begins, the patient is instructed to grasp one block at a time with the dominant hand, transport the block over the partition, and release it into the opposite compartment. The patient continues doing this for one minute. The number of blocks transported in 1 minute is recorded. The procedure should then be repeated with the non-dominant hand. The examiner should sit across the table from the participant to observe performance. Reliability in typically developing children and adults across age bins has been reported, and reliability in non-neuromuscular disease populations has also been reported. However, no reliability to date has been reported for patients with SMA.[97]

- **Scoring:** Number of blocks transported in 1 minute
- **Time to complete:** Maximal test duration is 1 minute for each upper extremity, with a rest break in between trials.
- **Equipment:** Box and Blocks Test (150 blocks, box, partition), adjustable table and chair, stop watch
- **Supportive evidence in SMA research:** The BBT has not to date been used in any SMA clinical trials.

Endurance Shuttle Box and Block Test (ESBBT)

Click here for test manual, proforma, and references

The ESBBT was developed for neuromuscular patients with upper extremity weakness to provide a measure of upper limb endurance for those who cannot participate in other endurance tests (six-minute walk test). This test, along with the ESNHPT assesses fatigability of both distal and proximal upper extremity musculature using a submaximal repetitive test protocol while pace is externally regulated. Participants are instructed to continuously perform the original BBT transferring 10 blocks over the partition as fast as possible before the beep at 75% of their individual maximum speed. They are encouraged to continue for as long as possible. Auditory cuing by set-speed metronome (at 75% max speed) is used to maintain speed. The test ends when the patient misses 2 consecutive beeps. Primary outcome parameter is time to limitation (Tlim), the time a task can be maintained at the pre-set intensity.[95] Construct, convergent and discriminant validity and reliability of the ESBBT has been demonstrated and supports use of the ESBBT to assess fatigability in patients with types II, III & IV SMA older than 10 years of age.[96]

- **Scoring:** Time to limitation in seconds when task continued at a preset speed
- **Time to complete:** Maximal test duration is 20 minutes. Test discontinued when T-lim is met.
- **Equipment:** Box and Blocks Test, 200 blocks, adjustable table and chair, metronome, stop watch
- **Supportive evidence in SMA research:** The ESBBT has not been used in past clinical trials. It is currently being utilized in a phase 2 study of pyridostigmine in SMA and the Scholar Rock Study of SKR-015, a latent myostatin inhibitor.

Bayley Scales of Infant Development III (BSID-III)/Bayley-4

See above under Non-Sitters

Ability Captured Through Interactive Video Evaluation (ACTIVE)

Click here for test manual, proforma, and references

The ACTIVE is a custom-designed 65 second video game that measures workspace volume (WSV) and quantifies upper extremity function in SMA. Workspace volume is defined as the area around a person within which she/he can reach and interact. The ACTIVE uses the skeletal tracking algorithm developed for the Microsoft Kinect camera. The ACTIVE measures function and responsiveness to treatment over time and should be considered for use as part of the outcome measure toolbox in SMA.[98]

- **Scoring:** A continuous scale of maximum WSV (reported in cubic meters) and scaled score per visit is provided.
- **Time to complete:** 15 minutes
- **Equipment:** Plug-and-play program, Microsoft Kinect camera, monitor
- **Supportive evidence in SMA research:** The ACTIVE was significantly correlated to the HFMSE and RULM ($p=0.85$ and $p=0.92$ respectively; $p<0.001$) in SMA types II and III. Relevance to patients and families was established by strong correlations to PROs. Responsiveness to change was demonstrated by significant change in scaled scores after treatment (median 15.9 points, Wilcoxon signed-rank test $p<0.01$).[98]

Tests Most Commonly Used for Walkers

Hammersmith Functional Motor Scale Expanded (HFMSE)

See above under Sitters.

Revised Hammersmith Scale (RHS)

See above under Sitters.

Six-minute Walk Test (6MWT)

Click here for test manual, proforma, and references

The 6MWT has been used in multiple clinical trials for ambulatory participants with SMA and measures the total distance walked in 6 minutes. Participants are asked to walk for 6 minutes (or as long as they can go) along a standardized 25-meter course. At the end of 25 meters they are instructed to walk around a cone and return to the start, repeating as often as they are able. Minute distance and total distance walked over 6 minutes is captured. This test can also provide an indication of fatigue as determined by the percent change in distance walked from the first to the last minute. Decrease in stride length, velocity and speed over time have also been described.[99-101] The test demonstrates excellent reliability and convergent validity in those with SMA as it correlates positively with other functional and clinical assessments such as the HFMSE, knee flexion HHD, stride length, lower extremity manual muscle testing and inversely with the 10MWRT.[102,103] Longitudinal data demonstrates age-related patterns of progression similar to other natural history motor function declines.[100]

- **Scoring:** Minute distances and total distance walked over 6 minutes is captured.
- **Time to complete:** 10 minutes
- **Equipment:** clear 30-meter walkway, tape measurement, stop watch, 2 orange cones, post-it flags
- **Supportive evidence in SMA research:** The 6MWT has been used in Cytokinetics' Reldesemtiv study and the Biogen's phase 2 open-label study of Nusinersen. In the Cytokinetics' study dose dependent changes in the 6MWT were reported at both time points post-baseline. In the 150 mg twice daily group vs placebo, mean increases of 10.86 meters (p=0.2531) at 4 weeks and 7.72 meters (p=0.4684) at 8 weeks post baseline were reported. In the 450mg BID group vs placebo, mean increases of 35.63 meters (p=0.0037) at 4 weeks and 24.89 meters (p=0.0584) at 8 weeks post baseline were reported.[104] There was also a statistically significant correlation between Reldesemtiv peak concentration and change from baseline in the 6MWT with a slope estimate of 9.53 meters/mg/mL.[104] In the Biogen study median distance walked increased over time by 17 meters at Day 253 and 98 meters at Day 1050, and mean fatigue decreased by -3.8%.[105] It is currently being used in Biogen, Roche, and Scholar Rock clinical trials.

Other Timed Function Tests (TFT)

See 9HPT, r9HPT, ESNHPT, BBT and ESBBT under sitters.

10-meter Walk/Run Test (10MWRT)

Click here for test manual, proforma, and references

The 10MWRT records the time taken to safely walk or run 10 meters on a marked 10-meter course. Time to complete discriminates between older and younger individuals with SMA and correlates with knee extensor and flexor strength and effectively measures walking ability with minimal endurance needs.[24,92] The 10MWRT is inversely correlated with the 6MWT distance.[102]

- **Scoring:** Time to complete in seconds
- **Time to complete:** Test discontinued if time > 180 seconds
- **Equipment:** 10-meter walkway, stop watch
- **Supportive evidence in SMA research**: Change in 10MWRT improved after 2 years of treatement on nusinersen.[106] The 10MWRT was used in the Carni-VAL type III study. No changes were reported from baseline to 6 months or 12 months.[24,107] It is currently being utilized in the Scholar Rock Study of SKR-015, a latent myostatin inhibitor as part of the RHS.

Timed Rise from Floor (TTR)

Click here for test manual, proforma, and references

The TTR assesses the time taken to rise from supine on the floor to standing upright.[24,92]

- **Scoring:** Time to complete test in seconds
- **Time to complete:** Test discontinued if time > 180 seconds
- **Equipment:** space to complete, floor mat, stop watch
- **Supportive evidence in SMA research:** Change in TTR improved after 2 years of treatement on nusinersen.[106] The TTR was used in the Carni-VAL type III study. No changes were reported from baseline to 6 months or 12 months.[24,107] It is currently being utilized in the Scholar Rock Study of SKR-015, a latent myostatin inhibitor as part of the RHS.[106]

Time to Climb 4 Stairs (TTC)

Click here for test manual, proforma, and references

The TTC assesses the time spent in the performance of a functional activity. Generally, the use of compensatory movements tends to increase the time spent in the performance of the activity tested and thus is indicative of worsening of functional status.

- **Scoring:** Time to complete in seconds
- **Time to complete:** Test discontinued if time > 180 seconds
- **Equipment:** stop watch, set of four 6" high steps with rails on both sides
- **Supportive evidence in SMA research:** Change in TTC improved after 2 years of treatment on nusinersen.[106] The TTC was used in an SMA natural history study[85] and the Carni-VAL type III clinical trial.[24,107] No changes were reported from baseline to 6 months or 12 months.[106]

Timed Up & Go (TUG)

Click here for test manual, proforma, and references

The TUG test is a quick measure of balance and mobility. The TUG scores correlate with clinical, functional, and strength assessment and decline linearly over time. Test-retest reliability was good to excellent for those with SMA. The TUG is correlated with total leg and knee flexor strength, the HFMSE, the 10MWRT, and 6MWT.[108]

- **Scoring:** Time to complete in seconds
- **Time to complete:** < 2 minutes
- **Equipment:** stop watch, chair with arms (seat height to allow for feet flat on floor and arms resting on arm rests), 3-meter pathway, marker cone
- **Supportive evidence in SMA research:** The TUG was used in Cytokinetics' study of Reldesemtiv, however, did not demonstrate significant differences between groups receiving Reldesemtiv vs placebo.[104]

30 Second Sit to Stand (30STS)

Click here for test manual, proforma, and references

The 30STS is used by researchers and clinicians as an assessment of functional lower limb strength[109] and has demonstrated good inter-tester and intra-tester reliability in adult populations using a standardized

protocol.[110] The test was modified for ambulatory SMA population and measures the total number of completed stands in 30 seconds.

- **Scoring:** Number of complete sit-to-stands are counted. Partial attempts or attempts when the participant does not fully obtain upright standing are not counted. Number of stands are recorded with the use of arms and without arms.
- **Time to complete:** 30 seconds
- **Equipment:** stop watch, bench without armrests
- **Supportive evidence in SMA research:** The 30STS has not yet been used in past clinical trials. It is currently being utilized in the Scholar Rock Study of SKR-015, a latent myostatin inhibitor.

Endurance Shuttle Walk Test (ESWT)

Click here for test manual, proforma, and references

The ESWT was developed for neuromuscular patients with lower extremity weakness to capture change in endurance in ambulatory patients. This test assesses fatigability and endurance capacity of lower extremity musculature using a submaximal repetitive test protocol while pace is externally regulated. Participants are instructed to continue walking on a 10meter shuttle course as fast as possible before the beep at 75% of their individual maximum speed. They are encouraged to continue for as long as possible until they are too tired or breathless. Walking speed was externally regulated by set-speed metronome (at 75% max speed) is used to maintain speed. The test is terminated prematurely when a participant fails two times in a row to reach the other side within time. Primary outcome parameter is time to limitation (Tlim), the time a task can be maintained at the pre-set intensity. The ESWT demonstrated good test-retest reliability and sensitivity to change after a seven-week rehabilitation program.[95] Construct, convergent and discriminant validity and reliability of the ESWT has been demonstrated and supports use of the ESWT to assess fatigability in ambulatory patients with types III & IV SMA older than 10 years.[95,96]

- **Scoring:** Time to limitation in seconds when task continued at a preset speed
- **Time to complete:** Maximal test duration is 20 minutes. Test discontinued when T-lim is met.
- **Equipment:** 10 meter shuttle course, metronome, stop watch
- **Supportive evidence in SMA research:** The ESWT has not been used in past clinical trials. It is currently being utilized in a phase 2 study of pyridostigmine in SMA.

Motor Function Measure (MFM-32, MFM-20)

See above under Sitters.

Hand Held Dynamometry (HHD)

See above under Sitters.

Revised Upper Limb Module (RULM)

See above under Sitters.

Tests for Presymptomatic Patients with SMA and/or Identified by NewBorn Screening (NBS)

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

See above under Non-Sitters.

Hammersmith Functional Motor Scale Expanded (HFMSE)

See above under Sitters.

Revised Hammersmith Scale (RHS)

See above under Sitters.

Hammersmith Infant Neurological Exam-Section 2, Motor Milestone (HINE-2)

See above under Non-Sitters.

World Health Organization Motor Milestones (WHO)

See above under Non-Sitters.

Six-minute Walk Test (6MWT)

See above under Walkers.

Peabody Developmental Motor Scales-2 (PDMS-2)

Click here for test manual, proforma, and references

The PDMS-2 is a standardized evaluation for children from birth to 72 months (6 years). The Gross Motor Composite includes 4 domains: reflexes, stationary, locomotion, and object manipulation. The Reflex Domain measures the child's ability to automatically react to environmental events. The Stationary Domain measures the child's ability to sustain control of his or her body within its center of gravity and retain equilibrium. The Locomotion domain measures the child's ability to transport his or her body from one base of support to another. The Object Manipulation Domain measures the child's ability to manipulate balls, i.e. throw, catch, and kick balls. The Fine Motor Composite includes 2 domains: Grasping and Visual-Motor Integration. The Grasping Domain measures a child's ability to use his or her hands and the Visual-Motor Integration Domain measures a child's ability to use his or her visual perceptual skills to perform complex eye-hand coordination tasks such as reaching and grasping for an object, building with blocks, and copying designs.[111]

Item scores are summed, and results of subtests may be used to generate three global indexes of motor performance or composites: a gross motor quotient, a fine motor quotient, and a total motor quotient. The scores are used to determine the child's performance compared with norms taken from typically developing children of their age. An age equivalent can also be determined. Reliability and validity are well established in multiple pediatric diagnoses and populations.[111-113]

- **Scoring:** Each item is scored as 0 (cannot or will not attempt item), 1 (emerging skill but does meet full criteria for mastery, or 2 (child performs according to criteria specified for mastery).
- **Time to complete:** 30-90 minutes, depending on age and subsets completed
- **Equipment:** The PDMS-2 test kit and manual, desk/table, adjustable seating, and additional materials as specified in kit manual such as rattle, soft plush toy, small toy on string, 8-inch ball, tennis ball, blunt scissors, washcloth, food pellets, stairs with 7" rise, mat, stopwatch, etc.
- **Supportive evidence in SMA research:** The PDMS-2 is currently being used in the Biogen NURTURE clinical trial.

Bayley Scales of Infant Development III (BSID-III)/Bayley-4

See above under Non-Sitters.

Test of Infant Motor Performance Screening Items (TIMPSI)

See above under Non-Sitters.

Harris Infant Neuromotor Test (HINT)

Click here for test manual, proforma, and references

The HINT is a brief, reliable and valid tool designed to differentiate between infants who are developing normally and those at increased risk for developmental delay.[114] The HINT is a family focused screening tool aimed at identifying neuromotor and/or cognitive/behavioral delays between the ages of 2.5 and 12.5 months of age. The test consists of 21 items including observations of motor behaviors in supine, prone, transitions from supine to prone, and sitting and observations of locomotion, posture, movements and behavioral state. Reliability and validity are excellent and there are no significant differences across US or Canadian groups and/or across ethnicities of white vs non-white groups. Concurrent validity with the MAI, AIMS and Ages and Stagers Questionnaire has been demonstrated.[114-118] Normative scores from 2.5 -12.5 months are included.[114,118,119]

- **Scoring:** Scores range from 76 to 0, with lower scores corresponding to more mature development
- **Time to complete:** 15-20 minutes
- **Equipment:** bright colored ring on an attached string, black and white contrasting pictures or picture book, tape measure, head circumference for age charts from CDC
- **Supportive evidence in SMA research:** It is currently being used in NBS testing for SMA infants.

Alberta Infant Motor Scale (AIMS)

Click here for test manual, proforma, and references

The AIMS is a norm referenced observational movement assessment scale, constructed to measure gross motor maturation in infants from birth through independent walking. The test consists of 58 items assessed by observation in 4 postures: prone, supine, sitting and standing.[120-122] The AIMS has good reliability and validity as well as scaling along the age continuum of development.[122] Correlation with the BSID-III[123,124] and between live and home video demonstrations have been demonstrated.[125] Normative scores initially established in 1994 were re-established in 2014.[120]

- **Scoring:** Items scored as present (1) or absent (0).
- **Time to complete:** 15-20 minutes
- **Equipment:** none
- **Supportive evidence in SMA research:** The AIMS was utilized in the SMA NeuroNEXT study and demonstrated significant deviation from typical progression in untreated infants with SMA[45] and is currently being used in NBS follow up studies in SMA as well as with infants treated presymptomatically.

Other Timed Function Tests (TFT)

See above under sitters and walkers for information on the 10MWRT, TTR, TTC, TUG, 9HPT, r9HPT, ESNHPT, BBT, and ESBBT.

Tests for Adult Patients with Chronic SMA

CHOP ATEND / Adult Test of Neuromuscular Disorders (ATEND)

Click here for test manual, proforma, and references

See above under Non-Sitters for CHOP INTEND. The CHOP ATEND was a new scale modified from the original CHOP INTEND and excluded items that cannot be performed with adults (items 11, 15, and 16). For older, weaker individuals with severe contractures, motor assessments are a challenge due to limitations in the ability to safely transfer or lie prone. The newer ATEND is a wheelchair-based functional motor outcome assessment for individuals with a neuromuscular disorder who are not able to sit or transfer out of the wheelchair. Work is on-going to collect data to further develop and refine the scale properties with future plans for modern psychometric analysis.

Hand Held Dynamometry (HHD) (grip/pinch)

See above under Sitters.

SMA Functional Rating Scale (SMAFRS)/Modified SMAFRS

Click here for test manual, proforma, and references

The SMAFRS was adapted from the ALS-FRS to assess function by patient and caregiver report in adults with SMA. The test demonstrates reliability and validity as SMAFRS scores are correlated with disease severity (strength and SMN2 copy number).[126] Ten items address questions related to eating, upper extremity dressing, lower extremity dressing, grooming, bathing, toileting, turning in bed and adjusting bed clothes, transfers, walking, and climbing stairs. A modified version (Modified SMAFRS) is available that has combined upper and lower body dressing to eliminate redundancy while adding an item on respiratory support.[127]

- **Scoring:** Patient or caregiver response is recorded based on a scale from 0 (fully dependent) to 5 (fully independent)
- **Time to complete:** 10-15 minutes
- **Equipment:** None-required
- **Supportive evidence in SMA research:** The SMAFRS was utilized as a secondary outcome in the adult gabapentin placebo-controlled trial[128] and the Modified SMAFRS was used in the adult Carni-Val trial[24] and demonstrated stability over a 12-month period.

Egen Klassification 2 (EK2)

Click here for test manual, proforma, and references

This EK2 test assesses functional abilities for those with SMA who are non-ambulatory. It examines activities and abilities such as transfers, trunk mobility, wheelchair use, bed mobility, cough, feeding, bulbar issues, distal hand function, and well-being. The CE evaluates function in conversation with the patient, to determine how certain items are normally performed by the patient and by asking the patient to demonstrate certain skills based on initial responses to a question. Some items such as 'ability to turn in bed', and 'physical well-being' are interview questions only. The test is an ordinal scale with 17 items. The EK scale is clinically relevant enabling clinicians to focus on practical issues and highlighting areas of concern. The EK2 scale demonstrates reliability and validity and can differentiate patients at Brooke levels 2 and 3, 3 and 4, and 4 and 5, but could not differentiate between the weakest patients at Brooke levels 5 and 6. However, it is uncertain whether the scale has sufficient sensitivity for application in clinical trials or whether the additional items are beneficial.[129,130]

- **Scoring:** Items are scored according to what an individual typically does. A few items require demonstration. Each item is scored 0-3, and the sum of all scores is the EK-sum score, with 0being the highest level of function and 51 being the lowest.
- **Time to complete:** 10-20 minutes
- **Equipment:** None required other than patient's wheelchair as needed
- **Supportive evidence in SMA research:** The EK2 has not to date been used in any SMA clinical trials.

Other Timed Function Tests (TFT)

See 9HPT, r9HPT, ESNHPT under sitters.

Pulmonary Outcome Measures

Pulmonary Function Tests (PFTS) (includes FVC, MIP, MEP, SNIP, PCF)

Click here for test manual, proforma, and references

The PFTs are non-invasive measures of lung volume, capacity, rates of flow and gas exchange. These tests may include Maximal Inspiratory Pressure (MIP), Maximal Expiratory Pressure (MEP), Sniff Nasal Inspiratory Pressure (SNIP), Peak Cough Flow (PCF) and Forced Vital Capacity (FVC). The FVC has demonstrated reliability in SMA[131] and is often measured using a spirometer with incentive visual reinforcement displayed on a computer screen. Three consecutive attempts are recorded, and the maximal result is taken as the measure of FVC.[131,132] Decline in respiratory and lung muscle function in those with type II occurs earlier than those with type III SMA as demonstrated by longitudinal assessment[133] with FVC and SNIP being the most feasible and accurate measure of this decline.

- **Scoring:** Output Varies by test
- **Time to complete:** Variable

- **Equipment:** Variable
- **Supportive evidence in SMA research:** The PFTs have been used in multiple SMA natural history studies as well as in several clinical trials. Natural history reports that patients with FVC ≥70% of predicted normal at baseline had a greater mean decline in pulmonary function at both 24 months ($p = 0.02$) and 36 months ($p = 0.007$) than subjects with FVC <70%. No other significant correlates for pulmonary function were found by subgroups defined by age, gender, SMA type, ambulatory status, baseline motor function, and baseline pulmonary function.[9]

Respiratory Inductance Plethysmography (RIP)

Click here for test manual, proforma, and references

The RIP can non-invasively measure and analyze precise patterns of thoracoabdominal chest and abdominal wall movements and synchrony. In a small study of infants with SMA type I (n=7) feasibility of use was demonstrated and reliable data were obtained safely for RIP phase angle and labored breathing index even in very weak infants. Data obtained corresponded to the clinical estimate of severity and predicted the need for respiratory support.[47]

- **Scoring:** Varies by test
- **Time to complete:** Variable, most protocols use 15-20 minutes of monitoring with RIP
- **Equipment:** The RIP test kit, various size chest bands, electrodes and laptop computer
- **Supportive evidence in SMA research:** The RIP is currently being used in Biogen and Roche clinical trials.

Patient-Reported Outcome Measures (PROs), including Quality of Life (QOL) (All Patients)

It is important to include the patient perspective in evaluations and assessments performed clinically and in research trials. Patient-reported outcomes establish what is meaningful to individuals and families affected by SMA and are intended to compliment, not replace, clinician-reported measures. Psychometrically sound, validated, flexible, and comprehensive assessments which are feasible in children and sensitive to change (e.g., PROMIS®) should be used as a framework to generate these patient-reported outcomes. A recent systematic review of quality of life in children with SMA noted that the PedsQL™ is the most commonly used in SMA studies, both the generic and neuromuscular modules. While there is a wide selection of measurement tools available in QOL literature, these are not disease-specific and there is not yet consensus on which tool is best for those with SMA.[42] The SMA specific modules or tools may be most sensitive to capture change across studies.

Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)

Click here for test manual, proforma, and references

The ACEND was developed and validated to specifically assess caregiver impact experienced by raising children severely affected by neuromuscular diseases.[134] While specifically developed for application to caregivers of patients undergoing orthopedic surgery, it has application to those with SMA. This PRO asks how much help the child requires to perform tasks in 7 domains including mobility, sitting/play, transfers, self-feeding, time burden, finance, and emotion.

- **Scoring:** Occurs on a 5 and 6-point Likert response scale representing the percentage of help required
- **Time to complete:** 10-15 minutes per module
- **Equipment:** paper and pen
- **Supportive evidence in SMA research:** No natural history study data has been published in SMA. The ACEND is currently being used in Biogen clinical trials.

ACTIVLIM

Click here for test manual, proforma, and references

The ACTIVLIM is a measure of activity limitations for patients with upper and/or lower limb impairments constructed using Rasch analyses. The scale measures a patient's ability to perform daily activities requiring the use of the upper and/or the lower limbs, with whatever strategies the participants choose. This 22-item scale can be used for patients from 6 to 80 years of age in such a way that the evolution of the disease course can be followed from the childhood to the adulthood. Reliability and construct validity have been established in the neuromuscular population.[135,136]

- **Scoring:** A 3-level response scale is presented to the adult patient and to the parents of the affected child. Patients are asked to rate their perception on the response scale as 'Impossible', 'Difficult' or 'Easy'.
- **Time to complete:** 10-15 minutes

- **Equipment:** paper and pen
- **Supportive evidence in SMA research:** The ACTIVLIM has not to date been used in any SMA clinical trials.

Egen Klassification 2 (EK2)

See above under Adults with Chronic SMA

Fatigue Severity Scale (FSS)

Click here for test manual, proforma, and references

The FSS is a unidimensional scale which focuses on the physical aspects of fatigue. It is a self-reported questionnaire developed to measure the impact of disabling fatigue on daily functioning and can be applied to patients with neuromuscular diseases.[137,138] It is composed of 9-items that cover several areas including physical, social, and cognitive effects.

