



CURE SMA

CLINICAL TRIAL READINESS TOOLKIT

THE BASICS OF SPINAL MUSCULAR ATROPHY
AND THE EFFECTIVE CONDUCT OF CLINICAL TRIALS IN SMA



Make today a
breakthrough.

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Authorship & Acknowledgements

The Cure SMA Industry Collaboration (SMA-IC) was established in 2016 to leverage the experience, expertise, and resources of pharmaceutical and biotechnology companies, as well as other nonprofit organizations involved in the development of spinal muscular atrophy (SMA) therapeutics to more effectively address a range of scientific, clinical, and regulatory challenges. It is currently comprised of our partners at Novartis Gene Therapies, Biogen, Genentech/Roche Pharmaceuticals, Scholar Rock, and SMA Europe. Funding for this project was provided by members of the 2018 - 2021 SMA-IC which included Biogen, Genentech/Roche Pharmaceuticals, Novartis Gene Therapies, Novartis Pharmaceuticals, Astellas Pharmaceuticals, Cytokinetics Inc., and Scholar Rock, Inc.

This document was prepared by Rosángel Cruz, MA; Mary Curry, ND, Ilse Peterson, MPH, Fatou Sarr, and Allison Mazzella. We wish to thank the Cure SMA Industry Collaboration for the funding that supported preparation of this document, and the numerous researchers and clinical trial coordinators who contributed input to help ensure that this document would be useful to clinical trial sites interested in conducting clinical trials in SMA.



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List of Abbreviations

ADR: Adverse drug reaction

AE: Adverse event

ASO: Antisense Oligonucleotides

CE: Clinical evaluators

CHOP-INTEND: Children's Hospital of Philadelphia infant test of neuromuscular disorders

CIOMS: Council for International Organizations of Medical Sciences

CMAP: Compound muscle action potential

CNS: Central nervous system

CRC: Clinical research coordinator

CRF: Case report form

CVS: Chronic villus sampling

DNA: Deoxyribose nucleic acid

DTR: Deep tendon reflexes

EMG: Electromyography

FDA: Food and Drug Administration

G: Gastrostomy

GCP: Good clinical practice

GERD: Gastroesophageal reflux disorder

HFMSE: Hammersmith functional motor scale-expanded

HHS: United States Department of Health and Human Services

HINE: Hammersmith infant neurological examination

IC: Industry collaboration

ICF: Informed consent form

IEC: Independent ethics committee

IRB: Institutional review board

IRDiRC: International Rare Disease Research Consortium

IT: Intrathecal

IV: Intravenous

M: Mean

MAGEC: MAGnetic expansion control

MFM: Motor function measure

MRCT: Multi-regional clinical trials

MUNE: Motor Unit Number Estimation

NG: Nasogastric

NIH: National Institute of Health

NJ: Nasojejunal

NV: Noninvasive ventilation

OT: Occupational Therapy

PCP: Primary care physician

PI: Principal investigators

PNCR: Pediatric Neuromuscular Clinical Research Network

PT: Physical therapist

RUSP: Recommended uniform screening panel

SAE: Serious adverse events

SMA: Spinal muscular atrophy

SMN: Survival motor Neuron

SC: Study coordinator

SOC: Standard of care

SOP: Standard operating procedure

TIMPSI/TIMP: Test for infant motor performance

US: United States

VEPTR: Vertical Expandable Prosthetic Titanium Rib

WHO: World Health Organization

WMA: World Medical Association



Introduction

Within the last decade, the treatment landscape for spinal muscular atrophy (SMA) has changed dramatically. With multiple FDA-approved therapies and more experimental treatments in clinical trials, patients have access to evidence-based treatments for a devastating disease that – until late 2016 – was managed solely via supportive and palliative care measures.

To better meet the needs of trial sponsors and the SMA patient community in the context of this evolving landscape, Cure SMA has launched a Clinical Trial Readiness Program with resources to support clinical trial site readiness throughout the United States (www.curesma.org/clinical-trial-readiness), including this toolkit.¹ These activities have been undertaken with the understanding that while clinical trials in general are extensive undertakings requiring significant preparation, time, and expense, clinical trials in SMA present unique challenges. In SMA trials, it is important to consider:

- the evolving natural history of SMA as the standard of care evolves and additional therapies become available;
- the multiple outcome measures that can be used to evaluate clinically meaningful changes, depending on SMA type; and
- the day-to-day burden that SMA places on patients and families, which can make their participation in clinical trials especially challenging.

This toolkit is part of Cure SMA's broader efforts to optimize site readiness for SMA clinical trials. It was developed to address major aspects of preparing for and conducting clinical trials, as well as specific issues that may be likely to arise within clinical trials in SMA, and has three major sections:



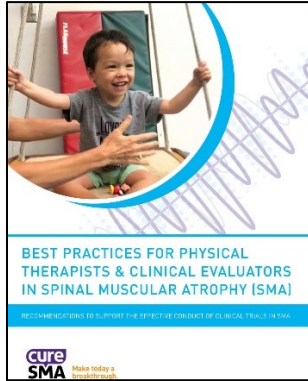

1. **"About Spinal Muscular Atrophy,"** which provides information on SMA as a disease, its diagnosis, classification, and disease management.
2. **"Conducting Clinical Trials in SMA,"** which delves into trial preparation and conduct, with discussion of SMA-specific considerations.
3. **"Appendices,"** with key terms and additional resources, including useful study templates to assist with protocol adherence that have been prepared by other organizations and individuals.

Sites are encouraged to view this toolkit as a guide, and one of many resources that can be helpful – noting that guidance from clinical trial sponsors, institutional review boards (IRBs), and regulatory authorities should always take precedence when planning for, conducting, and closing trials.

Updated September 2021

¹ For more details on the Cure SMA Clinical Trial Readiness Program refer to the Peterson et al. (2020) publication entitled: "The SMA Clinical Trial Readiness Program: creation and evaluation of a program to enhance SMA trial readiness in the United States" published in the Orphanet Journal of Rare Diseases (doi: 10.1186/s13023-020-01387-8).

Additional Resources in This Series

Toolkits on SMA, Clinical Evaluation, and Clinical Research Coordination		
Toolkits can be downloaded at: www.curesma.org/clinical-trial-readiness .		
 <p>CURE SMA CLINICAL TRIAL READINESS TOOLKIT THE BASICS OF SPINAL MUSCULAR ATROPHY AND THE EFFECTIVE CONDUCT OF CLINICAL TRIALS IN SMA</p>	 <p>BEST PRACTICES FOR CLINICAL RESEARCH COORDINATORS IN SPINAL MUSCULAR ATROPHY (SMA) RECOMMENDATIONS TO SUPPORT THE EFFECTIVE CONDUCT OF CLINICAL TRIALS IN SMA</p>	 <p>BEST PRACTICES FOR PHYSICAL THERAPISTS & CLINICAL EVALUATORS IN SPINAL MUSCULAR ATROPHY (SMA) RECOMMENDATIONS TO SUPPORT THE EFFECTIVE CONDUCT OF CLINICAL TRIALS IN SMA</p>
Basics of SMA and the Effective Clinical Trial Conduct	Best Practices for Clinical Research Coordinators in SMA	Best Practices for Clinical Research Coordinators in SMA
Webinars And Workshops:		
Webinars and workshops relevant to the SMA clinical research community are available on the Cure SMA Clinical Trial Readiness Program YouTube playlist .		
Evaluations And Checklists:		
For educational readiness evaluation checklists that help sites and physical therapists assess their readiness for clinical trials, email clinicaltrialreadiness@curesma.org .		
Information on External Training Resources:		
	Cure SMA has compiled reference guides for external resources on SMA, genetic diseases, and clinical research topics, which are also available on the Clinical Trial Readiness Program hub at www.curesma.org/clinical-trial-readiness .	



Part 1

About Spinal Muscular Atrophy

PART 1: ABOUT SPINAL MUSCULAR ATROPHY

What is Spinal Muscular Atrophy?

SMA (spinal muscular atrophy) is a rare, genetic, neuromuscular disease affecting motor neurons. While rare, SMA is one of the most common autosomal recessive inherited disorders and – prior to approval of treatments in 2016 – was the number one genetic cause of death for infants. SMA is characterized by progressive loss of alpha motor neurons leading to muscle weakness of the limb and trunk, followed by muscle atrophy (wasting) that can result in paralysis and premature death (Lefebvre et al., 1995, Wirth, 2000, Arnold et al., 2012, Kolb & Kissel, 2011, Kolb & Kissel, 2015; Kolb et al., 2016, Kolb et al., 2017). Genetically, SMA is caused by deletions or mutations in the Survival Motor Neuron 1 (*SMN1*) gene. SMA is a devastating disease that can take away a person’s ability to walk, eat, or breathe – but the prognosis is changing with the availability of disease-modifying therapies (Finkel et al., 2017, De Vivo et al., 2017, Glascock et al., 2020). Terms commonly used to describe SMA include “genetic disease”, “autosomal recessive genetic disorder”, “motor-neuron disease” or “neuromuscular disease.”



Video 1: Spinal muscular atrophy - causes, symptoms, diagnosis, treatment, pathology by Osmosis (Osmosis, 2017).

Etiology and Epidemiology

SMN1, the gene associated with SMA, is found on chromosome 5q13 (Lefebvre et al., 1995, Zerres, 1995, Zerres et al., 1997, Wirth et al., 1999). In a healthy person, this gene produces the survival motor neuron (SMN) protein. SMN is critical to the function of motor neurons that control and sustain our muscles. Without the SMN protein, motor neurons cannot properly function and eventually die, leading to debilitating and potentially fatal muscle weakness. SMA occurs in approximately one in 10,000 to 11,000 live births and roughly one in every 40-50 Americans is a genetic carrier (Prior, 2008, Sugarman et al., 2012, Verhaart et al., 2017). Because SMA is an autosomal recessive condition, both parents must be carriers for a child to inherit the condition. If both parents are carriers, then each of their children has a one in four chance of having the disease. SMA can affect any race or gender.

Historically, SMA has been classified into four clinical subtypes based on age of onset and highest physical milestone achieved (Zerres, 1995, Wirth et al., 1999, Wirth et al., 2006, Russman, 2007, Arnold et al., 2012, Wang et al. 2007, Wadman, et al., 2017). Individuals with SMA may have difficulty performing the basic functions of life, like breathing and swallowing. However, SMA does not affect a person’s ability to think, learn, and build relationships with others. For a more detailed description of SMA types, see [Classification of Spinal Muscular Atrophy](#) and [Clinical Presentation](#). For a document describing the burden of SMA by type, as described by patients and caregivers, you may refer to the [Spinal Muscular Atrophy Voice of the Patient Report](#) (Cruz et al., 2018). For an overview of SMA, including cause, symptoms, diagnosis, and treatment, you may also see the video in the callout box



above. When considering SMA subtype classification, it should be noted that the relevance of these subtype classifications is diminishing as drug treatments are increasingly modifying disease trajectories.



Genetics

The region containing the gene responsible for SMA was localized to the long arm of chromosome 5 in 1992. Subsequent worldwide efforts resulted in the identification of mutations in the survival motor neuron 1 (*SMN1*) gene as the cause for SMA in 1995. (Lefebvre et al., 1995; Wirth, 2000). In humans, a nearly identical copy of this gene, *SMN2*, is also present. The *SMN2* gene also makes SMN protein, but at greatly reduced efficiency leading to lower than normal levels of the protein.

The major difference between *SMN1* and *SMN2* is a single nucleotide (C for *SMN1* and T for *SMN2*) in exon 7 (Figure 1a). This missense mutation in *SMN2* disrupts a splicing control region while maintaining the protein coding. Thus, while *SMN1* mRNA transcript includes exon 7, the *SMN2* mRNA transcript generally excludes exon 7 which results in a nonfunctional protein. However, the splicing defect in *SMN2* is not perfect and allows a small percentage of *SMN2* transcripts to have normal splicing of exon 7, with normal SMN protein production. The amount of SMN protein produced from the *SMN2* gene is a critical modifier of disease severity and more copies of *SMN2* are correlated with later disease onset and decreased severity.

As SMA is an autosomal recessive disorder, individuals with SMA typically have inherited a faulty (mutant) *SMN1* gene from each of their parents. The majority of mutations responsible for 5q-SMA are deletions or gene conversions (Figure 1). A deletion involves partial or complete removal of the *SMN1* gene (Figure 1a). In a conversion, the *SMN1* gene is “converted” into an *SMN2*-like gene when the nucleotide cytosine (“C”) in exon 7 is changed into thymine (“T”) (Figure 1b). With both deletions and conversions, *SMN1* exon 7 is missing (homozygous absence of *SMN1* exon 7). As a result, affected persons make insufficient amounts of full-length (exon 7 containing) SMN protein. The remaining mutations that cause SMA are point mutations that affect only a few nucleotides of the *SMN1* gene. These point mutations result in the production of non-functional or unstable SMN protein (Figure 1c). Because deletions and gene conversion mutations are frequent and point mutations are rare, about 95% of SMA patients are homozygous for deletion and gene conversion mutations. About 5% of SMA-affected individuals are compound heterozygotes: they have a deletion or conversion on one copy of chromosome 5 and a point mutation on the other copy.

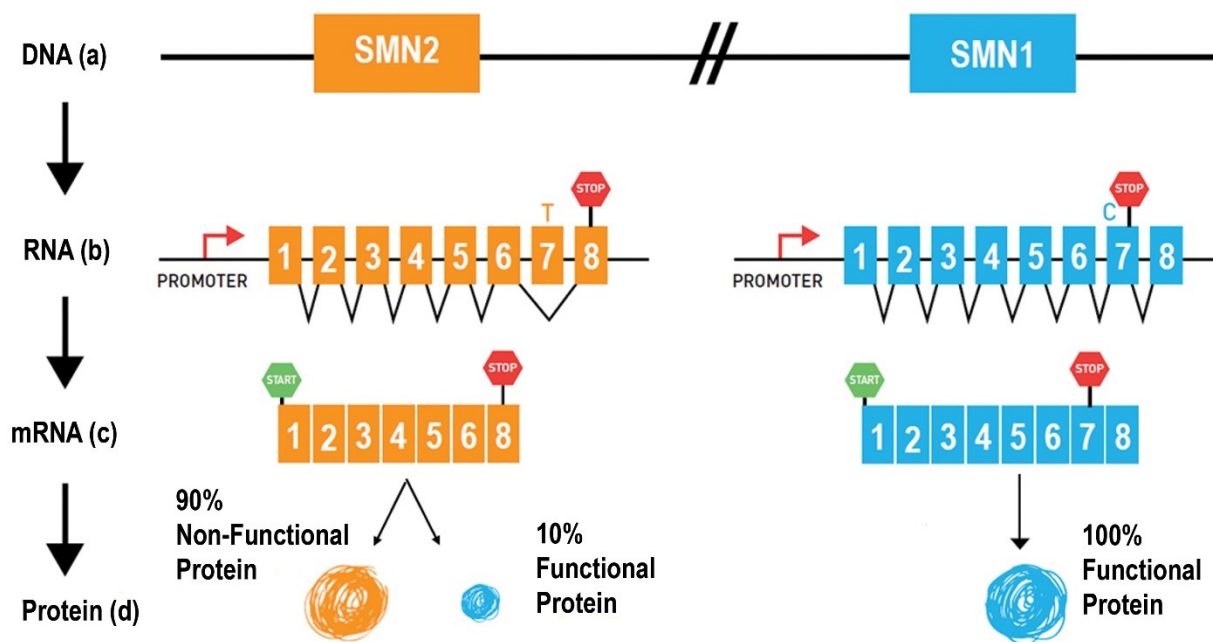


Figure 1a-c: Schematic of a portion of chromosome 5 that contains the two *SMN* genes.

The major difference between the two *SMN* gene copies is the C (*SMN1*) to T (*SMN2*) nucleotide change in exon 7, in which occurs during ore-mRNA splicing. Because of this difference, *SMN2* mostly makes an mRNA message that excludes exon 7 and produces a smaller, unstable *SMN* protein. *SMN1* makes mRNA message that includes exon 7 and makes functioning full-length *SMN* protein. This process is explained below. (a) The *SMN1* and *SMN2* gene organization on chromosome 5. (b) the *SMN* genes are turned on by their respective promoters (areas of DNA that turn genes on) in a process called transcription. Transcription results in a preliminary RNA that contains an intermediate blueprint for protein production. RNA splicing removes segments of RNA called introns from the preliminary message, which are not part of the protein blueprint. The remaining blueprint regions are called exons. Notice exon 7 is missing from the *SMN2* mRNA, due to defective RNA splicing. (d) The final mRNA message that results from the splicing process is used as the template for protein productions in a process called translation (retrieved from https://www.curesma.org/wp-content/uploads/2020/09/09172020_Genetics-of-SMA_vWeb.pdf).

The unique genetics of SMA provided an important clue for development of therapies targeting increased normal splicing of *SMN2* (Lorson et al., 2010, Arnold et al., 2012, Kolb and Kissel, 2011, Finkel et al., 2014, Finkel et al. 2017). Many drug development efforts focused on increasing SMN protein production by correcting the splicing error in the *SMN2* gene (Hua et al., 2007; see also [SMA Drug Pipeline](#)). These efforts culminated in the approval of the first *SMN2* modulator for SMA, nusinersen, in 2016 and a second *SMN2* modulator, risdiplam, in 2020.

SMA Carriers

Most people have two functioning copies of the *SMN1* gene. People with one faulty copy and one functioning copy are called “carriers” of SMA. SMA carriers do not have symptoms of SMA, but can

pass the faulty gene on to their children. Approximately one in 50 people is a genetic carrier for SMA. Most don't know they are carriers until they have a child or relative born with SMA (Ogino et al., 2002; Prior, 2008, Sugarman et al., 2012). When both parents are carriers ([Figure 2](#)), there is:

- A 25% chance that their child will be unaffected
- A 50% chance that their child will be a carrier
- A 25% chance that their child will have SMA

If only one parent is a carrier, the child is usually not at risk for SMA. Rarely, however, new mutations in the *SMN1* gene occur during egg or sperm production. In other rare instances, two copies of *SMN1* may be found on a single chromosome. A person with 2 copies of *SMN1* on a single chromosome is known as a silent carrier and will not be detected in traditional carrier screening, but may pass along the chromosome without the *SMN1* gene to children. In addition, a small percentage of carriers have a mutation that cannot be identified through current testing. In this case, the disease will appear to have been caused by a single carrier.

