CURE SMA

CLINICAL TRIAL READINESS TOOLKIT

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

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<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>ASO</td>
<td>Antisense Oligonucleotides</td>
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<td>CE</td>
<td>Clinical evaluators</td>
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<tr>
<td>CHOP-INTEND</td>
<td>Children’s Hospital of Philadelphia infant test of neuromuscular disorders</td>
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<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
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<tr>
<td>CMAP</td>
<td>Compound muscle action potential</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>CRC</td>
<td>Clinical research coordinator</td>
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<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>CVS</td>
<td>Chronic villus sampling</td>
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<tr>
<td>DNA</td>
<td>Deoxyribose nucleic acid</td>
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<tr>
<td>DTR</td>
<td>Deep tendon reflexes</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>G</td>
<td>Gastrostomy</td>
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<tr>
<td>GCP</td>
<td>Good clinical practice</td>
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<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disorder</td>
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<tr>
<td>HFMSE</td>
<td>Hammersmith functional motor scale-expanded</td>
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<tr>
<td>HHS</td>
<td>United States Department of Health and Human Services</td>
</tr>
<tr>
<td>HINE</td>
<td>Hammersmith infant neurological examination</td>
</tr>
<tr>
<td>IC</td>
<td>Industry collaboration</td>
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<tr>
<td>ICF</td>
<td>Informed consent form</td>
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<tr>
<td>IEC</td>
<td>Independent ethics committee</td>
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<tr>
<td>IRB</td>
<td>Institutional review board</td>
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<tr>
<td>IRdIRC</td>
<td>International Rare Disease Research Consortium</td>
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<td>IT</td>
<td>Intrathecal</td>
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<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>M</td>
<td>Mean</td>
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<tr>
<td>MAGEC</td>
<td>MAGnetic expansion control</td>
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<tr>
<td>MFM</td>
<td>Motor function measure</td>
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<tr>
<td>MRCT</td>
<td>Multi-regional clinical trials</td>
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<td>MUNE</td>
<td>Motor Unit Number Estimation</td>
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<td>NG</td>
<td>Nasogastric</td>
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<tr>
<td>NIH</td>
<td>National Institute of Health</td>
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<td>NJ</td>
<td>Nasojejunal</td>
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<tr>
<td>NV</td>
<td>Noninvasive ventilation</td>
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<tr>
<td>OT</td>
<td>Occupational Therapy</td>
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<tr>
<td>PCP</td>
<td>Primary care physician</td>
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<tr>
<td>PI</td>
<td>Principal investigators</td>
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<tr>
<td>PNCR</td>
<td>Pediatric Neuromuscular Clinical Research Network</td>
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<tr>
<td>PT</td>
<td>Physical therapist</td>
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<tr>
<td>RUSP</td>
<td>Recommended uniform screening panel</td>
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<tr>
<td>SAE</td>
<td>Serious adverse events</td>
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<tr>
<td>SMA</td>
<td>Spinal muscular atrophy</td>
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<tr>
<td>SMN</td>
<td>Survival motor Neuron</td>
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<tr>
<td>SC</td>
<td>Study coordinator</td>
</tr>
<tr>
<td>SOC</td>
<td>Standard of care</td>
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<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
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<tr>
<td>TIMPSI/TIMP</td>
<td>Test for infant motor performance</td>
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<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>VEPTR</td>
<td>Vertical Expandable Prosthetic Titanium Rib</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WMA</td>
<td>World Medical Association</td>
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Introduction

Within the last decade, the treatment landscape for spinal muscular atrophy (SMA) has changed dramatically. With several experimental treatments in clinical trials and two approved therapies on the market, patients now have the opportunity to access evidence-based treatments for a devastating disease that – until late 2016 – had no approved treatments and was solely managed via supportive and palliative care measures. As more experimental compounds move from early stage research into clinical trials, there will be a growing need for clinical trial sites that are well-equipped to work in SMA and can serve a geographically dispersed patient population. Based on a study of the SMA drug pipeline conducted by Cure SMA, roughly 1,630 SMA trial participants, globally, would have been enrolled in 27 clinical trials by end of 2018; an additional 1,100 patients will need to be recruited for new trials worldwide from 2019-2022, and at least 55 trial centers will be needed in the United States (US).

