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

RECOMMENDATIONS TO SUPPORT THE EFFECTIVE CONDUCT OF CLINICAL TRIALS IN SMA
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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.
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<th>Outcome Measure</th>
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<tr>
<td>SMA</td>
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<tr>
<td>SMAFRS/Modified SMAFRS</td>
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<tr>
<td>Pediatric Quality of Life Inventory (PedsQL™)</td>
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<td>Neuromuscular Module</td>
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<tr>
<td>Multidimensional Fatigue Scale</td>
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<tr>
<td>Pediatric Evaluation of Disability Inventory (PEDS)</td>
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<tr>
<td>Fatigue Severity Scale (FSS)</td>
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<tr>
<td>ACTIVLIM</td>
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<tr>
<td>Respiratory Inductance Plethysmography (RIP)</td>
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<tr>
<td>Pulmonary Function Tests (PFTS) (includes FVC, MIP, MEP, SNIP, PCF)</td>
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<tr>
<td>Patient-Reported Outcome Measures (PROs), including Quality of Life (QOL) (All Patients)</td>
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<tr>
<td>Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)</td>
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<tr>
<td>HFMSE/RHS</td>
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<tr>
<td>RHS</td>
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<tr>
<td>Six-minute Walk Test (6MWT)</td>
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<tr>
<td>Other Timed Function Tests (TFT)</td>
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<tr>
<td>10-meter Walk/Run Test (10MWRT)</td>
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<tr>
<td>Timed Rise from Floor (TTR)</td>
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<tr>
<td>Time to Climb 4 Stairs (TTC)</td>
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<tr>
<td>Timed Up &amp; Go (TUG)</td>
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<td>30 Second Sit to Stand (30STS)</td>
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<tr>
<td>MFM</td>
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<tr>
<td>HHD</td>
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<tr>
<td>RULM</td>
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Tests Most Commonly Used for Walkers

1. WHO
2. Motor Function Measure (MFM-32, MFM-20)
3. Hand Held Dynamometry (HHD)
4. Timed Function Tests (TFT)
5. Nine Hole Peg Test (9HPT)
6. Repeated (5 times) Nine-hole peg test (r9HPT)
7. Endurance Shuttle Nine Hole Peg Test (ESNHPT)
8. Box and Blocks Test (BBT)
9. Endurance Shuttle Box and Block Test (ESBBT)
10. BSID-III

Tests for Presymptomatic Patients with SMA

1. Peabody Developmental Motor Scales-2 (PDMS-2)
2. Egen Klassification 2 (EK2)
3. Other Timed Function Tests (TFT)

Tests for Adult Patients with Chronic SMA

1. CHOP INTEND
2. HFMSE/RHS
3. 6MWT
4. WHO
5. Peabody Developmental Motor Scales-2 (PDMS-2)
6. BSID-III
7. Other Timed Function Tests (TFT)

Pulmonary Outcome Measures

1. Pulmonary Function Tests (PFTS) (includes FVC, MIP, MEP, SNIP, PCF)
2. Respiratory Inductance Plethysmography (RIP)
3. Patient-Reported Outcome Measures (PROs), including Quality of Life (QOL) (All Patients)
4. Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)

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Fatigue

Falls

Fractures

Vital signs

Fasting and nutrition

Pain

Positioning limitations due to contractures and scoliosis

Transfers

Clothing

Considerations for Evaluating Chronic Adults

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Time of day

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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 (Arnold 2015; Wadman 2017). 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 (Lefebvre 1995; Kolb & Kissel 2015). 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, with hope for a cure. Figure 1 provides a historical timeline highlighting important milestones toward development of SMA treatments.

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

How did we get where we are today?
From mice to men, past to present: Classic 5q Spinal Muscular Atrophy
The Role of the Physical Therapist/Clinical Evaluator in SMA

Individuals with 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 (Finkel 2018; Mercuri 2018; Wang 2007). The role of the Physical Therapist is, as such, vital in the optimal functioning and management of patients with SMA.

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 (APTA 2014). The role of PTs is multifaceted and include injury prevention, health maintenance, restoration of function/rehabilitation, among others. In addition to restoring and maintaining physical function, PTs are also involved in promoting wellness and fitness and optimal quality of life as it relates to movement and health (APTA 2014). PTs provide care across multiple settings, including hospitals/medical centers, private practices, outpatient clinics, schools, sports and fitness facilities, and other settings. When managing the care of children and adults with SMA, PTs keenly focus on promoting function and mobility, positioning and bracing, and stretching. PTs may also recommend equipment such as adaptive seating, strollers, wheelchairs, standers, and gait trainers.

PTs may also play a central role in clinical research as clinical evaluators (CE) and may be involved in the evaluation and assessment of patients with a wide range of diagnoses, including various neuromuscular and rare diseases such as SMA. Physical therapy assessments in SMA may involve impairment-based measures to assess body structure and function, as well as capacity and/or performance-based measures to assess activity limitations. These assessments may include but are not limited to muscle strength, range of motion, cardiopulmonary function, gait, pain, postural alignment, and gross motor function testing, among others. PTs may also participate in many aspects of research including study design, protocol development, data management and analysis, presentation, and manuscript preparation and publication (Reference: https://clinicalcenter.nih.gov/rmd/pt/ptclinresearch.html). Examples of studies and research protocols in SMA where PTs have played a pivotal role include, but are not limited to:

**Natural History & Biomarker Studies**

- Natural History Studies – longitudinal evaluation of the progressive nature of SMA including weakness and motor function declines (Kaufmann 2011, 2012; Finkel 2014; Mercuri 2016; De Sanctis 2018; Montes 2018; Wadman 2018; Chabanon 2018)
- NeuroNEXT (Natural History/Biomarker study) – proof of concept for trials with SMA type I children with a duration of more than 1 year (Kolb 2016; Kolb 2017; Bartlett 2018)
- BforSMA – pilot study to identify a marker or panel of markers in the blood or urine from a wide range of SMA patients that segregates with measures of clinical severity (Finkel 2012; Crawford 2012; Kobayashi 2013)

**Therapeutic Trials – Phase I to III Clinical Trials (Pivotal Trials)**

- Ionis/Biogen trials (Nusinersen), SMA types (I-III), children and teens, including pre-symptomatic studies, (Antisense Oligonucleotide (ASO), SMN2 splicing modulator/enhances SMN protein production centrally, via intrathecal (IT) administration) – led to FDA-approval of Spinraza™ on December 23, 2016 (Chiriboga 2016; Finkel 2016, 2017; Mercuri 2018; Darras 2019)
AveXis trials (AVXS-101), with infants and young children SMA type I and II (Gene Therapy, SMN1 gene replacement, intravenous (IV) and IT administration); One-time only administration – led to FDA-approval of Zolgensma® on May 24, 2019 (Mendell 2017, 2019)

Genentech/Roche trials (Risdiplam), SMA types (I-III), (small molecule, SMN2 splicing modulator/enhances SMN protein production, systemic, oral administration) (Kletzl 2019)

Trophos trial (Olesoxime), non-ambulatory SMA type II and III (neuroprotective and neuroregenerative of motor nerve degeneration, oral administration) (Bertini 2017)

Cytokinetics trial (Reldesemtiv), children and adults with SMA type II and III, (muscle activator, oral administration)

Novartis trial (Branaplam), infants with SMA type I (SMN2 RNA splicing modulator, oral administration)

Scholar Rock trial (SRK-015), children and adults with SMA type II and III, (inhibitor of myostatin activation, IV administration)

With the nature of the SMA clinical research landscape, evolving therapeutic pipeline, and two 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.

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 F3: 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 Clinical Evaluators in Clinical Trials

Physical Therapists play a critical role as clinical evaluators (CEs) in the effective conduct of clinical trials in general and an especially pivotal role in the successful execution of clinical trials in SMA. In SMA clinical trials, CEs evaluate patients across multiple health dimensions using a variety of motor function scales and patient reported outcomes (PROs), to 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. CEs must perform each assessment in a consistent, reliable and standardized manner with all trial participants, such that the data collected is deemed valid and reproducible and as such may be used to assess critical endpoints in a given clinical trial.

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 the conduct of the study. All research team members including CEs ensure the effective conduct of clinical trials using good clinical practice (GCP).

As a CE, you are responsible for promoting consistency across the course of a clinical study. This includes using standardized clinical outcome measures while following published manuals of procedures (MOP). The outcome measures to be used in a trial are dictated by a study protocol.

- PTs 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: the primary and back-up evaluators. It is very important for the same CE to administer the 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 in the event the primary evaluator is unavailable. However, if possible, the primary and back-up evaluators are encouraged to work together both in clinical and research settings to promote alignment in administration and scoring for future testing.

- Standardization of evaluations are critical to maintain consistency. This will require the CE to follow the manuals of procedures and instructions as written, including the following:
  - 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, testing time of day, rest breaks, and parental involvement can be confounding factors that affect the ability to have a reliable and repeatable evaluation to maintain consistency.
**Becoming a Clinical Evaluator in a Clinical Trial: What is Required?**

**Education and Training**

Becoming a Lead CE or Back-up CE in a clinical trial requires robust training methods (including didactic lecturing, hands-on training, and competency evaluations) to promote education and to ensure consistency and quality assurance among all participating CEs and assessments.

- Formal sponsor-led CE trainings are required to ensure reliability and the standardization of administration and scoring of outcome measures. This formal training is designed to decrease variability across visit assessments and between CEs. This formal training 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, training, and preparation of future CEs to increase confidence in robustness of data and help to accelerate study start-up.

- Clinical trial preparation and training will lead to high quality, reproducible data, which is essential for trial success.