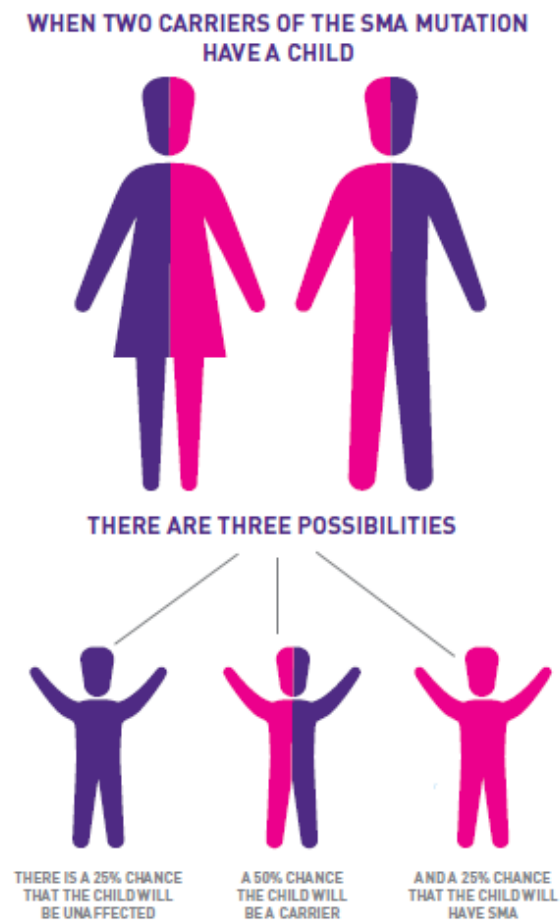




Figure 2: Schematic of the transmission of the defective *SMN1* gene.

SMA is an autosomal recessive genetic disorder, which means an affected individual must have two defective copies of the disease-causing gene. The figure shows SMA recessive inheritance between 2 people who are carriers of SMA. Each parent has one functioning *SMN1* gene and are without symptoms. For each pregnancy there is a 25% chance of having a child with SMA and two defective copies of the *SMN1* gene, a 50% chance of having a child who is a carrier of SMA and not have a disease, and a 25% chance of having a child who has two normal *SMN1* genes and does not have SMA. Having a child with SMA can also occur between a carrier of SMA and a person with SMA, or between 2 people with SMA (retrieved from https://www.curesma.org/wp-content/uploads/2020/09/09172020_Genetics-of-SMA_vWeb.pdf).



Diagnosis & Classification of SMA

A healthcare provider may suspect SMA when a child is noticeably weak, hypotonic (floppy), or delayed in meeting developmental milestones such as achievement of head control, rolling over, sitting independently, standing or walking. Given that SMA is rare and its hallmark symptoms overlap with other neuromuscular diseases (i.e., metabolic myopathies such as Pompe, congenital myopathies, congenital myasthenic syndromes, among others), SMA is often misdiagnosed or missed and many parents undergo an arduous and prolonged diagnostic journey (Lin, Kalb, & Yeh, 2015, Qian et al., 2015; McGraw, 2017).

Diagnosing SMA

SMA is suspected when an infant or toddler displays one or more of the following:

- Progressive, symmetrical muscle weakness and is more severe proximally (in the upper arms & legs) than distally (hands and feet). Symptoms are preceded by an asymptomatic period (except in the most severe of the types, SMA type 0) (see [Classification of SMA](#))
- Flattening of the chest wall and expanding the abdomen when breathing, rapid diaphragmic or belly breathing (paradoxical breathing), difficulty breathing
- Hypotonia, floppy baby, low muscle tone associated with absent deep tendon reflexes (DTRs)
- Weak cry and cough
- Limited movement of limbs and trunk; limited antigravity movements (particularly lower limbs)
- Swallowing and/or feeding difficulty
- Delayed or missed milestones (inability to sit, stand, or walk)
- Regression or loss of milestones (i.e., loss of head control, sitting, crawling, walking, etc.)
- Alert, socially engaging, and normal cognition

For more comprehensive information on clinical symptoms see Wirth, 2002, Wang, 2007, Arnold, 2015, and Kolb and Kissel, 2015.

Genetic testing is used to confirm a diagnosis of SMA. A blood test is used to detect homozygous deletion of the *SMN1* gene. Approximately 95% of SMA patients possess homozygous deletion of *SMN1* that is easily detected by the diagnostic test identifying *SMN1* copy number. About 5% of patients with 5q-SMA have rare point mutations that are not detected by the common *SMN1* deletion tests (Lebeuvre et al, 1995; Wirth et al, 1999) and will have *SMN1* gene testing results with one *SMN1* gene with exon 7 missing (a deletion) and a second *SMN1* gene present suggesting they are an SMA carrier. However, anyone with symptoms of SMA and one copy of *SMN1* should have further genetic testing with *SMN1* gene sequencing to determine whether they have a point mutation (Lebeuvre et al, 1995; Wirth et al, 1999). One must identify *SMN1* mutations in both genes to confirm the diagnosis of



5q-SMA. Therefore, it is said that the sensitivity of the common *SMN1* deletion tests is about 95% (Lebeuvre et al, 1995).

Historically, genetic testing focused on the *SMN1* gene, and most patients did not have *SMN2* copy number testing. However, with the FDA approved treatments and with newborn screening programs identifying patients in a pre-symptomatic phase of disease, *SMN2* testing for prognosis and treatment planning has become standard of care. Most commercial testing for SMA now includes both *SMN1* and *SMN2* copy numbers.

There are two types of tests for SMA:

1. **Diagnostic Tests:** Confirms if an individual has SMA.
2. **Carrier Test:** Confirms whether you are a carrier of SMA, with the possibility of passing on a *SMN1* gene mutation to an offspring. This test is offered to individuals with a family history of SMA or to a partner of a known SMA carrier.

Prenatal Testing

Prenatal testing can be used to determine if a fetus has inherited a genetic disorder such as SMA. Two different procedures can be used to obtain DNA for the test:

- Amniocentesis: In amniocentesis, the most common form of prenatal testing, a very fine needle is inserted into the woman's abdomen and uterus and amniotic fluid is extracted (Shulman & Elias, 1993). This fluid contains fetal DNA that can be tested for SMA (Shulman & Elias, 1993). Amniocentesis can be performed after the 14th week of pregnancy and is associated with a risk of miscarriage that may be as high as 1 in 200 (Verp, 1992; Shemmer & Johnson, 1993; Shulman & Elias, 1993).
- Chorionic Villus Sampling (CVS): This procedure can often be performed as early as the 10th week of pregnancy (Shulman & Elias, 1993). Chorionic villi are small, fingerlike structures that form the placenta. Chorionic villi contain fetal DNA that can be extracted and tested for SMA (Milunsky and Cheney, 1999). CVS is associated with a risk of miscarriage that may be as high as 1 in 100 (Verp, 1992).

Newborn Screening

In July 2018, the federal government added SMA to the Recommended Uniform Screening Panel (RUSP) — the list of recommended conditions that states should screen for within their statewide universal newborn screening programs. Cure SMA and its advocates have made tremendous progress. By the end of 2021, Cure SMA estimates that 80% of states will have implemented SMA newborn screening representing 9 in every 10 babies born in the U.S being screened for SMA. In most cases, newborn screening programs test only for deletions in the *SMN1* gene, so patients with point mutations (~5%) will be missed by newborn screening. Newborn screening is usually obtained during the first 2



days of life and results are available within 1 week of birth. Each state has different referral practices for reporting newborn screening results, but most focus on urgent referral for positive SMA newborn screening to neuromuscular centers where confirmatory testing for SMA is completed and treatments can be initiated quickly.

The SMA Diagnostic Journey: The Patient & Parent Perspectives

Although newborn screening is helping to reduce diagnostic delay, it is still common in SMA. This may be attributable to the relatively low incidence of the disease and the historical lack of treatments for the underlying cause of SMA. Cure SMA has committed to further understanding the diagnostic experience of affected individuals and their families with SMA (Qian et al., 2015, Cure SMA, 2015). Since 2014, Cure SMA has partnered with the community and scientists to shed light on the experiences of individuals with SMA and their families. In March 2016, Cure SMA launched a survey for newly diagnosed families to capture information on the diagnostic journey including age of symptom presentation, timing of symptom onset, time to diagnosis, SMA type, and diagnosing physician. (Belter et al., 2018). See a summary report below, from 2016.

- Average (mean) age of diagnosis (M)
 - Type I: 4.4 (3.9) months
 - Type II: 16.0 (12.1) months
 - Type III: 103.2 (138.4) months
- Questions
 - Physician information
 - Diagnosis information
 - Motor function, nourishment, breathing
 - Diagnostic journey
- 214 responses
 - Type I: 44.4%
 - Type II: 33.2%
 - Type III: 13.6%
 - Other/unknown: 9.9%
- Type of clinician making the correct dx
 - Pediatric neurologist – 61.7%
 - Genetics specialist/counselor – 19.6%
 - Pediatrician or family practitioner- 3.7%
 - Adult neurologist – 2.8%
 - Therapist – 0.5%
 - Neuromuscular specialist – 0.5%
 - Other – 11.2%

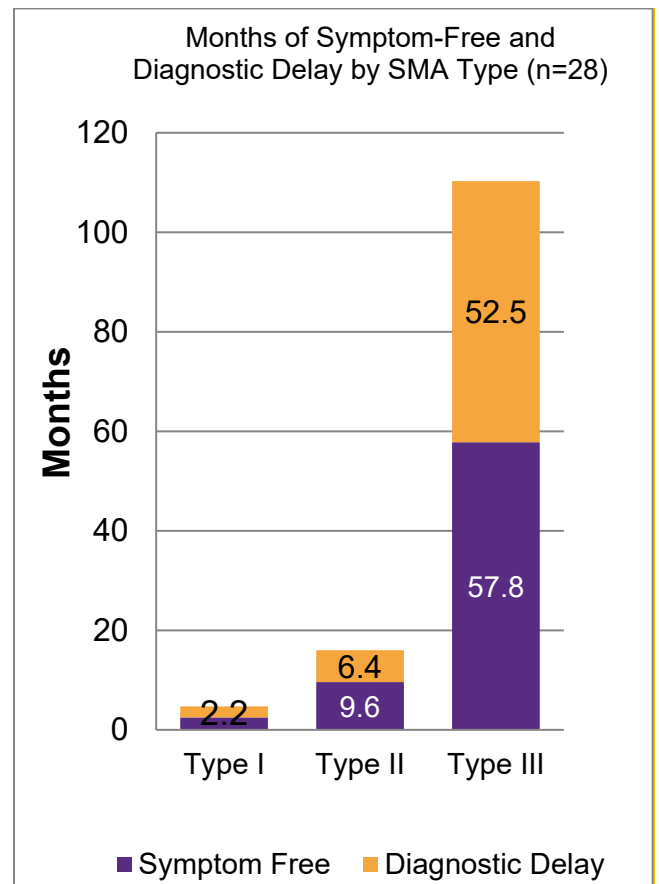


Figure 3: Results of Cure SMA Newly Diagnosed Survey (2016-2021)



Cure SMA also partnered with the research community to further explore issues around diagnostic delay (Qian et al., 2015). In 2015 Cure SMA worked with Dr. Yeh and others to pursue a qualitative study with individuals affected by SMA types I, II and III; parents of those affected; and clinicians. The research consisted of 16 focus group sessions and 37 interviews in the US with 96 participants including: 21 individuals with SMA, 64 parents and 11 clinicians. Families reported substantial diagnostic delays attributed to many factors including lack of awareness and knowledge about SMA; the difficulty of distinguishing normal from abnormal development; and the challenge of differential diagnosis.

The lack of awareness and knowledge among primary care physicians (PCPs) and some neurologists made it challenging for families to arrive at a diagnosis.

"We spent 3-4 years trying to find a diagnosis and we didn't have any luck, so we were jumping from doctor to doctor...the local doctors, they didn't have a clue of what could be wrong so we basically were struggling to find somebody to help us understand the problem" - Parent of type III child (Qian et al., 2015).

In addition, parents involved in these interviews consistently reported a "lack of sensitivity" from physicians communicating the diagnosis. This work also further explored families' attitudes toward newborn screening as well as the psychosocial impact of living with SMA, and:

- Confronting premature death
- Making difficult treatment choices
- Fearing the loss of functional ability
- Coming to terms with lost expectations
- Loss of sleep and stress
- Stigma
- Limitations on social activities
- Independence
- Uncertainty and helplessness
- Family finances

Study results reiterated that the effects of managing and coping with SMA are significant and multifaceted. Individuals with SMA and their families are affected in physical, psychosocial, emotional, financial and practical ways.

Efforts to Reduce Diagnostic Delays

As increasing numbers of therapeutic options become available to treat the underlying cause of SMA - it is imperative that clinicians, patient advocacy groups, professional organizations, and the community at large diligently work together to promote education and awareness to significantly reduce diagnostic delay in SMA (Glascock, 2018). As a leading genetic cause of death in infants, the diagnosis of SMA, especially type I, is a medical emergency. In infants with SMA type I, the onset of irreversible denervation occurs within the first 3 months of life with loss of 90% of motor units occurring within 6 months of age (Swoboda et al., 2005). This has been further supported by both, preclinical studies and clinical trials which have shown that early introduction of a therapy (at ≤ 12 weeks of disease duration); ideally, soon after symptoms' onset and most optimally, presymptomatically (Finkel et al., 2017, De



Vivo 2017; De Vivo et al., 2019), dramatically alters survival and other important outcomes such as respiratory and motor function.

In 2018, SMA was added to the list of conditions on the recommended uniform screening panel (RUSP), which includes conditions recommended for screening at birth. This was an important step toward shortening the diagnostic journey in SMA and improving outcomes and quality of life. As of June 2021, 38 states are screening for SMA with 85% of newborns in the US screened at birth (refer to the Cure SMA website: <https://www.curesma.org/newborn-screening-for-sma/>). For a review of the “Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening”, please see Glascock et al., 2020.

To promote reduction of diagnostic delays, Cure SMA launched [SMART Moves](https://smartmoves.curesma.org/), a disease awareness and educational campaign to empower parents, pediatricians, and other health care professionals to promptly recognize and diagnose the early signs of SMA. Central to [SMART Moves](https://smartmoves.curesma.org/) are resources dedicated to HCPs that detail current diagnostic criteria, educational resources, and treatment options and protocols. In addition, parents also have access to an easy-to-use website that encourages them to trust their instincts if they suspect a motor delay, because missed milestones may be a sign of a serious medical condition like SMA. On the site, parents can review the early signs of motor delays, watch instructional videos, and download a checklist including the hallmark signs of SMA to share with their doctor and help address their concerns. Learn more at <https://smartmoves.curesma.org/>.



Historical Classifications of Spinal Muscular Atrophy

No two people with SMA have identical experiences. Even among those with the same type or the same *SMN2* copy number, the progression of the disease can differ. The number of copies of the *SMN2* gene varies in the population. In general, the severity of SMA in people living with the disease inversely correlates with the number of *SMN2* gene copies, but there are exceptions (see [Table 1](#)).

More copies of *SMN2* = less severe phenotype

Every person living with SMA has at least one copy of the *SMN2* gene.



Although the availability of disease-modifying therapies is making the classification by type less relevant, SMA has historically been classified into four primary types: I, II, III, and IV. SMA Type has been based on age of onset and the highest physical milestones achieved. (Zerres et al., 1995, Wirth, 2002, Russman et al., 2007, Wadman et al., 2017, Darras & De Vivo, 2018). Information about each of these types and their natural history *without therapeutic intervention* is presented below.

Type	Age at Symptom Onset	Incidence	Prevalence	Maximum Motor Function Achieved	SMN2 Copy Number	Life Expectancy
1	<6 months	60%	15%	Never sits	1,2,3	<2 years
2	6 -18 months	25%	50%	Never walks	2,3,4	20-40 years
3	1.5 – 10 years	15%	35%	Walks, regression	3,4,5	Normal
4	>35 Years	<1%	<1%	Slow decline	4,5	Normal

Table 1: Classification of SMA based upon typical age of onset and maximal motor function achieved. Subtypes for types 1 to 4 are listed. The most common number of copies of the *SMN2* gene and typical life expectancy for each type of SMA is highlighted. Table adopted from EMA Briefing Document (SMA Europe; Treat-NMD, 2016)

SMA Type I (Infantile)

Type I—the most severe and the most common, comprising 60% of SMA cases—is usually diagnosed during an infant’s first six months. Babies with SMA type I, which is also known as Werdnig-Hoffmann disease, face many physical challenges, including severe muscle weakness and difficulty breathing, coughing, and swallowing. These children are never able to sit without support and typically need breathing assistance, a feeding tube and invasive supportive care, and without aggressive respiratory or nutrition supportive care or treatment, type I is often fatal early on in life. Depending on the time of symptom onset, and *SMN2* copy number, SMA type I has been further classified as type IA (symptom onset occurs within the first month, and typically have 1 *SMN2* copy, IB (typically have 2 *SMN2* copies and symptom onset before 3 months of age), or IC (usually has 2 or 3 copies and symptom onset after 3 months of age) (Thomas et. al., 1994; Finkel et al., 2014; EMA Briefing 2016).

SMA Type II (Intermediate)

Type II is usually diagnosed after six months of age, but before two years of age. The first sign is often a delay in meeting motor milestones, loss of already achieved milestones, or failing to meet milestones entirely. Individuals affected by SMA type II can sit up and stay seated without help, though as the disease progresses (without treatment or intervention), they may need assistance getting into a seated position. These children never stand or walk independently, but some patients are able to stand with the assistance of bracing or standing frame. Children with type II SMA will require a wheelchair for mobility. With disease progression, other signs may include hypoventilation during sleep, difficulty



swallowing, or eating difficulties due to muscle fatigue which may ensue when chewing meals. With treatment and improved standard of care, survival into adulthood is expected (Munsat et al., 1996, Zerres et al. 1997, Tangsrud et al., 2001).

SMA Type III (Juvenile)

Type III, also referred to as Kugelberg-Welander disease or juvenile SMA, is usually diagnosed after 18 months of age; on the weaker end of the spectrum, type IIIa patients are typically diagnosed before three years of age whereas type IIIb may present after the age of 3 years. However, SMA type III can be diagnosed as late as the teenage years. Individuals affected by SMA type III are initially able to walk but have increasingly limited mobility as they grow; eventually, many individuals with SMA type III need to use a wheelchair for ambulation (Munsat et al., 1996, Zerres et al., 1995, 1997; Darras and De Vivo, 2018).