- **Scoring:** Scores range from 1 = "strongly disagree" to 7 = "strongly agree". A higher score represents greater fatigue. A global score is a mean score of individual item scores. A score of >4 indicates abnormal fatigue and a score of >5 indicates severe fatigue.
- **Time to complete:** 5-10 minutes
- **Equipment:** paper and pen

  Supportive evidence in SMA research: Perceived fatigue in patients with SMA type II, type III[139,140] and congenital myopathies has recently been shown to be captured using the FSS.[138] Test-rest for the FSS in SMA was highly consistent.[138]

Patient-Reported Outcomes Measurement Information System (PROMIS®)

Click here for test manual, proforma, and references

The PROMIS® is a set of person-centered measures that evaluates and monitors physical (including fatigue), mental, and social health in adults and children.[141,142] It includes over 300 measures and can be used with the general population and with individuals living with chronic conditions. The PROMIS® measures are copyrighted. All English and Spanish PROMIS® measures are publicly available for use in one's individual research, clinical practice, educational assessment, or other application without licensing or royalty fees.

- **Scoring:** HealthMeasure score available in three ways: 1) Use a data collection tool that automatically calculates scores; 2) Use the FREE HealthMeasure's Scoring Service, powered by Assessment

Center℠ to score PROMIS®, ASCQ-Me®, Neuro-QoL™, and NIH Toolbox® Emotion measures; 3) Score by hand using a Scoring Manual for self-report and proxy-report short forms

- **Time to complete:** 10-15 minutes per module
- **Equipment:** On paper with pen (short forms and profiles only), computer, or app
- **Supportive evidence in SMA research:** No natural history study data has been published in SMA. The PROMIS® is currently being utilized in the Scholar Rock Study of SKR-015, a latent myostatin inhibitor.

Pediatric Evaluation of Disability Inventory – Computer Adaptive Test (PEDI-CAT)

Click here for test manual, proforma, and references

The PEDI-CAT is a questionnaire typically completed by the parent/caretaker that assesses a patient's ability to perform daily functions.[143] The PEDI-CAT is completed by the parent/legal guardian. The test is suitable to assess function in newborns to 21-year-olds with established reliability and validity for multiple pediatric populations.[144,145] Properties of the PEDI-CAT are under study for those with SMA.

- **Scoring:** The answers are scored on a 4-point scale (unable to easy). The PEDI-CAT provides two types of transformed summary scores: normative scores and scaled scores. Separate summary scores are calculated for each of the four domains. There is no total score that sums across all four domains.
- **Time to complete:** 10-20 minutes
- **Equipment:** iPad or tablet to allow user to complete at clinic visit, must purchase PEDI-CAT software to administer and complete scoring
- **Supportive evidence in SMA Research:** The PEDI-CAT has been used in natural history clinical trials where Rasch analysis revealed that the distribution of abilities for the Mobility and Daily Activities (upper extremity tasks) domains were best represented for those with type III SMA and distribution of abilities in the Daily Activities domain also represented those with type II SMA. Less difficult items need to be added to increase the sensitivity and validity for those with type I and II SMA.[146] It is currently being utilized in the Scholar Rock Study of SKR-015, a latent myostatin inhibitor.

Pediatric Quality of Life Inventory (PedsQL™), Neuromuscular Module and Multidimensional Fatigue Scale

Click here for test manual, proforma, and references

The PedsQL™ is a disease-specific questionnaire intended to evaluate the patient's perception of the neuromuscular disease state for children ages 2 to 18 years, including SMA.[147,148] The PedsQL™ Neuromuscular Module is a 25-item scale that encompasses three subscales: About My/My Child's Neuromuscular Disease (seventeen items), Communication (three items), and About Our Family Resources (five items). The format, instructions, Likert response scale, and scoring method for the Neuromuscular Module are identical to the Generic module.[149]

The PedsQL™ Multidimensional Fatigue Scale was designed to measure perceived fatigue in pediatric patients ages 2–18 and later expanded to include greater than age 18 years. The 18-item scale is comprised of 3 subscales: general fatigue (6 items), sleep/rest fatigue (6 items), and cognitive fatigue (6 items). It is a generic symptom-specific instrument that includes a child self-report and parent proxy-report

- **Scoring:** A five-point Likert response scale is utilized (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items are reverse- scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicated better health-related quality of life. Scale scores are computed as the sum of the items divided by the number of items answered.
- **Time to complete:** 5-10 minutes per module
- **Equipment**: paper and pen
- **Supportive evidence in SMA research:** The PedsQL™ Neuromuscular Module and Multidimensional Fatigue Scale have been utilized in natural history clinical trials with minimal data published on longitudinal assessments. Data supports the feasibility, reliability and validity of the PedsQL™ Generic and Neuromuscular Modules in pediatric patients with SMA.[132,149-151] The PedsQL™ Neuromuscular Module is currently being used in the Biogen clinical trial.

SMA Functional Rating Scale (SMAFRS)/Modified SMAFRS

See above under tests for Adults with Chronic SMA.

SMA-Health Index (SMA-HI)

Click here for test manual, proforma, and references

The SMA-HI is a patient-reported outcome measure that is comprehensive, easily utilized, and capable of measuring a patient's perception of their total disease burden and 15 areas of SMA sub-health.

- **Scoring:** Not available in the public domain
- **Time to complete:** Not available in the public domain
- **Equipment:** Index available for purchase
- **Supportive evidence in SMA research:** No data has been published on the validity or reliability of the SMA-HI. The SMA-HI was used in the Cytokinetics' study of Reldesemtiv. Study results not yet published.

Many of the above available outcome measures have been used in the SMA population. A summary of outcome measure clinical properties for use in SMA are outlined in Table 5 below.

Table 5: Summary of Clinical Properties of Outcome Measures

	CLINICALLY REPORTED OUTCOME MEASURES FOR SMA								
Outcome measures used in SMA	CHOP INTEND	TIMPSI	HFMS	HFMSE	RHS	MFM	RULM	6MWT	TFT*
Clinical subgroups	Type I	Type I	Type II	Type II, III	Type II, III	Type II, III	Type II, III	Type III	Type II
Functional subgroups	Non-sitter	Non-sitter	Sitter	Sitter/ Walker	Sitter/ Walker	Sitter/ Walker	Sitter/ Walker	Walker	Sitter/ Walker
Supports mechanism of action	Specific to therapeutic agent under investigation								
Conceptual framework fits SMA	Y	Y	Y	Y	Y	Y	Y	Y	Y
Reliability	Y	Y	Y	Y	Y	Y	Y	Y	**
Validation with other measures	Y	Y	Y	Y	Y	Y	Y	Y	**

Normative ranges	NA	Y	NA	NA	NA	NA	NA	Y	Y
Natural history studies	Y	Y	Y	Y		Y	Y	Y	Y
Multicenter studies	Y	Y	Y	Y	Y	Y	Y	Y	Y
Clinical trials	Y	Y	Y	Y	Y	Y	Y	Y	Y
Responsiveness to treatment	Y		Y	Y		Y	Y	Y	
Clinical meaningfulness				Y				Y	

*TFT= TUG, Time to climb 4 stairs, time to rise from floor, 10MWRT, 9HPT, r9HPT,BBT, ESNHPT, ESBBT

**clinical properties described here as a whole for details specific to each TFT measure see Section 3 above.

Y = Yes

NA = Not Applicable

Blank = Data not published

Important Aspects of a Research Evaluation

Scoring Considerations for Outcome Measures

One should score all items based on best performance. However, patients with SMA often utilize substitutions and compensations to complete tasks. In scoring, one should be cognizant of item-scoring criteria and use the rule of thumb "when in doubt score down***."***

Assessment for Inclusion and Exclusion Criteria

Each study will set inclusion/exclusion criteria that are often based on a minimum or maximum performance level on at least one if not multiple motor function tests. This can help prevent ceiling or floor effects of the outcome measures and endpoints used for the trial. The inclusion/exclusion criteria may also be based on degree of contracture or scoliosis development in some cases as these impairments can limit a patient's ability to perform on outcome measures as well (see Biomechanics of Movement in SMA). It is very important that you are aware of these criteria and assess the patient and adhere to these guidelines during your screening visit. Adhering to these criteria may also mean that a potential participant may be excluded from enrollment based on scores on specific motor outcomes or secondary impairments. Communication amongst study team members (PI, CE, coordinator, etc.) is essential to identifying appropriate/eligible study participants. Discussions should occur at the screening visit if functional status, contractures, scoliosis, or motor function cut-offs are a concern. The utilization of telemedicine opportunities is becoming increasingly more common to "pre-screen" unknown patients to reduce the number of screen failures of ineligible patients. It is the PIs role to communicate outcomes to the participant and family so that they understand why they may have been excluded. Clear communication will support the success of the clinical trial and help the greater SMA community.

Blinding

As a CE participating in a clinical trial, you may be blinded to the assigned treatment intervention (specific treatment arm/placebo) in a controlled study so that you cannot be influenced by that knowledge. In addition, you will be asked to maintain a blind to your previous study assessments and to not look back on previous test scores as this may bias or impact your scoring for the current assessment. You may also be asked to maintain blinding to the patients' therapies or routines to reduce ascertainment bias to your evaluations.

Time and Budget Planning: Estimates of Your Time for Assessments, Trainings, Webinars, and Related Activities

Clinical evaluators should understand the time it takes to complete assessments and required trainings for SMA clinical trials. This will help for planning and scheduling adequate time to be released from clinic duties as well as budgeting for interdepartmental fund transfers to cover time release. Estimated times to complete the most common assessments are noted above under assessments. Clinical evaluators should also estimate that there will be some set-up/clean-up, rest periods, and completion of case report form time as part of each assessment. In addition to time for direct evaluations, CEs should plan on 1-2 days (8-16 hrs.) to attend the initial investigator meeting for each clinical study. There are also ongoing evaluator training requirements that may vary from on-site to web-based activities from 1-2 hours quarterly or biannually. There may also be time outside of the direct trainings (max 60-90 minutes) necessary to complete post training reliability assessments. While these are broad estimates, they are provided so that you can best estimate what time might be required to fully partake in a clinical trial as a CE. Across clinical trials there is variability in outcomes that will be used, as well as training requirements. Protocol specifics should be discussed with the study sponsor prior to the start/initiation of the study, during the budget planning phase to assure that your time is adequately covered.

Difficulty Maintaining Consistency with Rotating Hospital PT Positions

It is important to maintain consistency amongst evaluators who are trained and collecting data in a clinical trial. Rotating staff positions make this difficult to accomplish. If you are currently assigned to a rotating position and wish to participate in a clinical trial as a CE, you may need to negotiate specific time that allows you to be available to the study team for assessments on a consistent and regular basis. This is best discussed up front with your clinical manager and the study's PI.

Commonly Used Equipment Needed in the Clinical/research Setting

Below is a list of the common equipment needs you may require for evaluations. A clinical trial site should be able to request any additional or missing equipment from the clinical trial sponsor.

- Benches, chairs, table (should be adjustable)
- Set of standard height stairs
- Test kits (e.g., BSID-III/Bayley-4, RULM, RIP, PDMS-2, etc.)
- Stopwatch and cones for 6MWT
- Standard toys to use for CHOP INTEND or HFMSE
- Camera or iPad, tripods, memory cards

Rules for Equipment Use Outside of Clinical Trial

Study sponsors are responsible for providing equipment and materials needed for clinical trials at your institution. Standardized tools, test kits and equipment such as toys, cameras, stairs, benches, tables, cones for 6-minute walk test, etc., should be provided by the sponsor. It is important to understand that equipment provided must be safely stored and used only for those patients participating in that sponsor's clinical trial. At the end of a study some equipment may need to be returned or destroyed, and other equipment may be allocated back to your site for permanent non-study use. It is important to clarify these equipment guidelines for each study and sponsor as they do vary.

KEY POINTS: EVALUATION IN THE RESEARCH SETTING

- It is important to be familiar with the multitude of common clinical outcomes used across the phenotypic spectrum of SMA. Outcomes selected for a clinical assessment or research clinical trial may vary based on type of SMA, current functional status, age at assessment, stage of disease and/or mechanism of intervention/drug being assessed.
- Progress in development of clinical assessments for those with SMA is ongoing with ultimate aims to minimize burden while providing a comprehensive assessment using tools across multiple domains including gross and fine motor function, cognition, balance, speed, and fatigue. Additionally, evaluation of performance-based measures includes both Quality of Life (QOL) and Patient Reported Outcome Measures (PROMs).

Section 4: Additional Considerations for Patient Safety, Performance of Outcome Measures, and Adult Populations

The Clinical Evalluator in the Context of the Care Team

A multidisciplinary team is key to the management of patients with SMA and different aspects of care should not be managed in isolation. Physical therapists work with other health care professionals to assess the musculoskeletal system and related functional impairments. To monitor function that reflects activities of daily living, the selection of assessments used should include strength and range of motion measures, relevant motor functional scales, and timed tests. Physical therapists should evaluate patients with SMA with these assessments routinely every 6 months to allow regular monitoring and identify recommendations and changes in management and interventions.[6] Communication of these recommendations and changes should occur with the appropriate providers of the multidisciplinary team (including Occupational and Speech Therapy, Rehab Medicine, Orthopedics, Orthotists, Neurology, etc.).

Considerations for Standard of Care and Supportive Care

A rehabilitation standard of care consensus statement for SMA was originally published in 2007 and was revised in 2018.[6,7] These guidelines include a review of evidence and expert consensus that have been widely adopted by clinicians all over the world. Increasing evidence of improvements in the natural history as well as with disease modifying therapies have promoted a more proactive, anticipatory approach to rehabilitation management and it has been observed that regular physical therapy sessions may influence trajectories of progression.[6,7]

The rehabilitation section of this manuscript[6] describes rehabilitation goals for the 3 different functional classifications: Non-Sitter, Sitters, and Walkers. Each functional group has intervention recommendations for stretching, positioning, mobility, and exercise as well as care considerations and assessment options that have been thoroughly reviewed.[6]

Safety Considerations in SMA with Physical Assessments

When assessing patients with SMA, there are numerous safety considerations that must be recognized prior to and during your evaluation and treatment, and that should also guide your plan of care recommendations:

Fatigue

Most patients with SMA report severe perceived fatigue and have physiological fatigue. This fatigue can impact their ability to participate in daily activities, physical therapy, and in community and school settings. Modifications to their daily schedule or modifications to their daily activities in general are recommended to minimize the impact of fatigue on their daily life and routine. Patients with SMA are advised to recognize and report fatigue so adequate breaks and rest periods can be implemented to prevent worsening of fatigue or potential risk for injury.[94-96,99,103,105,138-140,152,153]

Falls

Ambulatory patients are at risk of falling. This may be related to stride length. Most falls occur indoors and are associated with intrinsic and extrinsic factors including weakness, loss of balance, tripping, or slipping. Falling puts patients at risk for bruises, sprains, and even fractures.[152,153] Many walkers report frequent falls and an inability to get themselves up off the floor. Non-ambulatory patients are at risk of falling over when sitting without support (may need contact guard or close supervision) due to poor postural control and trunk strength and inability to utilize protective and righting reactions. They may fall out of their mobility and positioning devices if not safely secured in.

Fractures

Due to disuse (muscle weakness and lack of exercise), osteoporosis, and low vitamin D levels, non-ambulatory patients are at risk of fragility fractures.[6] These fractures can occur during transfers, stretching, and accidents in their mobility devices or from a fall. Ambulatory patients are at risk of fractures with a fall while walking in the home or out in the community, especially when on uneven surfaces.

Vital Signs

When assessing patients with SMA with respiratory insufficiency, a review of vital signs including oxygen desaturation and tachycardia using pulse oximetry with heart rate monitoring should be used to monitor their respiratory status during evaluation and testing. This is most important with non-sitters and some weak sitters.[5] Upright supported sitting, standing, and prone suspension may put these patients at risk for acute respiratory distress and should be monitored very closely and should be performed with extreme caution when performing functional motor assessments and during therapy intervention.

Fasting and Nutrition

Fasting can impact motor performance during testing and should be kept to a minimum. Less than 6 hours of fasting is recommended for acute care for non-sitters to prevent metabolic acidosis, fatty acid metabolism abnormalities, and hyper/hypoglycemia.[6] Allowing the patient and family to take frequent rest breaks and allowing for proper nutrition should take priority.

Pain

Numerous orthopedic issues can lead to pain including hip instability, severe contractures, limited mobility secondary to lack of movement, and the development of scoliosis. Pain management as well as appropriate referrals should be considered when assessing a patient who is in extreme pain with movement and transfers. Additionally, post-operative pain should always be taken into consideration when evaluating and assessing patients.[6]

Positioning Limitations Due to Contractures and Scoliosis

Contractures are common in SMA and result from decreased range of motion, prolonged static positioning, and an imbalance in agonist-antagonist muscle groups.[6] Severe contractures of the upper and lower extremities, as well as the neck, may impact the patient's ability to obtain or maintain start positions and end positions when using a functional motor scale assessment. Most scales have the ability to highlight and comment on these limitations by item as well as their impact on function.

Sixty to ninety percent of non-ambulatory patients with SMA develop scoliosis of the spine and are monitored by spinal radiographs.[6] Scoliosis can impact patient positioning as well as functional abilities and should be taken into consideration on the impact of testing and activities of daily living.[154] Scoliosis can create notable asymmetries impacting the evaluation and motor function assessments.

Transfers

Non-ambulatory, older patients with SMA may require equipment to assist with safe transfers. This may be determined when the caregivers and CEs are unable to dependently transfer a patient out of their mobility device. Transfer boards, lift systems including Hoyer and ceiling lifts, and sheets may be used for optimal transfers and bed mobility to support safety and decrease the risk of injury. During transfers without equipment, take care to fully support a child and limit abrupt movement. Always ask the child and parent or caretaker for preferred transfer methods to avoid upsetting a child or creating discomfort. Remember to communicate that you are going to transfer the child/adolescent/adult before doing so to minimize apprehension, especially in those that are weaker and less mobile.

Clothing

When evaluating and assessing a patient, it is ideal to see as much of their body as possible for easy examination. Infants and small children should be evaluated with diaper only. Children and adults should have shorts and t-shirt to clearly see their limbs and trunk. When removing clothing be cognizant of room temperature with young infants and also respectful of cultural beliefs. Ideally the patients should be barefoot during assessments, however, if performing gait assessments including the 6MWT, rubber soled shoes are recommended. Socks, sandals/flip-flops, and Crocs are not recommended to be worn during evaluations. It is good practice to ask your study coordinator to remind the family to bring the correct clothing and shoes to each appointment.

Considerations for Evaluating Chronic Adults

SMA is a progressive disease and chronic adults continue to lose muscle strength and motor function with increasing age.[2,155] Quality of life and participation may be impacted by worsening of contractures, bulbar dysfunction, respiratory involvement and functional limitations. Some outcome measures have been outlined and highlighted for use in assessing older patients however the standard SMA-specific motor function assessment may not best describe their functional abilities (potential floor effects). Non-ambulatory adults may require a lift device to promote safe transfers; without one, they may refuse to transfer out of their wheelchair or mobility devices for testing. Ambulatory adult patients may have difficulty getting up from the floor or sitting down on the floor safely. Ultimately optimizing function and maintaining independence is the primary goal for these adult patients.

Considerations for Illness, Handwashing Protocols for Safety and Equipment Cleaning

Patients with SMA have respiratory compromise leaving them susceptible to viral infections and illnesses. These illnesses often lead to acute hospitalizations and can exacerbate diffuse muscle weakness. It is essential that patients are not exposed to others with an illness and do not make direct contact with equipment from a previously ill person. Standard safety protocols for the prevention of illness must be upheld with regular handwashing and cleaning of equipment and examination tables. Masks should be worn and avoidance of contact with ill providers should be implemented. If a patient is already ill, their ability to undergo evaluation and assessment of their motor function should be carefully assessed. If assessment is undertaken when a patient is ill, be sure to document such on the CRF, scoresheet or proforma.

Best Practices and Testing Considerations for Best Performance

Time of Day

Ideally, patients should be tested first thing in the morning to prevent the impact of fatigue on their evaluation and assessments from their daily activities and routines. This time of day should be maintained for all evaluations and functional assessments throughout the course of the study. Patients may require rest periods and/or naps during testing to allow for optimal assessment and this should be considered when scheduling visit appointments.

Nutrition

Patients should be fed within 1 hour prior to evaluation and testing. They should be well fed and satiated to prevent the effects of fasting on their performance. Breaks for a snack or drink during assessments should be provided as needed.

Travel

When patients are traveling long distances, it may be amendable to have them stay overnight to allow for testing in the morning. Scheduling arrivals the day prior to allow for a good night's sleep prior to assessment is

also important. Long travel can impact fatigue and their ability to accomplish motor function tasks increasing their variability from day to day. The effects of long travel should be avoided and kept to a minimum.

Location and Equipment

All evaluations and motor function testing should be performed in the same location and room when possible to prevent any variability in environments. Maintaining consistency with the room, examination tables, and equipment will promote best results. If the testing location or equipment changes, this should be recorded and any impact on function should be noted.

Coordinating with the Team and Family in Planning Visits for Consistency over Time

The CE will need to coordinate with the research team as well as the family to plan for the ideal time and set-up for their evaluations and motor assessments. Communication to prioritize these assessments is key to optimizing testing conditions and getting the best performance from the patient. All testing considerations listed above should be discussed with the research study team and family to identify the most optimal window of time.

Rescheduling and Abiding by Study Windows

If a patient is unable to attend a study visit, protocol specific study windows should allow for rescheduling for a certain number of days/weeks before or after their scheduled visit. It is important to try and maintain their evaluations and assessments within this window of time to prevent protocol deviations and the proper management of the patient. Assessing outside those windows should be discussed with the study team and reported to site managers.

KEY POINTS: ADDITIONAL CONSIDERATIONS FOR SMA EVALUATIONS

- PTs are an integral part of the multidisciplinary care team that selects assessments to monitor functional abilities that reflect activities of daily living. Routine physical therapy evaluations should occur every 6 months to allow regular monitoring and to identify changes in management and interventions.
- Increasing evidence of improvements in the natural history with proactive care as well as with disease modifying therapies has promoted a more proactive, anticipatory approach to rehabilitation management as outlined in the revised rehabilitation standard of care consensus statement in SMA.
- There are numerous safety considerations that must be recognized prior to and during your evaluation and treatment, that should also guide your plan of care recommendations including fatigue, falls, fractures, vital signs, etc.
- To establish optimal performance and success, best practice standards and testing considerations must be applied when assessing a patient with SMA including time of day, nutrition, travel, etc.

Conclusion

Clinical evaluators play an essential role in clinical trials, and this is especially true in SMA. Through close collaboration with their team, effective execution of their responsibilities, and adoption of a patient-focused approach that builds trust and rapport, CEs can help trials to run more smoothly, and ensure that patients have a more positive experience.

Over time, CEs may find that they want to extend the approaches described in this document to the larger, community of therapists treating those with SMA, and find ways to engage with the SMA community more broadly, for instance through professional workshops and conferences (see Table A5: Professional Development: Meetings for Continuing Education), and other means. Such engagement may enable CEs to continue to learn about challenges and strategies to improve clinical trial site readiness and enhance the patient's experience in clinical trials. Clinical evaluators may also discover opportunities for learning methods and practices for the best care and management of patients with SMA from experienced SMA physicians and caregivers and even the patients themselves. Finally, given the opportunity, CEs in SMA trials can help contribute to the success of SMA trials by being active collaborators in trial design and feedback processes.

References

1. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle Nerve.* 2015;51(2):157-167.
2. Wadman RI, Stam M, Gijzen M, et al. Association of motor milestones, SMN2 copy and outcome in spinal muscular atrophy types 0-4. *Journal of neurology, neurosurgery, and psychiatry.* 2017;88(4):365-367.
3. Kolb SJ, Coffey CS, Yankey JW, et al. Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. *Annals of Clinical and Translational Neurology.* 2016;3(2):132-145.
4. Lefebvre S, Bürglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell.* 1995;80(1):155-165.
5. Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscular disorders : NMD.* 2018;28(3):197-207.
6. 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. *Neuromuscular disorders : NMD.* 2018;28(2):103-115.
7. Wang CH, Finkel RS, Bertini ES, et al. Consensus Statement for Standard of Care in Spinal Muscular Atrophy. *Journal of Child Neurology.* 2007;22(8):1027-1049.
8. APTA. The physical therapist scope of practice. 2014; http://www.apta.org/scopeofpractice/ Accessed June 4, 2019.
9. Kaufmann P, McDermott MP, Darras BT, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. *Neurology.* 2012;79(18):1889.
10. Bartlett A, Kolb SJ, Kingsley A, et al. Recruitment & retention program for the NeuroNEXT SMA Biomarker Study: Super Babies for SMA! *Contemporary clinical trials communications.* 2018;11:113-119.
11. Krosschell KJ, Bosch M, Nelson L, et al. Motor Function Test Reliability During the NeuroNEXT Spinal Muscular Atrophy Infant Biomarker Study. *Journal of neuromuscular diseases.* 2018;5:509-521.
12. Crawford TO, Paushkin SV, Kobayashi DT, et al. Evaluation of SMN Protein, Transcript, and Copy Number in the Biomarkers for Spinal Muscular Atrophy (BforSMA) Clinical Study. *PLOS ONE.* 2012;7(4):e33572.
13. Finkel RS, Crawford TO, Swoboda KJ, et al. Candidate Proteins, Metabolites and Transcripts in the Biomarkers for Spinal Muscular Atrophy (BforSMA) Clinical Study. *PLOS ONE.* 2012;7(4):e35462.
14. Kobayashi DT, Shi J, Stephen L, et al. SMA-MAP: A Plasma Protein Panel for Spinal Muscular Atrophy. *PLOS ONE.* 2013;8(4):e60113.
15. Al-Zaidy S, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatr Pulmonol.* 2019;54(2):179-185.
16. Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *The New England journal of medicine.* 2017;377(18):1713-1722.
17. Aartsma-Rus A. FDA Approval of Nusinersen for Spinal Muscular Atrophy Makes 2016 the Year of Splice Modulating Oligonucleotides. *Nucleic acid therapeutics.* 2017;27(2):67-69.
18. Albrechtsen SS, Born AP, Boesen MS. Nusinersen treatment of spinal muscular atrophy - a systematic review. *Danish medical journal.* 2020;67(9).
19. Baranello G, Darras BT, Day JW, et al. Risdiplam in Type 1 Spinal Muscular Atrophy. *New England Journal of Medicine.* 2021;384(10):915-923.
20. Dhillon S. Risdiplam: First Approval. *Drugs.* 2020;80(17):1853-1858.
21. Rudnicki SA, Andrews JA, Duong T, et al. Reldesemtiv in Patients with Spinal Muscular Atrophy: a Phase 2 Hypothesis-Generating Study. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics.* 2021.