To better meet the needs of trial sponsors and the SMA patient community as the number of SMA clinical trials increases, Cure SMA has taken on a series of initiatives to support increased clinical trial site capacity and optimized readiness throughout the United States. These activities include:

- the creation of new resources to help sites prepare for SMA clinical trials, including this toolkit and complementary toolkits for clinical research coordinators and physical therapists and clinical evaluators;
- the launch of new readiness evaluation and trainings for key research staff involved in SMA clinical trials (such as clinical research coordinators, and physical therapists who evaluate patient outcomes, and may need reliability training for these evaluations); and
- a voluntary educational readiness evaluation program to help sites assess their readiness for clinical trials, which was launched in 2018 to sites across the United States.

Each of these activities have been undertaken with the understanding that while clinical trials in general are extensive undertakings that require significant preparation, time, expense, and careful execution, clinical trials in SMA present unique challenges that require careful consideration on the part of trial sponsors, investigators, and research teams. In SMA trials, it is important to give consideration to:

- the evolving natural history of SMA as the standard of care also evolves and therapies become available and delivered pre-symptomatically through newborn screening;
- strategies for effective multi-disciplinary care and follow-up for patients with one underlying disease but multiple phenotypes and varied clinical presentation (with mild to severe/life-threatening severity);
- the variety of 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 one part of Cure SMA’s broader efforts to optimize site readiness for SMA clinical trials. It was developed by Cure SMA with the goal of providing sites with a resource for research teams that addresses major aspects of preparing for and conducting clinical trials in general, as well as specific issues that may be likely to arise within clinical trials in SMA. To this end, it 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 the preparation for and conduct of clinical trials, with a focus on potential SMA-specific challenges and potential methods for addressing these challenges.

3. “Appendices,” that provide additional information on key terms and additional resources, including useful study templates to assist with protocol adherence that have been prepared by other organizations and individuals.

With time, this toolkit will be updated to reflect changes in the science and the clinical trial landscape for SMA. Sites are encouraged to view it as a guide, recognizing that it is one of a wide number of different resources that can be helpful – and 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 November 2019*
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 characterized by progressive muscle weakness of the limb and trunk, followed by muscle atrophy (wasting) that in most cases, lead to 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). The symptoms of SMA are characterized by dysfunction and subsequent loss of alpha motor neurons in the spinal cord, caused by a deletion or mutations (changes) in the Survival Motor Neuron 1 gene (SMN1). SMA is a devastating disease that often takes away a person’s ability to walk, eat, or breathe. Today, SMA is the number one genetic cause of death for infants. But there is great reason for hope. We expect that with the availability and early administration of disease-modifying therapies, approved and on the horizon, the prognosis and natural history of this disease will greatly change (Finkel et al., 2017, De Vivo et al., 2017, Glascock et al., 2018). SMA is often referred to by several terms, including “genetic disease”, “autosomal recessive genetic disorder”, “motor-neuron disease” or a “neuromuscular disease.”

SMA is one of the most common autosomal recessive inherited disorders. SMA is caused by a mutation in the SMN1, 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 a protein that is critical to the function of the nerves (lower alpha motor neurons) that control and sustain the health of our muscles. Without the SMN protein, those nerve cells cannot properly function and eventually die, leading to debilitating and often fatal muscle weakness.

SMA occurs in approximately one in 10,000 to 11,000 live births, and about one in every 40-50 Americans is a genetic carrier (Prior, 2008, Sugarman et al., 2012, Verhaart et al., 2017). Because it is an autosomal recessive condition, generally both parents must be carriers for a child to inherit the condition. If both parents are carriers of the SMA gene, then each of their children has a one in four chance of having the disease. SMA can affect any race or gender.

SMA has been classified into four primary clinical subtypes—type I, II, III, and IV—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). Depending on the age of onset, SMA can lead to:

- Debilitating muscle weakness
- Inability to perform basic functions, such as walking, eating or breathing
- Death

Individuals with SMA often 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 or recap on SMA, including cause, symptoms, diagnosis, and treatment, you may click the video below.

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

Genetic linkage studies of families with a history of SMA allowed researchers to localize the region containing the gene responsible for SMA to the long arm of chromosome 5 in 1992. Worldwide efforts resulted in the identification of the SMA gene in 1995; this gene has been named SMN1 for the “survival motor neuron 1” gene (Lefebvre et al., 1995; Wirth, 2000). Humans have two nearly identical copies of this gene that have been named SMN1 and SMN2 (see Figure 1a). In a healthy person, the SMN1 gene produces survival motor neuron protein or SMN protein, which is critical to the function of the nerves that control and sustain muscle health. Without it, those nerve cells cannot properly function and eventually die, leading to debilitating and often fatal muscle weakness across all body systems (Lefebvre et al., 1995, Wirth, 2000, Arnold et al., 2012). In humans, a nearly identical copy of this gene, termed SMN2, is also present.