SMA Type IV (Adult-Onset)

Patients with SMA type IV are comparatively mildly affected with an age of onset later than 30 years; they have a normal life expectancy. This is a very rare form of SMA (Russman et al., 2007).

SMA Type 0 (Prenatal Onset)

Type 0 is the most severe of all types of SMA. Symptoms begin prenatally with contractures at birth and severe neonatal respiratory and motor impairment. SMA type 0 may also be characterized by reduced or absent fetal movements, noticed by mothers in the late stages of pregnancy.

Non-5q-Forms of SMA

A number of additional inherited motor neuron diseases occur that are caused by mutations in genes other than the *SMN1* gene. These are referred to as non-5q- SMA diseases, meaning that the genes causing these other forms of SMA are not located in the *SMN* region of chromosome 5. Like 5q-SMA, people with non- 5q-SMA also have early muscle weakness but with several features that differ from 5q-SMA. These features can include distal rather than proximal weakness, early contractures, diaphragmatic paralysis with early respiratory failure, and cerebellar degeneration. A subset of non-5q-SMA diseases can be diagnosed with DNA diagnostic tests, but for some this is still not possible as the affected genes have not yet been identified. A list of *some* non-5q-SMA diseases is presented in Table 2. For a comprehensive list of non-5q-SMA disease, please refer to the GeneTable of Nueromuscular Disorders (click [here](#) to access).

Name	Alternative titles and symbols	Mode of inheritance
Spinal Bulbar Muscular Atrophy	SBMA, SMAX1, X-linked 1, Kennedy Disease	X-linked recessive
Arthrogryposis Multiplex Congenita	AMC, SMAX2, X-linked 2	X-linked recessive
Spinal Muscular Atrophy, distal, X-linked	SMAX3, DSMAX, X-linked 3	X-linked recessive
Motor neuronopathy, distal with vocal cord paralysis	DHMNVP, type VII, HMN VII, HMN7 Harper-Young myopathy	Autosomal Dominant
Arthrogryposis Multiplex Congenita, neurogenetic type	AMCN	Autosomal Recessive
SMA, Distal, Type V	DSMAV, HMNV, dHMNV	Autosomal Dominant
SMA with respiratory distress 1	SMARD1, type VI, HMV VI	Autosomal Recessive
SMA, congenital, scapuloperoneal amyotrophy	SPSMA	Autosomal Dominant
SMA, proximal, adult	Finkel type	Autosomal Dominant

Table 2: Examples of Non-5q-Forms of SMA



Clinical Presentation

The clinical presentation, age of onset, degree of symptoms and rate of progression varies greatly, with differences generally based on the number of copies of the *SMN2* gene. In SMA, muscle weakness can cause an array of complications ranging from respiratory to musculoskeletal to nutritional complications. (see [Disease Management section below](#)). A high-level overview of changes that may occur in patients according to traditional type classifications and absent drug intervention (Lefebvre et al., 1995, Wirth, 2002, Wang et al., 2007, D'Amico et al, 2011, Wadman et al., 2017). The only muscle group spared by the effects of motor neuron loss in SMA are facial and eye muscles, though disease progression in SMA type I is typified by a child's inability to smile due to near complete muscle paralysis. SMA spares the diaphragm relative to the intercostal muscles (muscles between the ribs).

The effects of SMA on individuals and families is tremendous. Apart from the physical effects, the diagnosis can take a powerful emotional toll (Cruz et al., 2018, Cure SMA, 2015, Qian et al., 2015, McGraw, 2017).

SMA Type I

SMA Type I is characterized by the following presentation:

Decline in motor function: Motor function in type I SMA has been studied using motor function scales, including the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) and the Test for Infant Motor Performance Items (TIMPSI) (Glanzman et al., 2010, Krossschell et al., 2013, Krossschell et al., 2018, Kolb et al., 2017). The development of motor milestones, however, has not been examined as fully, as these infants, by definition, fail to gain independent sitting. Infants with SMA type I (with onset of symptoms after 3 months) are normal at birth and develop progressive hypotonia (low muscle tone) and weakness. This is followed by a predictable overall decline in motor function, sometimes with a brief plateau phase. More recently, the development of motor milestones has been examined (Kolb et al., 2017, Finkel et al, 2014). These infants fail to gain independent sitting and without treatment do not achieve motor skills beyond those present at the time of diagnosis.

Oral-motor dysfunction: If not already present at the time of diagnosis, oral-motor dysfunction (weak suck) typically evolves within the next few months. Failure to gain weight is often the subtle first sign of oral-motor dysfunction. Dysphagia (inability to swallow) can also lead to aspiration pneumonia, a potentially fatal condition in type I SMA infants. Supplemental tube feeding is available to support infants with dysphagia.

Respiratory insufficiency: Respiratory insufficiency typically evolves after feeding compromise is present. It may be the heralding event in the face of an acute respiratory illness, leading to hospitalization and initiation of the diagnostic effort. Supportive care options include nasal and oral suctioning, chest percussion to loosen airway secretions, cough assist device use to increase lung expansion and mobilize secretions, ventilation support – non-invasive and invasive respiratory support devices, and pulse oximetry monitoring.



SMA Type II

SMA type II patients typically survive longer – even absent drug treatment – than individuals with type I, due to greater motor strength in addition to availability of improved aggressive supportive care. Children with SMA type II usually do not have swallowing problems, but this can vary from child to child. They may have difficulty eating enough food by mouth to maintain their weight and grow, and a feeding tube may become necessary.

Respiratory Function: Children with SMA type II may also develop weakness of the muscles used for breathing and experience difficulty coughing and hypoventilation during sleep. Some may require equipment to support coughing especially with illness and support breathing during sleep.

Musculoskeletal Function: Weakness also leads to contractures. Stretching and bracing are often prescribed to preserve flexibility and prevent contractures. Problems with the spine and hips may lead to further loss of function. Severe curvature of the spine (scoliosis) can be managed with a brace to facilitate sitting upright and generally requires orthopedic surgical intervention with rod placement using a growing rod construct or a spinal fusion and fixed rods. . Bones are generally weaker and may break easily. A variety of therapeutic supports are available to help position children and adults with SMA type II comfortably. Adults with SMA type II often develop contractures, and limited mobility with disease progression necessitating the aid of caregivers or adaptive technology to perform activities of daily living (Haaker and Fajak, 2013, Mercuri et al., 2018, Cruz et al., 2018).

SMA Type III

Type III SMA is associated with onset between ages 18 months through adulthood. Standing or walking without support is achieved, although patients may lose the ability to walk with growth and/or disease progression. An abnormal gait is characteristic of SMA type III, as a result of compensation for weakness. Affected individuals may have difficulty walking, running, and climbing stairs; some will lose the ability to walk independently in childhood, while others may remain ambulatory into adolescence or adulthood. Supportive bracing help many to continue to walk despite severe weakness. Swallowing and coughing difficulties, along with breathing difficulty at night, may occur but are less common and present later than in SMA type II. Physical activity restrictions can also place children and adults with SMA type III at risk of becoming overweight. Fine shaking of the fingers and hands (tremors) can be seen in this type of SMA, and symptoms of joint aches, fatigue, and overuse frequently occur. Curvature of the spine may occur and can be managed with a brace and may require surgical intervention. Bones may be weak and break easily, and a variety of therapeutic supports are available to help position individuals comfortably and maintain mobility. Foot deformity may be seen in ambulatory patients. Lifespan is normal and a shift of the prevalence in favor of the Type III is observed among the SMA population with increasing age.

Disease Management and Current Treatments



The landscape of disease management and treatment for SMA has changed rapidly since the 2000s and continues to evolve with FDA approval of treatments and newborn screening adoption. While approaches vary depending upon individual needs and treatment options, disease management typically involves a combination of the following: interventions focused on preserving functions important to daily living, palliative care, and – if appropriate and available – drug treatment.

Standard of Care

An international, multidisciplinary SMA working group developed the initial standard of care guidelines for SMA in 2007. This included a detailed review of the pertinent literature and using the Delphi technique to generate consensus (or lack thereof) based upon expert opinion. This guideline has become a practical roadmap for clinicians and emphasized the need for coordinated, individualized, multidisciplinary care from neurologists, pulmonologists, orthopedic surgeons, gastroenterologists, dietitians, and physical, occupational and speech therapists, and with psychosocial support for the patient and the parents and caregivers (Wang, 2007, Wang et al., 2007, Finkel et al., 2018; Mercuri et al., 2018).

The standard of care was updated in 2016, and the updated version includes more input from patient and pharmaceutical representatives than the 2007 version (Finkel et al., 2018; Mercuri et al., 2018). Glascock et al. (2020), outlines treatment initiation recommendations for infants diagnosed via newborn screening by *SMN2* copy number. Affected individuals often receive care from a multidisciplinary healthcare team. Parents may have contact with specialists in neuromuscular conditions, palliative care, respiratory medicine, orthopedics, physiotherapy, occupational therapy, speech and language therapy, dietetics and a hospital or community consultant pediatrician. Type, level, and quality of care can vary greatly by country and region. The goal of supportive care is to enable people with SMA to enjoy a good quality of life at home with their family for as long as possible, with a minimum of hospital admissions while maintaining independence. However, keeping up with the recommended standards of care takes a considerable amount of effort, time and financial strain on parents and care givers (Cruz et al., 2018; Cure SMA, 2015; Qian, 2015).

Palliative Care

Palliative care begins at the time of diagnosis and emphasizes quality of life and comfort measures.

Respiratory Care

Breathing problems are the most common cause of illness and death for individuals with SMA. In healthy individuals, the muscles between the ribs—intercostal muscles—allow the chest to expand, filling the lungs with air. The diaphragm pulls the rib cage down, allowing the lungs to expand further. Individuals with SMA have very weak intercostal muscles and relatively stronger diaphragms in SMA type 1 and 2, which compromises breathing. This can result in:

- Weak respiratory muscles and underdeveloped chest wall



- Ribcage deformities
- A weak cough
- Severe risk of complications due to viral respiratory infections, even infections that only cause minor illness for healthy individuals
- Increased risk of pneumonia
- Aspiration of food or drink
- Hypoventilation, or shallow breathing, especially during sleep

Respiratory Support

For airway clearance and management, caregivers assist with coughing when needed using cough-assist devices and may also use:

- Chest physiotherapy to loosen mucus from the lungs
- Suction to remove secretions
- Medication to reduce secretions
- Respiratory support device to support ventilation during sleep to correct hypoventilation and to manage increased weakness associated with acute infection
- Invasive ventilation when non-invasive ventilation fails
- Pulse oximetry for in home monitoring

Musculoskeletal and Orthopedic Care

Generally, orthopedic complications are experienced by all SMA types; though the weaker types are most affected, and experienced many of these symptoms at a much younger age than those whose symptom presentations began later in life (Mercuri, et al, 2015). Common musculoskeletal issues experienced by most patients with SMA include contractures (tightening of muscles around joints due to lack of motion), which limit the range of motion in a joint; bone fractures (Osteoporosis is common in type IIs due to lack of weight bearing); hip dislocation; spinal deformities, such as scoliosis, lordosis, and kyphosis (Granata C, et al., 1989, Fajak et al., 2005, Rodillo, 1989, Haaker and Fajak, 2013, Mercuri et al., 2018).

Scoliosis is an abnormal curvature of the spine to the side—often "C-shaped"—that affects the balance of the trunk during sitting and/or standing. This spinal deformity can lead to obliquity at the base of the spine, the pelvis, which can lead to asymmetric and/or excessive pressure on hips and buttocks leading to skin breakdown and difficulty sitting. Scoliosis often results in twisting of the rib cage that impairs lung function by restricting motion of the chest and diaphragm during breathing. Spinal deformity may include a combination of scoliosis, lordosis (lumbar or cervical), and kyphosis. Kyphosis is an excessive forward flexion of the spine. Supportive care may involve modification of the wheelchair seating system, use of braces and if severe, surgical interventions that help straighten the spine and chest. These musculoskeletal issues can cause pain, as well as difficulty sitting, standing, or performing normal daily activities.



Many times, the musculoskeletal team will prescribe activities to be done at home. These may include:

- Daily exercises including aerobic activities, stretching, strengthening, and alignment to improve or maintain range of motion
- Use of equipment such as braces, a stander, or seating systems
- Supplemental calcium and vitamin D as part of the individual's nutrition plan to support bone health
- Bracing of the spine for sitting support
- Scoliosis corrective surgery

For more on this you may visit the Cure SMA website: <https://www.curesma.org/musculoskeletal/>

Gastrointestinal and Nutritional Care

Adequate nutrition is vital to maintaining proper muscle function and maintaining muscle mass in patients with SMA (Swoboda et al., 2007, 2014; Moore et al., 2016, Mercuri et al, 2018). Nutrition is also critical to fostering:

- **Improved Growth:** Gaining weight while growing in height is essential to good health. Having enough calories and protein support lung tissue and the heart muscle.
- **Better Breathing:** Growth in length helps with breathing, providing more room for the chest to expand. This is important because breathing problems are the leading cause of illness for children with SMA.
- **Preventing Illness:** Adequate nutrition helps to prevent and fight colds and viruses that could turn into a potentially threatening lower respiratory infection in the lungs (pneumonia).
- **Improved Motor Function:** Too much weight or too little weight can cause people with SMA to decline in both strength and ability to move.

Most patients with SMA experience various gastrointestinal and nutrition-related complications that make nutrition management a critical component of care. For instance, most patients with SMA, particularly those with type I and II, have low body weight relative to length and experience difficulty with feeding, chewing and/or swallowing. Most patients with SMA type I experience dysphagia or the inability to swallow that may often lead to choking issues or aspiration pneumonia (Wang, 2007, Kolb and Kissel, 2015, Martinez et al., 2018, Mercuri et al., 2018). Additionally, problems with constipation, reduced gastrointestinal motility, gastroesophageal reflux (GERD), malnutrition and low or high blood sugar have been reported. Swallowing studies are typically performed in SMA type I and II to evaluate swallow function.

It is recommended that the dietary intake of patients with SMA be monitored at least annually in consultation with a dietician experienced in management of patients with neuromuscular disorders or SMA specifically (Wang, 2007, Swoboda et al., 2007, Mercuri et al, 2018). Management is associated with:



- Evaluating weight, height and BMI
- Evaluating quality of diet and caloric need
- Evaluating nutrition laboratory studies

For more information on nutritional support and management, see [NUTRITION BASICS - Fostering Health and Growth for Spinal Muscular Atrophy](#); for a review on nutritional management, see, Kolb & Kissel, 2015, and Mercuri et al, 2018).

Physical (PT) and Aquatic Therapy

Physical therapy is recommended to maximize endurance, maintain mobility and flexibility, prevent contractures, improve or maintain range of motion and improve overall functioning and safety by incorporating activities such as swimming, aquatic therapy and adaptive sports. Neuromuscular fatigue appears to contribute to functional limitations in individuals with SMA (Montes et al., 2010). Such therapy may include:

- Passive exercises to enable movement and help circulation and prevent stiffening of the joints (contractures)
- Chest physiotherapy to help clear the chest when babies have difficulty coughing
- Aqua therapy – helps maintain cardiovascular function, range of motion and increased mobility and prevent contractures

For more information on SMA care, you may refer to the Cure SMA website (www.curesma.org).

Drug Treatments: Approved and Experimental

Therapeutic Approaches

The strength of the SMA drug discovery program is that it addresses SMA from multiple angles. Researchers have identified four distinct therapeutic approaches that show promise in treating SMA:

- **Replacement or correction** of the faulty *SMN1* gene. Gene Replacement Therapy restores the missing *SMN1* gene via a viral vector (Ex. AVXS-101/onasemnogene abeparvovec-xioi (Novartis Gene Therapies))
- **Modulation** of the low functioning *SMN2* "back-up gene"
 - ***SMN2* promoter activation** Cause the *SMN2* gene to be "on" more generating more *SMN* protein (Ex. RG3039 (Dcps Inhibitor, Cure SMA) or HDAC inhibitor (VPA))
 - ***SMN2* splicing modulation** Redirect splicing of *SMN2* to make more full-length transcripts containing exon 7 (e.g. Antisense Oligonucleotides (ASOs) or small molecules (Genentech/Roche and Novartis); Ex. nusinersen (Biogen))



- **Muscle protection and enhancement** to prevent or restore the loss of muscle and motor function in SMA (Ex. CK2127107 (Cytokinetics), Ex. SRK – 015 (Myostatin Inhibitor), (Scholar Rock))
- **Neuroprotection** of the motor neurons affected by loss of *SMN* protein. Aimed to protect against neuronal injury or degradation
- **Neuronal function** to enhance neuronal transmission
- **Combinations** of the above therapeutic approaches to address multiple aspects of the disease and improve patient outcomes (Ex. Spinraza + a muscle enhancer)

For an overview of these therapeutic approaches you may visit: <https://www.curesma.org/therapeutic-approaches/>.

Approved Drug Treatments:

There are currently three FDA-approved treatments for SMA that treat the underlying genetic cause of SMA through distinct mechanisms, to enhance the production and availability of *SMN* protein throughout the body. These treatments improve outcomes for SMA. None of these treatments are cures.

NUSINERSEN (SPINRAZA™)

Nusinersen (Spinraza), is an antisense oligonucleotide that works by correcting the *SMN2* transcript splicing, thereby improving functional *SMN* protein expression. Spinraza is administered via intrathecal (IT) injection, every four months and was approved for all types and ages of SMA. The treatment was approved on December 2016 based on data from studies involving more than 170 individuals with SMA, including data from ENDEAR, a Phase 3 controlled study evaluating SPINRAZA in infantile-onset, and open-label data from uncontrolled studies in pre-symptomatic and symptomatic patients with, or likely to develop, Types I, II and III SMA (Biogen, 2016; Finkel et al, 2017, De Vivo et al, 2017). For more on Spinraza, you may [click here](#).

Onasemnogene Apeparvovec-xioi (ZOLGENSMA)

Approved by the FDA in May 2019, Zolgensma is an *SMN*-enhancing therapy that works by replacing the missing or mutated *SMN1* gene. Zolgensma is given via intravenous infusion. A viral vector, AAV9, carries the replacement gene into the body. This vector “infects” the cells and deposits new DNA with the *SMN1* gene construct. Zolgensma is a type of treatment that is often called gene therapy or gene replacement therapy and is FDA-approved for infants with all types of SMA under 2 years of age based on an open label clinical trial of 15 infants with SMA type I (Mendell et al, 2017). Zolgensma was developed and marketed by AveXis/Novartis. Zolgensma is a one-time intravenous (IV) infusion. For more information on Zolgensma, you may [click here](#).