**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 the proper and effective conduct of a clinical research study 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, when assessing patients using various functional outcomes amongst all clinical site evaluators. This may include requirements for videography of assessments 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 quarterly) 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.
SUMMARY & RECOMMENDATIONS: ROLES AND RESPONSIBILITIES

- Physical Therapists/Clinical Evaluators are key members of the research team who hold a wide variety of responsibilities. CEs 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.

- In SMA clinical trials, CEs are responsible for assessing patients across multiple health dimensions, using a variety of motor function scales and patient reported outcomes (PROs), to assess baseline function and potential changes/improvements that may be captured over time, following the administration of a given therapeutic.

- Assessments in SMA may involve performance-based measures including but not limited to developmental milestones, muscle strength, gross motor function testing, range of motion, cardiopulmonary function, gait, distance walked, etc. CEs must perform each assessment, across all trial participants, in a consistent, reliable and standardized manner, such that the data collected is deemed valid and reproducible and as such may be used to assess critical endpoints in a given clinical trial.

- 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.
Section 2: Steps to Take Before Participating in a Trial

Clinical Evaluator Training and Development

Before CEs become actively involved in clinical trials, it is important to ensure that they have completed training to first and foremost support and ensure the ethical conduct of research. Additionally, as stated above, CEs must complete all the evaluator-related training required, per study protocol, to ensure reliability/standardization of administration and scoring of all trial-related outcome measures. This preparation begins with fundamental trainings required for participation in clinical research. Individual sites may have site-specific evaluator training requirements as well. For more information about fundamental trainings that CEs should complete as part of their professional training, please see Table F1: Recommended Regulatory Training for Clinical Evaluators for an overview of recommended trainings.

CEs 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 F2: 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 F3: 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, you may refer to the SMA Clinical Trials’ Toolkit, v.2, Part II, “Key Elements of Trial Management.”

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 the principles of GCP, including human subject protection (HSP) is universally required and recognized as a critical component of the ethical conduct of research involving human subjects (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 also includes proper completion of study case report forms (CRFs) used to collect patient information as data during a study. In clinical trials, information must be recorded in a way that is 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 a review on key principles of good documentation, including ALCOA, documentation, source, training, see Good documentation practice in clinical research (Bargaje 2011). You may also refer to, Table F1: Recommended Regulatory Training for Clinical Evaluators.

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

Below is a list of trainings/certifications related to the ethical and effective conduct of research required of the research team prior to the IRB-approval and conduct of a clinical trial. Certification that one has completed training in Human Subjects Protection 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.

- Research Ethics and Compliance Training provided by:
  - CITI Program (registration required)
  - IRBs at each academic institution
- US FDA Regulated Research Training includes:
  - FDA Regulatory Compliance
  - Human Subjects’ Protection/Research, including:
    - General requirements for the Informed Consent of Human Subjects / Key Elements of Informed Consent
  - Responsible Conduct of Research
  - Research with Minors
  - Conflicts of Interest
- GCP Certification
- Information Privacy & Security
  - Health Insurance Portability and Accountability Act (HIPAA) training specific for human subject research is also required

While this list may provide a helpful starting point for understanding relevant trainings for research study team members in clinical trials, it is not exhaustive. For a list of recommended regulatory training (including links describing the pertinent federal regulation), and other required forms that the CE must complete, prior to the conduct of research, please refer to Table F1: Recommended Regulatory Training for Clinical Evaluators.

Required Documentation and Forms for CEs

The following are required per GCP principles and US FDA regulations. For a comprehensive list of Essential Documents According to ICH E6(R2) guidelines, you may also refer to the SMA Clinical Trials’ Toolkit, v.2, Part II, section B2; also see, Table F1: 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 F1: Recommended Regulatory Training for Clinical Evaluators.
Professional state license, which demonstrates that you have the license to practice PT in your state of residence, per study protocol.

Professional certifications, which demonstrate that 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 (you may click this link for further instructions on completing Form 1572).

Financial Disclosure Form, a study-specific financial disclosure form is required (59 FR 48708) from each study team member involved in the research study (Weinfurt 2009, Boyd 2004). 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; and that 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 US FDA site at Financial Disclosures by Clinical Investigators.

Review of Study Protocol

As a critical member of the study team, CEs should have a solid understanding of the study protocol, including the purpose of the study (assess feasibility, safety, effectiveness), study methodology and design (e.g., single-arm, two-arm, open-label, placebo-controlled, blinded vs. double-blinded, etc.), schedule of procedures, trial endpoints, attributes of the investigational product being evaluated, and specific details, particularly those pertaining to your role and clinical evaluations (i.e., required outcome measures) and in a given trial. If you are interested in learning more about clinical trial design, you may refer to Clinical trial structures (Evans 2010) a publication which provides a good overview.

Investigator Meetings

To best prepare study members to conduct an effective trial, and given the complexities of running a clinical trial, sponsors hold an investigator meeting (IM), prior to beginning any study procedures. At the IM, the study team learns about the study protocol and all the steps required to maintain compliance and consistency in the protocol (review of inclusion/exclusion criteria, procedures performed at each study visit, adverse event reporting, lab procedures, regulatory issues, etc.). PIs, study coordinators, and CEs are typically required to attend from each clinical site to learn, ask questions, and prepare for participation and enrollment in the upcoming study. CEs may be asked to attend the initial full-study IM and may also have a separate study specific training to meet requirements for certification and participation. This 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. IMs are designed to encourage interactions and communication, provide education and training of the research initiative 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.

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

A collaborative, patient-focused approach is increasingly emphasized in health care and drug development. When the patient is not at the heart of all research activities (from the design of a research protocol to
interactions before recruitment and management of the trial), the outcome and success of the clinical trials are often compromised (Schliebner 2017, Xtalks 2018). A patient-focused approach may help not only to improve the patient experience, but may increase the success of clinical trials, and should be applied to all aspects of clinical trial operations (Schliebner 2017, Xtalks 2018). This approach emphasizes the needs of the patient and involves assessing trial design and operations from a patient’s perspective and can include integrating the SMA patient community input directly into the clinical trial design. As CEs are continually interacting with patients, families and caregivers, understanding and incorporating their perspectives may help coordinators and the research study team to be more effective in their role.

In SMA, a patient-focused approach can be particularly impactful. SMA 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 (Qian 2015, Cruz 2018). Families may be dealing with challenging complications and hospitalizations and need the research team to have a solid understanding of the presentation of the disease, including the multidisciplinary care required. Beyond understanding of the disease, patients and families may need extra reassurance, and someone who can listen to their questions, concerns, and struggles during the evaluation process. Furthermore, families, caregivers, and the patients themselves (children typically after 7 years of age must provide assent regarding participation in a trial) may want to be very involved in care and in the trial process.

Adopting a patient-focused approach through thoughtful, intentional listening and engagement can help patients, families, and caregivers to feel heard, supported, and engaged. CEs may also find shadowing families during their clinical visits helpful for gaining perspectives on the challenges and care needed when interacting with patients with different SMA types. 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.
Section 2: Summary & Recommendations

SUMMARY & RECOMMENDATIONS: 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.

- CEs 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. Certification that one has completed training in human subject protection in research is required of all faculty, investigators, study coordinators, CEs, and other individuals directly involved in human subjects’ research.

- In preparing for a trial, CEs must ensure that they attain a solid understanding of the study protocol, through participation in the Investigator Meeting 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.

- CEs 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. CEs 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 (Mercuri 2017). 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 (Mercuri 2017).

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 (Wang 2007). 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 (Mercuri 2017, 2018).

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 (Finkel 2018, Mercuri 2018, Wang 2007). Please see Table F3: 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. GCP 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 (Table 3) 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 1) 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 1.
### Table 1: Common Compensations and Biomechanics

<table>
<thead>
<tr>
<th>Sitting</th>
<th>Children and adults can display fixation or bracing techniques using their arms to support their weak trunk muscles in an upright sitting posture.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>
|                          | Excessive lateral trunk lean can occur when trying to use or lift the arm. 
<p>|                          | 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.). |
|                          | 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 rolling, it may be difficult to free the arms to move them out from under the body. |
|                          | 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. |
|                          | When in prone, patients may require the use of their arms to support their head upright when propped. |
|                          | 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 &amp; 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 |</p>
<table>
<thead>
<tr>
<th>Activity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standing</td>
<td>If a patient has difficulty standing unsupported, you may see them leaning their trunk on a support surface to stand. 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.</td>
</tr>
<tr>
<td>Walking</td>
<td>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.</td>
</tr>
<tr>
<td>Jumping</td>
<td>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. 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.</td>
</tr>
<tr>
<td>Stair Climbing</td>
<td>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.</td>
</tr>
<tr>
<td>Arm Function</td>
<td></td>
</tr>
</tbody>
</table>
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 2). 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 the research section below entitled, Table 2: Commonly Used Outcomes by SMA Functional Level/ Phenotype.