22. Place A. Apitegromab, a novel high-affinity anti-proMyostatin monoclonal antibody for treating spinal muscular atrophy: results of a phase 2 interim analysis. Paper presented at: MDA Clinical and Scientific Conference 2021; Virtual.
23. Kissel JT, Elsheikh B, King WM, et al. SMA valiant trial: a prospective, double-blind, placebo-controlled trial of valproic acid in ambulatory adults with spinal muscular atrophy. *Muscle Nerve.* 2014;49(2):187-192.
24. Kissel JT, Scott CB, Reyna SP, et al. SMA CARNI-VAL TRIAL PART II: A Prospective, Single-Armed Trial of L-Carnitine and Valproic Acid in Ambulatory Children with Spinal Muscular Atrophy. *PLOS ONE.* 2011;6(7):e21296.
25. Krosschell KJ, Kissel JT, Townsend EL, et al. Clinical trial of L-Carnitine and valproic acid in spinal muscular atrophy type I. *Muscle Nerve.* 2018;57(2):193-199.
26. Swoboda KJ, Scott CB, Crawford TO, et al. SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. *PLoS One.* 2010;5(8):e12140.
27. Montes J, Garber CE, Kramer SS, et al. Single-Blind, Randomized, Controlled Clinical Trial of Exercise in Ambulatory Spinal Muscular Atrophy: Why are the Results Negative? *Journal of neuromuscular diseases.* 2015;2(4):463-470.
28. Montes J, Garber CE, Kramer SS, et al. A Randomized, Controlled Clinical Trial of Exercise in Patients with Spinal Muscular Atrophy: Methods and Baseline Characteristics. *Journal of neuromuscular diseases.* 2014;1(2):151-161.
29. Lewelt A, Krosschell KJ, Stoddard GJ, et al. Resistance strength training exercise in children with spinal muscular atrophy. *Muscle Nerve.* 2015;52(4):559-567.
30. National Institute of Health. ClinicalTrials.gov website. n.d.; https://clinicaltrials.gov/ct2/results?cond=spinal+muscular+atrophy&term=&cntry=&state=&city=&dist%20.
31. Bargaje C. Good documentation practice in clinical research. *Perspectives in Clinical Research.* 2011;2(2):59-63.
32. Boyd EA, Lipton S, Bero LA. Implementation of financial disclosure policies to manage conflicts of interest. *Health affairs (Project Hope).* 2004;23(2):206-214.
33. Weinfurt KP, Hall MA, King NMP, Friedman JY, Schulman KA, Sugarman J. Disclosure of Financial Relationships to Participants in Clinical Research. *New England Journal of Medicine.* 2009;361(9):916-921.
34. Evans S. Clinical trial structures. *Journal of Experimental Stroke & Translational Medicine.* 2010;03.
35. Hand S. Patient-Focused clinical trial design for rare diseases like Duchenne muscular dystrophy. 2018; https://xtalks.com/patient-focused-clinical-trial-design-for-rare-diseases-like-duchenne-muscular-dystrophy/.
36. Schliebner S. The patient voice: engaging rare disease patients improves clinical trial enrollment & retention. 2017; https://prahs.com/insights/the-patient-voice-engaging-rare-disease-patients-improves-clinical-trial-enrollment-retention.
37. Cruz R, Lenz, M., Belter, L., Hobby, K., & Jarecki, J. . *Voice of the patient report: A summary report from an externally led patient focused drug development meeting reflecting the U.S. Food and Drug Adminstration (FDA), patient-focused drugs development initiative.* Cure SMA website. 2018.
38. Qian Y, McGraw S, Henne J, Jarecki J, Hobby K, Yeh W-S. Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study. *BMC Neurology.* 2015;15(1):217.
39. Mercuri E, Mazzone ES, Montes J, Messina S, Schroth MK. Chapter 23 - Spinal Muscular Atrophy Motor Functional Scales and Measures of Pulmonary Function. In: Sumner CJ, Paushkin S, Ko C-P, eds. *Spinal Muscular Atrophy.* Academic Press; 2017:371-382.

40. US Food and Drug Administration (FDA). Rare Diseases: Natural History Studies for Drug Development Guidance for Industry. March 2019; https://www.fda.gov/media/122425/download.
41. Sheehan J, Hirschfeld S, Foster E, et al. Improving the value of clinical research through the use of Common Data Elements. *Clinical Trials.* 2016;13(6):671-676.
42. Vaidya S, Boes S. Measuring quality of life in children with spinal muscular atrophy: a systematic literature review. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2018;27(12):3087-3094.
43. 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. *Neuromuscular disorders : NMD.* 2010;20(3):155-161.
44. Glanzman AM, McDermott MP, Montes J, et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association.* 2011;23(4):322-326.
45. Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. *Annals of neurology.* 2017;82(6):883-891.
46. De Sanctis R, Pane M, Coratti G, et al. Clinical phenotypes and trajectories of disease progression in type 1 spinal muscular atrophy. *Neuromuscular disorders : NMD.* 2018;28(1):24-28.
47. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology.* 2014;83(9):810-817.
48. Mercuri E, Lucibello S, Perulli M, et al. Longitudinal natural history of type I spinal muscular atrophy: a critical review. *Orphanet journal of rare diseases.* 2020;15(1):84.
49. De Vivo DC, Bertini E, Swoboda KJ, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscular disorders : NMD.* 2019;29(11):842-856.
50. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet (London, England).* 2016;388(10063):3017-3026.
51. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *New England Journal of Medicine.* 2017;377(18):1723-1732.
52. Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *New England Journal of Medicine.* 2017;377(18):1713-1722.
53. Mendell JR LK, McColly M, et al. AVXS-101 Gene-Replacement Therapy (GRT) in spinal muscular atrophy type I (SMA1): Long-term follow-up from the phase 1 clinical trial. Paper presented at: American Academy of Neurology Meeting. May 2019; Philadelphia, PA.
54. Baranello G SL, Day JW, et al. FIREFISH Part 1: Early clinical results following a significant increase in SMN protein in SMA type I babies treated with RG7916. Paper presented at: Child Neurology Society Meeting 2018; Chicago, IL.
55. Baranello G, Servais L, Day JW, et al. FIREFISH Part 1: 1-Year Results on Motor Function in Babies with Type 1 SMA (S25.003). Paper presented at: 71st American Academy of Neurology Annual Meeting. May 2019; Philadelphia, Pennsylvania.
56. Eeles AL, Olsen JE, Walsh JM, et al. Reliability of Neurobehavioral Assessments from Birth to Term Equivalent Age in Preterm and Term Born Infants. *Physical & Occupational Therapy In Pediatrics.* 2017;37(1):108-119.
57. Maitre NL, Chorna O, Romeo DM, Guzzetta A. Implementation of the Hammersmith Infant Neurological Examination in a High-Risk Infant Follow-Up Program. *Pediatric neurology.* 2016;65:31-38.

58. Romeo DM, Ricci D, Brogna C, Mercuri E. Use of the Hammersmith Infant Neurological Examination in infants with cerebral palsy: a critical review of the literature. *Dev Med Child Neurol.* 2016;58(3):240-245.
59. Bishop KM, Montes J, Finkel RS. Motor milestone assessment of infants with spinal muscular atrophy using the hammersmith infant neurological Exam—Part 2: Experience from a nusinersen clinical study. *Muscle Nerve.* 2018;57(1):142-146.
60. Wijnhoven TM, de Onis M, Onyango AW, et al. Assessment of gross motor development in the WHO Multicentre Growth Reference Study. *Food and nutrition bulletin.* 2004;25(1 Suppl):S37-45.
61. Bayley N. *Bayley scales of infant and toddler development.* 3rd ed. San Antonio, TX: Pearson; 2006.
62. Bayley N, Aylward GP. *Bayley 4 Scales of Infant and Toddler Development.* Bloomington, MN: NCS Pearson; 2019.
63. Campbell SK, Swanlund A, Smith E, Liao PJ, Zawacki L. Validity of the TIMPSI for estimating concurrent performance on the test of infant motor performance. *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association.* 2008;20(1):3-10.
64. Campbell SK, Kolobe THA, Osten ET, Lenke M, Girolami GL. Construct Validity of the Test of Infant Motor Performance. *Physical Therapy.* 1995;75(7):585-596.
65. Campbell SK, Kolobe THA, Wright BD, Linacre JM. Validity of the Test of Infant Motor Performance for prediction of 6-, 9- and 12-month scores on the Alberta Infant Motor Scale. *Developmental Medicine & Child Neurology.* 2002;44(4):263-272.
66. Krosschell KJ, Maczulski JA, Scott C, et al. Reliability and Validity of the TIMPSI for Infants With Spinal Muscular Atrophy Type I. *Pediatric Physical Therapy.* 2013;25(2).
67. Krosschell KJ V-TD, Sakonju A, Stevens A, Swoboda K. Electrophysiological (CMAP, MUNE) and motor function (TIMPSI) outcome association in infants with type I SMA. Paper presented at: International Cure SMA Research Meeting2014; Anaheim, CA.
68. O'Hagen JM, Glanzman AM, McDermott MP, et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. *Neuromuscular disorders : NMD.* 2007;17(9-10):693-697.
69. Glanzman AM, O'Hagen JM, McDermott MP, et al. Validation of the Expanded Hammersmith Functional Motor Scale in Spinal Muscular Atrophy Type II and III. *Journal of Child Neurology.* 2011;26(12):1499-1507.
70. Glanzman AM, Mazzone ES, Young SD, et al. Evaluator Training and Reliability for SMA Global Nusinersen Trials1. *Journal of neuromuscular diseases.* 2018;5(2):159-166.
71. Mercuri E, Finkel R, Montes J, et al. Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials. *Neuromuscular disorders : NMD.* 2016;26(2):126-131.
72. Mercuri E, Lucibello S, Pera MC, et al. Long-term progression in type II spinal muscular atrophy: A retrospective observational study. *Neurology.* 2019;93(13):e1241-e1247.
73. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. *The New England journal of medicine.* 2018;378(7):625-635.
74. Pera MC, Coratti G, Forcina N, et al. Content validity and clinical meaningfulness of the HFMSE in spinal muscular atrophy. *BMC Neurology.* 2017;17(1):39.
75. Ramsey D, Scoto M, Mayhew A, et al. Revised Hammersmith Scale for spinal muscular atrophy: A SMA specific clinical outcome assessment tool. *PLOS ONE.* 2017;12(2):e0172346.
76. 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(6):869-874.
77. Pera MC, Coratti G, Mazzone ES, et al. Revised upper limb module for spinal muscular atrophy: 12 month changes. *Muscle Nerve.* 2019;59(4):426-430.
78. Mazzone E, Bianco F, Martinelli D, et al. Assessing upper limb function in nonambulant SMA patients: Development of a new module. *Neuromuscular Disorders.* 2011;21(6):406-412.

79. Sivo S, Mazzone E, Antonaci L, et al. Upper limb module in non-ambulant patients with spinal muscular atrophy: 12 month changes. *Neuromuscular disorders : NMD.* 2015;25(3):212-215.
80. Bérard C, Payan C, Hodgkinson I, Fermanian J, The MFMCSG. A motor function measure scale for neuromuscular diseases. Construction and validation study. *Neuromuscular Disorders.* 2005;15(7):463-470.
81. Trundell D, Le Scouiller S, Gorni K, Seabrook T, Vuillerot C, the SMAMFMSG. Validity and Reliability of the 32-Item Motor Function Measure in 2- to 5-Year-Olds with Neuromuscular Disorders and 2- to 25-Year-Olds with Spinal Muscular Atrophy. *Neurology and Therapy.* 2020;9(2):575-584.
82. Trundell D, Le Scouiller S, Le Goff L, Gorni K, Vuillerot C. Assessment of the validity and reliability of the 32-item Motor Function Measure in individuals with Type 2 or non-ambulant Type 3 spinal muscular atrophy. *PLoS One.* 2020;15(9):e0238786.
83. de Lattre C, Payan C, Vuillerot C, et al. Motor Function Measure: Validation of a Short Form for Young Children With Neuromuscular Diseases. *Archives of Physical Medicine and Rehabilitation.* 2013;94(11):2218-2226.
84. Bertini E, Dessaud E, Mercuri E, et al. Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomised, double-blind, placebo-controlled phase 2 trial. *The Lancet Neurology.* 2017;16(7):513-522.
85. Chabanon A, Seferian AM, Daron A, et al. Prospective and longitudinal natural history study of patients with Type 2 and 3 spinal muscular atrophy: Baseline data NatHis-SMA study. *PLOS ONE.* 2018;13(7):e0201004.
86. Beenakker EAC, van der Hoeven JH, Fock JM, Maurits NM. Reference values of maximum isometric muscle force obtained in 270 children aged 4–16 years by hand-held dynamometry. *Neuromuscular Disorders.* 2001;11(5):441-446.
87. Escolar DM, Henricson EK, Mayhew J, et al. Clinical evaluator reliability for quantitative and manual muscle testing measures of strength in children. *Muscle Nerve.* 2001;24(6):787-793.
88. van der Ploeg RJ, Oosterhuis HJ. [Physical examination--measurement of muscle strength]. *Nederlands tijdschrift voor geneeskunde.* 2001;145(1):19-23.
89. Merlini L, Mazzone ES, Solari A, Morandi L. Reliability of hand-held dynamometry in spinal muscular atrophy. *Muscle Nerve.* 2002;26(1):64-70.
90. Escobar RG, Munoz KT, Dominguez A, Banados P, Bravo MJ. Maximal isometric muscle strength values obtained By hand-held dynamometry in children between 6 and 15 years of age. *Muscle Nerve.* 2017;55(1):16-22.
91. Hébert LJ, Maltais DB, Lepage C, Saulnier J, Crête M. Hand-Held Dynamometry Isometric Torque Reference Values for Children and Adolescents. *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association.* 2015;27(4):414-423.
92. Merlini L, Bertini E, Minetti C, et al. Motor function-muscle strength relationship in spinal muscular atrophy. *Muscle Nerve.* 2004;29(4):548-552.
93. Smith YA, Hong E, Presson C. Normative and Validation Studies of the Nine-Hole Peg Test with Children. *Perceptual and Motor Skills.* 2000;90(3):823-843.
94. Stam M, Wadman RI, Bartels B, et al. A continuous repetitive task to detect fatigability in spinal muscular atrophy. *Orphanet journal of rare diseases.* 2018;13(1):160.
95. Bartels B, Habets LE, Stam M, et al. Assessment of fatigability in patients with spinal muscular atrophy: development and content validity of a set of endurance tests. *BMC Neurology.* 2019;19(1):21.
96. Bartels B, de Groot JF, Habets LE, et al. Fatigability in spinal muscular atrophy: validity and reliability of endurance shuttle tests. *Orphanet journal of rare diseases.* 2020;15(1):75.
97. Mathiowetz V, Volland G, Kashman N, Weber K. Adult Norms for the Box and Block Test of Manual Dexterity. *American Journal of Occupational Therapy.* 1985;39(6):386-391.

98. Alfano LN, Miller NF, Iammarino MA, et al. ACTIVE (Ability Captured Through Interactive Video Evaluation) workspace volume video game to quantify meaningful change in spinal muscular atrophy. *Developmental Medicine & Child Neurology.* 2020;62(3):303-309.
99. Montes J, McDermott MP, Martens WB, et al. Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. *Neurology.* 2010;74(10):833.
100. Montes J, McDermott MP, Mirek E, et al. Ambulatory function in spinal muscular atrophy: Age-related patterns of progression. *PLOS ONE.* 2018;13(6):e0199657.
101. Montes J, Zanotto D, Dunaway Young S, Salazar R, De Vivo DC, Agrawal S. Gait assessment with solesound instrumented footwear in spinal muscular atrophy. *Muscle Nerve.* 2017;56(2):230-236.
102. Dunaway Young S, Montes J, Kramer SS, et al. Six-minute walk test is reliable and valid in spinal muscular atrophy. *Muscle Nerve.* 2016;54(5):836-842.
103. Montes J, Blumenschine M, Dunaway S, et al. Weakness and Fatigue in Diverse Neuromuscular Diseases. *Journal of Child Neurology.* 2013;28(10):1277-1283.
104. Day J. Update of CY-5021: A Phase 2 clinical trial of reldesemtiv, a fast slkeletal muscle troponin activator (FSTA), for the potential treatment of spinal muscular atrophy. Paper presented at: International Cure SMA Research Meeting. June 2018; Orlando, FL.
105. Montes J, Dunaway Young S, Mazzone ES, et al. Nusinersen improves walking distance and reduces fatigue in later-onset spinal muscular atrophy. *Muscle Nerve.* 2019;60(4):409-414.
106. Krosschell K, Brown L, Hoffman K, et al. SMA: REGISTRIES, BIOMARKERS & OUTCOME MEASURES: P.176 Longitudinal change over time on Timed Function Tests (TFTs) in ambulatory persons with SMA. *Neuromuscular Disorders.* 2020;30:S98.
107. Krosschell KJ SC, Maczulski, JA. Timed tests of function and relatedness to other outcomes in children with SMA. Report from SMA CARNI-VAL clinical trial. . Paper presented at: 13th Annual Spinal Muscular Atrophy International Research Meeting2009; Cincinatti, OH.
108. Dunaway S, Montes J, Garber CE, et al. Performance of the timed “up & go” test in spinal muscular atrophy. *Muscle Nerve.* 2014;50(2):273-277.
109. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Research quarterly for exercise and sport.* 1999;70(2):113-119.
110. Gill S, McBurney H. Reliability of performance-based measures in people awaiting joint replacement surgery of the hip or knee. *Physiotherapy Research International.* 2008;13(3):141-152.
111. Folio MR, Fewell RR. *Peabody Developmental Motor Scales: Examiner's manual.* Pro-Ed; 2000.
112. Connolly BH, Dalton L, Smith JB, Lamberth NG, McCay B, Murphy W. Concurrent validity of the Bayley Scales of Infant Development II (BSID-II) Motor Scale and the Peabody Developmental Motor Scale II (PDMS-2) in 12-month-old infants. *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association.* 2006;18(3):190-196.
113. Wuang YP, Su CY, Huang MH. Psychometric comparisons of three measures for assessing motor functions in preschoolers with intellectual disabilities. *Journal of intellectual disability research : JIDR.* 2012;56(6):567-578.
114. Harris SR, Backman CL, Mayson TA. Comparative predictive validity of the Harris Infant Neuromotor Test and the Alberta Infant Motor Scale. *Developmental Medicine & Child Neurology.* 2010;52(5):462-467.
115. Harris SR, Daniels LE. Content Validity of the Harris Infant Neuromotor Test. *Physical Therapy.* 1996;76(7):727-737.
116. Harris SR, Daniels LE. Reliability and validity of the Harris Infant Neuromotor Test. *The Journal of Pediatrics.* 2001;139(2):249-253.
117. Tse L, Mayson TA, Leo S, et al. Concurrent Validity of the Harris Infant Neuromotor Test and the Alberta Infant Motor Scale. *Journal of Pediatric Nursing.* 2008;23(1):28-36.

118. Westcott McCoy S, Bowman A, Smith-Blockley J, Sanders K, Megens AM, Harris SR. Harris Infant Neuromotor Test: Comparison of US and Canadian Normative Data and Examination of Concurrent Validity With the Ages and Stages Questionnaire. *Physical Therapy.* 2009;89(2):173-180.
119. Megens AM, Harris SR, Backman CL, Hayes VE. Known-Groups Analysis of the Harris Infant Neuromotor Test. *Physical Therapy.* 2007;87(2):164-169.
120. Darrah J, Bartlett D, Maguire TO, Avison WR, Lacaze-Masmonteil T. Have infant gross motor abilities changed in 20 years? A re-evaluation of the Alberta Infant Motor Scale normative values. *Developmental Medicine & Child Neurology.* 2014;56(9):877-881.
121. Darrah J, Piper M, Watt M-J. Assessment of gross motor skills of at-risk infants: predictive validity of the Alberta Infant Motor Scale. *Developmental Medicine & Child Neurology.* 1998;40(7):485-491.
122. Piper MC, Pinnell LE, Darrah J, Maguire T, Byrne PJ. Construction and validation of the Alberta Infant Motor Scale (AIMS). *Canadian journal of public health = Revue canadienne de sante publique.* 1992;83 Suppl 2:S46-50.
123. Albuquerque PL, Guerra MQF, Lima MC, Eickmann SH. Concurrent validity of the Alberta Infant Motor Scale to detect delayed gross motor development in preterm infants: A comparative study with the Bayley III. *Developmental neurorehabilitation.* 2018;21(6):408-414.
124. Williams MF. Movement Assessment of Infants and Alberta Infant Motor Scale prediction to Bayley-III outcome in extremely preterm infants. *Early human development.* 2016;103:83-84.
125. Boonzaaijer M, van Dam E, van Haastert IC, Nuysink J. Concurrent Validity Between Live and Home Video Observations Using the Alberta Infant Motor Scale. *Pediatric Physical Therapy.* 2017;29(2).
126. Elsheikh B, Prior T, Zhang X, et al. An analysis of disease severity based on SMN2 copy number in adults with spinal muscular atrophy. *Muscle Nerve.* 2009;40(4):652-656.
127. Elsheikh B, King W, Peng J, et al. Outcome measures in a cohort of ambulatory adults with spinal muscular atrophy. *Muscle Nerve.* 2020;61(2):187-191.
128. Miller RG, Moore DH, Dronsky V, et al. A placebo-controlled trial of gabapentin in spinal muscular atrophy. *Journal of the Neurological Sciences.* 2001;191(1):127-131.
129. Steffensen B, Hyde S, Lyager S, Mattsson E. Validity of the EK scale: a functional assessment of non-ambulatory individuals with Duchenne muscular dystrophy or spinal muscular atrophy. *Physiotherapy Research International.* 2001;6(3):119-134.
130. Steffensen BF, Lyager S, Werge B, Rahbek J, Mattsson E. Physical capacity in non-ambulatory people with Duchenne muscular dystrophy or spinal muscular atrophy: a longitudinal study. *Dev Med Child Neurol.* 2002;44(9):623-632.
131. Kaufmann P, McDermott MP, Darras BT, et al. Observational Study of Spinal Muscular Atrophy Type 2 and 3: Functional Outcomes Over 1 Year. *Archives of neurology.* 2011;68(6):779-786.
132. Iannaccone ST, and the American Spinal Muscular Atrophy Randomized Trials G. Outcome Measures for Pediatric Spinal Muscular Atrophy. *Archives of neurology.* 2002;59(9):1445-1450.
133. Khirani S, Colella M, Caldarelli V, et al. Longitudinal course of lung function and respiratory muscle strength in spinal muscular atrophy type 2 and 3. *European Journal of Paediatric Neurology.* 2013;17(6):552-560.
134. Matsumoto H, Clayton-Krasinski DA, Klinge SA, et al. Development and initial validation of the assessment of caregiver experience with neuromuscular disease. *Journal of pediatric orthopedics.* 2011;31(3):284-292.
135. Vandervelde L, Van den Bergh PY, Goemans N, Thonnard JL. ACTIVLIM: a Rasch-built measure of activity limitations in children and adults with neuromuscular disorders. *Neuromuscular disorders : NMD.* 2007;17(6):459-469.
136. Vandervelde L, Van den Bergh PYK, Goemans N, Thonnard J-L. Activity limitations in patients with neuromuscular disorders: A responsiveness study of the ACTIVLIM questionnaire. *Neuromuscular Disorders.* 2009;19(2):99-103.