RISDIPLAM (EVRYSDI ®)

Risdiplam (Evrysdi ®) is an oral small molecule that enhances normal SMN2 splicing. Risdiplam was approved by the FDA in April 2020 for patients 2 months of age and older. The molecule binds to two sites in the *SMN2* pre mRNA to promote *SMN2* exon 7 splicing. The treatment is orally administered once daily for life. The oral administration allows for peripheral distribution of the small molecule (Ojala et al., 2021). For more information on Evrysdi, you may [click here](#).

Experimental Drug Treatments: The SMA Drug Pipeline

To find a treatment and cure for SMA, we know it's crucial to attack SMA from all sides. As with all scientific research, it's difficult to predict which SMA drug programs might be successful. By investing in diverse approaches, we maximize our chances for success. If one drug candidate or one approach fails, we have others to take its place.

Therapeutic Programs and Strategies in SMA

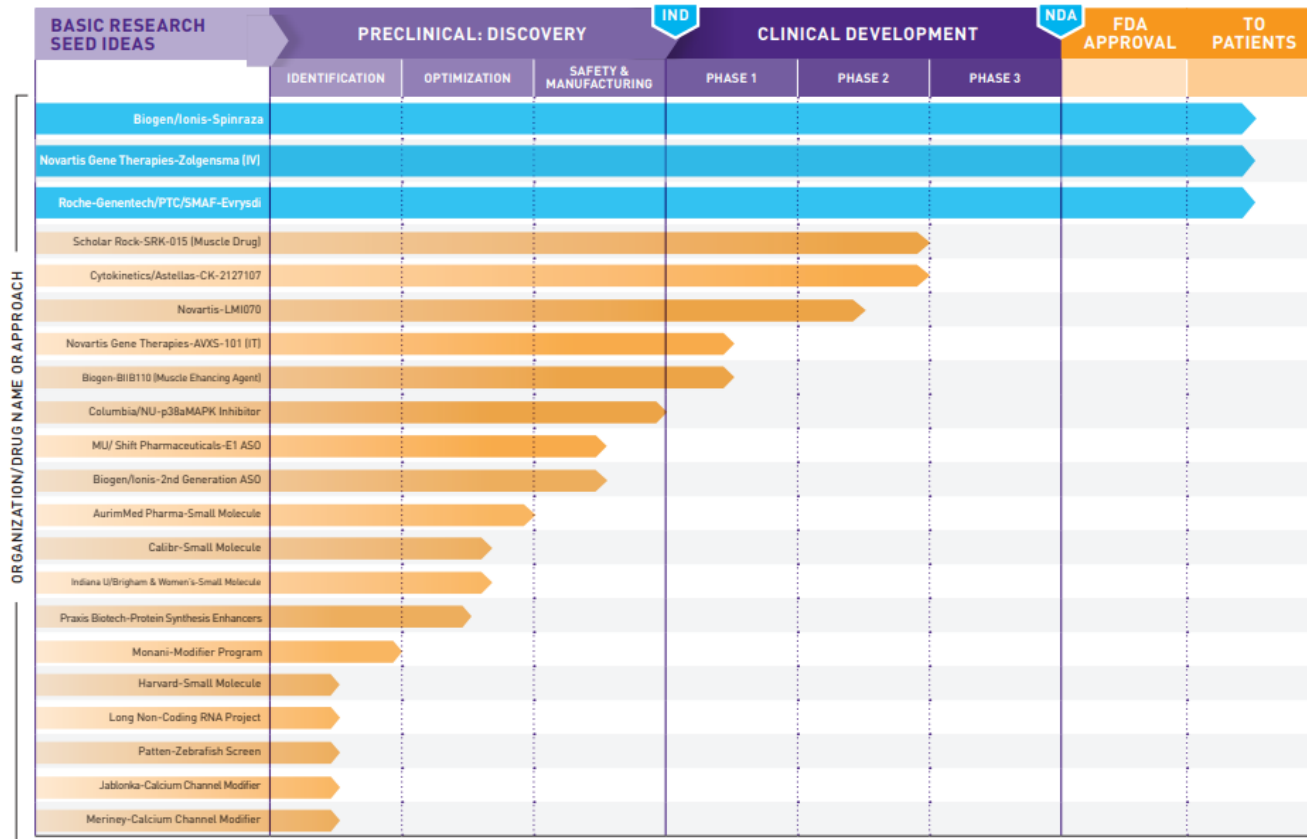
Cure SMA's research model funds drug programs at all stages of development. Basic research lays the groundwork for understanding the underlying cause of SMA, its pathophysiology and how and how it affects multiple body systems. This, in turn, improves our understanding of the natural history of SMA, including its clinical manifestations and disease progression. Continued investigation into the causes and biology of SMA is necessary to grow and improve our drug pipeline and is essential to the development of potential drugs to target the underlying cause and mechanisms of the disease. Promising pre-clinical projects create viable drugs that are then tested in humans to assess the safety, pharmacokinetics, pharmacodynamics, and efficacy of a drug for the treatment of SMA. Drug discovery converts what we have learned about the causes and biology of SMA through basic research into new drug candidates that can be tested in clinical trials.

Cure SMA funds groundbreaking research into the cause and treatment of SMA. In the last two decades, Cure SMA has invested over \$15 million in funding for 128 basic research grants and [nearly \\$20 million in funding for 12 drug development projects that have led to effective treatments for SMA](#).



SMA DRUG PIPELINE

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



IND = Investigational New Drug NDA = New Drug Application Last updated: April 2021

Table 3: Cure SMA Drug Pipeline



References for Part 1

- Arnold, W.D., Burghes, A.H. (2012). Spinal Muscular Atrophy: The Development and Implementation of Potential Treatments Running Head: Spinal Muscular Atrophy. *Ann Neurol.* 74(3), 10.1002/ana.23995. [[PMC free article](#)]
- Chen, Y.S., Shih, h.H., Chen, T.H., Kuo, C.H., & Jong, Y.J. (2012). Prevalence and risk factors for feeding and swallowing difficulties in spinal muscular atrophy types II and III. *J Pediatr.* 160(3):447–451. e1. [[PMC free article](#)]
- Cruz, R., Lenz, M., Belter, L., Hobby, K., & Jarecki, J. (2018). Voice of the patient report: A summary report from an externally led patient focused drug development meeting reflecting the U.S. Food and Drug Administration (FDA) patient-focused drug development initiative. <http://www.curesma.org/documents/advocacy-documents/sma-voice-of-the-patient.pdf>
- Cure SMA (2015) Voices of SMA, Retrieved from: <https://www.curesma.org/fda-engagement-update-the-voices-of-sma/>
- Darras B.T. & De Vivo, D.C. (2018). Precious SMA natural history data: A benchmark to measure future treatments successes. *Neurology.* 91 (8) 337-339; Doi: 10.1212/WNL.0000000000006026
- Belter, L., Cook, S.F., Crawford, T., Jarecki, J., Jones, C.C., Kissel, J.T.,....Hobby, K. (2018). An overview of the Cure SMA membership database: highlights of key demographic and clinical characteristics of SMA members. *J Neuromuscul Dis.* 5: 167–176
- Biogen. (2016). The first treatment for spinal muscular atrophy. Retrived from: <http://investors.biogen.com/news-releases/news-release-details/us-fda-approves-biogens-spinrazatm-nusinersen-first-treatment>
- D'Amico, A., Mercuri, E., tiziano, F.D., & Dertini, E. (2011). Spinal muscular atrophy. *Orphanet J Rare Dis.* 6:71. [[PMC free article](#)]
- De Vivo, D.C., Hwu, W.L., Reyna, S.P., Farwell, W., Gheuens, S., Sun, P..... Bertini, E. (2017). Interim efficacy and safety results from the Phase 2 NURTURE study evaluating Nusinersen in presymptomatic infants with spinal muscular atrophy. *Neurology.* Apr 2017, 88 (16 Supplement) S46.003. [[Neurology free article](#)]
- De Vivo, D.C., Bertini, E., Swoboda, K.J., Hwu, W.L., Crawford, T.O., Finkel, R.S.....Farwell, W. on behalf of the NURTURE Study Group. (2019). Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscul Dis.* doi: <https://doi.org/10.1016/j.nmd.2019.09.007>.
- Dunaway, Y.S., Montes, J., Kramer, S.S., Marra, J., Salazar, R., Cruz, R., Chiriboga, C.A., Garber, CE., De Vivo, D.C. (2016). Six-minute walk test is reliable and valid in spinal muscular atrophy. *Muscle Nerve.* 54(5):836– 842. doi: 10.1002/mus.25120.
- Farrar, M.A., Park, S.B., Vucic, S., Carey, K.A., Turner, B.J., Gillingwater, T.H.....Kiernan, M.C. (2017). Emerging therapies and challenges in spinal muscular atrophy. *Ann Neurol.* 81:355–68. [[Wiley Online Library free article](#)]

- Finkel, R., Bertini, E., Muntoni, F., & Mercuri, E. (2015). 209th ENMC international workshop: outcome measures and clinical trial readiness in spinal muscular atrophy 7-9 November 2014, Heemskerk, The Netherlands. *Neuromuscul Disord.* 25:593–602. [[Elsevier free article](#)]
- Finkel, R.S., McDermott, M.P., Kaufmann, P., Darras, B.T., Chung, W.K., Sproule, D.M.....De Vivo, D.C. (2014). Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology.* 83(9):810-7. [[Neurology free article](#)]
- Finkel, R.S., Mercuri, E., Darras, B.T., Connolly, A.M., Kuntz, N.L., Kirschner, J.....De Vivo, D.C. (2017). Nusinersen versus sham control in infantile onset spinal muscular atrophy. *N Engl J Med.* 377:1723-32. [[NEJM free article](#)]
- Finkel, R.S., Mercuri, E., Meyer, O.H., Simonds, A.K., Schroth, M.K., Graham, R.J.....Sejersen, T. (2018). Diagnosis and management of spinal muscular atrophy. Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord.* 28(3); 197-207 [[Elsevier free article](#)]
- Fujak, A., ingenhorst, A., Heuser, K., Forst, R., & Forst, J. (2005). Treatment of scoliosis in intermediate spinal muscular atrophy (SMA type II) in childhood. *Ortop Traumatol Rehabil.* 7(2):175–179. [PubMed: 17615511]
- Glanzman, A.M., Mazzone, E., Main, M., Pelliccioni, M., Wood, J., Swaboda, K.J.....Finkel, R.S. (2010). The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord* : NMD 2010;20:155-161.
- Glascok, J., Sampson, J., Haidet-Phillip, A., Connolly, A., Darras, B., Day, J..... Jarecki, J. (2018). Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. *J Neuromuscul Dis*, 2018. [[IOS full article](#)]
- Glascok, J., Sampson, J., Connolly, A.M., Darras, B.T., Day, J.W..... Jarecki, J. (2020). Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2. *J Neuromuscul Dis.* 7(2):97-100. doi: 10.3233/JND-190468. PMID: 32007960; PMCID: PMC7175931.
- Granata, C., Merlini, L., Magni, E., Marini, M.L., & Stagni, S.B. (1989). Spinal muscular atrophy: natural history and orthopaedic treatment of scoliosis. *Spine* (Phila Pa 1976). 14(7):760–762. [[ResearchGate abstract](#)]
- Haaker, G., & Fujak, A. (2013). Proximal spinal muscular atrophy: current orthopedic perspective. *Appl Clin Genet.* 2013; 6(11):113 120. [[DovePress free article](#)]
- Hua, Y., Vickers, T. A., Baker, B. F., Bennett, C. F., & Krainer, A. R. (2007). Enhancement of SMN2 exon 7 inclusion by antisense oligonucleotides targeting the exon. *PLoS biology*, 5(4), e73. doi:10.1371/journal.pbio.0050073
- Hypotonia. (2018). Wikipedia. Retrieved from: <https://en.wikipedia.org/wiki/Hypotonia>
- Kolb, S.J., Coffey, C.S., Yankey, J.W., Krosschell, K., Arnold, W.D., Rutkove, S.B..... NeuroNEXT Clinical Trial Network and on behalf of the NN101 SMA Biomarker Investigators. (2016). Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. *Ann Clin Transl Neurol.* 3(2):132-145. doi:10.1002/acn3.283/ [[PMC free article](#)]
- Kolb, S.J., & Kissel, J.T. (2011). Spinal muscular atrophy: a timely review. *Arch Neurol.* 68(8):979–984. [[JAMA full article](#)]

- Kolb, S. J., Coffey, C. S., Yankey, J. W., Krossschell, K. , Arnold, W. D., Rutkove, S. B..... NeuroNEXT Clinical Trial Network and on behalf of the NN101 SMA Biomarker Investigators. (2017). Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol.*, 82: 883-891. [[Wiley Online Library full article](#)]
- Kolb, S., & Kissel, J.T. (2015). Spinal Muscular Atrophy. *Neurol Clin.* 33(4): 831–846. [[Elsevier full article](#)]
- Krossschell, K.J., Maczulski, J.A., Scott, C., King, W., Hartman, J.T., Case, L.E.....Project Cure SMA Investigators Network. (2013). Reliability and validity of the TIMPSI for infants with spinal muscular atrophy type I. *Pediatr Phys Ther.* 25(2): 140-148. Doi: 10.1097/PEP.0b013e31828a205f.
- Krossschell, K.J., Bosch, M., Nelson, L., Duong, T., Lowes, L.P., Alfano, L.N....NeuroNEXT Clinical Trial Network and on behalf of the NN101 SMA Biomarker Investigators. (2018). Motor function test reliability during the NeuroNEXT spinal muscular atrophy infant biomarker study. *J Neuromuscul Dis.* 5(4): 509-521. Doi: 10.3233/JND-180327.
- Lefebvre, S., Burglen, L., Reboullet, S., Clermont, O., Burlet, P., Viollet, L.....Melki, J. (1995). Identification and characterization of a spinal muscular atrophy-determining gene. *Cell.* 80:155–65. [[Science Direct full article](#)]
- Lin, C.W., Kalb, S.J., & Yeh, W.S. (2015). Delay in Diagnosis of Spinal Muscular Atrophy: A Systematic Literature Review. *Pediatr Neurol.* 53(4):293-300. doi: 10.1016/j.pediatrneurol.2015.06.002.
- Lorson, C.L., Rindt, H., & Shababi, M. (2010). Spinal muscular atrophy: mechanisms and therapeutic strategies. *Hum Mol Genet.* 19(R1): R111–R118. [[PMC free article](#)]
- Mailman, M.D., Heinz, J.W., Papp, A.C., Snyder, P.J., Sedra, M.S., Wirth, B.....Prior, T.W. (2012). Molecular analysis of spinal muscular atrophy. *Genet Med* 35, 4 (suppl), 955-959.
- Martinez, E.E., Quinn, N., Arouchon, K., Anzaldi, R., Tarrant, S., Ma, S.....Mehta, N.M. (2018). Comprehensive nutritional and metabolic assessment in patients with spinal muscular atrophy: opportunity for an individual approach. *Neuromuscul Disord.* 28(6); 512-519 [doi: 10.1016/j.nmd.2018.03.009]
- McGraw, S., Qian, Y., Henne, J., Jarecki, J., Hobby, K., & Yeh, W.S. (2017). A qualitative study of perceptions of meaningful change in spinal muscular atrophy. *BMC Neurol.* 17: 68
- Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, Lowes L, Alfano L, Berry K, Church K, Kissel JT, Nagendran S, L'Italien J, Sproule DM, Wells C, Cardenas JA, Heitzer MD, Kaspar A, Corcoran S, Braun L, Likhite S, Miranda C, Meyer K, Foust KD, Burghes AHM, Kaspar BK. (2017). Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *N Engl J Med.* 377(18):1713-1722. doi: 10.1056/NEJMoa1706198. PMID: 29091557.
- Mercuri, E., Finkel, R.S., Muntoni, F., Wirth, B., Montes, J., Main, M..... SMA Care Group. (2018). Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord.* 28(2); 103-115 [doi: 10.1016/j.nmd.2017.11.005]
- Mercuri, E., Finkel, R., Montes, J., Mazzone, E.S., Sormani, M.P., Main, M.....De Vivo, D.C. (2016). Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials. *Neuromuscul Disord.* 26(2):126-31. doi: 10.1016/j.nmd.2015.10.006. Epub 2015 Dec 3.



- Milunsky, J.M. & Cheney, S.M. (1999). Prenatal diagnosis of spinal muscular atrophy by direct molecular analysis: Efficacy and potential pitfalls. *Genetic Testing*. <https://doi.org/10.1089/109065799316554>
- Montes, J., McDermott, M.P., Martens, W.B., Dunaway, S., Glanzman, A.M., Riley, S.,.....Finkel, R.S. (2010). Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. *Neurology*. 74(10):833–838. [\[PMC free article\]](#)
- Moore, G.E., Lindenmayer, A.W., McConchie, G.A., Ryan, M.M., & Davidson, Z.E. (2016). Describing nutrition in spinal muscular atrophy: A systematic review. *Neuromuscul Disord*, Volume 26, Issue 7, 395 – 404. [\[Elsevier abstract\]](#)
- Munsat, T., & Davies, K. (1995). Spinal muscular atrophy. 32nd ENMC International Workshop. Naarden, The Netherlands, 10-12 March 1995. *Neuromuscul Disord*. NMD 1996; 6:125-127. [\[Springer abstract\]](#)
- Munsat, T.L., & Davies, K.E. (1992). International SMA consortium meeting. (26–28 June 1992, Bonn, Germany) *Neuromuscul Disord*. 2(5–6):423–428
- Ojala, K. S., Reedich, E. J., DiDonato, C. J., & Meriney, S. D. (2021). In Search of a Cure: The Development of Therapeutics to Alter the Progression of Spinal Muscular Atrophy. *Brain sciences*, 11(2), 194. <https://doi.org/10.3390/brainsci11020194>
- Ogino, S., Leonard, D.G., Rennert, H., Ewens, W.J., & Wilson, R.B. (2002). Genetic risk assessment in carrier testing for spinal muscular atrophy. *Am J Med Genet*. 110(4):301-7. [\[Wiley Online Library abstract\]](#)
- Oskoui, M., Levy, G., Garland, C.J., Gray, J.M., O'Hagen, J., De Vivo DC, & Kaufmann, P. (2007). The changing natural history of spinal Muscular atrophy type 1. *Neurology*. 69(20):1931-6. [\[Neurology full article\]](#)
- Prior, T.W. (2008). Carrier screening for spinal muscular atrophy. *Genet Med*. 10(11):840-2.
- Qian, Y., McGraw, S., Henne, J., Jarecki, J., Hobby, K., & Yeh, W.S. (2015). Understanding the experiences and needs of individuals with spinal muscular atrophy and their parents: a qualitative study. *BMC Neurol*. 15: 217
- Qian, Y., McGraw, S., Henne, J., Jarecki, J., Hobby, K., & Yeh, W.S. (2015). Understanding the experiences and needs of individuals with spinal muscular atrophy and their parents: a qualitative study. *BMC Neurolgy*. 15(27)
- Reflexes. (2018). *Wikipedia*. Retrieved from: <https://en.wikipedia.org/wiki/Reflex>
- Rodillo, E., Marini, M.D., Heckmatt, J.Z. & Dubowitz, V. (1989). Scoliosis in spinal muscular atrophy: review of 63 cases. *J Child Neurol*. 4(2):118–123. [\[Sage abstract\]](#)
- Russman, B.S. (2007). Spinal muscular atrophy: clinical classification and disease heterogeneity. *Journal of child Neurology*. 22:946-951. [\[Sage abstract\]](#)
- Schemmer, G., Johnson, A. (1993). Genetic amniocentesis and chorionic villus sampling. *Obstet Gynecol Clin North Am*. 20:497-521.
- Shulman, L.P. & Elias, S. (1993). Amniocentesis and chorionic villus sampling. *West J Med*. Sep;159(3):260-8. PMID: 8236967; PMCID: PMC1011338.