Figure 2: Primary Areas for Assessment for Those With SMA

- Strength
- Contractures
- Symmetry and alignment
- Scoliosis and pelvic obliquity
- Fatigue
- Endurance
- Pain
- Pulmonary function
- Chest wall deformities
- Plagiocephaly
- Skin integrity
- Balance/Falls
- Fractures
- Hip dislocation

Function in everyday life
- Sitting tolerance/ability
- Reaching and grasping
- Postural control
- Achievement of motor milestones
- Balance
- Gait
- Speed/coordination
- Swallowing and feeding

Integration onto everyday life and activities with peers and family
- School
- Sports
- Community
**Figure 3: Commonly Used Assessments across Domains of the ICF**

- **Body Structure & Function**
  - Myometry/HHD (grip, pinch, elbow & knee flex/ext, etc)
  - MMT (MRC or individual muscles)
  - Myogrip, Myopinch
  - Fatigue (6MWT, ESIBIT, ESNAHT, +90ºP)
  - PFTs
  - Goniometry/ROM
  - Pain scales
  - RJP
  - Moviplate
  - Workspace volume (Active seated, Kinetix)
  - Balance measures (NESS, PBS, head & trunk-righting)

- **Activities**
  - CHOP INTEND
  - HINE-Section 2
  - WHO motor milestones
  - TIMPSI
  - HFMS/RHS
  - RULM
  - Timed tests of function
    - 6MWT, 10 meter walk/run, time to rise, time to climb, TUG, 9HPT, Box and Blocks
  - MFM (MFM-32, MFM-20)
  - Actiwatch, sensors
  - BSID-III
  - PDMS-2
  - CHOP ATEND
  - EK2

- **Participation**
  - PEDI-CAT for SMA
  - PedsQL™
  - Type 1 Caregiver Questionnaire
  - SMA Functional Rating Scale (SMAFRS/ Modified SMAFRS)
  - PROMIS
  - Fatigue scales
  - SMA-HI
  - ACTIVLIM
  - ACEND
  - CAPE/PAC

*Also provide information re: activity, personal factors, caregiver experience and environment

Infants and children
Adults
All ages

**Figure 4: Commonly Used Activity and Participation Functional Outcome Measures Across Functional Categories Of SMA**

- **Non-sitter**
  - CHOP INTEND/ATEND
  - TIMPSI

- **Sitter**
  - 6 min walk test
  - Hammersmith Expanded (HFMS/RHS)/Revised Hammersmith (RHS)

- **Walker**
  - BSID-III
  - PDMS-2
  - Revised Upper Limb Module (RULM)
  - Motor Function Measure (MFM)
  - Egan Klassification-2 (EK2)
  - Timed Function Tests (TFT)

- **Treated presymptomatically**
  - HINE (Section 2), WHO, BSID-III, ACEND, Fatigue Severity Scale (FSS), SMAFRS, PEDI-CAT, PedsQL, PROMIS, SMA-HI
SUMMARY & RECOMMENDATIONS: 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 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.

- 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 presymptomatic 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. 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 USA 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 (Mercuri 2017).

The National Institutes of Health (NIH) encourages the use of common data elements in clinical research and patient registries in order to improve data quality and allow opportunities for combination and comparison of electronic health records across multiple studies and centers. 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 would be 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 evolving change 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 2: Commonly Used Outcomes by SMA Functional Level/Phenotype with additional details found below in the next section and in Table F4: Outcome Measure and Evaluation Resources.
Table 2: Commonly Used Outcomes by SMA Functional Level/Phenotype

<table>
<thead>
<tr>
<th>Functional Level/Phenotype</th>
<th>Non-Sitters</th>
<th>Sitters</th>
<th>Walkers</th>
<th>Presymptomatic</th>
<th>Chronic Adult</th>
<th>Pulmonary Outcomes</th>
<th>Patient Reported Outcomes (PROs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHOP INTEND</td>
<td>HINE-2 Motor</td>
<td>WHO – Motor Milestones</td>
<td>BSID-III</td>
<td>TIMPSI</td>
<td>HFMSE/RHS</td>
<td>RULM</td>
</tr>
<tr>
<td></td>
<td>CHOP INTEND</td>
<td>HFMSE/RHS</td>
<td>WHO</td>
<td>6MWT</td>
<td>Other TFT (10MWRT, TTR, TTC, TUG, 30STS, 9HPT, r9HPT, ESNHPT, BBT, ESBBT)</td>
<td>MFM</td>
<td>HHD (grip/ pinch, elbow flex/ext, knee flex/ext, etc)</td>
</tr>
<tr>
<td></td>
<td>CHOP ATEND</td>
<td>HHD (grip/pinch)</td>
<td>Modified SMAFRS</td>
<td>EK2</td>
<td>TFT (9HPT, r9HPT, ESNHPT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFT</td>
<td>RIP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACEND</td>
<td>EK2</td>
<td>Fatigue (FSS, PedsQL, PROMIS)</td>
<td>Modified SMAFRS</td>
<td>PEDI-CAT</td>
<td>PedsQL</td>
<td>PROMIS</td>
</tr>
</tbody>
</table>

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2 In addition to functional level above if appropriate
3 Test in alphabetical order (can be administered to all types of SMA)
Tests Most Commonly Used for Non-Sitters

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

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. (Glazman 2010)

The test is valid and reliable (Glazman 2010) and sensitive to change (Glazman 2011) in SMA type I. 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 (The CHOP 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

[Link to test manual, proforma, and references](#)

- **Supportive evidence in SMA research:** CHOP INTEND scores in untreated children with SMA decline over time. A prospective, longitudinal natural history study (Kolb 2016, 2017) 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 (Finkel 2014; De Sanctis 2018) and a mean loss of -12.67 points was demonstrated over 2 years (Kolb 2017). 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 (Crawford 2018). 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 (Finkel 2017, 2016). 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 (Mendell 2017, 2019). In the FIREFISH study infants with type I SMA showed a median change from baseline of 16 points at 2 years of age (Baranello 2018).
Hammersmith Infant Neurological Exam - Section 2, Motor Milestone (HINE-2)

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 (Romeo 2016; Eeles 2016; Maitre 2016). 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 (Maitre 2016). 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 (Bishop 2018).

- 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

Link to test manual, proforma, and references

- 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. HINE-2 improvements were also correlated with changes in other neuromuscular outcome measures (Bishop 2018). 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%]) (Finkel 2017).

World Health Organization Motor Milestones (WHO)

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 USA, Ghana, India, Norway, and Oman (Wijnhoven 2004). 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. Biogen reported in an interim analysis that WHO motor milestones were on target for infants enrolled in the NURTURE presymptomatic study of Nusinersen (Crawford 2018).

Bayley Scales of Infant Development III (BSID-III)

The BSID-III 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. The test is intended to measure a child's level of development in multiple domains: cognitive, language, motor, and behavioral. 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 (Bayley 2006). 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 (Bayley 2006).

Scoring: Items are scored as able (1) or unable (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)

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 (Campbell 2008). It has demonstrated excellent reliability, sensitivity and validity when used in infants born prematurely and at high risk for poor motor performance (Campbell 1995, 2002). The TIMPSI is a shorter, screening version of the TIMP (Campbell 2008) 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 (Krosschell 2013, 2018; Kolb 2016, 2017). 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.

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

**Tests Most Commonly Used for Sitters**

**Hammersmith Functional Motor Scale Expanded (HFMSE)**

The HFMSE assesses motor function of those with both type II and type III SMA (O’Hagen 2007). 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 (O’Hagan 2007). The HFMSE is highly correlated with the GMFM and discriminates between SMA type, ambulatory function, and respiratory function (BiPAP use) (Glanzman 2011). Excellent inter and intra-rater reliability has been demonstrated across multiple multisite clinical trials (Glanzman 2018). Expected change in HFMSE scores with age and type of SMA has been established (Mercuri 2016; Kaufman 2012). 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 (Mercuri 2018). Content validity and clinical meaningfulness of the HFMSE has been established (Pera 2017).

Revised Hammersmith Scale (RHS)

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 (Ramsey 2017). 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 (Ramsey 2017).

- 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

Revised Upper Limb Module (RULM)

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 (Mazzone 2011, 2017; Sivo 2014).

- 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 F6: 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 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.

WHO

See above under Non-Sitters

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

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 (Bérand 2005). The MFM-32 is not suited to those younger than 7 as it is too long, and some items are too difficult in terms of cognitive or motor development. 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 (de Lattre 2013). 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

Hand Held Dynamometry (HHD)

(Hand grip/finger pinch, elbow flexion/extension, knee flexion/extension, etc.)

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.
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 (Merlini 2002). 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 (Escobar 2017; Hebert 2015; Beenakker 2001)

- Scoring: Quantitative measurement in kilogram, pounds, or newtons of force using a make or break test
- Time to complete: < 5 minutes per muscle group
- Equipment: Hand-held dynamometer

**Link to test manual, proforma, and references**

- **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 (Kissel 2011). There was no statistical difference in myometry from baseline to 6 or 12 months. HHD 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 (Lewelt 2015). Both studies reported high reliability (≥ 0.95), however, included small participant samples (n<20).

**Timed Function Tests (TFT)**

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)**

The originally validated and reliable 9HPT assessed fine motor dexterity in the distal upper extremity (Smith 2000). 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: 9HPT, adjustable chair and table, stop watch

**Link to test manual, proforma, and references**

- **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 (Kissel 2011).
**Repeated (5 times) Nine-hole peg test (r9HPT)**

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 (Stam 2017).

- **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:** 9HPT, 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 (Stam 2018).

**Endurance Shuttle Nine Hole Peg Test (ESNHPT)**

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 (Bartels 2019). Work on validity and reliability in a larger SMA study is underway (Bartels, B personnel communication).

- **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)

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 (Mathiowetz 1985).

- 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)

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 (Bartels 2019).

- 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.
Ability Captured Through Interactive Video Evaluation (ACTIVE)

ACTIVE is a custom-designed 65 second video game that measures workspace volume (WSV) and quantifies upper extremity function in SMA. WSV is defined as the area around a person within which she/he can reach and interact. 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 (Alfano 2019).

- 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 $p<0.01$) (Alfano 2019).

Tests Most Commonly Used for Walkers

HFMSE

See above under Sitters.

RHS

See above under Sitters.

Six-minute Walk Test (6MWT)

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 (Montes 2018, 2010, 2017). The test demonstrates excellent reliability and convergent validity in those with SMA as it correlates with other functional and clinical assessments (Dunaway Young 2016; Montes 2013). Longitudinal data demonstrates age-related patterns of progression similar to other natural history motor function declines (Montes 2018).

- 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

**Link to test manual, proforma, and references**

- **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 (Day 2018). 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 (Day 2018).