137. de Groot IJ, Voet NB, van Middendorp H, Knoop HJ, Rahbek J, van Engelen BG. 184th ENMC International Workshop: pain and fatigue in neuromuscular disorders: 20-22 May 2011, Naarden, The Netherlands. *Neuromuscular disorders : NMD.* 2013;23(12):1028-1032.
138. Werlauff U, Højberg A, Firla-Holme R, Steffensen BF, Vissing J. Fatigue in patients with spinal muscular atrophy type II and congenital myopathies: evaluation of the fatigue severity scale. *Quality of Life Research.* 2014;23(5):1479-1488.
139. Dunaway Young S, Montes J, Kramer SS, Podwika B, Rao AK, De Vivo DC. Perceived Fatigue in Spinal Muscular Atrophy: A Pilot Study. *Journal of neuromuscular diseases.* 2019;6(1):109-117.
140. Kizina K, Stolte B, Totzeck A, et al. Fatigue in adults with spinal muscular atrophy under treatment with nusinersen. *Scientific reports.* 2020;10(1):11069.
141. Gershon RC, Rothrock N, Hanrahan R, Bass M, Cella D. The use of PROMIS and assessment center to deliver patient-reported outcome measures in clinical research. *J Appl Meas.* 2010;11(3):304-314.
142. Tucker CA, Bevans KB, Teneralli RE, Smith AW, Bowles HR, Forrest CB. Self-reported pediatric measures of physical activity, sedentary behavior, and strength impact for PROMIS: item development. *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association.* 2014;26(4):385-392.
143. Haley SM, Raczek AE, Coster WJ, Dumas HM, Fragala-Pinkham MA. Assessing mobility in children using a computer adaptive testing version of the pediatric evaluation of disability inventory. *Arch Phys Med Rehabil.* 2005;86(5):932-939.
144. Dumas HM, Fragala-Pinkham MA, Haley SM, et al. Computer adaptive test performance in children with and without disabilities: prospective field study of the PEDI-CAT. *Disability and Rehabilitation.* 2012;34(5):393-401.
145. Haley SM, Coster WJ, Dumas HM, et al. Accuracy and precision of the Pediatric Evaluation of Disability Inventory computer-adaptive tests (PEDI-CAT). *Dev Med Child Neurol.* 2011;53(12):1100-1106.
146. Pasternak A, Sideridis G, Fragala-Pinkham M, et al. Rasch analysis of the Pediatric Evaluation of Disability Inventory–computer adaptive test (PEDI-CAT) item bank for children and young adults with spinal muscular atrophy. *Muscle Nerve.* 2016;54(6):1097-1107.
147. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Medical care.* 2001;39(8):800-812.
148. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. *Medical care.* 1999;37(2):126-139.
149. Iannaccone ST, Hynan LS, Morton A, Buchanan R, Limbers CA, Varni JW. The PedsQL in pediatric patients with Spinal Muscular Atrophy: feasibility, reliability, and validity of the Pediatric Quality of Life Inventory Generic Core Scales and Neuromuscular Module. *Neuromuscular disorders : NMD.* 2009;19(12):805-812.
150. Dunaway S, Montes J, Montgomery M, et al. Reliability of telephone administration of the PedsQL Generic Quality of Life Inventory and Neuromuscular Module in spinal muscular atrophy (SMA). *Neuromuscular disorders : NMD.* 2010;20(3):162-165.
151. Iannaccone ST, Hynan LS. Reliability of 4 outcome measures in pediatric spinal muscular atrophy. *Archives of neurology.* 2003;60(8):1130-1136.
152. Montes J, Dunaway S, Garber CE, Chiriboga CA, De Vivo DC, Rao AK. Leg muscle function and fatigue during walking in spinal muscular atrophy type 3. *Muscle Nerve.* 2014;50(1):34-39.
153. Montes J, Dunaway S, Montgomery MJ, et al. Fatigue leads to gait changes in spinal muscular atrophy. *Muscle Nerve.* 2011;43(4):485-488.
154. Dunaway Young S MJ, Mazzone E, et al. Scoliosis is negatively associated with motor function in children with later onset SMA type II. Paper presented at: Child Neurology Society Meeting2018; Chicago, IL.

155. Wadman RI, Wijngaarde CA, Stam M, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. *European journal of neurology*. 2018;25(3):512-518.

Appendices: Additional Resources for Clinical Evaluators

The tables below provide information on additional resources that may be helpful for clinical evaluators.

Table A1: Recommended Regulatory Training for Clinical Evaluators

There should be adequate training for all staff participating in the conduct of a study, and proper documentation that required training has been completed and it is up-to-date. Having proper documentation that the research staff/CE is qualified to perform the functions of their role, as delegated on study protocol and forms FDA 1572/delegation log is mandated by Regulators, Sponsor, and study site. This includes any new staff members that start after the study has begun.

Trainings	Description
GCP Certification	Certification may be provided by an academic institution, sponsor or certifying program such as, ➢ CITI Program [registration is required] ➢ FDA GCP Educational Materials or, ➢ Regulations: Good Clinical Practice and Clinical Trials ➢ Sponsor-specific GCP training
Regulatory/FDA Mandated Training	***FDA Regulatory Compliance:*** Training on the ethical conduct of research may be found, via the following resources: ➢ CITI Program [registration is required] ➢ Code of Federal Regulations, via US FDA website, CFR Title 21 [Food and Drugs] → Chapter I → Subchapter A [General Provisions]→ Part 50, includes: ○ Key Research Definitions – *e.g., Clinical investigation, Sponsor, Clinical Investigator, Human Subject, IRBs, etc.* ○ Subpart B—General requirements for the Informed Consent of Human Subjects / Key Elements of Informed Consent ➢ SOCRA: FDA Clinical Trial Requirements, Regulations, Compliance, and GCP Conference
	Human Subject Protection Research: Ensures the ethical conduct and protection of human subjects, including pediatric patients and other '*vulnerable populations'* – (e.g., children, prisoners, the medically fragile, etc.). ➢ Office for Human Research Protections - Online Education, includes links to: ○ Belmont Report –Provides the background behind the reason for the existence of these regulations. ○ Regulations on protecting human subjects in research ○ About research participation ○ Informational videos for research participants – on what is research, questions to ask, randomization, etc. ○ Upcoming educational events
	Responsible Conduct of Research: Describes specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving humans with food, investigational products and/or devices. See above.
	Research with Minors*:* There are special/additional considerations for the PI/research staff when conducting research with minors. If you are assigned as a primary/back-up CE in a clinical trial, involving minors, you must also complete this training. For a description of regulatory requirements to conduct research with children, refer to the following: ➢ Additional Safeguards for Children in Clinical Trials -(CRF) Title 21 → Chapter I → Subchapter D→ Part 50

	[for trials not involving greater than minimal risk; trials involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects; trials involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition]
	Financial Disclosure Form/Conflict of Interest: See description of form, including instructions for completion, below
Privacy and Security	***HIPAA for Clinicians & Non-clinicians with Research Responsibilities:*** May be certified through ➢ CITI Program [registration is required] ➢ Institutional training
Required Documentation for CEs	
Start Up Forms	***Updated Curriculum Vitae (CV)***
	Professional state license
	Professional certifications
Investigator Statements/ Agreements	***Form FDA 1572***: ➢ *See,* Instruction for Completing Form FDA 1572
Financial Disclosure Form	***Financial Disclosure Form* (59 FR 48708)**: ➢ See, Financial Disclosures by Clinical Investigators *Part of FDA regulations: CFR 54; 21 CF 312)

Table A2: SMA Seminal Paper Reference List

Standard of Care and Guidelines

Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord.* 2018;28(3):197-207.

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(2):103-115.

Takanashi JI, Takase N. Reader response: Evidence in focus: Nusinersen use in spinal muscular atrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2019;93(10):464.

Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol.* 2007;22(8):1027-1049.

Clinical Trial Readiness

Peterson I, Cruz R, Sarr F, Stanley AM, Jarecki J. The SMA clinical trial readiness program: creation and evaluation of a program to enhance SMA trial readiness in the United States. *Orphanet J Rare Dis.* 2020;15(1):118.

Cure SMA. Cure SMA clinical trial readiness toolkit. Elk Grove Village (IL): Cure SMA; 2018. Retrieved from: https://www.curesma.org/clinical-trial-readiness/

Cure SMA. Best practices for clinical research coordinators in spinal muscular atrophy (SMA). Elk Grove Village (IL): Cure SMA; 2018. Retrieved from: https://www.curesma.org/clinical-trial-readiness/

Natural History of SMA

Barois A, Mayer M, Desguerre I, et al. Spinal muscular atrophy. A 4-year prospective, multicenter, longitudinal study (168 cases). *Bull Acad Natl Chir Dent.* 2005;189:1181-98; discussion 98-9.

Borkowska J, Rudnik-Schoneborn S, Hausmanowa-Petrusewicz I, Zerres K. Early infantile form of spinal muscular atrophy (Werdnig-Hoffmann disease) with prolonged survival. *Folia Neuropathol.* 2002;40:19-26.

Chabanon A, Seferian AM, Daron A, et al. Prospective and longitudinal natural history study of patients with Type 2 and 3 spinal muscular atrophy: Baseline data NatHis-SMA study. *PLoS One.* 2018;13(7):e0201004.

Coratti G, Pera MC, Lucibello S, et al. Age and baseline values predict 12 and 24-month functional changes in type 2 SMA. *Neuromuscul Disord.* 2020;10.1016/j.nmd.2020.07.005.

Coratti G, Lucibello S, Pera MC, et al. Gain and loss of abilities in type II SMA: A 12-month natural history study. *Neuromuscul Disord.* 2020;10.1016/j.nmd.2020.07.004.

Choi YA, Suh DI, Chae JH, Shin HI. Trajectory of change in the swallowing status ispinal muscular atrophy type I. *Int J Pediatr Otorhinolaryngol.* 2020;130:109818.

Chung BH, Wong VC, Ip P. Spinal muscular atrophy: survival pattern and functional status. *Pediatrics.* 2004;114:e548-53.

De Sanctis R., Coratti G, Pasternak, A, et al. Developmental milestones in type I spinal muscular atrophy. *Neuromuscul Disord.* 2016;26(11), 754-759.

De Sanctis R, Pane M, Coratti G, et al. Clinical phenotypes and trajectories of disease progression in type 1 spinal muscular atrophy. *Neuromuscul Disord.* 2018;28(1):24-28.

Dunaway S, Montes J, McDermott MP, et al. Physical therapy services received by individuals with spinal muscular atrophy (SMA). *J Pediatr Rehabil Med.* 2016;9(1):35-44.

Dunaway S, Montes J, O'Hagen J, Sproule DM, Vivo DC, Kaufmann P. Independent mobility after early introduction of a power wheelchair in spinal muscular atrophy. *J Child Neurol.* 2013;28:576-582.

Dunaway S, Montes J, Ryan PA, Montgomery M, Sproule DM, De Vivo DC. Spinal muscular atrophy type III: trying to understand subtle functional change over time--a case report. *J of Child Neuro.* 2012;27:779-85.

Eng GD, Binder H, Koch B. Spinal muscular atrophy: experience in diagnosis and rehabilitation management of 60 patients. *Arch Phyl Med Rehabi.* 1984;65:549-53.

Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology*. 2014;83:810-817.

Finkel RS, Weiner DJ, Mayer OH, McDonough JM, Panitch HB. Respiratory muscle function in infants with spinal muscular atrophy type I. *Pediatr Pulmonol.* 2014;49(12):1234-1242.

Iannaccone ST, Browne RH, Samaha FJ, Buncher CR. Prospective study of spinal muscular atrophy before age 6 years. DCN/SMA Group. *Pediatr Neurol.* 1993;9:187-93.

Iannaccone ST, Russman BS, Browne RH, Buncher CR, White M, Samaha FJ. Prospective analysis of strength in spinal muscular atrophy. DCN/Spinal Muscular Atrophy Group. *J Child Neurol*. 2000;15:97-101.

Kaufmann P, McDermott MP, Darras BT, et al. Observational study of spinal muscular atrophy type 2 and 3: functional outcomes over 1 year. *Arch Neurol.* 2011;68:779-86.

Kaufmann P, McDermott MP, Darras BT, et al. A Prospective cohort study of spinal muscular atrophy types 2 and 3. *Neurology.* 2012;79(18),1889-1897.

Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol.* 2017;82(6):883-891.

Kolb SJ, Coffey CS, Yankey JW, et al. Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. *Ann Clin Transl Neurol.* 2016;3(2):132-145.

Kroksmark AK, Beckung E, Tulinius M. Muscle strength and motor function in children and adolescents with spinal muscular atrophy II and III. *Eur J Paediatr Neurol.* 2001;5:191-198.

Kruitwagen-van Reenen ET, van der Pol L, Schroder C, et al. Social participation of adult patients with spinal muscular atrophy: Frequency, restrictions, satisfaction, and correlates. *Muscle Nerve.* 2018;58(6):805-811.

Mazzone E, Bianco F, Main M, et al. Six minute walk test in type III spinal muscular atrophy: a 12 month longitudinal study. *Neuromuscul Disord.* 2013;23(8):624–628.

Mercuri E, Finkel R, Montes J, et al. Patterns of disease progression in type 2 and 3 SMA: implications for clinical trials. *Neuromuscul Disord.* 2016;26(2): 126–131.

Mercuri E, Lucibello S, Perulli M, et al. Longitudinal natural history of type I spinal muscular atrophy: a critical review. *Orphanet J Rare Dis.* 2020;15(1):84.

Mercuri E, Lucibello S, Pera MC, et al. Long-term progression in type II spinal muscular atrophy: A retrospective observational study. *Neurology.* 2019;93(13):e1241-e1247.

Montes J, McDermott MP, Mirek E, et al. Ambulatory function in spinal muscular atrophy: Age-related patterns of progression. *PLoS One*. 2018 Jun 26;13(6):e0199657. doi: 10.1371/journal.pone.0199657. eCollection 2018.

Oskoui M, Levy G, Garland CJ, et al. The changing natural history of spinal muscular atrophy type 1. *Neurology.* 2007;69:1931-1936.

Ou SF, Ho CS, Lee WT, et al. Natural history in spinal muscular atrophy Type I in Taiwanese population: A longitudinal study. *Brain Dev.* 2020;10.1016/j.braindev.2020.07.012.

Pane M, Palermo C, Messina S, et al. An observational study of functional abilities in infants, children, and adults with type 1 SMA. *Neurology.* 2018;91(8):e696-e703.

Russman BS, Buncher CR, White M, Samaha FJ, Iannaccone ST. Function changes in spinal muscular atrophy II and III. The DCN/SMA Group. *Neurology.* 1996;47:973-976.

Sivo S, Mazzone E, Antonaci L, et al. Upper limb module in non-ambulant patients with spinal muscular atrophy: 12 month changes. *Neuromuscul Disord.* 2015; 25(3),212-215.

van Bruggen HW, Wadman RI, Bronkhorst EM, et al. Mandibular dysfunction as a reflection of bulbar involvement in SMA type 2 and 3. *Neurology.* 2016;86(6):552-559.

van der Heul AMB, Cuppen I, Wadman RI, et al. Feeding and Swallowing Problems in Infants with Spinal Muscular Atrophy Type 1: an Observational Study. *J Neuromuscul Dis.* 2020;7(3):323-330.

Vazquez-Costa JF. Natural history data in adults with SMA. *Lancet Neurol.* 2020;19(7):564-565.

Wadman RI, Wijngaarde CA, Stam M, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. *Eur J Neurol.* 2018;25(3):512-518.

Wadman RI, Stam M, Gijzen M, et al. Association of motor milestones, SMN2 copy and outcome in spinal muscular atrophy types 0-4. *J Neurol Neurosurg Psychiatry.* 2017;88(4):365-367.

Wijngaarde CA, Stam M, de Kort FAS, Wadman RI, van der Pol WL. Limited maximal mouth opening in patients with spinal muscular atrophy complicates endotracheal intubation: An observational study. *Eur J Anaesthesiol.* 2018;35(8):629-631.

Wijngaarde CA, Veldhoen ES, van Eijk RPA, et al. Natural history of lung function in spinal muscular atrophy. *Orphanet J Rare Dis.* 2020;15(1):88.

Wijngaarde CA, Brink RC, de Kort FAS, et al. Natural course of scoliosis and lifetime risk of scoliosis surgery in spinal muscular atrophy. *Neurology.* 2019;93(2):e149-e158.

Willig TN, Bach JR, Rouffet MJ, Krivickas LS, Maquet C. Correlation of flexion contractures with upper extremity function and pain for spinal muscular atrophy and congenital myopathy patients. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists.* 1995;74:33-38.

Zerres K, Rudnik-Schoneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. *J Neurol Sci.* 1997;146:67-72.

Outcome Measure Development, Validation, and Reliability

Alfano LN, Miller NF, Iammarino MA, et al. ACTIVE (Ability Captured Through Interactive Video Evaluation) workspace volume video game to quantify meaningful change in spinal muscular atrophy. *Dev Med Child Neurol.* 2020;62(3):303-309.

Bartels B, Habets LE, Stam M, et al. Assessment of fatigability in patients with spinal muscular atrophy: development and content validity of a set of endurance tests. *BMC Neurol.* 2019;19(1):21.

Bartels B, de Groot JF, Habets LE, et al. Fatigability in spinal muscular atrophy: validity and reliability of endurance shuttle tests. *Orphanet J Rare Dis.* 2020;15(1):75.

Bertoli S, Foppiani A, De Amicis R, et al. Anthropometric measurement standardization for a multicenter nutrition survey in children with spinal muscular atrophy. *Eur J Clin Nutr.* 2019;10.1038/s41430-019-0392-2.

Bishop KM, Montes J, Finkel RS. Motor milestone assessment of infants with spinal muscular atrophy using the hammersmith infant neurological Exam-Part 2: Experience from a nusinersen clinical study. *Muscle Nerve.* 2018;57(1):142-146.

Buonsenso D, Berti B, Palermo C, et al. Ultrasound assessment of diaphragmatic function in type 1 spinal muscular atrophy. *Pediatr Pulmonol.* 2020;55(7):1781-1788.

Cano SJ, Mayhew A, Glanzman AM, et al. Rasch analysis of clinical outcome measures in spinal muscular atrophy. *Muscle Nerve.* 2014;49(3):422-430.

Dunaway S, Montes J, Garber CE, et al. Performance of the timed "up & go" test in spinal muscular atrophy. *Muscle Nerve.* 2014;50(2):273-277.

Dunaway Young S, Montes J, Kramer SS, et al. Six-minute walk test is reliable and valid in spinal muscular atrophy. *Muscle Nerve.* 2016;54(5):836-842.

Elsheikh B, King W, Peng J, et al. Outcome measures in a cohort of ambulatory adults with spinal muscular atrophy. *Muscle Nerve.* 2020;61(2):187-191.

Finkel, R., Bertini, E., Muntoni, F., & Mercuri, E. 209th ENMC International Workshop: Outcome measures and clinical trial readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands. *Neuromuscul Disord.* 2015;25(7):593-602.

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(3):155–161.

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(4):322-326.

Glanzman AM, O'Hagen JM, McDermott MP, et al. Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. *J Child Neuroly.* 2011;26(12):1499-1507.

Gomez-Garcia de la Banda M, Amaddeo A, Khirani S, et al. Assessment of respiratory muscles and motor function in children with SMA treated by nusinersen. *Pediatr Pulmonol.* 2020;10.1002/ppul.25142.

Goodwin AM, Cornett KMD, McKay MJ, et al. Limitations of 6-minute walk test reference values for spinal muscular atrophy. *Muscle Nerve.* 2020;61(3):375-382.

Iannaccone ST, Russman BS, Browne RH, Buncher CR, White M, Samaha FJ. Prospective analysis of strength in spinal muscular atrophy. DCN/Spinal Muscular Atrophy Group. *J Child Neurol.* 2000;15(2):97-101.

Khirani S, Amaddeo A, Fauroux B. Cough, sniff and maximal static pressure patterns in spinal muscular atrophy. *Respir Physiol Neurobiol.* 2020;271:103308.

Krosschell KJ, Maczulski JA, Scott C, et al. Reliability and validity of the TIMPSI for infants with spinal muscular atrophy type I. *Pediatr Phys Ther.* 2013 Summer;25(2):140-148; discussion 149.

Krosschell KJ, Scott CB, Maczulski JA, et al. Reliability of the Modified Hammersmith Functional Motor Scale in young children with spinal muscular atrophy. *Muscle Nerve.* 2011;44(2):246-251.

Krosschell KJ, Maczulski JA, Crawford TO, Scott C, Swoboda KJ. A modified Hammersmith functional motor scale for use in multi-center research on spinal muscular atrophy. *Neuromuscul Disord.* 2006;16(7):417-426.

Main M, Kairon H, Mercuri E, Muntoni F. 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(4):155-159.

Mazzone E, Bianco F, Martinelli D, et al. Assessing upper limb function in nonambulant SMA patients: development of a new module. *Neuromuscul Disord.* 2011;21(6):406–412.

Mazzone E, De Sanctis R, Fanelli L, et al. Hammersmith Functional Motor Scale and Motor Function Measure-20 in non ambulant SMA patients. *Neuromuscul Disord.* 2014;24(4):347-352.

Mazzone E, Montes J, Main M, et al. Old measures and new scores in spinal muscular atrophy patients. *Muscle Nerve.* 2015;52(3):435-437.

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(6):869-874.

Mercuri E, Messina S, Battini R, et al. Reliability of the Hammersmith functional motor scale for spinal muscular atrophy in a multicentric study. *Neuromuscul Disord.* 2006;16(2):93-98.

Mercuri E, Mazzone E, Montes J, Messina S, Schroth MK. Spinal muscular atrophy motor functional scales and measures of pulmonary function. In: Sumner CJ, Paushkin S, Ko C-P, eds. Spinal Muscular Atrophy: *Academic Press;* 2017:371-382.

Messina S, Frongia AL, Antonaci L, et al. A critical review of patient and parent caregiver oriented tools to assess health-related quality of life, activity of daily living and caregiver burden in spinal muscular atrophy. *Neuromuscul Disord.* 2019;29(12):940-950.

Montes J, Dunaway S, Garber CE, Chiriboga CA, De Vivo DC, Rao AK. Leg muscle function and fatigue during walking in spinal muscular atrophy type 3. *Muscle Nerve.* 2014;50(1):34-39.

Montes J, Glanzman AM, Mazzone ES, et al. Spinal muscular atrophy functional composite score: A functional measure in spinal muscular atrophy. *Muscle Nerve*. 2015;52(6):942-947.

Montes J, McDermott MP, Martens WB, et al. Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. *Neurology.* 2010;74(10):833–838.

Montes J, Young SD, Mazzone E, Main M, International Spinal Muscular Atrophy Consortium Clinical Evaluator Working G. *Neuromuscul Disord.* 2017;10.1016/j.nmd.2017.07.005.

Montes J, Dunaway Young S, Mazzone ES, et al. Nusinersen improves walking distance and reduces fatigue in later-onset spinal muscular atrophy. *Muscle Nerve.* 2019;60(4):409-414.

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(9-10):693-697.

Pasternak A, Sideridis G, Fragala-Pinkham M, et al. Rasch analysis of the Pediatric Evaluation of Disability Inventory-computer adaptive test (PEDI-CAT) item bank for children and young adults with spinal muscular atrophy. *Muscle Nerve.* 2016;54(6):1097-1107.

Pera MC, Coratti G, Forcina N, et al. Content validity and clinical meaningfulness of the HFMSE in spinal muscular atrophy. *BMC Neurol.* 2017;17(1):39.

Pera MC, Coratti G, Mazzone ES, et al. Revised upper limb module for spinal muscular atrophy: 12 month changes. *Muscle Nerve.* 2019;59(4):426-430.

Ramsey D, Scoto M, Mayhew A, et al. Revised Hammersmith Scale for spinal muscular atrophy: A SMA specific clinical outcome assessment tool. *PLoS One.* 2017;12(2):e0172346.

Ropars J, Barnerias C, Hully M, et al. Thoracic circumference: A new outcome measure in spinal muscular atrophy type 1? *Neuromuscul Disord.* 2019;29(6):415-421.

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;10.3233/JND-200534.

Stam M, Wadman RI, Bartels B, et al. A continuous repetitive task to detect fatigability in spinal muscular atrophy. *Orphanet J Rare Dis.* 2018;13(1):160.

Stepien A, Jedrzejowska M, Guzek K, Rekowski W, Stepowska J. Reliability of four tests to assess body posture and the range of selected movements in individuals with spinal muscular atrophy. *BMC Musculoskelet Disord.* 2019;20(1):54.

Stolte B, Bois JM, Bolz S, et al. Minimal clinically important differences in functional motor scores in adults with spinal muscular atrophy. *Eur J Neurol.* 2020;10.1111/ene.14472.

Tiziano FD, Bertini E, Messina S, et al. Hammersmith functional score correlates with the SMN2 copy number: a multicentric study. *Neuromuscul Disord.* 2007;17(5):400-403.

Trundell D, Le Scouiller S, Gorni K, Seabrook T, Vuillerot C, Group SMS. Validity and Reliability of the 32-Item Motor Function Measure in 2- to 5-Year-Olds with Neuromuscular Disorders and 2- to 25-Year-Olds with Spinal Muscular Atrophy. *Neurol Ther.* 2020;10.1007/s40120-020-00206-3.