- SMA Europe & TREAT-NMD. (2016). Briefing document to the clinical trial readiness in spinal muscular atrophy (SMA) SMA Europe, TREAT-NMD and European Medicines Agency Meeting. European Medicines Agency, London; 2016
- Sugarman, E.A., Nagan, N., Zhu, H., Akmaev, V.R., Zhou, Z., Rohlf, E.M.....Allitto, B.A. (2012). Pan-ethnic carrier screening and Prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet.* 20(1):27-32 [[PMC free article](#)]
- Swoboda, K. J., Prior, T. W., Scott, C. B., McNaught, T. P., Wride, M. C., Reyna, S. P., & Bromberg, M. B. (2005). Natural History of Denervation in SMA: Relation to Age, *SMN2* Copy Number, and Function. *Ann Neuro.* 57(5), 704–712. [[PMC free article](#)]
- Swoboda, K., & Hurst R. (2010). General Nutrition Guidelines for SMA Children. *Cure SMA website.* [[PDF](#)]
- Swoboda, K., & Smart A. (2007). Guidelines for Gastrostomy Tube Feeding for Infants with SMA type I. *Cure SMA.* [[PDF](#)]
- Tangsrud, S.E. Carlson, K.C.L., Lund-Petersen, I., & Carlson, K-H. (2001). Lung function measurements in young children with spinal muscle atrophy; a cross sectional survey on the effect of position and bracing. *Arch Dis Child.* 84(6):521–524. [[PDF full article](#)]
- Thomas, N.H., & Dubowitz, V. (1994). The natural history of type I (severe) spinal muscular atrophy. *Neuromuscul Disord.* 4(56):497-502. [[Elsevier abstract](#)]
- Verhaart, I.E., Robertson, A., Wilson, I.J., Aartsma-Rus, A., Cameron, S., Jones, C.C.....Lochmuller, H. (2017). Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. *Orphanet J Rare Dis.* 12(1):124. [[OJRD full article](#)]
- Verp, M.S. (1992). Prenatal diagnosis of genetic disorders. In: Gleicher N., ed. Principles and practice of medical therapy in pregnancy. 2nd ed. Norwalk, CT: Appleton and Lange, 159-70.
- Wadman, R.I., Stam, M., Gijzen, M., Lemmink, H.H., Snoeck, I.N., Wijngaarde, C.A.....Ludo Van Der Pol, W. (2017). Association of motor milestones, *SMN2* copy and outcome in spinal muscular atrophy types 0-4. *J Neurol Neurosurg Psychiatry.* 88:365-7. [[PDF full article](#)]
- Wang, C.H., Finkel, R.S., Bertini, E.S., Schroth, M., Simonds, A., Wong, B.....Participants of the International Sconference on SMA Standard of Care (2007). Consensus Statement for standard of care in spinal muscular atrophy. *J Child Neurol.* 22:1027-49. [Sage [abstract](#)]
- Wirth, B. (2002). Spinal muscular atrophy: state-of-the-art and therapeutic perspectives. *Amyotroph Lateral Scler Other Motor Neuron Disord.* 2002 Jun;3(2):87-95. Review.
- Wirth, B. (2000). An update of the mutation spectrum of the survival motor neuron gene (*SMN1*) in autosomal recessive spinal muscular atrophy (SMA), *Hum Mutat.* 15(3):228-37 [[Wiley Online Library abstract](#)]
- Wirth, B., Brichta, L., Schrank, B., Lochmuller, H., Blick, S., Baasner, A., & Heller, R., (2006). Mildly affected patients with spinal muscular atrophy are partially protected by an increased *SMN2* copy number. *Hum Genet.* 119:422–8. [[Springer abstract](#)]
- Wirth, B., Herz, M., Wetter, A., Moskau, S., Hahnen, E., Rudnik-Schoneborn, T.....Zerres, K. (1999). Quantitative analysis of survival motor neuron copies: identification of subtle *SMN1* mutations in



patients with spinal muscular atrophy, genotype-phenotype correlation, and implications for genetic counseling. *Am J Hum Genet.* 64:1340–56 [[PDF full text](#)]

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

Zerres, K., & Rudnik-Schoneborn, S. (1995). Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. *Arch Neurol.* 1995;52(5):518-23. [[JAMA abstract](#)]



Part 2

Conducting Clinical Trials in SMA



PART 2: CONDUCTING CLINICAL TRIALS IN SMA

As sites prepare to run clinical trials in SMA, it is essential that research teams understand the key elements of site readiness, including but not limited to: training (research, protocol, and specialty specific), regulatory/institutional (IRB) requirements, and the tools (such as SOPs, forms, templates, etc.) that are needed to support the team in the effective conduct of a trial, across a study life cycle. This also necessitates a healthy understanding of the patient community, with a complex rare disease. This next part of the toolkit addresses key attributes of site readiness and the types of things that sites will need to think about as they prepare for and conduct trials. Throughout, attention is given to specific considerations and challenges that may arise in the context of SMA clinical trials specifically, due to the nature of the disease and the needs of SMA patients.

Before You Begin: Adopting a Collaborative, Patient-Focused Approach

Before delving into the specifics of site readiness or the logistics of running a clinical trial, it can be helpful to think about the mindset with which you approach clinical trials, and how you can adopt a patient-focused mindset. Increasingly, collaborative, patient-focused approaches are being emphasized in health care and drug development. Taking a patient-focused approach has been shown to increase the success of clinical trials and can be applied to all aspects of clinical trial operations. This type of approach emphasizes the needs of the patient, involves assessing trial design and operations from a patient perspective and may in certain cases even include integrating SMA patient community input directly into the clinical trial design. In general, understanding patient perspectives may help sites involved in conducting trials to be more effective, and streamline the patient experience during trials.

In an SMA clinical trial, a patient-focused approach can be particularly impactful. SMA clinical trials may have more intensive protocols and procedures and can require significant commitments on behalf of the patients, their families, and their caregivers. This commitment is on top of the daily challenge that these patients and families have in managing care and coping with the implications of the patients' diagnosis with a progressive, degenerative neuromuscular disease. During the trial, patients and families may need reassurance; they may need someone who can listen to their questions, concerns and struggles. Furthermore, the families, caregivers, and the patients themselves tend to be very involved in care and want to be involved in the trial process.

In planning for and conducting clinical trials, trial sites can help to create a positive experience for patients by, as appropriate and feasible, taking a proactive approach to streamlining care and promoting a patient-focused mindset among key team members involved in trial conduct. This starts with trial planning and recruitment and carries through until the trial concludes.



Site Readiness for Clinical Trials in SMA

Although each clinical trial is unique and the needs of sponsors will vary from one trial to the next, there are a number of factors that are likely to impact a site's readiness for trials regardless of individual study needs. These include the site's infrastructure and ability to support clinical trials as well as the experience and abilities of key members of the research team and site staff. Before getting into the specifics of planning for and running a clinical trial in SMA, it may be helpful to review these factors to determine whether there are any steps that your site may need to take to become trial-ready.

The Cure SMA Clinical Trial Program is a voluntary, educational program designed to help sites - especially new SMA trial sites- assess their readiness and identify opportunities to increase their site and staff's readiness to run SMA clinical trials. This evaluation is part of ongoing efforts by Cure SMA and the SMA Industry Collaboration (IC) to increase trial site capacity and optimize readiness throughout the United States, to better meet the needs of trial sponsors and the SMA patient community as the number of SMA clinical trials increases. Participation in the readiness program helps sites to:

- a) access resources that equips clinical research staff to conduct SMA trials, including a PT Assessment and Readiness program, an SMA Best Practices Clinical Trials Toolkit for research staff, a Best Practices Clinical Evaluator Toolkit, and a Best-Practices for Clinical Evaluators in SMA (click [here](#) to access the toolkits), among others, and,
- b) acquire visibility with sponsors who may be seeking new trial sites.

If you are interested in learning more about this readiness evaluation process, please contact Cure SMA.



The Research Team: Key Players in SMA Trials

Principal Investigators

Principal investigators (PIs) are tasked with the responsibility of providing the primary level of oversight of clinical trial conduct by ensuring that all associated research staff comply the protocol as well as all IRB and FDA rules and regulations. PIs are also required to provide oversight of record management including documentation of informed consent, randomization, and protocol deviations. The use and distribution of investigational drug is also monitored by the PI. Should adverse events occur, the PI must also assess the status of the subject and provide notification to the sponsor as well as the IRB and FDA when applicable. Please note, although sites are encouraged to delegate study related procedures, the PI must ensure that staff is appropriately credentialed and trained to complete the assigned task (Baer, Devine, Beardmore, & Catalano, 2011; National Drug Abuse Treatment Clinical Trials Network, n.d.; International Council for the Harmonisation for International Requirements of Technical for Pharmaceuticals for Human Use (ICH), 2016).

For a detailed description of the role and responsibility of principal investigators please see section 4 of the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), and Baer, Devine, Beardmore, and Catalano, Clinical Investigator Responsibilities (2011).

Clinical Research Coordinators

Clinical Research Coordinators (CRCs), also known as Study Coordinators (SCs), work with principal investigators (PIs) to conduct clinical trials using good clinical practices (GCP). CRCs are the main communication liaison between the investigators and the study subjects, as well as the site and the sponsor. CRCs also handle a great deal of the everyday study activities. While every CRC's responsibilities may differ, key activities may also often include Institutional Review Board (IRB) submissions, negotiating contracts and budgets, and ensuring integrity and ethics in the study and site's conduct. The CRC role continues to increase in both amount of responsibility given, and tasks assigned, as well as overall importance. A high-performing clinical research coordinator (CRC) is critical to the success of any clinical trial, but this is especially true in SMA clinical trials given the complex needs of this patient community.

Because this position has such varied responsibilities and serves such a critical function in clinical trials, it is imperative that CRCs are properly trained and have access to a wide range of tools and resources. When supporting SMA clinical trials, CRCs may also encounter a number of specific disease-related challenges as well as challenges related to conducting clinical trials in rare diseases, and coordinators can benefit from the knowledge sharing of experienced SMA trial staff.

For more CRC-specific information and resources, please refer to the companion toolkit Best Practices for Clinical Research Coordinators in SMA (see callout box).



Physical Therapists

Physical therapists play an important role not only in disease management (as described in Part 1 of this toolkit), but also in assessing the effectiveness of a given therapeutic in a clinical trial. Using a variety of motor function measures, physical therapists (who should receive appropriate reliability training) may evaluate participants' mobility, strength, endurance, and their ability to achieve/maintain motor milestones independently or with assistance. This evaluation will help the researcher to identify changes in disease progression that may be occurring as a result of the treatment being studied.

For more PT-specific information and resources, please refer to the companion Best Practices for Physical Therapists and Clinical Evaluators (CEs) in SMA (see callout box).

Companion Resources: CRC and PT Toolkits



To help support coordinators who are new to SMA clinical trials, Cure SMA has developed **Best Practices for Clinical Research Coordinators in SMA**. This toolkit reviews CRC responsibilities, strategies, and tactics to support trial management, as well as tips on working with SMA-affected individuals and families. Cure SMA's **Best Practices for Physical Therapists and Clinical Evaluators (CEs) in SMA** was developed in collaboration with two PTs having significant experience in SMA. It is intended to help PTs/CEs—especially those new to SMA clinical trials—find productive ways to navigate challenges they may encounter in their work. The resource also includes appendices on additional resources, including seminal papers in SMA, manuals, and articles that delve further into SMA topics. Download both toolkits at www.curesma.org/clinical-trial-readiness.

Clinical Outcome Measures in SMA

Functional measures in SMA allow us to assess the impact of SMA and possible response to treatment. Types of outcome measures commonly used in evaluation of SMA patients include motor function scales, scales of motor development, electrophysiological measures, and pulmonary outcome measures. A comprehensive review of motor function outcomes is presented in the Best Practices for Physical Therapists and Clinical Evaluators (CEs) in SMA (click [here](#) to access the toolkits). Table A4 in the toolkit's appendices contains descriptions of outcome measures as well as links to procedure manuals, score sheets, and other external resources.



Key Elements of Trial Management

As sites and their research teams prepare for clinical trials in SMA, it will be helpful to ensure that research teams have a firm grasp on familiar elements of trial management – such as good clinical practice, standard operating procedures, recruitment and retention – and are sensitized to potential challenges that may arise in SMA clinical trials as a result of the complexity of the disease and patient needs. This next section provides an overview and information about suggested resources on good clinical practice, the ethical conduct of trials, standard operating procedures, documentation, monitoring and quality assurance, as well as key activities and issues related to patient recruitment and retention.

Good Clinical Practice

The principles of Good Clinical Practice (GCP) help to assure the safety, integrity, and quality of clinical trials by addressing elements related to the design, conduct, and reporting of clinical trials. Per the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice:

“Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.”

ICH E6(R2) provides extensive detail on GCP, including the roles and responsibilities of key parties including the institutional review board, investigators, and sponsors as well as information on the clinical trial protocol and investigator’s brochure. However, the principles of ICH GCP (as excerpted from ICH E6, for which ICH holds the copyright) are as follows:

- 2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
- 2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- 2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
- 2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
- 2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
- 2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.



2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

All research staff are required to complete and maintain certification in Good Clinical Practice. GCP training describes the responsibilities of investigators, sponsors, monitors, and IRBs in the conduct of clinical trials. A listing of free training resources can be found in the Certification and Training section of this document.

Ethical Conduct of Research: An Essential Element of Good Clinical Practice

Ethical considerations must be integrated into all aspects of clinical trials, from the training of health care professionals and staff prior to trial conduct, through the planning, conduct and completion of trials. These are a key part of Good Clinical Practice and important for protecting the welfare of research subjects. Key principles related to the ethical conduct of research include the social and clinical value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for potential and enrolled subjects.

To ensure that the individuals involved in planning and conducting trials understand and can identify key ethical issues that may arise in human subject's research, all staff members and health care professionals involved in human subject's research will be required to complete ethics training. In addition, an Institutional Review Board (IRB) must oversee and review the ethics of every clinical trial. Their goal is to protect human subject welfare. IRBs must be involved in the clinical trial process from the start, by reviewing all protocols and materials prior to the study.



Numerous external resources are available that address ethical considerations involved in human subject's research, so they will not be covered in detail here. Readers may wish to refer to the following resources as they delve further into this subject:

- The National Institutes of Health's webpage on "Ethical Guidelines & Regulations," which includes key guidelines as well as HHS and FDA regulations. (National Institute of Health (NIH): Research Involving Human Subjects, n.d.)
- The Belmont Report, which was written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and identifies basic ethical principles as well as guidelines addressing ethical issues that can arise in connection with human subject's research (U.S. Department of Health & Human Services: Office for Human Research Protections , 2016). The Declaration of Helsinki, which was developed by the World Medical Association "as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data." (World Medical Association (WMA), 2018)
- The "MRCT Ethics Essential Elements and Points to Consider Reference Document" from the Multiregional Clinical Trials Center of Harvard and Brigham and Women's Hospital. (Multi-Regional Clinical Trials (MRCT), n.d.)
- The Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO) "International Ethical Guidelines for Health-related Research Involving Humans" (Council for International Organizations of Medical Sciences (CIOMS); World Health Organization (WHO) , 2016)

Standard Operating Procedures

Standard operating procedures (SOPs) are policies that include a detailed set of instructions designed to regulate outcomes of routine activities. Frequently, SOPs are implemented to maintain uniform consistency while adhering to regulations, and institutional policies, in addition to providing greater clarity about workflow.

Development and implementation of standard operating procedures for all major aspects of clinical trial activities is strongly encouraged. Although sites will need to develop SOPs based upon their specific attributes and trial needs, SOPs should address, at a minimum:

- Trial participation recruitment and retention
- The informed consent process
- Document management, including filing and recordkeeping
- Institutional review board review
- Protocol deviation and violation documentation, resolution, and reporting
- Adverse event documentation, resolution, and reporting
- Study closure



For reference, links to sample SOPs are included in the [Appendix B.1](#) table located in this document.

Documentation

Trial sponsors and investigators participating in clinical trials must prepare and maintain a wide variety of documents during the lifecycle of a clinical trial. These documents play an important role in demonstrating that the investigator, sponsor and monitor are complying with the standards of Good Clinical Practice and all applicable regulatory requirements; they can also assist with successful trial management and confirming the validity of trial conduct and assuring data integrity.

Essential Documents Needed Before, During, and After Clinical Investigations

Section 8 of the [Integrated Addendum to ICH E6 \(R2\): Guideline for Good Clinical Practice](#) provides in-depth information on essential documents that should be prepared before, during, and after the conduct of a clinical trial. While it is important that investigators adhere to sponsor, IRB, and/or applicable regulatory body requests, this guideline provides baseline understanding of essential documents.