In the Biogen study median distance walked increased over time by 17 meters at Day 253 and 99 meters at Day 1050 (Montes 2018). 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)**

This test records the time taken to safely walk or run 10 meters on a marked 10-meter course. Time to complete correlates with knee extensor and flexor strength and effectively measures walking ability with minimal endurance needs (Merlini 2004; Kissel 2011).

- Scoring: Time to complete in seconds
- Time to complete: Test discontinued if time > 180 seconds
- Equipment: 10-meter walkway, stop watch

**Link to test manual, proforma, and references**

- **Supportive evidence in SMA research**: The 10MWRT was used in the Carni-VAL type III study. No changes were reported from baseline to 6 months or 12 months (Kissel 2011; Krosschell 2009). 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)**

The timed rise from floor assesses the time taken to rise from supine on the floor to standing upright (Merlini 2004; Kissel 2011).

- 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: The TTR was used in the Carni-VAL type III study. No changes were reported from baseline to 6 months or 12 months. (Kissel 2011; Krosschell 2009) It is currently being utilized in the Scholar Rock Study of SKR-015, a latent myostatin inhibitor as part of the RHS.

**Time to Climb 4 Stairs (TTC)**

The time to climb 4 stairs 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: The time to climb 4 stairs was used in an SMA natural history study (Chabanon 2018) and the Carni-VAL type III clinical trial (Kissel 2011; Krosschell 2009). No changes were reported from baseline to 6 months or 12 months.

**Timed Up & Go (TUG)**

The timed “up & go” (TUG) test is a quick measure of balance and mobility. 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 10MWR, and 6MWT (Dunaway Young 2014).

- **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 (Day 2018).

**30 Second Sit to Stand (30STS)**

The 30STS is used by researchers and clinicians as an assessment of functional lower limb strength (Jones 1999) and has demonstrated good inter-tester and intra-tester reliability in adult populations using a standardized protocol (Gill 2008). 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

**Link to test manual, proforma, and references**

- 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.

**MFM**

[See above under Sitters.]

**HHD**

[See above under Sitters.]

**RULM**

[See above under Sitters.]

**Tests for Presymptomatic Patients with SMA**

**CHOP INTEND**

[See above under Non-Sitters.]

**HFMSE/RHS**

[See above under Sitters.]

**6MWT**

[See above under Walkers.]

**WHO**

[See above under Non-Sitters.]

**Peabody Developmental Motor Scales-2 (PDMS-2)**

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 (Folio 2000).

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 (Connolly 2006; Folio 2000; Wuang 2012)

- 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: 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.

**Link to test manual, proforma, and references**

- Supportive evidence in SMA research: The PDMS-2 is currently being used in the Biogen NURTURE clinical trial.

BSID-III

See above under Non-Sitters.

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

See above under Non-Sitters for CHOP INTEND. A new version to be adapted for adults who are non-sitters is currently under development.

HHD (grip/pinch)

See above under Sitters.

SMA Functional Rating Scale/Modified SMAFRS (SMAFRS)

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) (Elsheikh 2009). 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 while adding an item on respiratory support.
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 (Miller 2001) and the Modified SMAFRS was used in the adult Carni-Val trial (Kissel 2011) and demonstrated stability over a 12-month period.

**Egen Klassification 2 (EK2)**

This 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 (Steffensen 2001, 2002).

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 'being the highest level of function and 51 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)**

Pulmonary function tests 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). FVC has demonstrated reliability in SMA (Kaufmann 2011) 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 \((\text{Kaufman 2011; Iannaccone 2002})\). 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 \((\text{Khirani 2013})\) 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

**Respiratory Inductance Plethysmography (RIP)**

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 \((\text{Finkel 2014})\).

- Scoring: Varies by test
- Time to complete: Variable, most protocols use 15-20 minutes of monitoring with RIP
- Equipment: RIP test kit, various size chest bands, electrodes and laptop computer

**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 (Vaidya 2018). SMA specific modules or tools may be most sensitive to capture change across studies.

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 (Matsumoto 2011). 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

Link to test manual, proforma, and references

- 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

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 (Vandervelde 2007, 2009).

- 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

Link to test manual, proforma, and references

- Supportive evidence in SMA research: The ACTIVLIM has not to date been used in any SMA clinical trials.

EK2

See above under Adults with Chronic SMA

Fatigue Severity Scale (FSS)

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 (de Groot 2013, Werlauff 2014). It is composed of 9-items that covers 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

**Link to test manual, proforma, and references**

- Supportive evidence in SMA research: Perceived fatigue in patients with SMA type II, type III (Dunaway Young 2019) and congenital myopathies has recently been shown to be captured using the FSS (Werlauff 2014). Test-rest for the FSS in SMA was highly consistent (Werlauff 2014).

**Patient-Reported Outcomes Measurement Information System (PROMIS®)**

PROMIS® is a set of person-centered measures that evaluates and monitors physical (including fatigue), mental, and social health in adults and children (Gershon 2010; Tucker 2014). It includes over 300 measures and can be used with the general population and with individuals living with chronic conditions. 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 CenterSM 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

**Link to test manual, proforma, and references**

- Supportive evidence in SMA research: No natural history study data has been published in SMA. 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)**

The PEDI-CAT is a questionnaire typically completed by the parent/caretaker that assesses a patient’s ability to perform daily functions (Haley 2005). 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 (Haley 2011; Dumas 2012). 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

**Link to test manual, proforma, and references**

- **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 (*Pasternak 2016*). 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**

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 (*Varni 1999, 2001*). 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 (*Iannaccone 2009*).

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

**Link to test manual, proforma, and references**

- **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 (*Iannaccone 2003, 2002, 2009; Dunaway 2010*). The PedsQL Neuromuscular Module is currently being used in the Biogen clinical trial.

**SMAFRS/Modified SMAFRS**

See above under tests for Adults with Chronic SMA.
SMA-Health Index (SMA-HI)

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

**Link to test manual, proforma, and references**

- 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 Reldesmtiv. 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 3** below.
### Table 3: Summary of Clinical Properties of Outcome Measures

<table>
<thead>
<tr>
<th>Outcome measures used in SMA</th>
<th>CHOP INTEND</th>
<th>TIMPSI</th>
<th>HFMS</th>
<th>HFMSE</th>
<th>RHS</th>
<th>MFM</th>
<th>RULM</th>
<th>6MWT</th>
<th>TFT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical subgroups</td>
<td>Type I</td>
<td>Type I</td>
<td>Type II</td>
<td>Type II, III</td>
<td>Type II, III</td>
<td>Type II, III</td>
<td>Type II, III</td>
<td>Type III</td>
<td>Type II</td>
</tr>
<tr>
<td>Functional subgroups</td>
<td>Non-sitter</td>
<td>Non-sitter</td>
<td>Sitter</td>
<td>Sitter/Walker</td>
<td>Sitter/Walker</td>
<td>Sitter/Walker</td>
<td>Sitter/Walker</td>
<td>Walker</td>
<td>Sitter/Walker</td>
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<tr>
<td>Supports mechanism of action</td>
<td>Specific to therapeutic agent under investigation</td>
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<tr>
<td>Conceptual framework fits SMA</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>Reliability</td>
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<td>Y</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>**</td>
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<tr>
<td>Validation with other measures</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>Normative ranges</td>
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<tr>
<td>Clinical trials</td>
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<td>Y</td>
<td>Y</td>
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<tr>
<td>Responsiveness to treatment</td>
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<tr>
<td>Clinical meaningfulness</td>
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Y=Yes, Blank = no or data not published; *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).
**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 rule of thumb when in doubt score down.

**Assessment for Inclusion and Exclusion Criteria**

Each study will set inclusion/exclusion criteria for entry to participate in the clinical trial that are often based on a minimum or maximum performance level on at least one if not multiple motor function tests. This is typically done to 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 above). 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 PI’s 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**

CEs 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. CEs 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., Bayley-III, RULM, RIP, PDMS-2, etc.)
- Stop watch and cones for 6MWT
- Standard toys to use for CHOP INTEND or HFMSE
- Camera, 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.
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: Considerations Related to Assessments and Patient Evaluation: Standards of Care, Supportive Care, and Multidisciplinary Care

The Clinical Evaluator 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. PTs 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. PTs should evaluate patients with SMA with these assessments routinely every 6 months to allow regular monitoring and identify changes in management and interventions (Mercuri 2018).

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. 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 (Mercuri 2018).

The rehabilitation section of this manuscript (Mercuri 2018, Section 2.4) 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 (Mercuri 2018).

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 (Dunaway Young 2019; Stam 2018; Montes 2010).

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 (Montes 2011, 2014). 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 and they may fall out of their mobility and positioning devices when 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 (*Mercuri 2018*). These fractures can occur during transfers, stretching, and accidents in their mobility devices or from a fall.

**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 (*Finkel 2018*). 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 (*Mercuri 2018*). 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 (*Mercuri 2018*).

**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 (*Mercuri 2018*). 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 (*Mercuri 2018*). 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 (*Dunaway Young 2018*). 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 CEIs 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 to easily examine. 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. Contractures, bulbar dysfunction, and respiratory involvement worsen, as well as increasing functional limitations which all can impact participation and quality of life. 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 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.
SUMMARY & RECOMMENDATIONS: 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

CEs 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 F5: 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. CEs 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 for this Appendix


Beenakker EA, 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. *Neuromuscul Disord.* 2001;11(5):441-446.


Day J. Update of CY-5021: A Phase 2 clinical trial of reldesemtiv, a fast skeletal muscle troponin activator (FSTA), for the potential treatment of spinal muscular atrophy. *International Cure SMA Research Meeting,* Orlando, June 2018.


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.