Veerapandiyan A, Eichinger K, Guntrum D, et al. Nusinersen for older patients with spinal muscular atrophy: A real-world clinical setting experience. *Muscle Nerve.* 2020;61(2):222-226.

Vuillerot C, Payan C, Iwaz J, Ecochard R, Berard C, MFM Spinal Muscular Atrophy Study Group. Responsiveness of the motor function measure in patients with spinal muscular atrophy. *Arch Phys Med Rehabil.* 2013;94(8):1555–1561.

Wijngaarde CA, Stam M, Otto LAM, et al. Muscle strength and motor function in adolescents and adults with spinal muscular atrophy. *Neurology.* 2020;10.1212/WNL.0000000000010540

Clinical Evaluator Training

Glanzman AM, Mazzone ES, Young SD, et al. Evaluator training and reliability for SMA global nusinersen trials. *J Neuromuscul Dis.* 2018;5(2):159-166.

Krosschell KJ, Bosch M, Nelson L, et al. Motor function test reliability during the NeuroNEXT Spinal Muscular Atrophy Infant Biomarker Study. *J Neuromuscul Dis.* 2018;5(4):509-521.

Clinical Trial Results and Real World Intervention Studies in SMA

Albrechtsen SS, Born AP, Boesen MS. Nusinersen treatment of spinal muscular atrophy - a systematic review. *Dan Med J.* 2020;67(9).

Al-Zaidy S, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatr Pulmonol.* 2019;54(2):179-185.

Al-Zaidy SA, Kolb SJ, Lowes L, et al. AVXS-101 (Onasemnogene Abeparvovec) for SMA1: Comparative Study with a Prospective Natural History Cohort. *J Neuromuscul Dis.* 2019;6(3):307-317.

Audic F, de la Banda MGG, Bernoux D, et al. Effects of nusinersen after one year of treatment in 123 children with SMA type 1 or 2: a French real-life observational study. *Orphanet J Rare Dis.* 2020;15(1):148.

Bertini E, Dessaud E, Mercuri E, et al. Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol.* 2017;16(7):513-522.

Chen TH. Comment on: "Myostatin inhibition in combination with antisense oligonucleotide therapy improves outcomes in spinal muscular atrophy" by Zhou et al. *J Cachexia Sarcopenia Muscle.* 2020;10.1002/jcsm.12607.

Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. *Neurology.* 2016;86(10):890-897.

Chiriboga CA, Marra J, LaMarca NM, et al. Lack of effect on ambulation of dalfampridine-ER (4-AP) treatment in adult SMA patients. *Neuromuscul Disord.* 2020;30(8):693-700.

Dabbous O, Maru B, Jansen JP, et al. Survival, Motor Function, and Motor Milestones: Comparison of AVXS-101 Relative to Nusinersen for the Treatment of Infants with Spinal Muscular Atrophy Type 1. *Adv Ther.* 2019;36(5):1164-1176.

Darras BT, Chiriboga CA, Iannaccone ST, et al. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies. *Neurology.* 2019;92(21):e2492-e2506.

Darras BT, Farrar MA, Mercuri E, et al. An Integrated Safety Analysis of Infants and Children with Symptomatic Spinal Muscular Atrophy (SMA) Treated with Nusinersen in Seven Clinical Trials. *CNS Drugs.* 2019;33(9):919-932.

De Vivo DC, Bertini E, Swoboda KJ, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscul Disord.* 2019;29(11):842-856.

Deymeer F. Nusinersen in SMA 2 and 3: Risks vs benefits. *Neurology.* 2020;95(4):151-152.

Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet.* 2016;388(10063):3017-3026.

Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med.* 2017;377(18):1723-1732.

Frongia AL, Natera-de Benito D, Ortez C, et al. Salbutamol tolerability and efficacy in patients with spinal muscular atrophy type II. *Neuromuscul Disord.* 2019;29(7):517-524.

Giovannetti AM, Pasanisi MB, Černiauskaitė M, Bussolino C, Leonardi M, Morandi L.Perceived efficacy of salbutamol by persons with spinal muscular atrophy: A mixed methods study. *Muscle Nerve.* 2016;54(5):843-849.

Hagenacker T, Wurster CD, Gunther R, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. *Lancet Neurol.* 2020;19(4):317-325.

Harada Y, Rao VK, Arya K, et al. Combination molecular therapies for type 1 spinal muscular atrophy. *Muscle Nerve.* 2020;10.1002/mus.27034.

Jochmann E, Steinbach R, Jochmann T, et al. Experiences from treating seven adult 5q spinal muscular atrophy patients with Nusinersen. *Ther Adv Neurol Disord.* 2020;13:1756286420907803.

Kissel JT, Elsheikh B, King WM, et al. SMA valiant trial: a prospective, double-blind, placebo-controlled trial of valproic acid in ambulatory adults with spinal muscular atrophy. *Muscle Nerve.* 2014;49(2):187-192.

Kissel JT, Scott CB, Reyna SP, et al. SMA CARNIVAL TRIAL PART II: a prospective, single-armed trial of L-carnitine and valproic acid in ambulatory children with spinal muscular atrophy. *PLoS One.* 2011;6(7):e21296.

Krosschell KJ, Kissel JT, Townsend EL, et al. Clinical trial of L-Carnitine and valproic acid in spinal muscular atrophy type I. *Muscle Nerve.* 2018;57(2):193-199.

Lee BH, Collins E, Lewis L, et al. Combination therapy with nusinersen and AVXS-101 in SMA type 1. *Neurology.* 2019;93(14):640-641.

LoMauro A, Mastella C, Alberti K, Masson R, Aliverti A, Baranello G. Effect of Nusinersen on Respiratory Muscle Function in Different Subtypes of Type 1 Spinal Muscular Atrophy. *Am J Respir Crit Care Med.* 2019;10.1164/rccm.201906-1175LE.

LoMauro A, Mastella C, Alberti K, et al. Reply to: Limited Assessment of Respiratory Muscle Response to Nusinersen Treatment in Infants with Spinal Muscular Atrophy. *Am J Respir Crit Care Med.* 2019;10.1164/rccm.201910-2022LE.

Lowes LP, Alfano LN, Arnold WD, et al. Impact of Age and Motor Function in a Phase 1/2A Study of Infants With SMA Type 1 Receiving Single-Dose Gene Replacement Therapy. *Pediatr Neurol.* 2019;98:39-45.

Matesanz SE, Curry C, Gross B, et al. Clinical Course in a Patient With Spinal Muscular Atrophy Type 0 Treated With Nusinersen and Onasemnogene Abeparvovec. *J Child Neurol.* 2020;35(11):717-723.

Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med.* 2017;377(18):1713-1722.

Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med.* 2018;378(7):625-635.

Mercuri E, Sansone V. Nusinersen in adults with spinal muscular atrophy: new challenges. *Lancet Neurol.* 2020;19(4):283-284.

Miller RG, Moore DH, Dronsky V, et al. A placebo-controlled trial of gabapentin in spinal muscular atrophy. *J Neurol Sci.* 2001;191(1-2):127-131.

Moshe-Lilie O, Visser A, Chahin N, Ragole T, Dimitrova D, Karam C. Nusinersen in adult patients with spinal muscular atrophy: Observations from a single center. *Neurology.* 2020;95(4):e413-e416.

Pane M, Coratti G, Sansone VA, et al. Nusinersen in type 1 spinal muscular atrophy: Twelve-month real-world data. *Ann Neurol.* 2019;86(3):443-451.

Pechmann A, Baumann M, Bernert G, et al. Treatment with Nusinersen - Challenges Regarding the Indication for Children with SMA Type 1. *J Neuromuscul Dis.* 2020;7(1):41-46.

Sansone VA, Albamonte E, Salmin F, et al. Intrathecal nusinersen treatment for SMA in a dedicated neuromuscular clinic: an example of multidisciplinary and integrated care. *Neurol Sci.* 2019;40(2):327-332.

Sansone VA, Pirola A, Albamonte E, et al. Respiratory Needs in Patients with Type 1 Spinal Muscular Atrophy Treated with Nusinersen. *J Pediatr.* 2020;219:223-228 e224.

Stam M, Wadman RI, Wijngaarde CA, et al. Protocol for a phase II, monocentre, double-blind, placebo-controlled, cross-over trial to assess efficacy of pyridostigmine in patients with spinal muscular atrophy types 2-4 (SPACE trial). *BMJ Open.* 2018;8(7):e019932.

Sugimoto M, Aiba K, Koyama N, Yokochi K, Nishio H. Nusinersen helps restore walking ability in childhood spinal muscular atrophy. *Pediatr Int.* 2019;61(7):728-729.

Swoboda KJ, Scott CB, Reyna SP, et al. Phase II open label study of valproic acid in spinal muscular atrophy. *PLoS One.* 2009;4(5):e5268.

Swoboda KJ, Scott CB, Crawford TO, et al. SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. *PLoS One.* 2010;5(8):e12140.

Szabo L, Gergely A, Jakus R, et al. Efficacy of nusinersen in type 1, 2 and 3 spinal muscular atrophy: Real world data from Hungarian patients. *Eur J Paediatr Neurol.* 2020;27:37-42.

Waldrop MA, Karingada C, Storey MA, et al. Gene Therapy for Spinal Muscular Atrophy: Safety and Early Outcomes. *Pediatrics.* 2020;146(3).

Walter MC, Drager B, Gunther R, et al. [Treatment evaluation in patients with 5q-associated spinal muscular atrophy : Real-world experience]. *Nervenarzt.* 2019;90(4):343-351.

Walter MC, Wenninger S, Thiele S, et al. Safety and Treatment Effects of Nusinersen in Longstanding Adult 5q-SMA Type 3 - A Prospective Observational Study. *J Neuromuscul Dis.* 2019;6(4):453-465.

Wurster CD, Winter B, Wollinsky K, et al. Intrathecal administration of nusinersen in adolescent and adult SMA type 2 and 3 patients. *J Neurol.* 2019;266(1):183-194.

Yeo CJJ, Simeone SD, Townsend EL, Zhang RZ, Swoboda KJ. Prospective Cohort Study of Nusinersen Treatment in Adults with Spinal Muscular Atrophy. *J Neuromuscul Dis.* 2020;7(3):257-268.

Zhou H, Meng J, Malerba A, et al. Myostatin inhibition in combination with antisense oligonucleotide therapy improves outcomes in spinal muscular atrophy. *J Cachexia Sarcopenia Muscle.* 2020;11(3):768-782.

Imaging & Biomarkers

Alves CRR, Zhang R, Johnstone AJ, et al. Serum creatinine is a biomarker of progressive denervation in spinal muscular atrophy. *Neurology.* 2020;94(9):e921-e931.

Baranello G, De Amicis R, Arnoldi MT, et al. Evaluation of body composition as a potential biomarker in spinal muscular atrophy. *Muscle Nerve.* 2020;61(4):530-534.

Barp A, Carraro E, Albamonte E, et al. Muscle MRI in two SMA patients on nusinersen treatment: A two years follow-up. *J Neurol Sci.* 2020;417:117067.

Buonsenso D, Berti B, Palermo C, et al. Ultrasound assessment of diaphragmatic function in type 1 spinal muscular atrophy. *Pediatr Pulmonol.* 2020;55(7):1781-1788.

Brogna C, Cristiano L, Verdolotti T, et al. MRI patterns of muscle involvement in type 2 and 3 spinal muscular atrophy patients. *J Neurol.* 2020;267(4):898-912.

Brogna C, Cristiano L, Verdolotti T, et al. Predominant distal muscle involvement in spinal muscular atrophy. *Neuromuscul Disord.* 2019;29(11):910-911.

Darras BT, Crawford TO, Finkel RS, et al. Neurofilament as a potential biomarker for spinal muscular atrophy. *Ann Clin Transl Neurol.* 2019;6(5):932-944.

Faravelli I, Meneri M, Saccomanno D, et al. Nusinersen treatment and cerebrospinal fluid neurofilaments: An explorative study on Spinal Muscular Atrophy type 3 patients. *J Cell Mol Med.* 2020;24(5):3034-3039.

Gunther R, Neuwirth C, Koch JC, et al. Motor Unit Number Index (MUNIX) of hand muscles is a disease biomarker for adult spinal muscular atrophy. *Clin Neurophysiol.* 2019;130(2):315-319.

Kariyawasam DST, D'Silva A, Lin C, Ryan MM, Farrar MA. Biomarkers and the Development of a Personalized Medicine Approach in Spinal Muscular Atrophy. *Front Neurol.* 2019;10:898.

Kollmer J, Hilgenfeld T, Ziegler A, et al. Quantitative MR neurography biomarkers in 5q-linked spinal muscular atrophy. *Neurology.* 2019;93(7):e653-e664.

Otto LAM, van der Pol WL, Schlaffke L, et al. Quantitative MRI of skeletal muscle in a cross-sectional cohort of patients with spinal muscular atrophy types 2 and 3. *NMR Biomed.* 2020;33(10):e4357.

Pucciarelli V, Gibelli D, Mastella C, et al. 3D Facial morphology in children affected by spinal muscular atrophy type 2 (SMAII). *Eur J Orthod.* 2019;10.1093/ejo/cjz071.

Querin G, El Mendili MM, Lenglet T, et al. The spinal and cerebral profile of adult spinal-muscular atrophy: A multimodal imaging study. *NeuroImage. Clinical.* 2019;21:101618.

Regensburger AP, Wagner AL, Hanslik G, et al. Ultra-high-frequency ultrasound in patients with spinal muscular atrophy: A retrospective feasibility study. *Muscle Nerve.* 2020;61(3):E18-E21.

Sleutjes B, Wijngaarde CA, Wadman RI, et al. Assessment of motor unit loss in patients with spinal muscular atrophy. *Clin Neurophysiol.* 2020;131(6):1280-1286.

Smith G, Bell SK, Sladky JT, Kang PB, Albayram MS. Lumbosacral ventral spinal nerve root atrophy identified on MRI in a case of spinal muscular atrophy type II. *Clin Imaging.* 2019;53:134-137.

Neuwirth C, Weber M. MUNIX in children with spinal muscular atrophy: An unexpected journey. *Muscle Nerve.* 2020;10.1002/mus.27053.

Stam M, Haakma W, Kuster L, et al. Magnetic resonance imaging of the cervical spinal cord in spinal muscular atrophy. *NeuroImage. Clinical.* 2019;24:102002.

Totzeck A, Stolte B, Kizina K, et al. Neurofilament Heavy Chain and Tau Protein Are Not Elevated in Cerebrospinal Fluid of Adult Patients with Spinal Muscular Atrophy during Loading with Nusinersen. *Inter J Molec Sci.* 2019;20(21).

Tiziano FD, Lomastro R, Abiusi E, et al. Longitudinal evaluation of SMN levels as biomarker for spinal muscular atrophy: results of a phase IIb double-blind study of salbutamol. *J Med Genet.* 2019;56(5):293-300.

Verma S, Forte J, Ritchey M, Shah D. Motor unit number index in children with later-onset spinal muscular atrophy. *Muscle Nerve.* 2020;10.1002/mus.26909.

Wurster CD, Gunther R, Steinacker P, et al. Neurochemical markers in CSF of adolescent and adult SMA patients undergoing nusinersen treatment. *Ther Adv Neurol Disord.* 2019;12:1756286419846058.

Wurster CD, Koch JC, Cordts I, et al. Routine Cerebrospinal Fluid (CSF) Parameters in Patients With Spinal Muscular Atrophy (SMA) Treated With Nusinersen. *Front Neurol.* 2019;10:1179.

Rehabilitation in SMA

Orthopedic Issues (ie. Contractures, Scoliosis, Hip dislocation)

Baranello G, Vai S, Broggi F, et al. Evolution of bone mineral density, bone metabolism and fragility fractures in Spinal Muscular Atrophy (SMA) types 2 and 3. *Neuromuscul Disord.* 2019;29(7):525-532.

Bernatz JT, Anderson PA, Halanski MA. Cervical Kyphosis in Spinal Muscular Atrophy: A Case Report. *JBJS Case Connect.* 2020;10(2):e1900341.

Chng SY, Wong YQ, Hui JH, Wong HK, Ong HT, Goh DY. Pulmonary function and scoliosis in children with spinal muscular atrophy types II and III. *J Paediatr Child Health*. 2003;39:673-676.

Davies NR, Galaretto E, Piantoni L, et al. Scoliosis in spinal muscular atrophy: is the preoperative magnetic resonance imaging necessary? *Spine Deform.* 2020;10.1007/s43390-020-00134-0.

de Groot IJ, de Witte LP. Physical complaints in ageing persons with spinal muscular atrophy. *J of Rehabil Med.* 2005;37:258-262.

Di Pede C, Salamon E, Motta M, Agosto C, Benini F, Ferrari A. Spinal bracing and lung function in type-2 spinal muscular atrophy. *Eur J Phys Rehabil Med.* 2018.

Dunaway Young S, Montes J, Salazar R, et al. Scoliosis Surgery Significantly Impacts Motor Abilities in Higher-functioning Individuals with Spinal Muscular Atrophy1. *J Neuromuscul Dis*. 2020;7(2):183-192.

Farber HJ, Phillips WA, Kocab KL, et al. Impact of scoliosis surgery on pulmonary function in patients with muscular dystrophies and spinal muscular atrophy. *Pediatr Pulmonol.* 2020;55(4):1037-1042.

Fujak A, Kopschina C, Forst R, Mueller LA, Forst J. Use of orthoses and orthopaedic technical devices in proximal spinal muscular atrophy. Results of survey in 194 SMA patients. *Disabil Rehabil Assist Technol*. 2011;6:305-311.

Fujak A, Kopschina C, Gras F, Forst R, Forst J. Contractures of the upper extremities in spinal muscular atrophy type II. Descriptive clinical study with retrospective data collection. *Ortop Traumatol Rehabil*. 2010;12:410-419.

Fujak A, Raab W, Schuh A, Richter S, Forst R, Forst J. Natural course of scoliosis in proximal spinal muscular atrophy type II and IIIa: descriptive clinical study with retrospective data collection of 126 patients. *BMC Musculoskelet Disord*. 2013;14:283.

Fujak A, Kopschina C, Forst R, Gras F, Mueller LA, Forst J. Fractures in proximal spinal muscular atrophy. *Arch Orthop Trauma Surg.* 2010;130(6):775-780.

Fujak A, Ingenhorst A, Heuser K, Forst R, Forst J. Treatment of scoliosis in intermediate spinal muscular atrophy (SMA type II) in childhood. *Ortop Traumatol Rehabil*. 2005;7(2):175-179.

Granata C, Magni E, Merlini L, Cervellati S. Hip dislocation in spinal muscular atrophy. *La Chirurgia Degli organi Di movimento*. 1990;75:177-184.

Hell AK, Braunschweig L, Tsaknakis K, et al. Children With Spinal Muscular Atrophy With Prior Growth-Friendly Spinal Implants Have Better Results After Definite Spinal Fusion in Comparison to Untreated Patients. *Neurosurgery*. 2020;10.1093/neuros/nyaa053.

Hensel N, Brickwedde H, Tsaknakis K, et al. Altered bone development with impaired cartilage formation precedes neuromuscular symptoms in Spinal Muscular Atrophy (SMA). *Hum Mol Genet.* 2020;10.1093/hmg/ddaa145.

Kruse T, Lehmann HC, Braumann B, Fink GR, Wunderlich G. The Maximum Bite Force for Treatment Evaluation in Severely Affected Adult SMA Patients-Protocol for a Longitudinal Study. *Front Neurol*. 2020;11:139.

Labianca L, Weinstein SL. Scoliosis and spinal muscular atrophy in the new world of medical therapy: providing lumbar access for intrathecal treatment in patients previously treated or undergoing spinal instrumentation and fusion. *J Pediatr Orthop B.* 2019;28(4):393-396.

Larson JE, Snyder B, et al. Short-term clinical outcomes of hip reconstructive surgery in patients with spinal muscular atrophy. *Pediatrics.* 2019;144 (2 Meeting Abstract) 761.

Luc M, Bensoussan L, Viton JM, et al. Gait recovery in a distal spinal muscular atrophy patient wearing a patellar tendon-bearing orthosis and orthopaedic shoes. *J Rehabil Med*. 2007;39:181-184.

Matsumoto H, Mueller J, Konigsberg M, et al. Improvement of Pulmonary Function Measured by Patient-reported Outcomes in Patients With Spinal Muscular Atrophy After Growth-friendly Instrumentation. *J Pediatr Orthop.* 2020;10.1097/BPO.0000000000001656.

Nasomyont N, Hornung LN, Wasserman H. Intravenous bisphosphonate therapy in children with spinal muscular atrophy. *Osteoporos Int.* 2020;31(5):995-1000.

Ness K, Apkon SD. Bone health in children with neuromuscular disorders. *J Pediatr Rehabil Med.* 2014;7(2):133-142.

Rodillo E, Marini ML, Heckmatt JZ, Dubowitz V. Scoliosis in spinal muscular atrophy: review of 63 cases. *J Child Neurol.* 1989;4:118-123.

Salazar R, Montes J, Dunaway Young S, et al. Quantitative evaluation of lower extremity joint contractures in spinal muscular atrophy: Implications for motor function. *Pediatr Phys Ther.* 2018;30(3):209-215.

Shen PC, Lu CC, Liang WC, et al. Predictors for Deformity Progression in a Spinal Muscular Atrophy Cohort After Scoliosis Correction Surgery. *Clin Spine Surg.* 2020;10.1097/BSD.0000000000000989.

Skalsky AJ, McDonald CM. Prevention and management of limb contractures in neuromuscular diseases. *Am J Phys Med Rehabil Clin N Am.* 2012;23(3):675-687.

Sporer SM, Smith BG. Hip dislocation in patients with spinal muscular atrophy. *J Pediatr Ortho.* 2003;23:10-4.

Sproule DM, Montes J, Dunaway S, et al. Adiposity is increased among high-functioning, non-ambulatory patients with spinal muscular atrophy. *Neuromuscul Disord.* 2010;20(7):448-452.

Stepien A, Mazurkiewicz L, Maslanko K, Rekowski W, Jedrzejowska M. Cervical rotation, chest deformity and pelvic obliquity in patients with spinal muscular atrophy. *BMC Musculoskelet Disord.* 2020;21(1):726.

Swarup I, MacAlpine EM, Mayer OH, et al. Impact of growth friendly interventions on spine and pulmonary outcomes of patients with spinal muscular atrophy. *Eur Spine J.* 2020;10.1007/s00586-020-06564-8.

Thacker M, Hui JH, Wong HK, Chatterjee A, Lee EH. Spinal fusion and instrumentation for paediatric neuromuscular scoliosis: retrospective review. *J Ortho Surgery.* 2002;10:144-151.

Thompson CE, Larsen LJ. Recurrent hip dislocation in intermediate spinal atrophy. *J Pediatr Orthop.* 1990;10:638-641.

Vai S, Bianchi ML, Moroni I, et al. Bone and spinal muscular atrophy. *Bone*. 2015;79:116-120.

Wang HY, Ju YH, Chen SM, Lo SK, Jong YJ. Joint range of motion limitations in children and young adults with spinal muscular atrophy. *Arch Rehabil Res Clin Transl.* 2004;85:1689-1693.

Willig TN, Bach JR, Rouffet MJ, Krivickas LS, Maquet C. Correlation of flexion contractures with upper extremity function and pain for spinal muscular atrophy and congenital myopathy patients. *Am J Phys Med Rehabil.* 1995;74(1):33-38.

Interventions

Abeleira MT, Limeres J, Outumuro M, et al. Benefits of Maxillary Expansion for a Patient With Spinal Muscular Atrophy Type 2. *Am J Phys Med Rehabil.* 2019;98(4):e32-e34.

Alves CRR. Exercise training: thinking ahead to counteract systemic manifestations of spinal muscular atrophy. *J Physiol.* 2019;597(24):5757-5758.

Bartels B, Montes J, van der Pol WL, de Groot JF. Physical exercise training for type 3 spinal muscular atrophy. *Cochrane Database Syst Rev.* 2019;3:CD012120.

Biondi O, Lopes P, Desseille C, et al. Physical exercise reduces cardiac defects in type 2 spinal muscular atrophy-like mice. *J Physiol.* 2012;590(22):5907-5925.

Bora G, Subaşı-Yıldız Ş, Yeşbek-Kaymaz A, Bulut N, Alemdaroğlu İ, Tunca-Yılmaz Ö, et al. Effects of arm cycling exercise in spinal muscular atrophy type II patients: A pilot study. *J Child Neurol*. 2018;33(3):209-215.

Bulut N, Yardimci BN, Ayvat E, Aran OT, Yilmaz O, Karaduman A. The effect of two different aerobic training modalities in a child with spinal muscular atrophy type II: a case report. *J Exerc Rehabil.* 2019;15(2):322-326.

Catteruccia C, Vaugier I, Leclair D, et al. Orthopedic management of scoliosis by Garches brace and spinal fusion in SMA type 2 children. *J Neuro Dis*. 2015;2:463-470.

Craig J, Hilderman C, Wilson G, Misovic R. Effectiveness of stretch interventions for children with neuromuscular disabilities: Evidence-based recommendations. *Pediatr Phys Ther.* 2016;28(3):262-275.