The following three tables have been extracted from the Integrated Addendum to ICH E6 (R2): Guideline for Good Clinical Practice and included in the Appendices of this toolkit for reference:

- **8.2 Before the Clinical Phase of the Trial Commences:** describes documents to be created and placed on file before the trial starts. These include documents such as the investigator's brochure, the study protocol, informed consent and Institutional Review Board documents, verification of regulatory authority approval of the protocol, information on the investigator, documentation related to medical procedure and the handling of trial-related materials, decoding procedures for blinded trials, and pre-trial and trial initiation monitoring reports.
- **8.3 During the Clinical Conduct of the Trial:** describes additional documents to be added to files as the trial progresses, and updates that should be captured if any of the original documents were revised or adapted. Revisions to the investigator's brochure, study protocol and CRF, ICF, other written information provided to subjects, and, if applicable, advertisement(s) for subject recruitment should be captured, as should IRB and regulatory approvals for changes, updates to study procedures or related information. New information that will need to be captured includes information such as monitoring visit reports, relevant communications, signed ICFs, source documents, CRFs, information related to serious adverse events, and information related to subject screening, enrollment, among several other documents.
- **8.4 After Completion or Termination of the Trial:** captures information about use of investigational products at the site and subsequent destruction, the completed subject identification code list, the audit certificate (if available), the final close-out monitoring report, documentation on treatment allocation and decoding, the final report by the investigator to the IRB and regulatory authorities, and the clinical study report.



Source Documentation

Source documentation is a part of the essential trial documents covered in Section 8.3 of the Integrated Addendum to ICH E6 (R2): Guideline for Good Clinical Practice. Source documents play critical roles in ensuring the capture of key information about subjects and substantiating the integrity of trial data. ICH defines source data and documents as follows:

- **Source Data:** All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- **Source Documents:** Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

The Principal Investigator and all research personnel are responsible for adherence to the source documentation guidelines as outlined in good clinical practice as well as those provided by the sponsor, IRB and/or any applicable regulatory body.

Monitoring and Quality Assurance

Trial monitoring and quality assurance take place throughout the clinical trial, and are an important part of ensuring that human subjects' rights are protected; trial data are accurate, complete, and verifiable; and that trial conduct complies with the protocol, GCP, and regulatory requirements. The study sponsor will be responsible for selecting qualified study monitors and ensuring adequate monitoring of the study; however, sites should also develop reliable quality control processes and an audit plan.

If deviations from the protocol, GCP, or regulatory requirements are identified, prompt action will be needed to address them. Corrective actions may involve staff training or creation of new SOPs, tools and, templates. All potential corrective actions should be tested prior to implementation to verify that they address the problem and can be incorporated within current procedures relatively easily.

Templates for internal audit tools are included within the Research Tools and Templates section of this document. Also, the Model for Improvement, * developed by Associates in Process Improvement offers the Quality Improvement [Essentials Toolkit](#) that includes a series of tools that can be used to guide those through the process of implementation (See [Institute for Healthcare Improvement \(2017\)\)](#).



Patient Recruitment, Screening, Consent, and Retention

Recruitment

Patient recruitment is one of the most important – yet also time-consuming and potentially costly – aspects of the clinical trial process. Under the guidance of the investigator, research staff are tasked with the responsibility of increasing awareness of clinical trial opportunities and identifying individuals eligible for enrollment in clinical trials. Without an effective patient recruitment strategy, sites may fail to connect with potentially eligible patients, miss deadlines due to low enrollment, or miss the opportunity of enrolling patients, all together, if site is involved in a competitive enrollment process (Tweet, 2011; Sugarman, 2012).

Challenges in Recruiting Patients for SMA Trials

Timely and efficient recruitment is vital to ensure an optimal trial outcome in a progressive rare disease such as SMA; however, the rarity of SMA means patients are often geographically dispersed. As such, it may be more difficult to connect with and recruit patients for trials. It also means that many patients will need to travel a significant distance to reach a trial site (Swoboda et al., 2007; TMJFF, 2011). In a disease that can take a significant physical and emotional toll and make even “the littlest of tasks monumental,” traveling to participate in a clinical trial can become an almost insurmountable burden (Cure SMA, 2018b).

Finding eligible patients for trials can also be challenging because SMA pediatric and neonate patients are also very heterogeneous in terms of their anatomy, metabolism, presentation of disease, diagnostic stage and progression, and possible secondary health problems. This heterogeneity can potentially confound clinical trial results and may further limit the already small pool of eligible patients (Grismund et al., 2015; Stevenson, 2015; Cure SMA, 2018a; Baer, n.d; CDER, 2017).

Strategies to Address Recruitment Challenges

To address these challenges, trial sites may find it helpful to have a communication plan and to incorporate innovative recruitment strategies into these plans. One way for sites and their staff to connect with a larger segment of the geographically disperse patient community and to increase opportunities for recruitment is by working with patient advocacy groups, local groups that provide support and services, and by engaging with the patient community (ACRP, n.d; AccrualNet, 2013). Patient advocacy groups may also maintain SMA patient contact registries to connect interested individuals with particular trials. Establishing good relationships with referring sites can also aid in recruitment.

Alternative advertising platforms, communication strategies, and consideration of patient barriers (e.g., travel challenges) can also help support efficient recruitment (Augustine, Adams, & Mink, 2014; International Rare Diseases Research Consortium (IRDRC), 2016; Tweet, 2011). For example, social media can provide a direct and cost-efficient advertising platform to target populations for clinical



research, thus increasing awareness of clinical trials and helping to inform potential participants of eligibility requirements—particularly for patients who are not located near Centers of Excellence (Krischer et al., 2017; Shpilber, 2017). However, there is a continuing discussion on the benefits of utilizing social media to engage prospective participants and on the ethical considerations that should be addressed when utilizing social media (Krischer et al., 2017; Gelinas et al., 2017).

Sites should be aware that social media is a powerful communication tool that parents and caregivers may turn to for input on clinical trials (SMA Europe, TREAT-NMD, & EMA, 2016; Murphy, 2016). However, the information that is shared by other patients on social media can lead to unrealistic expectations about interventions (SMA Europe, TREAT-NMD, & EMA, 2016). Research teams may wish to be prepared to address these potential misconceptions and to caution participants, parents, and caregivers about relying on unofficial results or feedback from other participants on social media.

The following resources regarding patient recruitment are freely accessible online, and may be helpful:

- **Patient Recruitment in Clinical Trials Steps to Develop a Successful Enrollment Strategy:** This eBook provides the opportunity for research personnel to learn best practices regarding development and implementation of successful recruitment campaigns, using metrics to identify and prevent under-enrollment. (Forte, n.d.)
- **The Expanding Web of Clinical Trial Patient Recruitment:** This report, by Industry Standard Reports, details the various platforms existing clinical trial sites use for patient recruitment, based off a survey. It also discusses the changing and expanding landscape of resources available for patient recruitment. (ISR Reports, 2014)

Screening

Before a research participant can enter a clinical trial, he/she must undergo a screening process. The screening process allows the study investigator/sponsor/team to determine if an individual is eligible to participate in a study. An IRB approved study protocol, including the study procedures to conduct during a screening visit, is used to ascertain the eligibility of potential research participants into a clinical trial. More information on the screening process is included in the Best Practices for Clinical Trial Coordinators Toolkit (click [here](#) to access the toolkits).

Informed Consent

At the outset of any interaction with an individual for research purposes, all staff must initiate the informed consent. Obtaining valid and appropriate informed consent is a crucial part of protecting human subjects' rights and welfare: every member of the research team must recognize this, and ensure that proper consent is obtained for all research subjects before any trial-related procedures are conducted.

Research teams are encouraged to view informed consent as a process that continues throughout the trial, and to regularly revisit aspects of informed consent relevant to activities being carried out as part



of the trial. For successful implementation, in addition to the provision of the consent document, it is crucial for staff to discuss the purpose of the protocol along with any benefits and risks to participation. Staff must also provide ample time for the individual to consider the information provided and discuss concerns with friends, family, and research staff especially the investigator. The FDA offers a comprehensive review of the informed consent process as follows:

“To many, the term informed consent is mistakenly viewed as the same as getting a research participant's signature on the consent form. FDA believes that obtaining a research participant's verbal or written informed consent is only part of the process. Informed consent involves providing a potential participant with:

- *Adequate information to allow for an informed decision about participation in the clinical investigation.*
- *Facilitating the potential participant's understanding of the information.*
- *An appropriate amount of time to ask questions and to discuss with family and friends the research protocol and whether you should participate.*
- *Obtaining the potential participant's voluntary agreement to participate.*
- *Continuing to provide information as the clinical investigation progresses or as the subject or situation requires.”*

(U.S. Food & Drug Administration , 2018)

For additional information linked to implementation of the informed consent process, please review additional FAQ's listed on the [FDA website](#).

Elements of Informed Consent

For studies conducted in the United States, according to 45 CFR 46.116(a), it is required that the informed consent address the following:

- a) Basic elements of informed consent. Except as provided in paragraph (d), (e), or (f) of this section [not included here], in seeking informed consent the following information shall be provided to each subject or the legally authorized representative:
 - 1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
 - 2) A description of any reasonably foreseeable risks or discomforts to the subject;
 - 3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
 - 4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

- 5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
 - 6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
 - 7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
 - 8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; and
 - 9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
 - a. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
 - b. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.
- b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject*:
- 1) A statement that the treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
 - 2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
 - 3) Any additional costs to the subject that may result from participation in the research;
 - 4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
 - 5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject;
 - 6) The approximate number of subjects involved in the study;

* Please note, the items in the aforementioned list are basic requirements and may not be inclusive of all requirements stipulated by your IRB; any additional conditions should be included within the informed consent document prior to use.



- 7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- 8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
- 9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen). (U.S. Department of Health & Human Services (HHS), 2009).

It can be difficult for some to ensure that all requirements have been achieved. The utilization of a checklist documenting the completion of each step with every research participant provides documentation of completion. An informed consent checklist as well as other tools that can assist with facilitation are included in the [Research Tools and Templates](#) section of this document. For additional guidance on how to initiate and complete the informed consent process, please see the [National Institute of Health's Good Clinical Practice Training](#) (NIH, 2017).

Considerations for the Informed Consent Process in SMA

For many SMA clinical trials, it is likely that parents of the SMA patients will provide the consent in order for the patients to participate in the clinical trial. Past clinical trials of rare diseases have found that due to the increased pressure and burden that the parents are dealing with, informed consent becomes a challenge. Some parents do not recall giving consent for their children to participate in clinical trials when initially approached (Yeung, n.d.). Understanding the challenges and ethical issues associated with the informed consent process for pediatric SMA patients—and understanding strategies for addressing these challenges—may help sites to more effectively navigate the informed consent process.

The following proposed strategies were developed to help research teams navigate the informed consent process:

- In terms of general approach, research teams may find it helpful to think about the informed consent process as a continuing dialogue with parents and patients throughout the clinical trial experience (Steinhillber, 2015; Joseph, Craig, & Caldwell, 2015).
- When obtaining consent, having a physician present – or having the physician obtain consent from the parents themselves – may help parents develop trust, which is essential to increasing the chances of consenting (Steinhillber, 2015). Other practical considerations—such as printing multiple copies of the informed consent form, one for the CRC and one for each caregiver, so that parents can follow along as the CRC reviews the form—can also be helpful.
- Flexibility is another factor to keep in mind when obtaining consent. Clear and consistent communication is important, and it may be possible for research staff to adjust how they



communicate key points based on each family and their circumstances (Steinhilber, 2015; Joseph, Craig, & Caldwell, 2015).

For more guidance on the informed consent process, research teams may find the following to be helpful: Basic Requirements for Starting a Research Site by the Association of Clinical Research Professionals (n.d.).

Safety and Adverse Events

ICH E6(R2) defines adverse drug reactions, adverse events, and serious adverse events as follows:

1.1 Adverse Drug Reaction (ADR) In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2 Adverse Event (AE) Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) Any untoward medical occurrence that at any dose:

- Results in death,
- Is life –threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Adverse events are taken seriously in clinical trials and must be documented and addressed in accordance with the trial protocol, GCP, and any applicable regulatory guidelines. Per section 4 of the Integrated Addendum to ICH E6 (R2): Guideline for Good Clinical Practice:



“4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).”

Adverse events can be of high concern in SMA clinical trials, as the often-fragile nature of patients' conditions may heighten the risk of adverse events. Young patients in particular – especially Type I infants – are often chronically, and severely, sick. They may be plagued by respiratory infections (pneumonia, viral, bacterial infections) that necessitate other supportive care interventions and weaken their immune systems. Maintaining awareness within the research team of these risks may help research teams to ensure that they are prepared to respond to adverse events if, and when they occur. For additional resources regarding reporting adverse events to IRBs, please see the FDA's Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection (FDA, 2009).



References for Part 2

- AccrualNet. (2013). Recruitment strategies for rare disease. Retrieved from https://accrualnet.cancer.gov/communities/conversation/recruitment_strategies_for_rare_diseases#.WtUlvYWcE_n
- American Society of Clinical Oncology. (2008). Basic Requirements for Starting a Research Site. Retrieved from: <https://www.asco.org/research-progress/clinical-trials/clinical-trial-resources/basic-requirements-starting-research-site>
- Association of Clinical Research Professionals. (n.d.). The Process of Informed Consent. Retrieved from: <https://www.acrpnet.org/wpcontent/uploads/2016/09/ACRPWhitePaperTheProcessofInformedConsent.pdf>
- Augustine, E. F., Adams, H. R., & Mink, J. W. (2013). Clinical trials in rare disease: Challenges and opportunities. *J Child Neurol*, 28(9), 1142–1150. doi: 10.1177/0883073813495959
- Baer, A. R., Devine, S., Beardmore, C. D., & Catalano, R. (2011). Clinical Investigator Responsibilities. *J Oncol*, 7(2):124-128.
- Baer, G.R. (n.d.) Neonates: Challenges and opportunities for clinical investigators. Retrieved from <https://www.fda.gov/downloads/NewsEvents/MeetingsConferencesWorkshops/UCM519812.pdf>
- Biogen. (2016). The First Treatment for Spinal Muscular Atrophy. Retrived from: <http://investors.biogen.com/news-releases/news-release-details/us-fda-approves-biogens-spinrazatm-nusinersen-first-treatment>
- Center for Drug Evaluation and Research (CDER). (2017). Rare diseases 2017 public workshop: Strategies, tools, and best practices for effective advocacy in rare diseases drug development. Retrieved from <https://www.fda.gov/downloads/Drugs/NewsEvents/UCM583517.pdf>
- Council for International Organizations of Medical Sciences (CIOMS); World Health Organization (WHO). International Ethical Guidelines for Health-related Research Involving Humans (2016). Retrieved from: <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>
- Cure SMA. (2018). Clinical care network & clinical data registry project & clinical trials' site expansion projects for SMA. Retrieved from <http://www.curesma.org/documents/32118-clinical-webinar-deck.pdf>
- Cruz, R., Lenz, M., Belter, L., Hobby, K., Jarecki, J. (2018). Voice of the patient report: A summary report from an externally led patient focused drug development meeting reflecting the U.S. Food and Drug Administration (FDA) patient-focused drug development initiative. Retrieved from <http://www.curesma.org/documents/advocacy-documents/sma-voice-of-the-patient.pdf>
- CURE SMA. (n.d.). *Living with SMA*. Retrieved from: <http://www.curesma.org/support-care/living-with-SMA/medical-issues/orthopedics/>.
- McGraw, D.J. M., Rene S. Cabral-Daniels, J. M., & B. Vindell Washington, M. M. (2017). An Individual's Right to Access and Obtain Their Health Information Under HIPAA. Retrieved from: https://www.medscape.org/viewarticle/876110?src=acdm part ocr-hhs_876110

- Forte. (2017). *Patient Recruitment in Clinical Trials: Steps to Develop a Successful Enrollment Strategy*. Retrieved from: https://cdn2.hubspot.net/hubfs/216272/eBooks/eBook_Patient_Recruitment_2017.pdf
- Gelinas, L., Pierce, R., Winkler, S., Cohen, I. G., Lynch, H. F., & Bierer, B. E. (2017). Using social media as a research recruitment tool: Ethical issues and recommendations. *The American Journal of Bioethics*, 17(3), 3–14. doi:10.1080/15265161.2016.1276644
- Glanzman, A.M., Mazzone, E., Main, M., Pelliccioni, M., Wood, J., Swaboda, K.J.....Finkel, R.S. (2010) The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *J Neuromuscul Dis*. 20:155-161.
- Glascok, J., Sampson, J., Haidet-Phillips, A., Connolly, A., Darras, B., Day, J.....Jarecki, J. (2018). Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screen. *J Neuromuscul Dis*. doi:10.3233/JND-180304
- Grimsrud, K., Sherwin, S., Constance, J., & Tak, C. (2015). Special population considerations and regulatory affairs for clinical trials. *Clinical Research and Regulatory Affairs* doi:10.3109/10601333.2015.1001900
- Harvard Catalyst. (2016). Research Resources. Retrieved from: <https://catalyst.harvard.edu/services/regbinder/>
- Harvard School of Public Health. (2014). Informed Consent Assessment Checklist. Retrieved from: https://www.hsph.harvard.edu/ohra-new/wp-content/uploads/sites/2102/2017/05/Informed-Consent_Assent-Checklist-and-observation-tool-8-1-2014.docx.
- Industry Standard Research. (2017). ISR Whitepaper: The Expanding Web of Clinical Trial Patient Recruitment. Retrieved from: <http://www.isrreports.com/wp-content/uploads/2014/04/ISR-The-Expanding-Web-of-Clinical-Trial-Patient-Recruitment-Whitepaper.pdf>
- Institute for Healthcare Improvement. (2017). Quality Improvement Essentials Toolkit. Retrieved from: <http://www.ihl.org/resources/Pages/Tools/Quality-Improvement-Essentials-Toolkit.aspx>
- Institute of Translational Health Sciences. (n.d.). Study Document Templates. Retrieved from ITHS: <https://www.iths.org/investigators/forms-templates/study-document-templates/>
- International Council for the Harmonisation for International Requirements of Technical for Pharmaceuticals for Human Use (ICH). (2016). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). Retrieved from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf
- International Rare Disease Research Consortium (IRDiRC). (2016). Small population clinical trial force workshop report and recommendations. Retrieved from http://www.irdirc.org/wp-content/uploads/2017/12/SPCT_Report.pdf
- ISR Reports. (2014). The Expanding Web of Patient Recruitment. Retrived from: <http://www.isrreports.com/wp-content/uploads/2014/04/ISR-The-Expanding-Web-of-Clinical-Trial-Patient-Recruitment-Whitepaper.pdf>
- Joseph, P. D., Craig, J. C., & Caldwell, P. H. (2013). Clinical trials in children. *British Journal of Clinical Pharmacology*, 79(3), 357–369. doi: 10.1111/bcp.12305