U.S. Food & Drug Administration. **Instructions for Filling Out FORM FDA 1572 – STATEMENT OF INVESTIGATOR.** Retrieved from: [https://www.fda.gov/media/79326/download](https://www.fda.gov/media/79326/download) (PDFs)


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. **Med Care.** 2001;39(8):800-812.


Appendices: Additional Resources for Clinical Evaluators

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

1. Table F1 Recommended Regulatory Training for Clinical Evaluators
2. Table F2 SMA Seminal Paper Reference List
3. Table F3 External Resources for SMA Education and Training
4. Table F4 Outcome Measure and Evaluation Resources
5. Table F5 Professional Development: Meetings for Continuing Education
6. Table F6 RULM Kit Supply List
7. F7 “How to Use” Toolkit Example Guide
Table F1: 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.

<table>
<thead>
<tr>
<th>Trainings</th>
<th>Description</th>
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<tbody>
<tr>
<td>GCP Certification</td>
<td>Certification may be provided by an academic institution, sponsor or certifying program such as,</td>
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<tr>
<td></td>
<td>- [CITI Program][registration is required]</td>
</tr>
<tr>
<td></td>
<td>- [FDA GCP Educational Materials][registration is required]</td>
</tr>
<tr>
<td></td>
<td>- [Regulations: Good Clinical Practice and Clinical Trials][registration is required]</td>
</tr>
<tr>
<td></td>
<td>- Sponsor-specific GCP training</td>
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<tr>
<td>FDA Regulatory Compliance</td>
<td>Training on the ethical conduct of research may be found, via the following resources:</td>
</tr>
<tr>
<td></td>
<td>- [CITI Program][registration is required]</td>
</tr>
<tr>
<td></td>
<td>- Key Research Definitions – e.g., Clinical investigation, Sponsor, Clinical Investigator, Human Subject, IRBs, etc.</td>
</tr>
<tr>
<td></td>
<td>- Subpart B—General requirements for the Informed Consent of Human Subjects / Key Elements of Informed Consent</td>
</tr>
<tr>
<td></td>
<td>- [SOCRA: FDA Clinical Trial Requirements, Regulations, Compliance, and GCP Conference][registration is required]</td>
</tr>
<tr>
<td>Regulatory/FDA Mandated Training</td>
<td><a href="https://www.hhs.gov/ohrp">Human Subject Protection Research:</a> Ensures the ethical conduct and protection of human subjects, including pediatric patients and other ‘vulnerable populations’ – (e.g., children, prisoners, the medically fragile, etc.).</td>
</tr>
<tr>
<td></td>
<td>- [Office for Human Research Protections - Online Education][registration is required]</td>
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<tr>
<td></td>
<td>- [Belmont Report][registration is required] Provides the background behind the reason for the existence of these regulations.</td>
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<td></td>
<td>- Regulations on protecting human subjects in research</td>
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<tr>
<td></td>
<td>- About research participation</td>
</tr>
<tr>
<td></td>
<td>- Informational videos for research participants – on what is research, questions to ask, randomization, etc.</td>
</tr>
<tr>
<td></td>
<td>- [Upcoming educational events][registration is required]</td>
</tr>
<tr>
<td></td>
<td><a href="https://www.fda.gov">Responsible Conduct of Research:</a> 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.</td>
</tr>
<tr>
<td></td>
<td><a href="https://www.fda.gov">Research with Minors:</a> 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</td>
</tr>
</tbody>
</table>
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 50.51-50.53
- **CFR 46 Subpart D** — Additional Protections for Children Involved as Subjects in Research

*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):**

[https://www.careereducation.columbia.edu/resources/what-curriculum-vitae](https://www.careereducation.columbia.edu/resources/what-curriculum-vitae)

**Professional state license**

**Professional certifications**

#### Investigator Statements/Agreements

**Form FDA 1572:**

- See, [Form FDA 1572](#)
- See, [Instructions for completing Statement of Investigator 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)*
### Standard of Care

<table>
<thead>
<tr>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>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. <em>Neuromuscul Disord.</em> 2018;28(3):197-207.</td>
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</tbody>
</table>

### Natural History of SMA

<table>
<thead>
<tr>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Finkel RS, Weiner DJ, Mayer OH, McDonough JM, Panitch HB. Respiratory muscle function in infants with spinal muscular atrophy type I. <em>Pediatr Pulmonol.</em> 2014;49(12):1234-1242.</td>
</tr>
</tbody>
</table>


**Outcome Measure Validation/Reliability**


**Clinical Trial Results in SMA**


<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
<th>Publication Information</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical Evaluator Training in SMA</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Rehabilitation in SMA</strong></td>
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<tr>
<td>Orthopedic Issues (i.e. Contractures, Scoliosis, Hip dislocation)</td>
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</tbody>
</table>