Cunha MC, Oliveira AS, Labronici RH, Gabbai AA. Spinal muscular atrophy type II (intermediary) and III (Kugelberg-Welander). Evolution of 50 patients with physiotherapy and hydrotherapy in a swimming pool. *Arq Neuropsiquiatr.* 1996;54:402-406.

Fehlings DL, Kirsch S, McComas A, Chipman M, Campbell K. Evaluation of therapeutic electrical stimulation to improve muscle strength and function in children with types II/III spinal muscular atrophy. *Dev Med Child Neurol.* 2002;44:741-744.

Frownfelter D, Stevens K, Massery M, Bernardoni G. Do abdominal cutouts in thoracolumbosacral orthoses increase pulmonary function? *Clin Orthop Relat Res.* 2014;472(2):720-726.

Gobbo M, Lazzarini S, Vacchi L, et al. Exercise Combined with Electrotherapy Enhances Motor Function in an Adolescent with Spinal Muscular Atrophy Type III. *Case Rep Neurol Med.* 2019;2019:4839793.

Granata C, Cornelio F, Bonfiglioli S, Mattutini P, Merlini L. Promotion of ambulation of patients with spinal muscular atrophy by early fitting of knee-ankle-foot orthoses. *Dev Med and Child Neurol.* 1987;29:221-224.

Hartley S, Stockley R. It's more than just physical therapy: reported utilization of physiotherapy services for adults with neuromuscular disorders attending a specialist centre. *Disabil Rehabi.* 2013;35:282-290.

Jones MA, McEwen IR, Hansen L. Use of power mobility for a young child with spinal muscular atrophy. *Phys Ther.* 2003;83:253-262.

Lemke D, Rothwell E, Newcomb TM, Swoboda KJ. Perceptions of equine-assisted activities and therapies by parents and children with spinal muscular atrophy. *Pediatr Physl Ther.* 2014;26:237-244.

Lewelt A, Krosschell KJ, Stoddard GJ, et al. Resistance strength training exercise in children with spinal muscular atrophy. *Muscle Nerve.* 2015;52:559-567.

Lloyd Morris EH, Estilow T, Glanzman AM, Cusack SV, Yum SW. Improving Temporomandibular Range of Motion in People With Duchenne Muscular Dystrophy and Spinal Muscular Atrophy. *Am J Occup Ther.* 2020;74(2):7402205080p7402205081 7402205080p7402205010.

Madsen KL, Hansen RS, Preisler N, Thogersen F, Berthelsen MP, Vissing J. Training improves oxidative capacity, but not function, in spinal muscular atrophy type III. *Muscle Nerve.* 2015;52:240-244.

Montes J, Garber, CE, Kramer SS, et al. Single-blind, randomized, controlled clinical trial of exercise in ambulatory spinal muscular atrophy: Why are the results negative? *J Neuro Dis.* 2015;2:463-470.

Montes J, Yoon LH. Commentary on "Stander Use in Spinal Muscular Atrophy: Results From a Large Natural History Database". *Pediatr Phys Ther.* 2020;32(3):242.

Peeters LHC, Janssen M, Kingma I, van Dieen JH, de Groot IJM. Patients With Spinal Muscular Atrophy Use High Percentages of Trunk Muscle Capacity to Perform Seated Tasks. *Am J Phys Med Rehabil.* 2019;98(12):1110-1117.

Rathore FA, Afridi A. Does physical exercise training improve functional performance in type 3 spinal muscular atrophy? A Cochrane Review summary with commentary. *Dev Med Child Neurol.* 2020;62(9):1014-1016.

Salem Y, Gropack SJ. Aquatic therapy for a child with type III spinal muscular atrophy: a case report. *Phys Occup Ther Pediatr.* 2010;30:313-324.

Stark C, Duran I, Cirak S, et al. Vibration-assisted home training program for children with spinal muscular atrophy. *Child Neurol Open.* 2018;5:2329048X18780477.

Tangsrud SE, Carlsen KC, Lund-Petersen I, Carlsen KH. Lung function measurements in young children with spinal muscle atrophy; a cross sectional survey on the effect of position and bracing. *Arch Dis Child.* 2001;84:521-524.

Townsend EL, Simeone SD, Krosschell KJ, Zhang RZ, Swoboda KJ, Project Cure SMA Investigator Network Stander Use in Spinal Muscular Atrophy: Results From a Large Natural History Database. *Pediatr Phys Ther.* 2020;32(3):235-241.

Trabacca A, Lucarelli E, Pacifico R, Vespino T, Di Liddo A, Losito L. The International Classification of Functioning, Disability and Health-Children and Youth as a framework for the management of spinal muscular atrophy in the era of gene therapy: a proof-of-concept study. *Eur J Phys Rehabil Med.* 2020;56(2):243-251.

Trenkle J, Brugman J, Peterson A, Roback K, Krosschell KJ. Filling the gaps in knowledge translation: Physical therapy recommendations for individuals with spinal muscular atrophy compared to standard of care guidelines. *Neuromuscul Disord*. 2021;31(5):397-408.

Vry J, Schubert IJ, Semler O, Haug V, Schonau E, Kirschner J. Whole-body vibration training in children with Duchenne muscular dystrophy and spinal muscular atrophy. *Euro J Padiatr Neurol.* 2014;18:140-149.

Falls

Montes J, McIsaac TL, Dunaway S, et al. Falls and spinal muscular atrophy: exploring cause and prevention. *Muscle Nerve.* 2013;47:118-123.

Fatigue

Binz C, Schreiber-Katz O, Kumpe M, et al. An observational cohort study on impact, dimensions and outcome of perceived fatigue in adult 5q-spinal muscular atrophy patients receiving nusinersen treatment. *J Neurol.* 2020;10.1007/s00415-020-10227

Dunaway Young S, Montes J, Kramer SS, Podwika B, Rao AK, De Vivo DC. Perceived fatigue in spinal muscular atrophy: A pilot study. *J Neuromuscul Dis.* 2019;6(1):109-117.

King W, Kissel JT, Montes J, De Vivo DC, Finkel RS. Six-minute walk test demonstrates motor fatigue in spinal muscular atrophy. *Neurology.* 2010;75(12):1121-1122; author reply 1122.

Kizina K, Stolte B, Totzeck A, et al. Fatigue in adults with spinal muscular atrophy under treatment with nusinersen. *Sci Rep.* 2020;10(1):11069.

McMillan HJ. Nusinersen: Evidence of sustained clinical improvement and lessened fatigue in older ambulatory patients with spinal muscular atrophy. *Muscle Nerve.* 2020;61(1):1-2.

Montes J, Blumenschine M, Dunaway S, et al. Weakness and fatigue in diverse neuromuscular diseases. *J Child Neurol.* 2013;28:1277-1283.

Montes J, Dunaway S, Garber CE, Chiriboga CA, De Vivo DC, Rao AK. Leg muscle function and fatigue during walking in spinal muscular atrophy type 3. *Muscle Nerve.* 2014;50:34-39.

Montes J, Dunaway S, Montgomery MJ, et al. Fatigue leads to gait changes in spinal muscular atrophy. *Muscle Nerve.* 2011;43:485-488.

Montes J, McDermott MP, Martens WB, et al. Six-minute walk test demonstrates motor fatigue in spinal muscular atrophy. *Neurology.* 2010;74:833-838.

Stam M, Wadman RI, Bartels B, et al. A continuous repetitive task to detect fatigability in spinal muscular atrophy. *Orphanet J Rare Dis.* 2018;13(1):160.

Pain

Lager C, Kroksmark AK. Pain in adolescents with spinal muscular atrophy and Duchenne and Becker muscular dystrophy. *Euro J Padiatr Neurol.* 2015;19:537-546.

Review

Canavese F, Sussman MD. Strategies of hip management in neuromuscular disorders: Duchenne muscular dystrophy, spinal muscular atrophy, Charcot-Marie-Tooth disease and arthrogryposis multiplex congenita. Hip International: the journal of clinical and experimental research on hip pathology and therapy. 2009;19 Suppl 6:S46-52.

Cuisset JM, Estournet B, French Ministry of H. Recommendations for the diagnosis and management of typical childhood spinal muscular atrophy. *Revue Neurologique.* 2012;168:902-909.

Haaker G, Fujak A. Proximal spinal muscular atrophy: current orthopedic perspective. *App Clin Genet.* 2013;6:113-120.

Merlini L, Granata C, Bonfiglioli S, Marini ML, Cervellati S, Savini R. Scoliosis in spinal muscular atrophy: natural history and management. *Dev Med and Child Neurol.* 1989;31:501-508.

Merlini L, Granata C. Rehabilitation of children with muscle disease. *Current Opinion in Neurol Neurosurg.* 1990;3:738-741.

Participation and Quality of Life, including Patient Reported Outcomes and Measures

Bach JR, Vega J, Majors J, Friedman A. Spinal muscular atrophy type 1 quality of life. *Am J Phys Med Rehabil*. 2003;82(2):137-142.

Beernaert K, Lovgren M, Jeppesen J, et al. Parents' experiences of information and decision making in the care of their child with severe spinal muscular atrophy: A population survey. *J Child Neurol.* 2019:883073818822900.

Belter L, Cruz R, Jarecki J. Quality of life data for individuals affected by spinal muscular atrophy: a baseline dataset from the Cure SMA Community Update Survey. *Orphanet J Rare Dis.* 2020;15(1):217.

Benini F, Salamon E, Divisic A, Maghini I, Agosto C. Acknowledging Limits: Statistics and the Child's Quality of Life in Spinal Muscular Atrophy. *J Paediatr Child Health.* 2020;56(6):995-996.

Chambers GM, Settumba SN, Carey KA, et al. Prenusinersen economic and health-related quality of life burden of spinal muscular atrophy. *Neurology.* 2020;95(1):e1-e10.

Cremers CH, Fischer MJ, Kruitwagen-van Reenen ET, et al. Participation and mental well-being of mothers of home-living patients with spinal muscular atrophy. *Neuromuscul Disord.* 2019;29(4):321-329.

Cruz R, Belter L, Wasnock M, Nazarelli A, Jarecki J. Evaluating Benefit-risk Decision-making in Spinal Muscular Atrophy: A First-ever Study to Assess Risk Tolerance in the SMA Patient Community. *Clin Ther.* 2019;41(5):943-960 e944.

Cruz R, Lenz M,Belter L, Hobby K, Jarecki J. The Voice of the Patient Report. Cure SMA 2018. https://www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf. Accessed 10.1.2020.

Fischer MJ, Asselman FL, Kruitwagen-van Reenen ET, et al. Psychological well-being in adults with spinal muscular atrophy: the contribution of participation and psychological needs. *Disabil Rehabil.* 2020;42(16):2262-2270.

Hjorth E, Kreicbergs U, Sejersen T, et al. Bereaved Parents More Satisfied With the Care Given to Their Child With Severe Spinal Muscular Atrophy Than Nonbereaved. *J Child Neurol.* 2019;34(2):104-112.

Hoot NR. Nusinersen for Type 1 Spinal Muscular Atrophy: A Father's Perspective. *Pediatrics.* 2019;144(4).

Hully M, Barnerias C, Chabalier D, et al. Palliative Care in SMA Type 1: A Prospective Multicenter French Study Based on Parents' Reports. *Front Pediatr.* 2020;8:4.

Gunther R, Wurster CD, Cordts I, et al. Patient-Reported Prevalence of Non-motor Symptoms Is Low in Adult Patients Suffering From 5q Spinal Muscular Atrophy. *Front Neurol.* 2019;10:1098.

Hunter M, Heatwole C, Luebbe E, Johnson NE. What matters most: A perspective from adult spinal muscular atrophy patients. *J Neuromuscul Dis*. 2016;3(3):425-429.

Kiefer P, Kirschner J, Pechmann A, Langer T. Experiences of caregivers of children with spinal muscular atrophy participating in the expanded access program for nusinersen: a longitudinal qualitative study. *Orphanet J Rare Dis.* 2020;15(1):194.

Kruitwagen-Van Reenen ET, Wadman RI, Visser-Meily JM, van den Berg LH, Schroder C, van der Pol WL. Correlates of health related quality of life in adult patients with spinal muscular atrophy. *Muscle Nerve.* 2016;54(5):850-855.

Landfeldt E, Edström J, Sejersen T, Tulinius M, Lochmüller H, Kirschner J. Quality of life of patients with spinal muscular atrophy: A systematic review. *Eur J Paediatr Neurol.* 2019;10.1016/j.ejpn.2019.03.004.

Lavie M, Nisnkorn H, Sagi L, Amirav I. Choosing Life with Spinal Muscular Atrophy Type 1. *Adv Ther.* 2020;37(5):1708-1713.

Lloyd AJ, Thompson R, Gallop K, Teynor M. Estimation Of The Quality Of Life Benefits Associated With Treatment For Spinal Muscular Atrophy. *Clinicoecon Outcomes Res.* 2019;11:615-622.

McGraw S, Qian Y, Henne J, Jarecki J, Hobby K, Yeh WS. A qualitative study of perceptions of meaningful change in spinal muscular atrophy. *BMC Neurol.* 2017;17(1):68.

Mercuri E, Messina S, Montes J, et al. Patient and parent oriented tools to assess health-related quality of life, activity of daily living and caregiver burden in SMA. Rome, 13 July 2019. *Neuromuscul Disord.* 2020;30(5):431-436.

Mongiovi P, Dilek N, Garland C, et al. Patient reported impact of symptoms in spinal muscular atrophy (PRISM-SMA). *Neurology.* 2018;91(13):e1206-e1214.

Osmanovic A, Ranxha G, Kumpe M, et al. Treatment expectations and patient-reported outcomes of nusinersen therapy in adult spinal muscular atrophy. *J Neurol.* 2020;267(8):2398-2407.

Pacione M, Siskind CE, Day JW, Tabor HK. Perspectives on Spinraza (Nusinersen) treatment study: Views of individuals and parents of children diagnosed with spinal muscular atrophy. *J Neuromuscul Dis.*2019;6(1):119-131.

Pena-Longobardo LM, Aranda-Reneo I, Oliva-Moreno J, et al. The Economic Impact and Health-Related Quality of Life of Spinal Muscular Atrophy. An Analysis across Europe. *Int J Environ Res Public Health.* 2020;17(16).

Qian Y, McGraw S, Henne J, Jarecki J, Hobby K, Yeh WS. Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study. *BMC Neurol.* 2015;15(1):217.

Vaidya S, Boes S. Measuring quality of life in children with spinal muscular atrophy: a systematic literature review. *Qual Life Res.* 2018;27(12):3087-3094.

Wan HWY, Carey KA, D'Silva A, et al. Health, wellbeing and lived experiences of adults with SMA: a scoping systematic review. *Orphanet J Rare Dis.* 2020;15(1):70.

Wan HWY, Carey KA, D'Silva A, Kasparian NA, Farrar MA. "Getting ready for the adult world": how adults with spinal muscular atrophy perceive and experience healthcare, transition and well-being. *Orphanet J Rare Dis.* 2019;14(1):74.

Weaver MS, Hanna R, Hetzel S, et al. A Prospective, Crossover Survey Study of Child- and Proxy-Reported Quality of Life According to Spinal Muscular Atrophy Type and Medical Interventions. *J Child Neurol.* 2020;35(5):322-330.

Newborn Screening

Baker M, Griggs R, Byrne B, et al. Maximizing the Benefit of Life-Saving Treatments for Pompe Disease, Spinal Muscular Atrophy, and Duchenne Muscular Dystrophy Through Newborn Screening: Essential Steps. *JAMA Neurol.* 2019;10.1001/jamaneurol.2019.1206.

Bozorg Qomi S, Asghari A, Salmaninejad A, Mojarrad M. Spinal Muscular Atrophy and Common Therapeutic Advances. *Fetal Pediatr Pathol.* 2019;38(3):226-238.

Brandsema JF, Gross BN, Matesanz SE. Diagnostic Testing for Patients with Spinal Muscular Atrophy. *Clin Lab Med.* 2020;40(3):357-367.

Cavdarli B, Ozturk FN, Guntekin Ergun S, Ergun MA, Dogan O, Percin EF. Intelligent Ratio: A New Method for Carrier and Newborn Screening in Spinal Muscular Atrophy. *Genet Test Mol Biomarkers.* 2020;24(9):569-577.

Dangouloff T, Burghes A, Tizzano EF, Servais L, Group NSS. 244th ENMC international workshop: Newborn screening in spinal muscular atrophy May 10-12, 2019, Hoofdorp, The Netherlands. *Neuromuscul Disord.* 2020;30(1):93-103.

Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. *J Neuromuscul Dis.* 2018;5(2):145-158.

Glascock J, Sampson J, Connolly AM, et al. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2. *J Neuromuscul Dis.* 2020;7(2):97-100.

Gyngell C, Stark Z, Savulescu J. Drugs, genes and screens: The ethics of preventing and treating spinal muscular atrophy. *Bioethics.* 2020;34(5):493-501.

Jalali A, Rothwell E, Botkin JR, Anderson RA, Butterfield RJ, Nelson RE. Cost-Effectiveness of Nusinersen and Universal Newborn Screening for Spinal Muscular Atrophy. *J Pediatr.* 2020;10.1016/j.jpeds.2020.07.033.

Kariyawasam DST, Russell JS, Wiley V, Alexander IE, Farrar MA. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. *Genet Med.* 2020;22(3):557-565.

Kay DM, Stevens CF, Parker A, et al. Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. *Genet Med.* 2020;22(8):1296-1302.

Ke Q, Zhao ZY, Mendell JR, et al. Progress in treatment and newborn screening for Duchenne muscular dystrophy and spinal muscular atrophy. *World J Pediatr.* 2019;15(3):219-225.

Kraszewski JN, Kay DM, Stevens CF, et al. Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. *Genet Med.* 2018;20(6):608-613.

Lopez-Chacon M, Buehner AN, Rao VK. Spinal Muscular Atrophy Diagnosed by Newborn Screening. *Pediatr Neurol Briefs.* 2019;33:5.

Muller-Felber W, Vill K, Schwartz O, et al. Infants Diagnosed with Spinal Muscular Atrophy and 4 SMN2 Copies through Newborn Screening - Opportunity or Burden? *J Neuromuscul Dis.* 2020;7(2):109-117.

Ross LF, Kwon JM. Spinal Muscular Atrophy: Past, Present, and Future. *Neoreviews.* 2019;20(8):e437-e451.

Saffari A, Kolker S, Hoffmann GF, Weiler M, Ziegler A. Novel challenges in spinal muscular atrophy - How to screen and whom to treat? *Ann Clin Transl Neurol.* 2019;6(1):197-205.

Serra-Juhe C, Tizzano EF. Perspectives in genetic counseling for spinal muscular atrophy in the new therapeutic era: early pre-symptomatic intervention and test in minors. *Eur J Hum Genet.* 2019;27(12):1774-1782.

The New Horizon

Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle Nerve.* 2015;51(2):157-167.

Chen TH. New and Developing Therapies in Spinal Muscular Atrophy: From Genotype to Phenotype to Treatment and Where Do We Stand? *International journal of molecular sciences.* 2020;21(9).

Ciafaloni E, Russman BS. Nusinersen for spinal muscular atrophy: Not just for babies? *Neurology.* 2019;92(21):985-986.

Dangouloff T, Servais L. Clinical Evidence Supporting Early Treatment Of Patients With Spinal Muscular Atrophy: Current Perspectives. *Ther Clin Risk Manag.* 2019;15:1153-1161.

Darras BT, Mammas IN, Spandidos DA. Spinal muscular atrophy, pediatric virology and gene therapy: A challenge of modern weakness and hope. *Exp Ther Med.* 2018;15(4):3671-3672.

D'Silva A, Farrar MA. Personalized medicine for children with spinal muscular atrophy: Toward the holy grail. *Muscle Nerve.* 2020;10.1002/mus.27030.

d'Ydewalle C, Sumner CJ. Spinal muscular atrophy therapeutics: Where do we stand? *Neurotherapeutics.* 2015;12(2):303-316.

Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy. *Ann Neurol.* 2017;81(3):355-368.

Farrar MA, Carey KA, Paguinto SG, Kasparian NA, De Abreu Lourenco R. "The Whole Game is Changing and You've Got Hope": Australian Perspectives on Treatment Decision Making in Spinal Muscular Atrophy. *Patient.* 2020;13(4):389-400.

Gidaro T, Servais L. Nusinersen treatment of spinal muscular atrophy: current knowledge and existing gaps. *Dev Med Child Neurol.* 2019;61(1):19-24.

Hensel N, Kubinski S, Claus P. The Need for SMN-Independent Treatments of Spinal Muscular Atrophy (SMA) to Complement SMN-Enhancing Drugs. *Front Neurol.* 2020;11:45.

Howell K, Gibbs RM, Rubin LL. Spinal Muscular Atrophy: Huge Steps. *Cerebrum.* 2019 Mar 1;2019:cer-03-19. eCollection Mar-Apr 2019.

Jedrzejowska M, Kostera-Pruszczyk A. Spinal muscular atrophy - new therapies, new challenges. *Neurol Neurochir Pol.* 2020;54(1):8-13.

Kariyawasam D, Carey KA, Jones KJ, Farrar MA. New and developing therapies in spinal muscular atrophy. *Paediatr Respir Rev.* 2018;28:3-10.

Kolb SJ, Kissel JT. Spinal muscular atrophy. *Neurologic clinics.* 2015;33(4):831-846.

Kolb SJ, Kissel JT. Spinal muscular atrophy: a timely review. *Arch Neurol.* 2011;68(8):979-984.

Messina S, Sframeli M. New Treatments in Spinal Muscular Atrophy: Positive Results and New Challenges. *J Clin Med.* 2020;9(7).

Meylemans A, De Bleecker J. Current evidence for treatment with nusinersen for spinal muscular atrophy: a systematic review. *Acta Neurol Belg.* 2019;119(4):523-533.

Pacak CA, Kang PB. The End of the Beginning: The Journey to Molecular Therapies for Spinal Muscular Atrophy. *Pediatr Neurol.* 2020;102:1-2.

Pera MC, Coratti G, Berti B, et al. Diagnostic journey in Spinal Muscular Atrophy: Is it still an odyssey? *PLoS One.* 2020;15(3):e0230677.

Ramdas S, Servais L. New treatments in spinal muscular atrophy: an overview of currently available data. *Expert Opin Pharmacother.* 2020;21(3):307-315.

Schorling DC, Pechmann A, Kirschner J. Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care. *J*

Neuromuscul Dis. 2020;7(1):1-13.

Smith M. Current and future treatments of spinal muscular atrophy. *Dev Med Child Neurol.* 2020;62(3):267.

Sumner CJ, Crawford TO. Two breakthrough gene-targeted treatments for spinal muscular atrophy: challenges remain. *J Clin Invest.* 2018;128(8):3219-3227.

Swoboda KJ, Kissel JT, Crawford TO, et al. Perspectives on clinical trials in spinal muscular atrophy. *J Child Neurol.* 2007;22(8):957-966.

Tizzano EF, Finkel RS. Spinal muscular atrophy: A changing phenotype beyond the clinical trials. *Neuromuscul Disord.* 2017;27(10):883-889.

Tizzano EF. Treating neonatal spinal muscular atrophy: A 21st century success story? *Early Hum Dev.* 2019;138:104851.

Vu-Han TL, Weiss C, Pumberger M. Novel Therapies for Spinal Muscular Atrophy are Likely Changing the Patient Phenotype. *Spine J.* 2020;10.1016/j.spinee.2020.08.013.

Williams L. Spinal Muscular Atrophy in the Age of Gene Therapy. *AACN Adv Crit Care.* 2020;31(1):86-91.

Wirth B, Karakaya M, Kye MJ, Mendoza-Ferreira N. Twenty-Five Years of Spinal Muscular Atrophy Research: From Phenotype to Genotype to Therapy, and What Comes Next. *Annu Rev Genomics Hum Genet.* 2020;21:231-261.

Waldrop MA, Elsheikh BH. Spinal Muscular Atrophy in the Treatment Era. *Neurologic clinics.* 2020;38(3):505-518.

Yong J, Moffett M, Lucas S. Implementing a Global Expanded Access Program (EAP) for Infantile-Onset Spinal Muscular Atrophy (Type I): Understanding the Imperative, Impact and Challenges. *J Neuromuscul Dis.* 2019;6(2):227-231.

Professional or Pharmacologic Guidelines, and Cochrane Reviews

Ganesh A, Galetta S. Editors' note: Evidence in focus: Nusinersen use in spinal muscular atrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2019;93(10):464.

Kirschner J, Butoianu N, Goemans N, et al. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. *Eur J Paediatr Neurol.* 2020;10.1016/j.ejpn.2020.07.001.

Michelson D, Ciafaloni E, Ashwal S, et al. Evidence in focus: Nusinersen use in spinal muscular atrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;91(20):923-933.

Takanashi JI, Takase N. Reader response: Evidence in focus: Nusinersen use in spinal muscular atrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2019;93(10):464.

Wadman RI, van der Pol WL, Bosboom WM, et al. Drug treatment for spinal muscular atrophy types II and III. *Cochrane Database Syst Rev.* 2020;1:CD006282.