- Krischer, J., Cronholm, P. F., Burroughs, C., McAlear C. A., Borchin, R., Easley, E.,... Vasculitis Clinical Research Consortium. (2017). Experience with direct-to-patient recruitment for enrollment into a clinical trial in a rare disease: A web-based study. *Journal of Medical Internet Research*, 19(2), e50. doi: [10.2196/jmir.6798](https://doi.org/10.2196/jmir.6798)
- MRCT Center at Harvard Ethics Workgroup. (2014). Toolkit: MRCT Ethics Essential Elements and Points to Consider Reference Document. Retrieved from: <http://mrctcenter.org/resources/2014-11-14-training-material-mrct-ethics-essential-elements-and-points-to-consider-reference-document/>
- Murphy, M. F. (2016). Rare diseases: Meeting the unique challenges of orphan drug development. *Applied Clinical Trials*. Retrieved from <http://www.appliedclinicaltrialsonline.com/rare-diseases-meeting-unique-challenges-orphan-drug-development>
- National Archives and Records Administration's Office of the Federal Register (OFR). (2018). Title 21. Retrieved from: https://www.ecfr.gov/cgi-bin/text-idx?SID=3ee286332416f26a91d9e6d786a604ab&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl
- National Archives and Records Administration's Office of the Federal Register (OFR). (2018). Title 45. Retrieved from: https://www.ecfr.gov/cgi-bin/text-idx?SID=bec24c15274dbc44c282650ddb6d7846&mc=true&tpl=/ecfrbrowse/Title45/45tab_02.tpl
- National Center for Complementary and Integrative Health (NCCIH). (2018). NCCIH Clinical Research Toolbox. Retrieved from: <https://nccih.nih.gov/grants/toolbox#templates>
- National Drug Abuse Treatment Clinical Trials Network (NIDA). (n.d.). Roles and Resources. Retrieved from: <https://gcp.nidatraining.org/modules/9/pdf>
- National Institute of Health. (n.d.). What Makes Clinical Research Ethical? Retrieved from: <https://crt.nihtraining.com/ethics/index.php?p=22>
- National Institute of Aging. (n.d.). Clinical Research Study Investigator's Toolbox: Informed Consent. Retrieved from: <https://www.nia.nih.gov/research/dgcr/clinical-research-study-investigators-toolbox/informed-consent>
- National Institute of Health (NIH). (2017). Good Clinical Practice Training. Retrieved from <https://grants.nih.gov/policy/clinical-trials/good-clinical-training.htm>
- National Institute of Health (NIH): Research Involving Human Subjects. (n.d.). Ethical Guidelines & Regulations. Retrieved from: <https://humansubjects.nih.gov/ethical-guidelines-regulations>
- NIH CC Office of Clinical Research Training and Medical Education. (n.d.). Clinical Research Training. Retrieved from: <https://crt.nihtraining.com>
- Osmosis. (2017). Spinal muscular atrophy - causes, symptoms, diagnosis, treatment, pathology. Retrieved from: <https://www.youtube.com/watch?v=Ax89gbbC-4g>
- Shpillber, S. (2017) Social media for clinical trial patient recruitment: The comprehensive guide. *AMWA Journal*. 32(4), 162-165. Retrieved from https://cdn.ymaws.com/www.amwa.org/resource/resmgr/journal/Spotlight/2017v32n4_SocialMedia.pdf
- SMA Europe and TREAT-NMD. (2016). Briefing Document to the Clinical Trial Readiness in Spinal Muscular Atrophy (SMA) SMA Europe, TREAT-NMD and European Medicines Agency meeting.



London: European Medicines Agency. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500217553.pdf

Steinhilber, G. (2015). 10 Lessons learned in recruitment for pediatric trials. Forte Research. Retrieved from <https://forteresearch.com/news/10-lessons-learned-in-recruitment-for-pediatric-trials/>

Stevenson, D. (2015). Clinical trials for rare diseases—finding and keeping patients. BHD Foundation. Retrieved from <https://www.bhdsyndrome.org/forum/bhd-research-blog/clinical-trials-for-rare-diseases-finding-and-keeping-patients/>

Swoboda, K. J., Kissel, J. T., Crawford, T. O., Bromberg, M. B., Acsadi, G., D'Anjou, G., & Simard, L. R. (2007). Perspectives on clinical trials in spinal muscular atrophy. *J Child Neurol*, 22(8), 957–966. <http://doi.org/10.1177/0883073807305665>

The Global Health Network. (2012). Downloadable Templates and Tools for Clinical Research. Retrieved from: <https://globalhealthtrainingcentre.tghn.org/articles/downloadable-templates-and-tools-clinical-research/>

The Global Health Network. (n.d.). ELearning: Short Courses. Retrieved from: <https://globalhealthtrainingcentre.tghn.org/elearning/short-courses/>

The Global Health Network. (n.d.). ELearning: Modular Courses. Retrieved from: <https://globalhealthtrainingcentre.tghn.org/elearning/modular-courses/>

The Michael J. Fox Foundation (MJFF). (2011). Clinical trials recruitment best practices manual. Retrieved from https://www.michaeljfox.org/files/MJFF_Recruitment_Best_Practices_manual.pdf

Tufts Office of the Vice Provost for Research, Health Sciences IRB. (n.d.). Checklists and Worksheets. Retrieved from: <http://viceprovost.tufts.edu/HSIRB/checklists-and-worksheets/>

Tweet, M. S. (2011). Social media aided in recruiting for clinical trial in rare disease. Healio. Retrieved from <https://www.healio.com/hematology-oncology/practice-management/news/online/%7B6ddd9104-4636-46f7-b22e-29e2dfd0d13%7D/social-media-aided-in-recruiting-for-clinical-trial-in-rare-disease>

U.S. Department of Health & Human Services (HHS). (2009). 45CFR 46. Retrieved from: <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.116>

U.S. Department of Health & Human Services: Office for Human Research. (2018). Research. Retrieved from: <https://www.hhs.gov/hipaa/for-professionals/special-topics/research/index.html>

U.S. Department of Health & Human Services: Office for Human Research Protections . (2016). THE Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Retrieved from: <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html>

U.S. Department of Health & Human Services: Office for Human Research Protections. (2017). Informed Consent FAQs. Retrieved from: <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/index.html>

U.S. Department of Health and Human Services, Food and Drug Administration. (2009). Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs - Improving Human



Subject Protection. Retrieved from:

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079753.pdf>

U.S. Food & Drug Administration . (2018). Informed Consent for Clinical Trials. Retrieved from:

https://www.fda.gov/ForPatients/ClinicalTrials/InformedConsent/default.htm#What_is_Informed_Consent

U.S. Food & Drug Administration. (2014). Informed Consent Info Sheet. Retrieved from:

https://www.fda.gov/ForPatients/ClinicalTrials/InformedConsent/default.htm#What_is_Informed_Consent_

University of Alabama at Birmingham Center for Clinical and Translational Science. (n.d.). Standard Operating Procedure (SOP) Library. Retrieved from:

https://www.uab.edu/ccts/images/SOP_Library_Documents/RM_XX.XX_Sponsor_CRO_and_Internal_Audits.docx

Vick, M. (2010). SOP Writing for Clinical Research. Institute of Translational Health Sciences. Retrieved from: <https://www.iths.org/wp-content/uploads/ITHS-SOPs-for-Clinical-Research-03-03-10.pdf>

World Health Organization. (n.d.). Informed Consent Templates. Retrieved from:

http://www.who.int/rpc/research_ethics/informed_consent/en/

World Medical Association (WMA). (2018). Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Retrieved from: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>



Part 3

Appendices



PART 3: APPENDICES

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Appendix A. Glossary of Commonly Used Terms

A.1. Commonly Used Clinical Research Terms

Excerpted from Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice

Adverse Drug Reaction (ADR) In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Adverse Event (AE) Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Amendment (to the protocol) (See [Protocol Amendment](#))

Applicable Regulatory Requirement(s) Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Approval (in relation to Institutional Review Boards) The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Audit Certificate A declaration of confirmation by the auditor that an audit has taken place.

Audit Report A written evaluation by the sponsor's auditor of the results of the audit.



Audit Trail Documentation that allows reconstruction of the course of events.

Blinding/Masking A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF) A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial/Study Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical Trial/Study Report A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

Comparator (Product) An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Compliance (in relation to trials) Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Confidentiality Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Contract A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Coordinating Committee A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

Coordinating Investigator An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

Contract Research Organization (ORO) A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.



Direct Access Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

Documentation All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Essential Documents Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

Good Clinical Practice (GCR) A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee) An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Impartial Witness A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Independent Ethics Committee (IEC) An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

Informed Consent A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to



the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Institution (medical) Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Institutional Review Board (IRB) An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim Clinical Trial/Study Report A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Investigational Product A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. (See also [Sub investigator](#)).

Investigator/Institution An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

Investigator's Brochure A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigator's Brochure).

Legally Acceptable Representative An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Monitoring The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).



Monitoring Report A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

Multicenter Trial A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Nonclinical Study Biomedical studies not performed on human subjects.

Opinion (in relation to Independent Ethics Committee) The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

Original Medical Record See Source Documents.

Protocol document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

Protocol Amendment A written description of a change(s) to or formal clarification of a protocol.

Quality Assurance {QA} All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC) The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Randomization The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments to reduce bias.

Regulatory Authorities Bodies having the power to regulate. In the ICH GCP Guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see I .29). These bodies are sometimes referred to as competent authorities.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect



(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Source Data All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Sponsor-Investigator An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Standard Operating Procedures (SOPs) Detailed, written instructions to achieve uniformity of the performance of a specific function.

Sub investigator Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). (See also [Investigator](#)).

Subject/Trial Subject An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Subject Identification Code A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

Trial Site The location(s) where trial-related activities are conducted.

Unexpected Adverse Drug Reaction An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)



(See the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Vulnerable Subjects Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Well-being (of the trial subjects) The physical and mental integrity of the subjects participating in a clinical trial.

ADDENDUM

Certified Copy A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Monitoring Plan A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

Validation of Computerized Systems A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.



A.2. Glossary of Common Terms Related to SMA

The following is a basic glossary of acronyms and vocabulary associated with SMA. For more information about SMA, please see the opening of the toolkit, or refer to the Cure SMA website at www.curesma.org. Excerpted also taken from the [GeneReviews®](#).

Amniocentesis A type of prenatal testing that can be done as early as the 14th week of pregnancy. Amniocentesis can detect SMA in a fetus, but is associated with a risk of miscarriage that may be as high as 1 in 200.

Aspiration the inhalation of food or liquid into the lungs while eating.

Autosomal Recessive mode of disease inheritance which requires two copies of the mutated gene for the condition to develop. In SMA, the child who is affected by SMA inherits two copies of a mutated gene, one copy from each parent; while not typically affected by SMA, each parent carries one copy of the mutated SMA gene.

Bell-Shaped Chest Children with SMA may appear to have “bell-shaped” chests, which look wider at the bottom than at the top. This happens because the weak intercostal muscles do not help the upper chest to expand (or go out) normally during breathing, and the diaphragm pulls the chest and rib cage down.

Bi-level positive airway pressure (BiPAP) A machine that provides breathing assistance through a mask over the nose, or nose and mouth. The machine provides higher pressure and an increased volume of air when the individual inhales, and lowers its pressure automatically when the individual exhales. Often recommended for SMA patients as opposed to CPAP.

Bone mineral density (BMD) a test that measures the density of minerals (such as calcium) in your bones using a special x-ray called a DEXA. This information is used to estimate the strength of bones.

Chromosome DNA carrying structures located within the nucleus of cells.

Compound Muscle Action Potential (CMAP) electrophysiological examination of muscle function.

Computerized tomography (CT scan) specialized x-ray study that looks at different views of a structure, which gives more detail than a regular x-ray.

Contractures fixed tightness around joints, caused by abnormal shortening of muscle tissue due to limited mobility that are most commonly found at the ankles, knees, hips, elbows, forearms, and wrists.

Chorionic villus sampling (CVS) A type of prenatal testing that can be done as early as the 10th week of pregnancy. CVS can detect SMA in a fetus, but is associated with a risk of miscarriage that may be as high as 1 in 100.



Cough Machine used to help your child inhale and exhale. The machine forces air into the lungs at a preset pressure and then sucks the air out of the lungs at a preset pressure.

Deletion Mutation Genetic mutation caused by a deletion of part of the chromosome that can vary in severity.

Dual Energy X-ray Absorptiometry (DEXA) an x-ray that measures the amount of bone mineral content (BMC) in the femur, spine, radius, or whole body.

Exon Coding portions of DNA sequences.

Fracture a bone that is broken.

Gastronomy (G) Tube a tube surgically placed directly into the stomach to help with feeding.

Gene Conversion transfer of DNA sequences between two similar genes.

Growth Rods surgically implanted hardware in younger children with severe scoliosis that allows for growth of the spine through periodic adjustments for growth.

Hammersmith Functional Motor Scale (HFMS) - a motor assessment developed by Main and colleagues, used to evaluate motor function and specifically developed for SMA Type 2 and 3 patients. There are multiple versions of the HFMS being used and validated, including the Expanded and Modified HFMS.

Heterozygous carrying two different copies of the same allele.

Hip abduction if hips are abducted, they are spread away from the center of the body.

Hip Dislocation the head of the femur bone is out of the hip socket.

Hip Dysplasia shallow hip socket (acetabulum).

Hip Subluxation femoral head is not covered completely by the hip socket.

Homozygous carrying two identical copies of the same allele.

Hypotonia - commonly known as floppy baby syndrome, is a state of low muscle tone (the amount of tension or resistance to stretch in a muscle), often involving reduced muscle strength.

Hypoventilation breathing is too shallow or too slow. The lungs are not taking in (inhaling) enough oxygen or giving off (exhaling) enough carbon dioxide to meet the needs of the body. Hypoventilation during sleep is often one of the earliest signs of breathing difficulty in SMA.

Intercostal Muscles the muscles lying between the ribs that help to move the chest wall by expanding and contracting to facilitate breathing.



Intron Noncoding portions of DNA sequences.

Kyphosis spinal curve forward (hunchback).

Lordosis spinal curve of the low back inward (swayback).

Motor Neuron a neuron (nerve cell that sends and receives messages) that facilitates muscle contraction; arises from the spinal cord and control the muscles that are used for activities such as breathing, crawling, walking, head and neck control, and swallowing. A neuron is a to and from parts of the body. In SMA, the motor-neurons in the spinal cord do not have enough of a certain protein, called **SMN** protein. As a result, these motor-neurons do not function normally and may die, resulting in muscle weakness and atrophy (shrinkage).

Motor Unit Count Estimate (MUNE) electrophysiological examination of muscle function

Muscle Atrophy also known as muscle wasting; in the case of SMA, it is due to denervation (loss of nerve supply) of the muscle.

Nasoduodenal (ND) Tube a small flexible tube inserted in the nose that runs down to the duodenum of the small intestine.

Nasogastric (NG) Tube a small flexible tube inserted in the nose that runs down to the stomach to help with feeding.

Nasojejunal (NJ) Tube a small flexible tube inserted in the nose that runs down the jejunum of the small intestine to help with feeding.

Neuromuscular Disease (NMD) a disease that affects the peripheral nervous system, which includes the motor-neuron cell body (located within the spinal cord), motor-neuron axons (projections from the cell body to muscles), neuromuscular junctions (the connection between the motor-neuron axons and muscles), or the muscles themselves. The central nervous system includes the brain and the spinal cord. The peripheral nervous system includes everything outside the brain and the spinal cord. The job of the peripheral nervous system is to send information to and from the central nervous system to regulate muscle activity.

Nissen Fundoplication A surgical procedure in which the top of the stomach (fundus) is wrapped around the lower esophagus to support the function of the lower esophageal sphincter (LES); treats acid reflux and GERD.

Non-invasive (NIV) Respiratory Treatment Non-invasive describes a care intervention that does not cut into or go inside the body. Non-invasive respiratory care offers breathing assistance via the use of a mask over the nose.

Nucleotide the basic unit of nucleic acids including DNA.



Osteopenia mild to moderate decrease in bone mineral density.

Osteoporosis severe decrease in bone mineral density that is associated with a higher chance of a fracture.

Osteotomy surgery where the bone is cut and the alignment is changed

Palliative care Palliative means relieving or soothing symptoms without curing the underlying disease. Though palliative care is usually associated with end-of-life decisions, it is broader than that. Palliative care aims to provide comfort for children and families, and to uphold quality of life: physically, psychologically, socially, emotionally, and spiritually.

Point Mutation a mutation in which a single nucleotide is altered.

Pectus Excavatum when the sternum, the bone in the middle of the chest, appears to be sunken. When the diaphragm pulls the rib cage down, the sternum is also pulled in.

Scoliosis curvature of the spine to the side.

Six-minute walk test (6MWT) A standardized way of measuring a patient's mobility. It involves measuring how far a person can walk in six minutes.

SMN Protein Survival Motor Neuron protein - produced from both the *SMN1* and *SMN2* genes, the *SMN* protein is required for the survival of lower motor neurons. If there is no *SMN* protein in a cell, the cell will die. Of all the different cell types, the lower motor neurons seem to be most affected by low levels of *SMN* protein.

Spine Fusion a surgery performed to fuse the spine straighter, usually using metal rods.

Standard of Care (SOC) specifics regarding diagnosis and treatment in which all providers should adhere when interacting with patient with a specific diagnosis; SOC changes as new evidence based practices are developed. This document offers a summary of SOC practices for the diagnosis and treatment of SMA. However, to access the original documents please see [Treatment algorithm for Infants Diagnosed with Spinal Muscular Atrophy through New Born Screening](#) (Glascok et al, 2018), [218th ENMC International Workshop: Revisiting the consensus on standards of care in SMA Naarden, The Netherlands, 19–21 February 2016](#) (Finkel et al, 2016), and [Consensus Statement for Standard of Care in Spinal Muscular Atrophy](#) (Wang et al, 2007; Finkel et al., 2017; Mercuri et al., 2017).

Stomach (Belly) Breathing Children with SMA breathe differently. Their intercostal muscles between the ribs are weak. Their diaphragms are stronger and become the major muscle used for breathing. With weak intercostal muscles, the rib cage does not expand outward during breathing. The diaphragm, however, stays strong and pulls the rib cage downward. This causes what appears to be “stomach breathing”— when the child expands the stomach while breathing, instead of the chest.

Supportive Care (See [Palliative Care](#))



Survival motor neuron gene 1 (SMN1) A gene that produces a protein—called survival motor neuron protein or *SMN* protein—that is critical to the function of the nerves that control an individual's muscles. SMA is caused by a mutation in this gene. When *SMN* protein is not produced correctly, those nerve cells cannot properly function and eventually die, leading to debilitating and often fatal muscle weakness.