**Interventions**


**Falls**


**Fatigue**


**Pain**


**Review**


**Participation and Quality of Life**


**Newborn Screening**


**The New Horizon**


**Professional or Pharmacologic Guidelines**


**Miscellaneous**


### Table F3: 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.

<table>
<thead>
<tr>
<th>Resources</th>
<th>Title</th>
<th>Resource Description</th>
<th>Resource Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard of Care Documents</td>
<td>Consensus statement for standard of care in spinal muscular atrophy. 2007</td>
<td>In 2007, an International Conference on the Standard of Care for SMA published a consensus statement on SMA standard of care that has been widely used throughout the world. (Wang et al, 2007)</td>
<td><a href="https://journals.sagepub.com/doi/abs/10.1177/0883073807305788">Link</a></td>
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<tr>
<td></td>
<td>Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. 2018</td>
<td>Updated Standards of Care (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.</td>
<td><a href="https://www.sciencedirect.com/science/article/pii/S0960896617312841?via%3Dihub">Link</a></td>
</tr>
<tr>
<td></td>
<td>Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. 2018</td>
<td>Updated Standards of Care (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.</td>
<td><a href="https://www.sciencedirect.com/science/article/pii/S0960896617312907?via%3Dihub">Link</a></td>
</tr>
<tr>
<td>Standards of Care for Families</td>
<td>A Family Guide to the Consensus Statement for Standard of Care in SMA</td>
<td>This Family Guide to the Consensus Statement for Standard of Care in SMA was prepared by advocates for families impacted by SMA.</td>
<td><a href="https://www.smafoundation.org/pdf/A-Guide-to-SMA-Standard-of-Care-(English).pdf">Link</a></td>
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<tr>
<td>APTA Academy of Pediatric PT (APPT) - SMA Fact Sheet. 2012</td>
<td>APTA Academy of Pediatric PT (APPT) - SMA Fact Sheet. 2012</td>
<td>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.</td>
<td><a href="https://pediatricapta.org/includes/factsheets/pdfs/PEDS_Factsheet_SMA.pdf">https://pediatricapta.org/includes/factsheets/pdfs/PEDS_Factsheet_SMA.pdf</a></td>
</tr>
<tr>
<td>Cure SMA Care Series, Musculoskeletal System</td>
<td>Cure SMA Care Series, Musculoskeletal System</td>
<td>This is a Cure SMA booklet specifically regarding issues with the musculoskeletal system in SMA. It reviews orthopedic concerns including contractures, hips, and spine.</td>
<td><a href="https://www.curesma.org/wp-content/uploads/2019/07/the-musculoskeletal-system.pdf">https://www.curesma.org/wp-content/uploads/2019/07/the-musculoskeletal-system.pdf</a></td>
</tr>
<tr>
<td>Exercise and Spinal Muscular Atrophy – website</td>
<td>Exercise and Spinal Muscular Atrophy – website</td>
<td>SMA UK article on studies from the past few years investigating the benefits of exercise with regards to SMA.</td>
<td><a href="https://smauk.org.uk/exercise-and-spinal-muscular-atrophy">https://smauk.org.uk/exercise-and-spinal-muscular-atrophy</a></td>
</tr>
<tr>
<td>The Role of Therapy in your child’s life. Being a part of the team!</td>
<td>The Role of Therapy in your child’s life. Being a part of the team!</td>
<td>These slides were originally presented at the 2017 Annual Cure SMA Conference. Designed for parents and families of children with SMA, the presentation details the importance of being involved and informed in PT. This presentation</td>
<td><a href="https://www.curesma.org/wp-content/uploads/2019/07/pt-ot-conf-2018.pdf">https://www.curesma.org/wp-content/uploads/2019/07/pt-ot-conf-2018.pdf</a></td>
</tr>
<tr>
<td>General SMA Resources</td>
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<tr>
<td><strong>Cure SMA</strong></td>
<td>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.</td>
<td><a href="http://www.curesma.org/">http://www.curesma.org/</a></td>
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<tr>
<td><strong>Muscular Dystrophy Association</strong></td>
<td>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.</td>
<td><a href="https://www.mda.org/">https://www.mda.org/</a></td>
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<tr>
<td><strong>Spinal Muscular Atrophy Foundation</strong></td>
<td>The mission of the SMA Foundation is to accelerate the development of a treatment for Spinal Muscular Atrophy.</td>
<td><a href="http://www.smafoundation.org/">http://www.smafoundation.org/</a></td>
<td></td>
</tr>
<tr>
<td><strong>Orthopedic Management of Spinal Deformities in Spinal Muscular Atrophy</strong></td>
<td>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.</td>
<td><a href="https://www.curesma.org/wp-content/uploads/2019/07/orthopedic-management-2018conf.pdf">https://www.curesma.org/wp-content/uploads/2019/07/orthopedic-management-2018conf.pdf</a></td>
<td></td>
</tr>
<tr>
<td><strong>Medical Management of Adults with SMA</strong></td>
<td>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.</td>
<td><a href="https://www.curesma.org/wp-content/uploads/2019/07/adult-med-management-conf2018-presentation.pdf">https://www.curesma.org/wp-content/uploads/2019/07/adult-med-management-conf2018-presentation.pdf</a></td>
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<tr>
<td><strong>SMA and Exercise</strong></td>
<td>Brief article providing an overview of SMA exercise research and highlighting a few studies regarding the benefits of swimming, strength tests, and resistance training.</td>
<td><a href="https://smanewstoday.com/sma-and-exercise/">https://smanewstoday.com/sma-and-exercise/</a></td>
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<tr>
<td><strong>Treat-NMD Neuromuscular Network</strong></td>
<td>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.</td>
<td><a href="https://treat-nmd.org/">https://treat-nmd.org/</a></td>
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<td><strong>ChildMuscleWeakness.org - National Task Force for Early Identification of Childhood Neuromuscular Disorders</strong></td>
<td>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.</td>
<td><a href="https://www.childmuscleweakness.org/">https://www.childmuscleweakness.org/</a></td>
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<tr>
<td><strong>National Organization for Rare Disorders (NORD)</strong></td>
<td>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 diseases.</td>
<td><a href="https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/">https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/</a></td>
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<tr>
<td>Resource</td>
<td>Description</td>
<td>Website</td>
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<tr>
<td>SMA News Today</td>
<td>SMA News Today is strictly a news and information website about the disease.</td>
<td><a href="https://smanewstoday.com/">https://smanewstoday.com/</a></td>
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<tr>
<td>SMArt Moves – Cure SMA</td>
<td>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.</td>
<td><a href="http://www.SMArtMoves.CureSMA.org">http://www.SMArtMoves.CureSMA.org</a></td>
<td></td>
</tr>
<tr>
<td>SMA Care and Management</td>
<td>SMA: Disease Mechanisms and Therapy, 1st Edition</td>
<td>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.</td>
<td><a href="https://www.elsevier.com/books/spinal-muscular-atrophy/sumner/978-0-12-803685-3?dgclid=EAIaIQobChMIn8f2nJf33QIVgsBkC_h3fkw21EAYYASABgLWvD_BwE">https://www.elsevier.com/books/spinal-muscular-atrophy/sumner/978-0-12-803685-3?dgclid=EAIaIQobChMIn8f2nJf33QIVgsBkC_h3fkw21EAYYASABgLWvD_BwE</a> <a href="http://www.sciencedirect.com/science/article/pii/B9780128036853000239">http://www.sciencedirect.com/science/article/pii/B9780128036853000239</a></td>
</tr>
<tr>
<td>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</td>
<td>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.”</td>
<td><a href="https://www.curesma.org/sma-industry-collaboration-releases-spinal-muscular-atrophy-voice-of-the-patient-vop-report/">https://www.curesma.org/sma-industry-collaboration-releases-spinal-muscular-atrophy-voice-of-the-patient-vop-report/</a></td>
<td></td>
</tr>
<tr>
<td>Spinal muscular atrophy - causes, symptoms, diagnosis, treatment, pathology</td>
<td>Video by Osmosis</td>
<td><a href="https://www.youtube.com/watch?v=Ax89gbbC-4g">https://www.youtube.com/watch?v=Ax89gbbC-4g</a></td>
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<tr>
<td>SMA and the drug that fights it, explained</td>
<td>Video By Cold Spring Harbor Laboratory</td>
<td><a href="https://www.youtube.com/watch?v=YLuVwg_y4">https://www.youtube.com/watch?v=YLuVwg_y4</a></td>
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<tr>
<td>Together in SMA</td>
<td>Biogen’s information page on SMA and treatment</td>
<td><a href="https://www.togetherinsma-hcp.com/?cid=aff-tisma-header-hp">https://www.togetherinsma-hcp.com/?cid=aff-tisma-header-hp</a></td>
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<td></td>
<td>FDA product label for Spinraza</td>
<td><a href="https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf">https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf</a></td>
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<tr>
<td>Area of Interest</td>
<td>Resource</td>
<td>Website Link</td>
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<tr>
<td>The First SMA Gene Therapy in Human Trials</td>
<td>AveXis’ information page on SMA treatment</td>
<td><a href="https://www.avexis.com/research-and-development">https://www.avexis.com/research-and-development</a></td>
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<tr>
<td>Spinal Muscular Atrophy (SMA) Fact Sheet</td>
<td>FDA product label for Zolgensma</td>
<td><a href="https://www.fda.gov/media/126109/download">https://www.fda.gov/media/126109/download</a></td>
<td></td>
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<tr>
<td>Understanding SMA</td>
<td>Roche’s article on SMA</td>
<td><a href="https://www.roche.com/research_and_development/what_we_are_working_on/neuroscience/approaching-sma.htm">https://www.roche.com/research_and_development/what_we_are_working_on/neuroscience/approaching-sma.htm</a></td>
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</tr>
<tr>
<td>Area of Interest: SMA - Risdiplam, PTC Therapeutics</td>
<td>PTC Therapeutics article on Risdiplam</td>
<td><a href="https://www.ptcbio.com/our-pipeline/areas-of-interest/sma/">https://www.ptcbio.com/our-pipeline/areas-of-interest/sma/</a></td>
<td></td>
</tr>
<tr>
<td>Spinal Muscular Atrophy</td>
<td>Cytokinetics information page on SMA</td>
<td><a href="https://cytokinetics.com/our-focus/spinal-muscular-atrophy/">https://cytokinetics.com/our-focus/spinal-muscular-atrophy/</a></td>
<td></td>
</tr>
<tr>
<td>Cut and Paste: Treating Spinal Muscular Atrophy with Nusinersen</td>
<td>Video by Youreka Science</td>
<td><a href="https://www.youtube.com/watch?v=wN-BRrzZ5E">https://www.youtube.com/watch?v=wN-BRrzZ5E</a></td>
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<tr>
<td>SMA Clinical Trials</td>
<td>SMA Type I: How Gene Therapy Works</td>
<td>Video by Nationwide Children’s</td>
<td><a href="https://www.youtube.com/watch?v=iBmyXr_o1hU&amp;t=22s">https://www.youtube.com/watch?v=iBmyXr_o1hU&amp;t=22s</a></td>
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<tr>
<td>SMA Clinical Trials</td>
<td>SMA Trial Readiness Toolkit</td>
<td>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 information, as well as the Cure SMA website for parent- and family-friendly materials.</td>
<td><a href="https://www.curesma.org/clinical-trial-readiness/">https://www.curesma.org/clinical-trial-readiness/</a></td>
</tr>
<tr>
<td>Cure SMA Clinical Trials Drug Development/Pipeline</td>
<td>Cure SMA Clinical Trials Drug Development/Pipeline</td>
<td>Graphics outline of therapeutic pipeline for SMA (updated frequently)</td>
<td><a href="http://www.curesma.org/research/latest-advances/">http://www.curesma.org/research/latest-advances/</a></td>
</tr>
<tr>
<td>Common Data Elements for Spinal Muscular Atrophy</td>
<td>Common Data Elements for Spinal Muscular Atrophy</td>
<td>National Institute of Neurological Disorders &amp; 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. CDEs also allow for comparison of results across studies to allow for effective aggregation of information into more significant metadata results.</td>
<td><a href="https://www.commondataelements.ninds.nih.gov/Spinal%20Muscular%20Atrophy">https://www.commondataelements.ninds.nih.gov/Spinal%20Muscular%20Atrophy</a></td>
</tr>
<tr>
<td>Mandatory Core Dataset for TREAT-NMD SMA Registries</td>
<td>This project was carried out to expand the mandatory core dataset for the SMA Registries affiliated to the TREAT-NMD network. This work was done so that the TREAT-NMD Global SMA Registry can better inform on the natural history of SMA, provide context to understand the safety and effectiveness of new treatments, and support post marketing surveillance (PMS) for those new treatments.</td>
<td><a href="https://treat-nmd.org/what-is-a-patient-registry/registries-tool-kit/mandatory-core-dataset-for-treat-nmd-sma-registries/">https://treat-nmd.org/what-is-a-patient-registry/registries-tool-kit/mandatory-core-dataset-for-treat-nmd-sma-registries/</a></td>
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<tr>
<td>Cure SMA Resources</td>
<td>Education Resources from Cure SMA</td>
<td>Cure SMA Conference Medical Presentations, SMA Clinical Care Evidence, and Medical Education Tools</td>
<td><a href="https://www.curesma.org/current-educational-programs/">https://www.curesma.org/current-educational-programs/</a></td>
</tr>
<tr>
<td>Tool</td>
<td>Description</td>
<td>Manual of Procedures</td>
<td>Score Sheet</td>
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<tr>
<td>Ability Captured Through Interactive Video Evaluation (ACTIVE)</td>
<td>ACTIVE is a custom-designed video game that measures workspace volume and quantifies upper extremity function in SMA.</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ACTIVLIM</td>
<td>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.</td>
<td><a href="http://rssandbox.iescagilly.be/activlim-instructions.html">http://rssandbox.iescagilly.be/activlim-instructions.html</a></td>
<td><a href="http://rssandbox.iescagilly.be/activlim-downloads.html">http://rssandbox.iescagilly.be/activlim-downloads.html</a></td>
</tr>
<tr>
<td>Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)</td>
<td>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.</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bayley Scales of Infant and Toddler</td>
<td>The Bayley-III is a standardized test series of measurements used primarily to assess the</td>
<td>Available for purchase with test kit</td>
<td>Available for purchase with test kit</td>
</tr>
<tr>
<td>Test Name</td>
<td>Description</td>
<td>Reference(s)</td>
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<tr>
<td>Box and Block Test (BBT, ESBBT)</td>
<td>The BBT is a standardized, quantitative test assessing unilateral gross manual dexterity of the upper extremity.</td>
<td><a href="https://www.sralab.org/sites/default/files/2017-06/Box%20and%20Blocks%20Test%20Instructions.pdf">https://www.sralab.org/sites/default/files/2017-06/Box%20and%20Blocks%20Test%20Instructions.pdf</a></td>
<td></td>
</tr>
<tr>
<td>Fatigue Severity Scale (FSS)</td>
<td>The FSS is a patient-reported outcome measure to evaluate the impact of fatigue.</td>
<td>NA</td>
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</tr>
</tbody>
</table>