COVID 19

Alghamdi F, Alshaikh N, Bamaga AK, et al. A consensus statement on spinal muscular atrophy management in Saudi Arabia in the context of COVID-19. *Neurosciences (Riyadh).* 2020;25(3):230-237.

Veerapandiyan A, Connolly AM, Finkel RS, et al. Spinal muscular atrophy care in the COVID-19 pandemic era. *Muscle Nerve.* 2020;62(1):46-49.

Zafeiriou D. Gene therapy for spinal muscular atrophy: Solomon's consensus in Covid times. *Eur J Paediatr Neurol.* 2020;10.1016/j.ejpn.2020.08.005.

Registries

Finkel RS, Day JW, De Vivo DC, et al. RESTORE: A Prospective Multinational Registry of Patients with Genetically Confirmed Spinal Muscular Atrophy - Rationale and Study Design. *J Neuromuscul Dis.* 2020;7(2):145-152.

Hodgkinson VL, Oskoui M, Lounsberry J, et al. A National Spinal Muscular Atrophy Registry for Real-World Evidence. *Can J Neurol Sci.* 2020;10.1017/cjn.2020.111:1-6.

Mercuri E, Finkel R, Scoto M, et al. Development of an academic disease registry for spinal muscular atrophy. *Neuromuscul Disord.* 2019;29(10):794-799.

Pechmann A, Konig K, Bernert G, et al. SMArtCARE - A platform to collect real-life outcome data of patients with spinal muscular atrophy. *Orphanet J Rare Dis.* 2019;14(1):18.

Miscellaneous

Abreu NJ, Waldrop MA. Overview of Gene Therapy in Spinal Muscular Atrophy and Duchenne Muscular Dystrophy. *Pediatr Pulmonol.* 2020;10.1002/ppul.25055.

Aragon-Gawinska K, Daron A, Ulinici A, et al. Sitting in patients with spinal muscular atrophy type 1 treated with nusinersen. *Dev Med Child Neurol.* 2020;62(3):310-314.

Ball LJ, Chavez S, Perez G, et al. Communication skills among children with spinal muscular atrophy type 1: A parent survey. *Assist Technol.* 2019;10.1080/10400435.2019.1586788:1-11.

Bose M, Parab SD, Patil SM, Pandey NA, Pednekar GV, Saini SS. Exploring spinal muscular atrophy and its impact on functional status: Indian scenario. *Indian J Public Health.* 2019;63(3):254-257.

Chacko A, Sly PD, Gauld L. Limited Assessment of Respiratory Muscle Response to Nusinersen Treatment in Infants with Spinal Muscular Atrophy. *Am J Respir Crit Care Med.* 2020;201(5):624.

Elsheikh B, Prior T, Zhang X, et al. An analysis of disease severity based on SMN2 copy number in adults with spinal muscular atrophy. *Muscle Nerve.* 2009;40(4):652-656.

Elsheikh BH, Zhang X, Swoboda KJ, et al. Pregnancy and delivery in women with spinal muscular atrophy. *Int J Neurosci.* 2017;127(11):953-957.

Gidaro T, Servais L. Nusinersen treatment of spinal muscular atrophy: current knowledge and existing gaps. *Dev Med Child Neurol.* 2019;61(1):19-24.

Iyer AA, Barzilay JR, Tabor HK. Patient and family social media use surrounding a novel treatment for a rare genetic disease: a qualitative interview study. *Genet Med*. 2020 Nov;22(11):1830-1837. doi: 10.1038/s41436-020-0890-6. Epub 2020 Jun 30.

Mayer OH. Turning the tide in spinal muscular atrophy: A different respiratory course. *Pediatr Pulmonol.* 2019;54(7):935-936.

Murrell DV, Crawford CA, Jackson CT, Lotze TE, Wiemann CM. Identifying opportunities to provide Family-centered care for families with children with type 1 spinal muscular atrophy. *J Pediatr Nurs.* 2018;43:111-119.

Polido GJ, de Miranda MMV, Carvas N, et al. Cognitive performance of children with spinal muscular atrophy: A systematic review. *Dement Neuropsychol.* 2019;13(4):436-443.

Tizzano EF, Zafeiriou D. Prenatal aspects in spinal muscular atrophy: From early detection to early presymptomatic intervention. *Eur J Paediatr Neurol.* 2018;22(6):944-950.

Vukovic S, McAdam L, Zlotnik-Shaul R, Amin R. Putting our best foot forward: Clinical, treatment-based and ethical considerations of nusinersen therapy in Canada for spinal muscular atrophy. *J Paediatr Child Health.* 2019;55(1):18-24.

Wijngaarde CA, Stam M, Otto LAM, et al. Population-based analysis of survival in spinal muscular atrophy. *Neurology.* 2020;94(15):e1634-e1644.

Economics of SMA

Darba J, Marsa A. Patient characteristics and hospitalisation costs of spinal muscular atrophy in Spain: a retrospective multicentre database analysis. *BMJ Open.* 2019;9(11):e031271.

Droege M, Sproule D, Arjunji R, Gauthier-Loiselle M, Cloutier M, Dabbous O. Economic burden of spinal muscular atrophy in the United States: a contemporary assessment. *J Med Econ.* 2020;23(1):70-79.

Lee M, Jr., Franca UL, Graham RJ, McManus ML. Pre-Nusinersen Hospitalization Costs of Children With Spinal Muscular Atrophy. *Pediatr Neurol.* 2019;92:3-5.

Tan H, Gu T, Chen E, Punekar R, Shieh PB. Healthcare Utilization, Costs of Care, and Mortality Among Patients With Spinal Muscular Atrophy. *J Health Econ Outcomes Res.* 2019;6(3):185-195.

Zuluaga-Sanchez S, Teynor M, Knight C, et al. Cost Effectiveness of Nusinersen in the Treatment of Patients with Infantile-Onset and Later-Onset Spinal Muscular Atrophy in Sweden. *Pharmacoeconomics.* 2019;37(6):845-865.

Table A3: External Resources for SMA Education and Training

The table below categorizes external resources for SMA education and training into the following subsections: Standards of Care Documents, Standards of Care for Families, Physical Therapy Specific SMA Resources, General SMA Resources, SMA Care and Management, Pharmaceutical Related Resources, SMA Clinical Trials, and Cure SMA Resources. This list encompasses many resources but is not fully comprehensive; it is intended as a guide for further information. Each resource is captured with a title, source description, and a resource link if applicable.

	Title	Resource Description	Resource Link
Standard of Care (SOC) Documents	Consensus statement for standard of care in spinal muscular atrophy. 2007	In 2007, an International Conference on the SOC for SMA published a consensus statement on SMA standard of care that has been widely used throughout the world. (Wang et al., 2007)	https://journals.sagepub.com/doi/abs/10.1177/0883073807305788
	Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. 2018	Updated SOC in SMA (Mercuri et al., 2018), expands on the topics covered in the 2007 SOC recommendations and includes information on the most updated, best practices in care for SMA. Part 1 focuses on the methods used to achieve SOC recommendations, and an update on diagnosis, rehabilitation, orthopedic and spinal management. It also covers nutritional, swallowing and gastrointestinal management.	https://www.sciencedirect.com/science/article/pii/S0960896617312841?via%3Dihub
	Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. 2018	Updated SOC in SMA (Finkel et al., 2018), expands on the topics covered in the previous recommendations and includes information on the most updated, best practices in care for SMA. Part 2 focuses on pulmonary management, acute care, other organ involvement, ethical issues, medications, and the impact of new treatments for SMA.	https://www.sciencedirect.com/science/article/pii/S0960896617312907?via%3Dihub
Standards of Care for Families	A Family Guide to the Consensus Statement for Standard of Care in Spinal Muscular Atrophy. 2007	This Family Guide to the Consensus Statement for SOC in SMA was prepared by advocates for families impacted by SMA including the SMA Foundation, Cure SMA (then Families of SMA), MDA, and Fight SMA.	https://www.mda.org/sites/default/files/publications/SMA_Family_Guide_Care_Standards.pdf
	A guide to the 2017 International SMA Standards of Care - published in 2019 (Treat NMD)	A user-friendly précis and a comprehensive outline of the standard of care recommendations.	https://treat-nmd.org/wp-content/uploads/2019/06/uncategorized-A-Guide-to-the-2017-International-Standards-of-Care-for-SMA_UKEnglish_Digital-v2L.pdf

Physical Therapy Specific SMA Resources	Physical Therapist's Guide to Spinal Muscular Atrophy - Move Forward PT, APTA. 2014	Consumer e-newsletter of the American Physical Therapy Association (APTA). Article provides a general, high level overview of SMA including a description of signs and symptoms, diagnosis, how a PT may help, real life experiences, etc.	https://www.choosept.com/symptomsconditionsdetail/physical-therapy-guide-to-spinal-muscular-atrophy
	APTA Academy of Pediatrics PT (APPT) - SMA Fact Sheet. 2021	Useful fact sheet for PTs working with SMA patients. It includes quick and easily accessible information on SMA signs and symptoms, diagnosis and intervention strategies.	https://pediatricapta.org/includes/fact-sheets/pdfs/PEDS_Factsheet_SMA.pdf
	Cure SMA Care Series, Musculoskeletal System	This is a Cure SMA booklet specifically regarding issues with the musculoskeletal system in SMA. It reviews orthopedic concerns including contractures, hips, and spine.	https://curesma.wpengine.com/wp-content/uploads/2019/07/the-musculoskeletal-system.pdf
	Exercise and Spinal Muscular Atrophy - website	SMA UK article on studies from the past few years investigating the benefits of exercise with regards to SMA.	https://smauk.org.uk/exercise-spinal-muscular-atrophy
	Management of Spinal Deformities in Spinal Muscular Atrophy	These slides were originally presented at the 2018 Annual Cure SMA Conference. Details surgical and nonsurgical options for treating spinal deformities that often occur in SMA, such as scoliosis.	https://curesma.wpengine.com/wp-content/uploads/2019/07/orthopedic-management-2018conf.pdf
	Medical Management of Adults with SMA	These slides were originally presented at the 2018 Annual Cure SMA Conference. They give an overview of the standards of care for adult SMA patients, as well as a discussion of the upcoming drug pipeline options for this population.	https://curesma.wpengine.com/wp-content/uploads/2019/07/adult-med-management-conf2018-presentation.pdf
	SMA and Exercise	Brief article providing an overview of SMA exercise research and highlighting a few studies regarding the benefits of swimming, strength tests, and resistance training.	https://smanewstoday.com/sma-and-exercise/
	APTA Section on Neurology Fact Sheet: Spinal Muscular Atrophy in Adults	Useful fact sheet for PTs working with SMA adult patients. It includes quick and easily accessible information about the adult form of SMA and how physical therapy can help.	https://www.neuropt.org/docs/degenerative-diseases-sig/spinal-muscular-atrophy-in-adults.pdf?sfvrsn=8d2aae96_2

	Spinal Muscular Atrophy Teaching and Excellence for Physiotherapists an International Network (STEP IN)	STEP IN aims to develop training expertise and shared educational resources for physiotherapists who provide clinical care or research for SMA patients.	https://www.stepinsma.org/
	Summit of Strength Virtual Program: Physical Therapy at Home	This installment of the Summit of Strength webinar series focused on Physical Therapy at Home.	https://www.youtube.com/watch?v=7l8nMQIXbfs&feature=youtu.be
	Physio with Marion	Online web series related to physiotherapy treatment and equipment	https://www.treatsma.uk/physio-with-marion/
General SMA Resources	Cure SMA	Cure SMA is dedicated to the treatment and cure of SMA, the number one genetic cause of death for infants. We fund groundbreaking research and provide families the support they need for today.	http://www.curesma.org/
	Muscular Dystrophy Association	Families are at the heart of MDA's mission. A caring and concerned group of families started MDA in 1950, and they continue to relentlessly pursue the promise to free families from the life-threatening effects of muscular dystrophy and muscle-debilitating diseases today.	https://www.mda.org/
	Spinal Muscular Atrophy Foundation	The mission of the SMA Foundation is to accelerate the development of a treatment for Spinal Muscular Atrophy.	http://www.smafoundation.org/
	Treat-NMD Neuromuscular Network	TREAT-NMD is a network for the neuromuscular field that provides an infrastructure to ensure that the most promising new therapies reach patients as quickly as possible. Since its launch in January 2007 the network's focus has been on the development of tools that industry, clinicians and scientists need to bring novel therapeutic approaches through preclinical development and into the clinic, and on establishing best-practice care for neuromuscular patients worldwide.	http://www.treat-nmd.eu/

	Treat Spinal Muscular Atrophy	Treat SMA is a UK charity made up of people living with SMA and their parents and carers who joined hands to improve the diagnostics, standard of care, social support, and access to treatments in this severe genetic disorder.	https://www.treatsma.uk/
	ChildMuscleWeakness.org - National Task Force for Early Identification of Childhood Neuromuscular Disorders	The National Task Force for Early Identification of Childhood Neuromuscular Disorders convened in 2009 to address the delay that families frequently experience between symptom onset and diagnosis of neuromuscular disorders. The Task Force aims to increase clinicians' awareness of peripheral neuromuscular disease as a cause of developmental delay in young children, and to help providers in primary care, rehabilitation medicine, and physical therapy identify the early symptoms of neuromuscular disorders.	https://www.childmuscleweakness.org/
	The Gene: An Intimate History	Documentary series unravels history of the human genome and explores the ethical implications of groundbreaking developments in genetics. SMA is discussed in episode 2.	https://www.kpbs.org/news/2020/apr/06/gene-intimate-history/
	Genetics Home Reference from the U.S. National Library of Medicine (NIH)	Genetics Home Reference provides consumer-friendly information about the effects of genetic variation on human health.	https://ghr.nlm.nih.gov/condition/spinal-muscular-atrophy
	About Spinal Muscular Atrophy	NIH National Human Genome Research Institute	https://www.genome.gov/Genetic-Disorders/Spinal-Muscular-Atrophy
	Spinal Muscular Atrophy	The American Society of Gene & Cell Therapy is the primary professional membership organization for gene and cell therapy.	https://www.asgct.org/education/spinal-muscular-atrophy
	National Organization for Rare Disorders (NORD)	NORD, a 501(c)(3) organization, is a patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 280 patient organization members, is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.	https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/

	Learn About Spinal Muscular Atrophy	DNA Learning Center – Cold Spring Harbor	http://www.learnaboutsma.org/
	Nusinersen (Spinraza TM): The First FDA Approved Treatment for SMA	Cold Spring Harbor Laboratories CanadaGairdner Awards	https://www.youtube.com/watch?v=2zFP331gmQo
	NeurologyLive | Direct Access to Expert Insight in Neurology	NeurologyLive™ offers a print and digital media platform to busy healthcare professionals treating neurological diseases to deliver practice-changing news and insight directly from top medical conferences and researchers.	https://www.neurologylive.com/search?keywordTerm=spinal+muscular+atrophy
	SMA Europe	SMA Europe provides a framework to stimulate collaboration and accelerate translational research pathways in SMA and promote patient care.	https://www.sma-europe.eu/
	SMA News Today	SMA News Today is strictly a news and information website about the disease.	https://smanewstoday.com/
	Spinal Muscular Atrophy	UpToDate Wolters Kluwer Health webpage	https://www.uptodate.com/contents/spinal-muscular-atrophy
	Spinal Muscular Atrophy	Medscape information page	https://emedicine.medscape.com/article/1181436-overview
	SMArt Moves – Cure SMA	Website designed to improve families and health care professionals' understanding of SMA motor delays, especially around the importance of an SMA early diagnosis and early treatment. The website delivers helpful resources about the critical signs, the need for rapid action, and the life-saving benefits possible for so many children given access to swift and crucial treatments.	http://events.curesma.org/site/PageNavigator/SmartMoves/SmartMoves.html

	Spinal Muscular Atrophy	Baby's First Test is the nation's newborn screening education resource center. Baby's First Test provides current educational and family support and services information, materials, and resources about newborn screening at the local, state, and national levels.	https://www.babysfirsttest.org/newborn-screening/conditions/spinal-muscular-atrophy
SMA Care and Management	SMA: Disease Mechanisms and Therapy, 1st Edition Editors: Charlotte Sumner Sergey Paushkin Chien-Ping Ko	This book provides a comprehensive accounting of recent advances in basic and clinical research that covers SMA clinical features and standards of care, multifaceted aspects of SMN protein functions and SMA disease pathology, various animal models, and biomarkers, as well as current therapeutic development. Chapter 23 reviews SMA Motor Functional Scales and Measures of Pulmonary Function	https://www.elsevier.com/books/spinal-muscular-atrophy/sumner/978-0-12-803685-3?dgcid=shopping_low_priority&gclid=EAIaIQobChMIn8f2nJf33QIVgsBkCh3fkw21EAYYASABEgLW6vD_BwE http://www.sciencedirect.com/science/article/pii/B9780128036853000239
	Understanding Spinal Muscular Atrophy (SMA)	Information on understanding SMA from the Cure SMA Care Series Booklet	https://www.curesma.org/wp-content/uploads/2020/08/08262020_Understanding_SMA_vWeb.pdf
	VOICE OF THE PATIENT REPORT: A summary report resulting from an Externally Led Patient-Focused Drug Development Meeting reflecting the U.S. Food and Drug Administration (FDA) Patient-Focused Drug Development Initiative	This document is a report of the Cure SMA's April 2017 Externally Led Patient-Focused Drug Development (PFDD) Meeting with FDA. The report details SMA patient/ parent/ caregiver perspectives on treatment and clinical trials for SMA patients. The report was developed as a resource for the FDA and drug development community to help "researchers, clinicians, payers and other related organizations, to provide a better understanding of the needs, hopes and goals of [the SMA] community."	https://www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf
	Spinal muscular atrophy - causes, symptoms, diagnosis, treatment, pathology	Video by Osmosis	https://www.youtube.com/watch?v=Ax89gbbC-4g

	SMA and the drug that fights it, explained	Video By Cold Spring Harbor Laboratory	https://www.youtube.com/watch?v=YLluIVwg_y4
Pharmaceutical Related Resources	New Treatments for Spinal Muscular Atrophy — Neurodegenetic Diseases	2020 Science Writers' Boot Camp: Johns Hopkins Webinar: Dr. Charlotte Sumner	https://www.youtube.com/watch?v=iAvPCsz3Q7I
	SMA Therapeutics: A Comparative Overview of Drugs Approved and in Development	Presentation outlining targets for therapeutic intervention in SMA	http://www.smafoundation.org/wp-content/uploads/2017/07/Comparative-Overview-of-SMA-Drugs-1.pdf
	Biogen SMA Scientific Lounge	A dynamic evolving online hub including enduring digital resources to ensure access to leading SMA science and resources.	https://www.biogensmalounge.eu/
	Together in SMA	Biogen's information page on SMA and treatment	https://www.togetherinsma-hcp.com/?cid=aff-tisma-header-hp
	Clinical Development Program for SMA	Novartis (AveXis) information page on SMA treatment	https://www.avexis.com/research-and-development
	Spinal Muscular Atrophy (SMA) Fact Sheet	Novartis' fact sheet on SMA	https://www.novartis.com/news/media-library/spinal-muscular-atrophy-sma-factsheet
	Spinal Muscular Atrophy: bringing patient support to a rare disease	Roche's article on SMA	https://www.roche.com/research_and_development/what_we_are_working_on/neuroscience/approaching-sma.htm

	Roche in spinal muscular atrophy: Making a difference for families	Video from Roche	https://www.youtube.com/watch?v=Fp7MQlZGpKI
	Our Pipeline, PTC Therapeutics	PTC Therapeutics approved medicines	https://www.ptcbio.com/our-pipeline/approved-medicines/
	Understanding SMA	Genentech article and video on understanding SMA	https://www.gene.com/stories/understanding-sma https://www.youtube.com/watch?v=5mI_ZsWkkc4
	Pipeline SRF-015 for Spinal Muscular Atrophy	Scholar Rock SMA drug trial pipeline	https://scholarrock.com/our-pipeline/spinal-muscular-atrophy/
	Spinal Muscular Atrophy	Cytokinetics information page on SMA	https://cytokinetics.com/our-focus/spinal-muscular-atrophy/
	Cut and Paste: Treating Spinal Muscular Atrophy with Nusinersen	Video by Youreka Science	https://www.youtube.com/watch?v=wrN-BRrzZ5E
	SMA Type 1: How Gene Therapy Works	Video by Nationwide Childrens	https://www.youtube.com/watch?v=iBmyXr_o1hU&t=22s
SMA Clinical Trials	SMA Trial Readiness Toolkit Hub	This comprehensive trial readiness toolkit was created by Cure SMA and is intended to help equip new SMA clinical trial sites in the effective conduct of SMA clinical trial. It has content on SMA diagnosis, treatment, clinical presentation, and on every aspect of the clinical trial process and how it pertains to SMA. Cure SMA encourages CEs and all research staff to peruse the entire toolkit for more	https://www.curesma.org/clinical-trial-readiness/

		information, as well as the Cure SMA website for parent- and family friendly materials.	
	Cure SMA Clinical Trials Drug Development/Pipeline	Graphics outline of therapeutic pipeline for SMA (updated frequently)	https://www.curesma.org/sma-drug-pipeline/
	Current List of SMA Clinical Trials	List of ongoing SMA Clinical Trials from the National Institutes of Health (NIH) (updated frequently)	https://clinicaltrials.gov/ct2/results?cond=Spinal+Muscular+Atrophy&term=&cntry=&state=&city=&dist=
	Common Data Elements for Spinal Muscular Atrophy	National Institute of Neurological Disorders & Stroke (NINDS) Common Data Elements Standardized data collection elements recommended for use in SMA clinical trials and registries to allow for harmonized data collection so that data is consistently captured and recorded across studies. The CDEs also allow for comparison of results across studies to allow for effective aggregation of information into more significant metadata results.	https://www.commondataelements.ninds.nih.gov/Spinal%20Muscular%20Atrophy#pane-157
	Core Dataset for Spinal Muscular Atrophy (SMA)	This page contains information about core dataset for TREAT-NMD registries which are collecting data on people with SMA. This dataset was expanded in September 2018 in order to better inform on the natural history of SMA, and provide data to support post-marketing surveillance (safety and effectiveness) for new treatments.	https://treat-nmd.org/patient-registries/treat-nmd-core-datasets/sma-core-dataset/
Cure SMA Resources	Education Resources from Cure SMA	Cure SMA Clinical Care Evidence and Medical Education Tools	https://www.curesma.org/about-sma-for-hcps/ and https://www.curesma.org/educational-opportunities-for-providers/
	Cure SMA Youtube Channel (Free)	Cure SMA's YouTube channel is home to a variety of Cure SMA webinars and other videos that may be of interest to those who want to learn more about SMA and how it affects those with the disease.	https://www.youtube.com/channel/UCECjEl49gy32nz8wWeb2AFQ

Table A4: Outcome Measures and Evaluation Resources (Alphabetical Order)

Tool	Description	Manual of Procedures	Score Sheet	Resources
Ability Captured Through Interactive Video Evaluation (ACTIVE)	The ACTIVE is a custom-designed video game that measures workspace volume and quantifies upper extremity function in SMA.	NA	NA	https://onlinelibrary.wiley.com/doi/full/10.1111/dmcn.14230
ACTIVLIM	The ACTIVLIM is a measure of activity limitations for patients with upper and/or lower limb impairments. The scale measures a patient's ability to perform daily activities requiring the use of the upper and/or the lower limbs, whatever the strategies involved.	http://rssandbox.iescagilly.be/activlim-instructions.html	http://rssandbox.iescagilly.be/activlim-downloads.html	http://rssandbox.iescagilly.be/activlim.html https://www.nmd-journal.com/article/S0960-8966(08)00703-7/fulltext
Adult Test of Neuromuscular Disorders (ATEND)	The ATEND is a wheelchair-based functional motor outcome assessment for individuals with a neuromuscular disorder who are not able to sit or transfer out of the wheelchair.	https://med.stanford.edu/day-lab/atend.html	https://med.stanford.edu/day-lab/atend.html	https://www.nmd-journal.com/article/S0960-8966(20)30387-4/fulltext
Alberta Infant Motor Scale (AIMS)	The AIMS is a norm-referenced assessment of gross infant motor skills from ages 0-18 months. It evaluates weight bearing, posture, and antigravity movements of infants.	https://www.elsevier.com/books/motor-assessment-of-the-developing-infant/piper/978-0-7216-4307-6	https://www.us.elsevierhealth.com/alberta-infant-motor-scale-score-sheets-aims-9780721647210.html	https://pubmed.ncbi.nlm.nih.gov/1468050/ https://content.iospress.com/articles/journal-of-neuromuscular-diseases/jnd180327

Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)	The ACEND was developed and validated to specifically assess caregiver impact experienced by raising children severely affected by neuromuscular diseases. While specifically developed for application to patients undergoing orthopedic surgery it has application to those with SMA and is currently being assessed in larger patient populations.	NA	NA	https://journals.lww.com/pedorthopaedics/Fulltext/2011/04000/Development_and_Initial_Validation_of_the.11.aspx
Bayley Scales of Infant and Toddler Development (BSID-III/ Bayley-4	The BSID-III/Bayley-4 is a standardized test series of measurements used primarily to assess the development of infants and toddlers, ages 1–42 months.	Available for purchase with test kit	Available for purchase with test kit	https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Behavior/Adaptive/Bayley-Scales-of-Infant-and-Toddler-Development-%7C-Third-Edition/p/100000123.html https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Cognition-%26-Neuro/Bayley-Scales-of-Infant-and-Toddler-Development-%7C-Fourth-Edition/p/100001996.html https://www.sciencedirect.com/topics/medicine-and-dentistry/bayley-scales-of-infant-development

Box and Block Test (BBT, ESBBT)	The BBT is a standardized, quantitative test assessing unilateral gross manual dexterity of the upper extremity.	https://www.sralab.org/sites/default/files/2017-06/Box%20and%20Blocks%20Test%20Instructions.pdf	NA	https://www.performancehealth.com/box-and-blocks-test https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-019-1244-3 (Additional File 2) https://bmjopen.bmj.com/content/8/7/e019932 https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-1348-2
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)	The CHOP INTEND is a reliable and valid measure of motor skills in weaker patients with SMA type I and neuromuscular disorders presenting in infancy.	http://columbiasma.org/docs/cme-2010/CHOP-INTEND-for-SMA-Type-I-Manual-of-Procedures.pdf	http://columbiasma.org/docs/cme-2010/CHOP%20INTEND%20for%20SMA%20Type%20I%20-%20Score%20Sheet.pdf	https://www.nmd-journal.com/article/S0960-8966(09)00698-1/fulltext
Egen Klassifikation Scale Version 2 (EK2)	The EK2 is a question-based scale of 17 items relating to an individual's "own functioning" in the home.	https://rcfm.dk/wp-content/uploads/sites/2/2021/01/EK2_Manual_Revised070618_Engelsk.pdf	https://rcfm.dk/wp-content/uploads/sites/2/2021/01/EK2_engelsk.pdf	https://onlinelibrary.wiley.com/doi/10.1002/pri.221
Endurance Shuttle Walk Test (ESWT)	The ESWT assesses fatigability and endurance capacity in ambulatory patients with neuromuscular disease.	NA	NA	https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-019-1244-3 https://bmjopen.bmj.com/content/8/7/e019932 https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-1348-2

Fatigue Severity Scale (FSS)	The FSS is a patient-reported outcome measure to evaluate the impact of fatigue.	NA	https://www.sralab.org/sites/default/files/2017-06/sleep-Fatigue-Severity-Scale.pdf	https://jamanetwork.com/journals/jamaneurology/article-abstract/589466 https://link.springer.com/article/10.1007%2Fs11136-013-0565-8 https://content.iospress.com/articles/journal-of-neuromuscular-diseases/jnd180342 https://www.nature.com/articles/s41598-020-68051-w
Hammersmith Functional Motor Scale Expanded (HFMSE)	The HFMSE allows for assessment of higher functioning sitters and walkers (SMA types II and III). Ease of administration and correlation with established motor function measures and excellent validity and reliability justify use for those with SMA in clinical trials.	http://columbiasma.org/docs/HFMSE_2019_Manual.pdf	http://columbiasma.org/docs/HFMSE_2019_Proforma.pdf	https://journals.sagepub.com/doi/10.1177/0883073811420294 https://www.nmd-journal.com/article/S0960-8966(07)00186-1/abstract
Hammersmith Infant Neurological Examination (HINE) - Motor Section Part 2	The HINE is an easily performed and relatively brief clinical neurological examination for infants aged between 2 and 24 month. The motor section Part 2 has been used to record milestone achievement in SMA.	https://hammersmith-neuro-exam.com/	https://hammersmith-neuro-exam.com/wp-content/uploads/2019/02/HINE-proforma_08.02.19.pdf	https://onlinelibrary.wiley.com/doi/10.1002/mus.25705 https://www.nmd-journal.com/article/S0960-8966(16)30816-1/fulltext https://www.sciencedirect.com/science/article/pii/S0887899416305653 https://www.jpeds.com/article/S0022-3476(99)70016-8/pdf

Harris Infant Neuromotor Test (HINT)	The HINT is a neuromotor screening test that can be used with low-risk (typically developing) or high-risk infants ranging in age from 2.5 to 12.5 months.	https://www.thetimp.com/products-for-therapists#!/HINT-Products/c/100058132	https://www.thetimp.com/products-for-therapists#!/HINT-Products/c/100058132	https://www.thetimp.com/about-our-tests https://www.thetimp.com/products-for-therapists https://journals.lww.com/iycjournal/Abstract/2003/04000/Development_and_Standardization_of_the_Harris.6.aspx
Motor Function Measure (MFM)	The MFM is designed to measure functional motor abilities in neuromuscular diseases. It is a validated and usable from 6 to 60 years old.	https://mfm-nmd.org/get-a-user-manual/?lang=en	Available for purchase	https://mfm-nmd.org/?lang=en https://www.archives-pmr.org/article/S0003-9993(13)00098-1/fulltext
Neuromuscular Gross Motor Outcome (GRO)	The Neuromuscular GRO is a gross motor outcome measure designed to assess whole body strength, motor development and function for all levels of ability across the lifespan in those diagnosed with neuromuscular disease.	NA	NA	https://www.nationwidechildrens.org/research/areas-of-research/center-for-gene-therapy/lowes-lab/neuromuscular-gross-motor-outcome-gro

Nine Hole Peg Test (NHPT, r9HPT, ESNHPT)	The NHPT is a brief, standardized, quantitative test of upper extremity function.	NA	NA	https://www.performancehealth.com/jamar-9-hole-peg-test-kit https://ojrd.biomedcentral.com/articles/10.1186/s13023-018-0904-5 https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-019-1244-3 https://bmjopen.bmj.com/content/8/7/e019932 https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-1348-2
Patient-Reported Outcomes Measurement Information System (PROMIS®)	The PROMIS® is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. It can be used with the general population and with individuals living with chronic conditions.	http://www.healthmeasures.net/explore-measurement-systems/promis/obtain-administer-measures	http://www.healthmeasures.net/score-and-interpret/interpret-scores/promis	http://www.healthmeasures.net/explore-measurement-systems/promis https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01498-2
Peabody Developmental Motor Scales (PDMS-2)	The PDMS2 is composed of six subtests that measure interrelated motor abilities of children from birth through age 5.	Available for purchase with test kit	Available for purchase with test kit	https://www.pearsonclinical.com/therapy/products/100000249/peabody-developmental-motor-scales-secondedition-pdms-2.html

Pediatric Evaluation of Disability Inventory – Computer Adaptive Test (PEDI-CAT)	The PEDI-CAT is a caregiver-reported outcome measure that evaluates functional skills in the domains of self-care, mobility, social/cognitive and responsibility from birth to 21 years old.	Available for purchase with software	Available for purchase with software	https://www.pedicat.com/ https://onlinelibrary.wiley.com/doi/full/10.1002/mus.25164?scrollTo=references
Pediatric Quality of Life Inventory (PedsQL™) Neuromuscular Module and Multidimensional Fatigue Scale	The PedsQL™ was designed to measure health related quality of life dimensions specific to children ages 2 to 18 years with neuromuscular disorders, including SMA.	http://www.pedsql.org/pedsqladmin.html	Available for purchase	http://www.pedsql.org/ http://www.pedsql.org/PedsQL-Scoring.pdf https://www.nmd-journal.com/article/S0960-8966(09)00623-3/abstract
Pulmonary Function Tests (PFT)	The PFTs are noninvasive tests that measure lung volume, capacity, rates of flow, and gas exchange.	NA	NA	https://www.sciencedirect.com/science/article/pii/S1090379813000615 https://jamanetwork.com/journals/jamaneurology/fullarticle/782727 https://jamanetwork.com/journals/jamaneurology/fullarticle/503374
Respiratory Inductance Plethysmography (RIP)	The RIP can non-invasively measure and analyze precise patterns of chest and abdominal wall movements.	NA	NA	https://onlinelibrary.wiley.com/doi/full/10.1002/ppul.22997
Revised Hammersmith Scale (RHS)	The RHS is a psychometrically sound and versatile clinical outcome assessment to test the broad range of physical abilities of patients with type II and III SMA.	http://www.smareachuk.org/information-for-professionals/category/revised-hammersmith-scale	http://www.smareachuk.org/information-for-professionals/category/revised-hammersmith-scale	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0172346

Revised Upper Limb Module (RULM)	The RULM scale shows good reliability and validity, making it a suitable tool to assess upper extremity function in the SMA population.	http://columbiasma.org/docs/cme-2010/RULM-Generic-Manual-16-Dec-2014.pdf	http://columbiasma.org/docs/cme-2010/RULM-Generic-Score-16-Dec-2014.pdf	https://onlinelibrary.wiley.com/doi/full/10.1002/mus.25430 RULM Kit Supply List
Six-Minute Walk Test (6MWT)	The 6MWT measures ambulatory function as well as fatigue. It is widely accepted from a regulatory perspective and shows validity and reliability for those with SMA.	https://journals.sagepub.com/doi/suppl/10.1177/0883073813493663 (supplemental file)	NA	https://n.neurology.org/content/74/10/833?ijkey=0dc2b7ddbd62c23ddd3a01b5282b826db73e6990&keytype2=tf_ipsecsha https://onlinelibrary.wiley.com/doi/full/10.1002/mus.25120 https://onlinelibrary.wiley.com/doi/10.1002/mus.26794
SMA Functional Rating Scale (SMAFRS)	The SMAFRS was developed to assess function in ambulatory adults with SMA. The modified SMAFRS was developed to eliminate redundancy.	NA	NA	https://onlinelibrary.wiley.com/doi/10.1002/mus.21350 https://n.neurology.org/content/90/15_Supplement/P4.452 https://onlinelibrary.wiley.com/doi/10.1002/mus.26756
SMA Health Index (SMA-HI)	The SMA-HI is patient-reported outcome measure that is highly comprehensive, easily utilized, and capable of measuring a patient's perception of their total disease burden and 15 areas of SMA sub-health.	NA	NA	https://onlinelibrary.wiley.com/doi/10.1002/mus.27223?af=R

Strength Assessments	Hand-Held Dynamometry (HHD) is a quantitative and objective method for assessment of muscular strength using a portable handheld dynamometer and demonstrates reliability and validity in those with SMA. Maximal voluntary isometric contraction testing (MVICT) is a standardized method for measurement of muscle strength using a quantitative muscle assessment system in patients with neuromuscular disease.	NA	NA	https://onlinelibrary.wiley.com/doi/10.1002/mus.10166 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0140822 https://onlinelibrary.wiley.com/doi/10.1002/mus.26756
Ten-Meter Walk/Run Test (10MWRT)	The 10MWRT assess walking speed as a measure of ambulatory function over a shorter distance and has established reliability and validity in SMA.	http://smaoutcomes.org/hammersmith_manual/pdf/timed_test_module	NA	https://onlinelibrary.wiley.com/doi/full/10.1002/mus.20018
Test of Infant Motor Performance Screening Items (TIMPSI)	The TIMPSI is a shorter, screening version of the TIMP which is psychometrically valid, well-constructed scale used to assess motor performance in infants born preterm through 4 months of age.	Available for purchase	Available for purchase	https://www.thetimp.com/about-our-tests https://www.thetimp.com/products-for-therapists https://journals.lww.com/pedpt/Fulltext/2013/25020/Reliability_and_Validity_of_the_TIMPSI_for_Infants.4.aspx

Thirty Second Sit to Stand (30STS)	The 30STS measures the number of sit to stands a person can complete in 30 seconds, rather than the amount of time to complete a pre-determined number of repetitions.	https://www.cdc.gov/steadi/pdf/STEADI-Assessment-30Sec-508.pdf	https://www.cdc.gov/steadi/pdf/STEADI-Assessment-30Sec-508.pdf	
Time to Climb 4 Stairs (TTC)	The TTC assesses the time spent in the performance of a functional activity.	NA	NA	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0201004 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0021296
Timed Rise from Floor (TTR)	The TTR assesses the time taken to rise from supine on the floor to standing upright.	http://smaoutcomes.org/hammersmith_manual/pdf/timed_test_module	NA	https://onlinelibrary.wiley.com/doi/full/10.1002/mus.20018
Timed "up & go" (TUG) Test	The TUG is a quick measure of balance and mobility. The TUG scores correlate with clinical, functional, and strength assessment.	https://www.cdc.gov/steadi/pdf/TUG_Test-print.pdf	https://www.cdc.gov/steadi/pdf/TUG_Test-print.pdf	https://onlinelibrary.wiley.com/doi/full/10.1002/mus.24153
World Health Organization (WHO) Motor development milestones	The WHO measures six motor milestones from birth to age 18 months. It relies on parent and evaluator assessment, and is used longitudinally.	https://www.who.int/childgrowth/mgrs/en/fnb_motor_37_45.pdf?ua=1	NA	https://www.who.int/childgrowth/standards/motor_milestones/en/

Table A5: Professional Development: Meetings for Continuing Education

	Title	Resource Description	Resource Link
Organizations	American Academy of Neurology (AAN)	The AAN Annual Meeting offers innovative, unique, and creative experiences throughout the week served up in exciting and inspirational formats to fuel your mind, body, and spirit.	https://www.aan.com/conferences-community/annual-meeting/
	American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM)	The AANEM is a nonprofit membership association dedicated to the advancement of neuromuscular (NM), musculoskeletal, and electrodiagnostic (EDX) medicine.	http://www.aanem.org/Meetings/Annual-Meeting
	American Physical Therapy Association (APTA)	A collaborative effort between APTA and our 18 specialty sections (Combined Sections Meeting).	https://www.apta.org/your-career/courses-and-events
	Child Neurology Society (CNS)	The CNS Annual Meeting is the meeting of choice for child neurologists and professionals in other fields of study related to neurologic and neurodevelopmental disorders in children and adolescents.	https://www.childneurologysociety.org/meetings
	Cure SMA	The annual conference brings together researchers, healthcare professionals, and families to network, learn, and collaborate.	http://www.curesma.org/get-involved/conference/
	Muscular Dystrophy Association (MDA)	The long-standing clinical and scientific conferences leverage MDA's extensive reach into the scientific, clinical research and clinical practice communities to bring together the world's leading experts in neuromuscular disease as it represents the full spectrum of scientific researchers, medical professionals and decision makers.	https://www.mda.org/conferences
	Muscle Study Group (MSG)	The MSG, is a consortium of scientific investigators from academic and research centers who are committed to the cooperative planning, implementation, analysis and reporting of controlled clinical trials and of other research for muscle and other neuromuscular diseases.	https://musclestudygroup.org/
	SMA Europe	SMA Europe provides a framework to stimulate collaboration and accelerate translational research pathways in SMA and promote patient care.	https://www.sma-europe.eu/newscat/meetings-and-conferences/

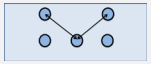
	Spinal Muscular Atrophy Teaching and Excellence for Physiotherapists an International Network (STEP IN)	STEP IN aims to develop training expertise and shared educational resources for physiotherapists who provide clinical care or research for SMA patients.	https://www.stepinsma.org/
	TREAT-NMD Neuromuscular Network	TREAT-NMD is a network for the neuromuscular field that provides an infrastructure to ensure that the most promising new therapies reach patients as quickly as possible.	https://treat-nmd.org/engagement/
	World Muscle Society (WMS)	The activities of WMS shall be open to all professionals working in the neuromuscular field, irrespective of nationality, race and political opinion. It shall be a multidisciplinary Society, reflecting in particular the different disciplines involved in the study of neuromuscular disorders and the management of patients with these disorders.	https://www.worldmusclesociety.org/
Continuing Medical Education Opportunities	Addressing the Needs of Adults With Spinal Muscular Atrophy: Expanding Approaches, Improving Care	Online course	https://sma.cme-lms.com/
	Advances in Neuromuscular Disorder Management	Ology Medical Education is an independent, expert-led educational resources in neurology and neuromuscular diseases (Free). It is Access to a regularly updated sourcerange of CME-accredited activities, provided by Ology Medical Education, including webcasts, infographics, and interactive patient cases, to promote best practices for the covering clinical and management of SMA, patient case discussions, and more.	https://ologyeducation.org/ https://ologyeducation.org/neuromusculardisorders/ https://ologyeducation.org/page/2/?s=sma
	Assessing functional changes in adult patients with SMA	Interactive Infographic	https://ologyeducation.org/blog/2020/05/01/assessing-functional-changes-in-adult-patients-with-sma-interactive-infographic/
	Case discussions on specialist care in adult SMA – EXPRESS expert presentation series	Educational online activity	https://ologyeducation.org/courses/case-discussions-on-specialist-care-in-adult-sma-

			express-expert-presentation-series/
	Continuing Medical Education (CME) for SMA	Current Educational Programs provided by Cure SMA	https://www.curesma.org/educational-opportunities-for-providers/
	Critical Insights on Recent Advances in Spinal Muscular Atrophy	On Demand webcast	https://www.mycme.com/courses/critical-insights-on-recent-advances-in-spinal-muscular-atrophy-7019
	The France Foundation	Courses on SMA	https://www.francefoundation.com/education/disease-area/spinal-muscular-atrophy
	Integrating neurological and pulmonary care for adolescents with SMS	On Demand Webcast and Interactive Patient Cases	https://ologyeducation.org/courses/integrating-neurological-and-pulmonary-care-for-adolescents-with-sma/
	Interactive ePatient Case: Spinal Muscular Atrophy (SMA) in Adults	Course on Lippincott CME Connection	https://cme.lww.com/public/modules/12913/steps/30289
	Learning Center Progress in Spinal Muscular Atrophy Management	CME activities provided by Office of Continuing Medical Education Elsevier and Ology Medical Education Course on MedPage Today	https://sma.elsevierresource.com/cme-activities
	Navigating the Therapeutic Advances for Spinal Muscular Atrophy	On Demand webcast	https://www.youtube.com/watch?v=lVSoRGPytSs
	Nusinersen Shows Benefit in Later-Onset Spinal Muscular Atrophy	Course on MedPage Today	https://www.medpagetoday.com/neurology/generalneurology/79447

	Obtaining Support and Ongoing Care for Children with SMA after Gene Replacement Therapy	On Demand webcast including 6 modules	https://www.neurocarelive.com/sma/
	Post-Gene Replacement Treatment SMA Phenotypes and Multidisciplinary Care	On Demand webcast available at Neuro Series Live – Requires log in to access	https://www.neuroserieslive.com/presentation-cme/?q=2021_SMA_CME
	Presentation, diagnosis and management of SMA: Multidisciplinary perspectives	Expert opinion online course	https://touchneurology.com/spinal-muscular-atrophy/
	Recent Developments in the Spinal Muscular Atrophy Treatment Landscape	Peer-to-Peer Professional Educational Webinar provided by MDA	https://gateway.on24.com/wcc/experience/elitemda/1962960/2159472/mda-grand-rounds-webinars
	Spinal Muscular Atrophy	Online course modules	https://checkrare.com/learning-center/p-spinal-muscular-atrophy/
	Spinal Musuclar Atrophy in Focus	Course on MedPage Today	https://www.medpagetoday.com/resource-centers/spinal-muscular-atrophy-focus
	Spinal Muscular Atrophy: Best Practices for SMA in an Evolving Era: Advantages & Challenges of Multidisciplinary Care	Internet enduring material from the virtual conference on December 3-5, 2020, sponsored by Stanford University School of Medicine	https://stanford.cloud-cme.com/course/courseoverview?P=3000&EID=40071
	Spinal Muscular Atrophy: Current Advances in Treatment and Recommendations for Evaluation and Rehabilitation Online	Internet enduring material from the live conference on December 6-7, 2019, sponsored by Stanford University School of Medicine	https://stanford.cloud-cme.com/default.aspx?P=0&EID=35514

	Spinal Muscular Atrophy: Evaluation and Management for the Rehabilitation Specialist	Recap of Continuing Medical Education Course, held October 20-21, 2017 at CUIMC. Must fill out a brief form to view videos of the presentations and discussions.	https://cumc.co1.qualtrics.com/jfe/form/SV_cVjVY0DNwBo9mhD
	SMA Newborn Screening and Early Intervention	Peer-to-Peer Professional Educational Webinar provided by MDA	https://gateway.on24.com/wcc/experience/elitemda/1962960/2159472/mda-grand-rounds-webinars
	Spinal Muscular Atrophy (SMA) Symposium on Optimizing Care	Audio recordings of 2016 symposium	https://soundcloud.com/user-5816643
	The role of the physical therapist in SMA management: patient cases from the clinic	On Demand Webcast and Interactive Patient Cases	https://ologyeducation.org/courses/the-role-of-the-physical-therapist-in-sma-management-patient-cases-from-the-clinic/

Table A6: RULM Kit Supply List (as of September 2020)[4]

Item	Description	Image	Source/Vendor Link
One Tablecloth marked with circles	White non-friction surface. Dimensions specified in Appendix 1 of RULM manual		Make signs. www.Makesigns.com Design #: 200120115902
2 or 3 Standard pencil	Standard lead pencil		Can be sourced locally. https://www.staplesadvantage.com/webapp/wcs/stores/servlet/StplShowItem?cust_sku=476919&catalogId=4&item_id=51852728&langId=-1&currentSKUNbr=476919&storeId=10101&itemType=1&addWE1ToCart=true&documentID=e886f43878250d3a5f259d0b939e54fd572e068d
2 Coins/Tokens	24 mm diameter		https://www.amazon.com/gp/product/B01EKMI000/ref=oh_aui_detailpage_o06_s00?ie=UTF8&psc=1
40 plastic cups (vending cups) one placed inside the other	The RULM was standardized with European standard cups. Capacity: 200 ml/8 oz *Upper ∅ 7 cm/2.7in* *Lower ∅ 4,5 cm/1.7 in* *Height: 8 cm/ 3,1*		Can be sourced locally in UK (Maddison's) https://www.maddisonsuk.com/epages/BT4896.sf/en_GB/?ObjectPath=/Shops/BT4896/Products/%22CUP/008%22
One calibration metric weight	200 g		https://www.amazon.com/MAGIKON-Precision-Calibration-Weight-Single/dp/B08S3HVN42/ref=rvi_6/140-7631865-9430533?pd_rd_w=gS5U5&pf_rd_p=c0296674-5a83-4ad6-b035-0702d2b359df&pf_rd_r=5GC925ZB25BC0F99XT21&pd_rd_r=0de2de7e-afd1-48fb-939e-40a33793a6c2&pd_rd_wg=sm9K3&pd_rd_i=B08S3HVN42&psc=1
One calibration metric weight	500 g		https://www.amazon.com/gp/product/B00SSK3YNO/ref=od_aui_detailpages00?ie=UTF8&psc=1

[4] Cure SMA is not endorsing any specific item by providing the links in the table. The links provided in the table should only be used as a reference for the supply described.

One calibration metric weight	1 kg		https://www.amazon.com/Calibration-Weight-0-16gm-Chrome-Scales/dp/B07SY8GTMY/ref=sr_1_4?dchild=1&keywords=1kg+metal+calibration+weight&qid=1624929523&s=industrial&sr=1-4
500 g. gym sand weight	Make sure it can be fastened into a ring shape		https://www.amazon.com/TheraBand-Weights-Adjustable-Strengthening-Physical/dp/B0029U8CXG/ref=sr_1_1?keywords=B0029U8cxg&qid=1583245017&sr=8-1
Take and Toss bowls or plastic round container with lid that has lip (8 oz)	Top ∅: 10cm/4 in Bottom ∅: 7,5 cm/3 in h: 5cm/2 in		https://www.amazon.com/dp/B000096M2Z/ref=dp_cerb_1
Push light button	∅ 6,7 cm/2.6 in h: 1,5 cm/0.6 in		https://www.amazon.com/gp/product/B074XG1C57/ref=ppx_yo_dt_b_asin_title_o03_s00?ie=UTF8&psc=1
Plain A4 paper	Size A4: 21cm/8.3 in X 29,7cm/11.7 in Paper weight: 80 gsm		Can be sourced locally. https://www.amazon.com/Premium-8-3-11-7-Printer-Paper/dp/B07FTXJCYF/ref=sr_1_3_sspa?dchild=1&keywords=a4+paper+for+printer&qid=1597685367&sr=8-3-spons&psc=1&spLa=ZW5jcnlwdGVkUXVhbGlmaWVyPUEzUDlHVzNWTEozSjMzJmVuY3J5cHRlZElkPUEwNzU1ODg2MTBTUlhEOEVEOU0yOSZlbmNyeXB0ZWRBZElkPUEwMjkyNTQxMjJGUVJZVVBZTEFBWSZ3aWRnZXROYW1lPXNwX2F0ZiZhY3Rpb249Y2xpY2tSZWRpcmVjdCZkb05vdExvZ0NsaWNrPXRydWU

twitter.com/cureSMA

@curesmaorg

facebook.com/cureSMA

youtube.com/user/FamiliesofSMA1

www.linkedin.com/company/families-of-sma

cure SMA

925 Busse Road, Elk Grove Village, IL 60007

800.886.1762 • Fax 847.367.7623 • info@cureSMA.org • cureSMA.org