Survival motor neuron gene 2 (SMN2) Also called the SMA “back-up gene.” This gene also produces *SMN* protein, but the protein produced by *SMN2* lacks a key building block normally produced by *SMN1*. Many potential SMA treatments focus on prompting *SMN2* to produce more protein, or to produce a complete protein.

Thoracic-Lumbar-Sacral Orthosis (TLSO) body jacket, also known as a brace, that provides external support to the spine

Tracheostomy a procedure in which the doctor creates a small, surgical hole in the neck and inserts a breathing tube (tracheostomy tube) through this hole. This breathing tube, therefore, bypasses the mouth and vocal cords, sparing them long-term damage by going directly into the trachea and lungs.

Vertical Expandable Prosthetic Titanium Rib (VEPTR) System hardware that is surgically implanted in younger children with severe scoliosis that allows for growth of the spine through periodic adjustments for growth.

Z-score the result of the DEXA is referred to as a Z-score and is the measure of how close or far the result is from that of the average child of the same sex and age.



Appendix B. Resources to Assist with Protocol Adherence

B.1. Tools and Templates

The tools listed within the following table were provided to assist with protocol adherence. These documents do not supersede those required by your facility or the sponsor; these tools should be considered an additional resource. The templates themselves have been obtained from a variety of sources as indicated within each document and the associated footnote.

The tools provided below are not requirements, but merely included as a potential resource which can be customized to meet the needs of each institution and protocol and to help you to optimize the collection and organization of required documentation throughout the clinical trial lifecycle. Additional information about similar tools and templates can be found in the appendices of our complementary toolkits for study coordinators and clinical evaluators.

Please note: If an FDA audit were to occur, all research staff must adhere to those SOPs that are implemented at your site. Routine internal audits and applicable staff training should be utilized to verify use.

Title	Tools, Templates, & SOPs (hyperlinks to external resources)
Adverse Event (AE) reporting	Adverse Event Log Adverse Events Record Template Safety assessment and reporting SOP
Audit / Quality Control	File Review Checklist Regulatory File Review Checklist Routine Self Audit SOP
Case Report Form	Case Report Form Template (Generic)
Activities for study close out	Study Close Out and Early Termination Checklist Site Close Out SOP
Communication documents*	Communication Log Meeting Minutes

Title	Tools, Templates, & SOPs (hyperlinks to external resources)
Concomitant Medications	Concomitant Medications Log <i>*Maintaining accurate, well-documented medication logs is an especially important part of recordkeeping.</i>
Drug accountability and storage	Pharmacy Accountability Form Managing Investigational Drug SOP
IND Safety Report	IND Safety Report Log
Informed consent process	Informed Consent Template Informed Consent Checklist Informed Consent Version Tracker Informed Consent SOP
Training Log	Research Staff Training Log
Protocol Deviation	Protocol Deviation Log
Regulatory Binder	Regulatory Binder Instructions
Screening & Enrollment	Recruitment and Enrollment SOP Subject Screening Log Subject Identification Log
Site Initiation	Site Initiation SOP
Staff Training and Study Handover	Staff Training and Study Handover SOP
Standard Operating Procedures (SOPs)	SOP for Preparing SOPs SOP Template SOP Management SOP Log

B.2. Essential Documents According to ICH E6(R2)

The following three tables describing essential documents that should be prepared before, during, and after the conduct of a clinical trial have been excerpted from the Integrated Addendum to ICH E6 (R2): Guideline for Good Clinical Practice. Copyright for the content contained within these tables is held by International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

ICH E6(R2) - 8.2 Before the Clinical Phase of the Trial Commences

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
8.2.1	INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	INFORMATION GIVEN TO TRIAL SUBJECT - INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent	X	X
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
8.2.4	FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5	INSURANCE STATEMENT (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.: - investigator/institution and sponsor - investigator/institution and CRO - sponsor and CRO - investigator/institution and authority(ies) (where required)	To document agreements	 X X X	 X X (where required) X X
8.2.7	DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment	To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s)	X	X

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
	(if used) - subject compensation (if any) - any other documents given approval/ favorable opinion			
8.2.8	INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL (where required)	To document appropriate authorization/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and/or ranges of the tests	X	X
8.2.12	MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS - certification or - accreditation or	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
	<ul style="list-style-type: none"> - established quality control and/or external quality assessment or - other validation (where required) 			
8.2.13	SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects	X	
8.2.14	INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
8.2.15	SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16	CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED	To document identity, purity, and strength of investigational product(s) to be used in the trial	X	
8.2.17	DECODING PROCEDURES FOR BLINDED TRIALS	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for	X	X (3rd party if applicable)

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
		the remaining subjects' treatment		
8.2.18	MASTER RANDOMISATION LIST	To document method for randomization of trial population		X (3rd party if applicable)
8.2.19	PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X



ICH E6(R2) - 8.3 During the Clinical Conduct of the Trial

Documents included in the table below should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
8.3.1	INVESTIGATOR'S BROCHURE UPDATES	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	ANY REVISION TO: - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
8.3.3	<p>DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</p> <ul style="list-style-type: none"> - protocol amendment(s) - revision(s) of: - informed consent form - any other written information to be provided to the subject - advertisement for subject recruitment <p>(if used)</p> <ul style="list-style-type: none"> - any other documents given approval/favorable opinion - continuing review of trial (where required) 	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favorable opinion. To identify the version number and date of the document(s).	X	X
8.3.4	<p>REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:</p> <ul style="list-style-type: none"> - protocol amendment(s) and other documents 	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)	(see 8.2.10)	X	X

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
8.3.6	UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT	(see 8.2.15.)	X	X
8.3.9	CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS	(see 8.2.16)		X
8.3.10	MONITORING VISIT REPORTS	To document site visits by, and findings of, the monitor		X

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
8.3.11	<p>RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS</p> <ul style="list-style-type: none"> - letters - meeting notes - notes of telephone calls 	<p>To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting</p> <p>-NOTE: This is highly important, and can be inadvertently neglected due to the complexity of protocols and high volume of activity associated with trials. As such, special attention should be paid to ensuring that appropriate records are maintained.</p>	X	X
8.3.12	SIGNED INFORMED CONSENT FORMS	<p>To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)</p>	X	

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
8.3.13	SOURCE DOCUMENTS	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject. NOTE: See note in 8.3.11	X	
8.3.14	SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	DOCUMENTATION OF CRF CORRECTIONS	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
8.3.17	NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2	X (where required)	X
8.3.18	NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	SUBJECT SCREENING LOG	To document identification of subjects who entered pre-trial screening	X	X (where required)

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
8.3.21	SUBJECT IDENTIFICATION CODE LIST	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22	SUBJECT ENROLLMENT LOG	To document chronological enrollment of subjects by trial number	X	
8.3.23	INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	SIGNATURE SHEET	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	X	X
8.3.25	RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)	To document location and identification of retained samples if assays need to be repeated	X	X



ICH E6(R2) - 8.4 After Completion or Termination of the Trial

All of the documents identified in Sections 8.2 and 8.3 should be in the file together with the following after completion of the trial:

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
8.4 .1	INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4 .2	DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4 .3	COMPLETED SUBJECT IDENTIFICATION CODE LIST	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4 .4	AUDIT CERTIFICATE (if available)	To document that audit was performed		X
8.4 .5	FINAL TRIAL CLOSE-OUT MONITORING REPORT	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4 .6	TREATMENT ALLOCATION AND DECODING DOCUMENTATION	Returned to sponsor to document any decoding that may have occurred		X

	Title of Document	Purpose	Located in Files of:	
			Investigator	Sponsor
8.4 .7	FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)	To document completion of the trial	X	
8.4 .8	CLINICAL STUDY REPORT	To document results and interpretation of trial	X (if applicable)	X

(ICH, 2016)



Appendix C: Relevant Certifications and External Resources for Key Members of the Research Team

Certification	Relevant For
Association of Clinical Research Professionals Clinical Research Certification for PIs (Certified Principal Investigator)	PIs
Association of Clinical Research Professionals Clinical Research Coordinator Certification	CRCs
Society of Clinical Research Associates Clinical Research Certification	CRCs

Resources on SMA, Genetic Disease, and Clinical Research Topics

This Appendix offers information about various training resources that may be of interest for research teams working on clinical trials for spinal muscular atrophy (SMA). Cure SMA also maintains information about trainings specifically for clinical research coordinators, available on the Cure SMA Trial Readiness Hub (www.curesma.org/clinical-trial-readiness).

Resources on SMA Diagnosis and Management

Cure SMA: CME Podcast Series (Free)

Cure SMA collaborated with expert clinical care stakeholders to develop a series of podcast presenting on options for management, novel therapies, and approaches for functional assessments for SMA.
<https://soundcloud.com/user-5816643>

The France Foundation: Urgency for Early Diagnosis and Treatment of SMA (Free)

The France Foundation collaborated with Cure SMA to present on the importance and impact of early diagnosis of SMA. The presentation is accompanied with a pre/post-test and various resources (e.g. toolkits, reference guides, etc.) related to the early detection and diagnosis of SMA.
https://www.francefoundation.com/content/curesma/splash/story_html5.html

NeuroSeries Live: Spinal Muscular Atrophy: Best Practices in Diagnosis and Management (Free)

Expert healthcare providers present on best clinical practices and consensus guidelines for optimized management and diagnosis of SMA.
https://www.neuroserieslive.com/app/signup/121219_NSL_SMA_CME_Reg/formPage/0?refCode=PAR_CureSMA_SMA_ICYMI_121219

NACCME: Navigating the Therapeutic Advances for Spinal Muscular Atrophy (Free)

NACCME hosts a webinar to discuss the clinical, economic, and psychosocial burdens of SMA, new and emerging therapies, and strategies to increase detection, diagnosis, and treatment of SMA.
<https://www.naccme.com/program/19-mcIn-209>

Ology Medical Education: Advances in Neurological Disorder Management (Free)



An NMD learning center provides access to various CME-accredited activities, including webcasts, patient case discussions, to promote best practices for the management of neuromuscular disorders.

<https://ologyeducation.org/neuromusculardisorders/>

Stanford Medicine: Spinal Muscular Atrophy: Current Advances in Treatment and Recommendations for Evaluation and Rehabilitation (Free)

The Stanford Center for Continuing Medical Education developed an online course to educate healthcare providers on the clinical perspective of SMA and how providers, outside of specialized SMA centers, can manage rehabilitation and assess SMA patients. <https://stanford.cloud-cme.com/default.aspx?P=0&EID=35514>

Cure SMA Youtube Channel (Free)

Cure SMA's Youtube channel is home to a variety of Cure SMA webinars and other videos that may be of interest to those who want to learn more about SMA and how it affects those with the disease. The channel includes Cure SMA's SMART Moves Video Resources, which teach viewers about the warning signs of SMA, videos from affected individuals about living with SMA – including videos on clinical meaningfulness and the impact of SMA on teens – and webinars from Cure SMA, among other videos.

<https://www.youtube.com/channel/UCECjEI49gy32nz8wWeb2AFQ>

Resources on Genetic Diseases and Rare Diseases

PBS: The Gene: An Intimate History (Free)

A documentary series that discusses the history of the human genome and diagnosis and treatment of genetic diseases. SMA is discussed in episode two. <https://www.kpbs.org/news/2020/apr/06/gene-intimate-history/>.

Rare University Courses: Understanding Genetic Concepts and Drug Development (Free)

Global Genes has created two online courses that will be of interest for those new to rare disease clinical trials. The first, "Genetic Concepts for Rare Disease Patients and Families" is a series of over two dozen online lectures presented in four sections: genetic concepts, heredity and family, genetic testing, and scientific advances. The second, "Understanding Drug Development" reviews the drug development process; the roles of patients, funders, researchers, and regulators; steps in development and clinical evaluation; regulatory review; and considerations specific to rare diseases. Courses are free with a free account. <https://rareuniversity.com/courses>

Resources on Clinical Research Topics & Related Trainings

ACRP Resources (Cost varies; some resources are free)

The Association of Clinical Research Professionals (ACRP) has an array of training resources for entry level, intermediate, and senior clinical research professionals. For online resources, users of their website can sort resources based on role, knowledge level, contact hours (if continuing education credits are needed), type of resource, and competency area. Many trainings are free to members, although others require payment for both members and nonmembers. ACRP also offers periodic in-person meetings and training workshops.

<https://acrpnnet.org/training/>

SOCRA ONLINE Educational Offerings for Clinical Research Education (Cost varies)



The Society of Clinical Research Associates (SOCRA) offers in-person and online training resources. Information about in-person meetings and training workshops can be found on the SOCRA website. Online courses are “intended to provide access to training and continuing education that will promote quality clinical research, protect the welfare of research participants and improve global health.” The courses – which are in the form of webinars – focus on essential concepts in clinical research. The cost of the meetings and online courses varies, and some are free to members. <https://www.socra.org/conferences-and-education/online-courses/>

Transcelerate Multimedia Library (Free)

The Transcelerate video library offers videos on a variety of important and emerging issues in clinical research, which are free to view and may be of particular interest to those who want to learn about innovations in clinical research approaches. <https://transceleratebiopharmainc.com/video/>

CITI Program

Offers a wide range of key trainings for those involved in clinical research. <https://about.citiprogram.org/en/homepage/>

Global Health Network

Includes a variety of free training opportunities, including short courses and modular courses. Certificate is provided upon completion of each course. <https://tghn.org/>

NIH Training Center (NIH, n.d.)

Offers free training on ethical issues, roles and responsibilities of the institution and the investigator, regulatory issues and media. <https://crt.nihtraining.com/>

HHS.gov

Provides a comprehensive overview of HIPAA and confidentiality issues. <https://www.hhs.gov/hipaa/for-professionals/special-topics/research/index.html>

An Individual’s Right to Access and Obtain Their Health Information Under HIPAA

FREE CME that reviews patient rights related to HIPAA. https://www.medscape.org/viewarticle/876110?src=acdmpt_ocr-hhs_876110

Other External Resources

Coursera Courses and Specializations (Cost varies; some courses are free)

Coursera offers a wide range of courses in clinical research, drug development, and project management topics. Individuals can search their website to learn more about specific offerings and identify courses relevant to their level of experience and professional development objectives. www.coursera.org

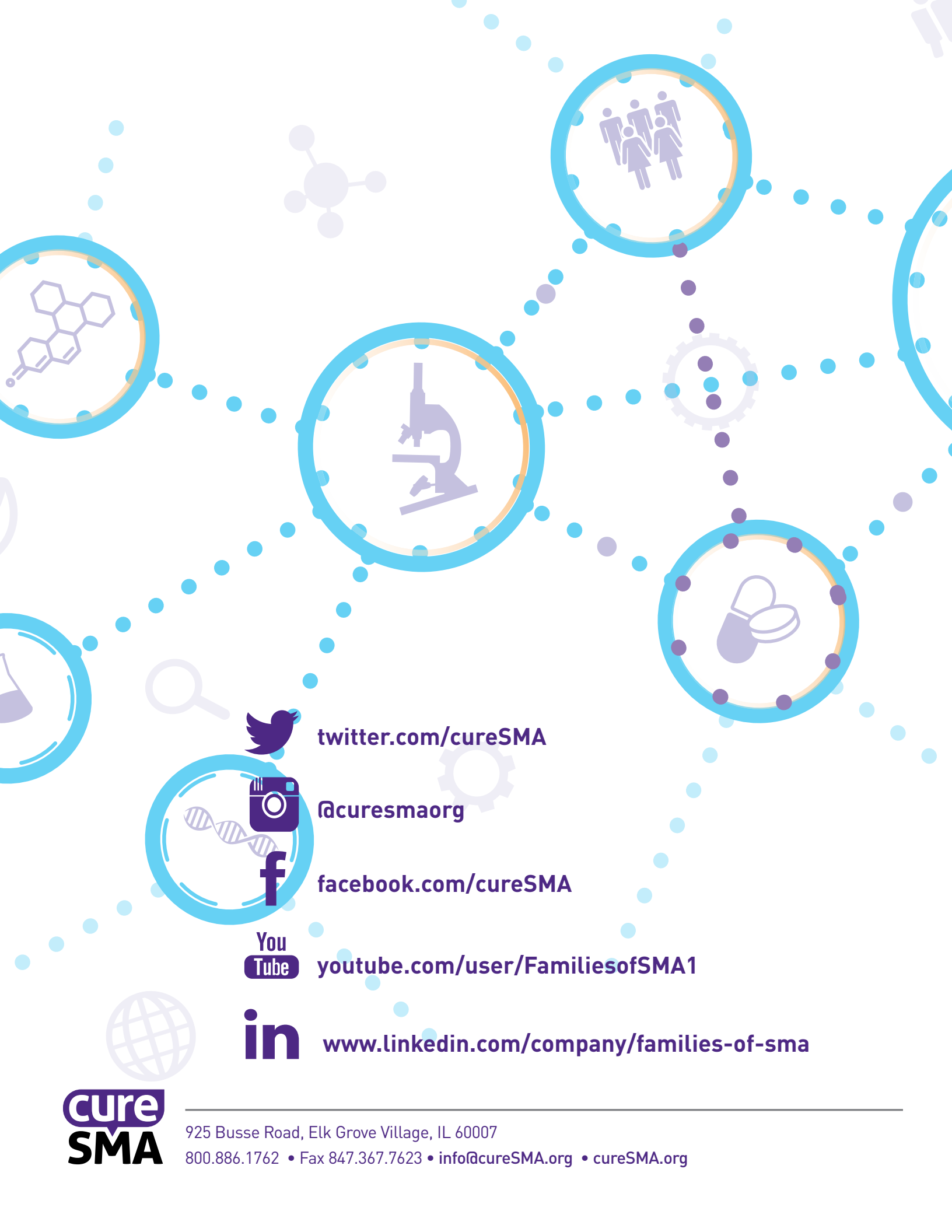
EdX Courses, Programs, and Degrees (Cost varies; some courses are free)



EdX has a diverse set of courses, programs, and degrees in a large number of topics including data sciences, the life sciences, and physical sciences. EdX is both non-profit and open source. <https://www.edx.org/>

LinkedIn Learning (Requires account; some courses are free)

LinkedIn Learning offers an ever-growing array of courses. Some courses are free, while others require a subscription. <https://www.linkedin.com/learning/>.



twitter.com/cureSMA



[@curesmaorg](https://www.instagram.com/curesmaorg)



facebook.com/cureSMA



youtube.com/user/FamiliesofSMA1



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



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