For more detailed information, please visit the provided references.
<table>
<thead>
<tr>
<th>Test Name</th>
<th>Description</th>
<th>Manual/Proforma</th>
<th>Online Link 1</th>
<th>Online Link 2</th>
<th>Online Link 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammersmith Infant Neurological Examination (HINE) - Motor Section Part 2</td>
<td>The HINE is an easily performed and relatively brief clinical neurological examination for infants aged between 2 and 24 months. The motor section Part 2 has been used to record milestone achievement in SMA.</td>
<td>NA</td>
<td><a href="https://www.jpeds.com/article/S0022-3476(99)70016-8/pdf">https://www.jpeds.com/article/S0022-3476(99)70016-8/pdf</a></td>
<td><a href="https://onlinelibrary.wiley.com/doi/10.1002/mus.25705">https://onlinelibrary.wiley.com/doi/10.1002/mus.25705</a></td>
<td><a href="https://www.nmd-journal.com/article/S0960-8966(16)30816-1/fulltext">https://www.nmd-journal.com/article/S0960-8966(16)30816-1/fulltext</a></td>
</tr>
<tr>
<td>Hand-Held Dynamometry (HHD)</td>
<td>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.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td><a href="https://onlinelibrary.wiley.com/doi/10.1002/mus.10166">https://onlinelibrary.wiley.com/doi/10.1002/mus.10166</a></td>
</tr>
<tr>
<td>Nine Hole Peg Test (NHPT, r9HPT, ESNHPT)</td>
<td>The NHPT is a brief, standardized, quantitative test of upper extremity function.</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td><a href="https://www.performancehealth.com/jamar-9-hole-peg-test-kit">https://www.performancehealth.com/jamar-9-hole-peg-test-kit</a></td>
</tr>
<tr>
<td><strong>Patient-Reported Outcomes Measurement Information System (PROMIS®)</strong></td>
<td>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.</td>
<td><a href="http://www.healthmeasures.net/explore-measurement-systems/promis/obtain-administer-measures">http://www.healthmeasures.net/explore-measurement-systems/promis/obtain-administer-measures</a></td>
<td><a href="http://www.healthmeasures.net/score-and-interpret/interpret-scores/promis">http://www.healthmeasures.net/score-and-interpret/interpret-scores/promis</a></td>
<td><a href="http://www.healthmeasures.net/explore-measurement-systems/promis">http://www.healthmeasures.net/explore-measurement-systems/promis</a></td>
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<tr>
<td><strong>Pediatric Evaluation of Disability Inventory – Computer Adaptive Test (PEDI-CAT)</strong></td>
<td>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.</td>
<td>Available for purchase with software</td>
<td>Available for purchase with software</td>
<td><a href="https://www.pedicat.com/">https://www.pedicat.com/</a></td>
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<tr>
<td><strong>Pediatric Quality of Life Inventory (PedsQL) Neuromuscular Module and</strong></td>
<td>The PedsQL was designed to measure health related quality of life dimensions specific to children ages 2 to 18 years with</td>
<td><a href="http://www.pedsql.org/pedsqladmin.html">http://www.pedsql.org/pedsqladmin.html</a></td>
<td>Available for purchase</td>
<td><a href="http://www.pedsql.org/">http://www.pedsql.org/</a> <a href="http://www.pedsql.org/PedsQL-Scoring.pdf">http://www.pedsql.org/PedsQL-Scoring.pdf</a></td>
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<tr>
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<tr>
<td><strong>Multidimensional Fatigue Scale</strong></td>
<td>neuromuscular disorders, including SMA.</td>
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</tr>
</tbody>
</table>
| **Pulmonary Function Tests (PFT)** | 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 |
| **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.smareachu.org/information-for-professionals/category/revised-hammersmith-scale | http://www.smareachu.org/information-for-professionals/category/revised-hammersmith-scale | https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0172346 |
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 | https://journals.sagepub.com/doi/suppl/10.1177/0883073813493663/suppl_file/Supplemental.pdf | NA | https://n.neurology.org/content/75/12/1121.2
and shows validity and reliability for those with SMA.

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<tr>
<th>Test Name</th>
<th>Description</th>
<th>NA</th>
<th>NA</th>
<th>Source</th>
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</tr>
</thead>
<tbody>
<tr>
<td>SMA Functional Rating Scale (SMAFRS)</td>
<td>The SMAFRS was developed to assess function in ambulatory adults with SMA.</td>
<td>NA</td>
<td>NA</td>
<td><a href="https://onlinelibrary.wiley.com/doi/10.1002/mus.21350">https://onlinelibrary.wiley.com/doi/10.1002/mus.21350</a></td>
<td><a href="https://n.neurology.org/content/90/15_Supplement/P4.452">https://n.neurology.org/content/90/15_Supplement/P4.452</a></td>
</tr>
<tr>
<td>SMA Health Index (SMA-HI)</td>
<td>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.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Test of Infant Motor Performance Screening Items (TIMPSI)</td>
<td>The TIMPSI is a shorter, screening version of the TIMP which is psychometrically valid, well-constructed scale used assess motor performance in infants born preterm through 4 months of age.</td>
<td>Available for purchase</td>
<td>Available for purchase</td>
<td><a href="https://www.thetimp.com/about-our-tests">https://www.thetimp.com/about-our-tests</a></td>
<td><a href="https://www.thetimp.com/products-for-therapists">https://www.thetimp.com/products-for-therapists</a></td>
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<tr>
<td>Test Description</td>
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<tr>
<td>Thirty Second Sit to Stand (30STS)</td>
<td>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.</td>
<td><a href="https://www.cdc.gov/steady/pdf/STEADI-Assessment-30Sec-508.pdf">https://www.cdc.gov/steady/pdf/STEADI-Assessment-30Sec-508.pdf</a></td>
<td><a href="https://www.cdc.gov/steady/pdf/STEADI-Assessment-30Sec-508.pdf">https://www.cdc.gov/steady/pdf/STEADI-Assessment-30Sec-508.pdf</a></td>
<td><a href="https://journals.lww.com/pedpt/Fulltext/2013/25020/Reliability_and_Viability_of_the_T1MPSI_for_Infants.4.aspx">https://journals.lww.com/pedpt/Fulltext/2013/25020/Reliability_and_Viability_of_the_T1MPSI_for_Infants.4.aspx</a></td>
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<tr>
<td>Time to Climb 4 Stairs (TTC)</td>
<td>The time to climb 4 stairs assesses the time spent in the performance of a functional activity.</td>
<td>NA</td>
<td>NA</td>
<td><a href="https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0201004">https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0201004</a></td>
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<tr>
<td>Organizations</td>
<td>Title</td>
<td>Resource Description</td>
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<td>American Academy of Neurology (AAN)</td>
<td>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.</td>
<td><a href="https://www.aan.com/conferences-community/annual-meeting/">https://www.aan.com/conferences-community/annual-meeting/</a></td>
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<td>American Association of Neuromuscular &amp; Electrodiagnostic Medicine (AANEM)</td>
<td>The AANEM is a nonprofit membership association dedicated to the advancement of neuromuscular (NM), musculoskeletal, and electrodiagnostic (EDX) medicine.</td>
<td><a href="http://www.aanem.org/meetings/Annual-Meeting">http://www.aanem.org/meetings/Annual-Meeting</a></td>
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<td></td>
<td>American Physical Therapy Association (APTA)</td>
<td>A collaborative effort between APTA and our 18 specialty sections (Combined Sections Meeting).</td>
<td><a href="https://www.apta.org/Conferences/">https://www.apta.org/Conferences/</a></td>
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<td></td>
<td>Child Neurology Society (CNS)</td>
<td>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.</td>
<td><a href="https://www.childneurologysociety.org/">https://www.childneurologysociety.org/</a></td>
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<td></td>
<td>Cure SMA</td>
<td>The annual conference brings together researchers, healthcare professionals, and families to network, learn, and collaborate.</td>
<td><a href="https://www.curesma.org/sma-researcher-meeting/">https://www.curesma.org/sma-researcher-meeting/</a></td>
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<td></td>
<td>Muscular Dystrophy Association (MDA)</td>
<td>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.</td>
<td><a href="https://www.mda.org/conferences">https://www.mda.org/conferences</a></td>
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<td>Muscle Study Group (MSG)</td>
<td>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</td>
<td><a href="https://musclestudygroup.org/">https://musclestudygroup.org/</a></td>
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controlled clinical trials and of other research for muscle and other neuromuscular diseases.

| **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. | [http://www.treat-nmd.eu/about/events/](http://www.treat-nmd.eu/about/events/) |
| **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/](https://www.worldmusclesociety.org/) |

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<p>| <strong>Continuing Medical Education Opportunities</strong> |  |
| The 2017 Update of the Standard of Care Recommendations for Spinal Muscular Atrophy | On Demand Webcast | <a href="https://courses.elseviercme.com/sma17/760">https://courses.elseviercme.com/sma17/760</a> |
| Evolving SMA Treatment Landscape | Interactive eLearning | <a href="https://courses.elseviercme.com/elearn/778a#group-tabs-node-course-default1">https://courses.elseviercme.com/elearn/778a#group-tabs-node-course-default1</a> |</p>
<table>
<thead>
<tr>
<th>How Gene Replacement Therapy is Changing the Way We Manage Spinal Muscular Atrophy and Other Neurologic Diseases</th>
<th>Office of Continuing Medical Education elsivercme.com</th>
<th><a href="https://courses.elseviercme.com/sma/756">https://courses.elseviercme.com/sma/756</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Muscular Atrophy: Evaluation and Management for the Rehabilitation Specialist</td>
<td>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.</td>
<td><a href="https://cumc.co1.qualtrics.com/jfe/form/SV_cVjVY0DNwBo9mhD">https://cumc.co1.qualtrics.com/jfe/form/SV_cVjVY0DNwBo9mhD</a></td>
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<tr>
<td>Tablecloth for circles</td>
<td>Please contact Chris Yun at <a href="mailto:chrisyun07@live.com">chrisyun07@live.com</a> to source pre-printed tablecloths</td>
<td></td>
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<tr>
<td>Standard pencil</td>
<td><a href="https://www.staplesadvantage.com/webapp/wcs/stores/servlet/StplShowItem?cust_sku=476919&amp;catalogId=4&amp;item_id=51852728&amp;langId=-1&amp;currentSKU=476919&amp;storeId=10101&amp;itemType=1&amp;addWE1ToCart=true&amp;documentId=e886f43878250d3a5f259d0b939e54fd572e068d">https://www.staplesadvantage.com/webapp/wcs/stores/servlet/StplShowItem?cust_sku=476919&amp;catalogId=4&amp;item_id=51852728&amp;langId=-1&amp;currentSKU=476919&amp;storeId=10101&amp;itemType=1&amp;addWE1ToCart=true&amp;documentId=e886f43878250d3a5f259d0b939e54fd572e068d</a></td>
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<td>Tokens</td>
<td><a href="https://www.amazon.com/gp/product/B01EKMI000/ref=oh_aui_detailpage_o06_s00?ie=UTF8&amp;psc=1">https://www.amazon.com/gp/product/B01EKMI000/ref=oh_aui_detailpage_o06_s00?ie=UTF8&amp;psc=1</a></td>
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<tr>
<td>20CC standard European plastic vending cups</td>
<td>2 Plastic cups (vending cup) one placed inside the other. <a href="https://www.maddisonsuk.com/epages/4896.sf/en_GB/?ObjectPath=/Shops/4896/Products/%22CUHP/008%22">https://www.maddisonsuk.com/epages/4896.sf/en_GB/?ObjectPath=/Shops/4896/Products/%22CUHP/008%22</a></td>
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<tr>
<td>200g metal weight</td>
<td><a href="https://www.amazon.com/American-Weigh-Scales-200WGT-Calibration/dp/B002ULILIK/ref=psd_sim_328_3?encoding=UTF8&amp;pd_rd_i=B002ULILIK&amp;pd_rd_r=0d031875-fa59-11e8-91ac-c7886f307111&amp;pd_rd_w=KlmoO&amp;pd_rd_wg=blkQ6&amp;pf_rd_p=18bb0b78-4200-49b9-ac91-f141d61a1780&amp;pf_rd_r=0KT5TGK07FCPD7ZGM5JR&amp;pf_rd_r=0KT5TGK07FCPD7ZGM5R&amp;psc=1&amp;refRID=0KT5TGK07FCPD7ZGM5R">https://www.amazon.com/American-Weigh-Scales-200WGT-Calibration/dp/B002ULILIK/ref=psd_sim_328_3?encoding=UTF8&amp;pd_rd_i=B002ULILIK&amp;pd_rd_r=0d031875-fa59-11e8-91ac-c7886f307111&amp;pd_rd_w=KlmoO&amp;pd_rd_wg=blkQ6&amp;pf_rd_p=18bb0b78-4200-49b9-ac91-f141d61a1780&amp;pf_rd_r=0KT5TGK07FCPD7ZGM5JR&amp;pf_rd_r=0KT5TGK07FCPD7ZGM5R&amp;psc=1&amp;refRID=0KT5TGK07FCPD7ZGM5R</a></td>
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<td>500g metal weight</td>
<td><a href="https://www.amazon.com/gp/product/B00SSK3YN0/ref=od_aui_detailpages00?ie=UTF8&amp;psc=1">https://www.amazon.com/gp/product/B00SSK3YN0/ref=od_aui_detailpages00?ie=UTF8&amp;psc=1</a></td>
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<tr>
<td>1 kg metal weight</td>
<td><a href="https://www.amazon.com/B002UL9ZEO?keywords=1%20kg%20calibration%20weight&amp;qid=1443710919&amp;ref=sr_1_1&amp;sr=8-1">https://www.amazon.com/B002UL9ZEO?keywords=1%20kg%20calibration%20weight&amp;qid=1443710919&amp;ref=sr_1_1&amp;sr=8-1</a></td>
<td></td>
</tr>
<tr>
<td>Take and Toss bowls (8 oz)</td>
<td><a href="https://www.amazon.com/gp/product/B00GXGQR7Y/ref=oh_aui_detailpage_o00_s00?ie=UTF8&amp;psc=1">https://www.amazon.com/gp/product/B00GXGQR7Y/ref=oh_aui_detailpage_o00_s00?ie=UTF8&amp;psc=1</a></td>
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F7 “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:

A sponsor reaches out to your site for participating in a new clinical trial in SMA.

1. Your coordinator and PI ask you to complete regulatory trainings for the IRB
   - Section 2: Steps to Take Before Participating in a Trial
     - Clinical Evaluator Training and Development - For more information about fundamental trainings that CEs should complete as part of their professional training, please see Table F1: Recommended Regulatory Training for Clinical Evaluators for an overview of recommended trainings.
   - Table F1: Recommended Regulatory Training for Clinical Evaluators
     - GCP certification through CITI Program
     - HIPPA training through CITI Program
     - If working with a pediatric population, please review, CFR 46 Subpart D—Additional Protections for Children Involved as Subjects in Research

2. You have a SMA patient who may be eligible for the study
   - Section 2: Steps to Take Before Participating in a Trial
     - 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 F2: SMA Seminal Paper Reference List for a comprehensive reference list on SMA Seminal Papers)
   - Table F2: SMA Seminal Paper Reference List
     - Standard of Care articles to read
     - Patient may have an orthopedic issue that could impact participation
       - Articles on Orthopedic Issues (i.e. Contractures, Scoliosis, Hip dislocation)
   - Section 3A: Evaluation in the Clinical Setting
     - 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 1.

3. The protocol says the SMA type 2 sitter cohort will use the MFM and the RULM during the course of the study
   - Section 3B: Evaluation of Study Participants in Research Setting
     - Available Motor Function Outcome Measures by Phenotype - Some of the most common outcome measures for SMA are listed in order of prioritization in Table 2: Commonly Used Outcomes by SMA Functional Level/ Phenotype
       - MFM – Information about test and use in SMA
         - Link provided to access to manual, proforma and relevant articles in Table F4
       - RULM – Information about test and use in SMA
4. Your coordinator approaches you with how much time you require as they are creating the budget
   o Use Table of Contents to access each outcome measure in the study to get estimated time of assessments

5. You have CME requirements and are interested in applying it to SMA education and training
   o Table F5: Professional Development: Meetings for Continuing Education – see online e-learning modules and an upcoming conferences

Intermediate CE Example:

Newborn screening for SMA gets approved in your state.

1. You get a referral to your clinical from SMA newborn screening
   o Section 3B: Evaluation of Study Participants in Research Setting
     ▪ Available Motor Function Outcome Measures by Phenotype – Some of the most common outcome measures for SMA are listed in order of prioritization in Table 2: Commonly Used Outcomes by SMA Functional Level/ Phenotype
     ▪ Can assess which pre-symptomatic measures are appropriate based on age
       • 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.
         o Link provided to access to manual, proforma and relevant articles in Table F4
       • WHO – Biogen reported in an interim analysis that WHO motor milestones were on target for infants enrolled in the NURTURE presymptomatic study of Nusinersen.
         o Link provided to access to manual, proforma and relevant articles in Table F4
       • 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.
         o Link provided to access to order test kit in Table F4

2. A patient asks you about a clinical trial they saw in a newsletter
   o Table F3: External Resources for SMA Education and Training
     ▪ 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
     ▪ Pharmaceutical Related Resources – SMA Therapeutics: A Comparative Overview of Drugs Approved and in Development, a presentation outlining targets for therapeutic intervention in SMA

3. Your coordinator asks when is the best time to schedule the research patient for testing
   o Section 4: Considerations Related to Assessments and Patient Evaluation: Standards of Care, Supportive Care, and Multidisciplinary Care
     ▪ Best Practices and Testing Considerations for Best Performance – to refer to for optimal testing and communication to patient
Advanced CE Example:

A sponsor contacts your center for participation in a new clinical trial in SMA.

1. You receive the protocol and see new fatigability testing you are unfamiliar with for their cohort of non-ambulatory SMA.
   - **Section 3B: Evaluation of Study Participants in Research Setting**
     - Available Motor Function Outcome Measures by Phenotype – Some of the most common outcome measures for SMA are listed in order of prioritization in **Table 2: Commonly Used Outcomes by SMA Functional Level/ Phenotype**
       - **ESNHPT** – read description of the test, read the evidence in SMA
         - Link provided to order test kit to practice in clinic, and related articles in SMA in **Table F4**
       - **PRO for fatigue** – read description of test, read the evidence in SMA
         - **FSS** – read description of test, get access to resources and related articles in SMA, **Table F4**

2. You are interested in networking and attending an upcoming conference that highlights SMA and neuromuscular diseases to learn about the late-breaking research
   - **Table F5: Professional Development: Meetings for Continuing Education**
     - Organizations – **World Muscle Society** – sounds interesting and click to learn when is the next conference