The major difference between the SMN1 and SMN2 genes is found in exon 7. There is a single nucleotide difference at the beginning of exon 7 (C for SMN1 and T for SMN2, (see Figure 1a)) which is important for SMN RNA splicing. Thus, the SMN1 mRNA includes exon 7 whereas the SMN2 mRNA generally excludes exon 7.

The presence of exon 7 is critical to the production of fully functional and stable SMN protein. Because the mRNA from the SMN2 gene excludes exon 7, protein made from the SMN2 gene lacks a chunk of the normal protein. Thus, the SMN2 gene alone cannot provide sufficient amounts of fully functional (full-length exon 7-containing) SMN protein that is necessary to maintain survival of motor neurons.

The genetics of SMA provides a unique opportunity for therapeutic development (Lorson et al., 2010, Arnold et al., 2012, Kolb and Kissel, 2011, Finkel et al., 2014, Finkel et al. 2017). While SMA patients lack the functional SMN1 gene, they have a “backup” gene, SMN2. The SMN2 gene also makes SMN protein, but at greatly reduced efficiency/quantity, leading to lower than normal levels of the protein. SMN2 provides an attractive target for developing SMA therapies, and most drug development efforts in the field are focused on increasing SMN protein production by correcting the splicing error in the SMN2 gene (Hua et al., 2007; see also SMA Drug Pipeline).

As SMA is an autosomal recessive disorder, individuals with this disease typically have inherited a faulty (mutant) SMN1 gene from each of their parents. The majority of mutations responsible for 5q-SMA are either deletions or gene conversions (see Figure 1):

- A deletion involves partial or complete removal of the SMN1 gene (see Figure 1a).
- In a gene conversion, the SMN1 gene is “converted” into an SMN2-like gene because the “C” in exon 7 is changed into a “T” (see Figure 1b).

In both cases, (deletion and gene conversion) SMA patients are missing SMN1 exon 7, referred to as homozygous absence of SMN1 exon 7. Therefore, SMA patients 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 (see Figure 1c). Because deletions and gene conversion
mutations are very frequent and point mutations are very rare, about 95% of SMA patients are homozygous for deletion/gene conversion mutations: they have deletion/gene conversion mutations on both their chromosome 5’s. Some rare SMA patients (about 5%) are compound heterozygotes: they have a deletion/gene conversion mutation on one of their chromosome 5’s and a point mutation on the other chromosome 5.

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 pre-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 chunks 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/2019/07/genetics-of-sma.pdf).

Carriers

Most people have two functioning copies of the SMN1 gene. People with one faulty copy and one functioning copy are called “carriers.” Even though carriers don’t have SMA themselves, they can still pass the faulty gene on to their children. Approximately 1 in 40-50 people is a genetic carrier for SMA. Most have no idea they are carriers until they have a child born with SMA (Ogino et al., 2002; Prior, 2008, Sugarman et al., 2012).

SMA is a recessive disease, which means that, generally, a child will only have SMA if both parents pass on the SMN1 mutation. When two parents are carriers (see 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 (though they do have a 50% risk of being a carrier). However, in very rare cases, mutations in the SMN1 gene can occur during egg or sperm production. In these cases, SMA can be the result of a new mutation in the SMN1 gene. In other rare instances, 2 copies of SMN1 may be found on a single allele. A person with 2 copies of SMN1 on a single allele is known as a silent carrier as they may pass along their allele without the SMN1 gene to any children, but they will not be detected in traditional carrier screening tests. In addition, a small percentage of carriers have a mutation that cannot be identified through current testing. In this case, it will appear as though the disease has been caused by a single carrier.

Figure 2: Schematic of the transmission of the defective SMN gene. SMA is an autosomal recessive genetic disorder, which means an affected individual must have two defective copies of the disease-causing gene. One copy of the defective gene is inherited from each parent. This scenario is illustrated here. N designates a normal SMN1 gene and a faulty SMN1 gene. (a) Parents of an affected individual are typically carriers of one defective copy of the disease-causing gene and are unaffected by the disease. (b) Chromosomes carrying the SMN gene are passed down to offspring from one generation to the next to produce affected (SMA SMA), unaffected SMA carriers (SMA N, or N SMA), or unaffected non-carrier individuals (NN). In a family where both parents are carriers (SMA N), there is a 25% chance that each of their children will have two defective copies of the SMN1 gene and have SMA, a 50% chance each of their children will be carriers and not have a disease, and a 25% chance that each of their children will have two normal SMN1 genes and not have the disease (retrieved from https://www.curesma.org/wp-content/uploads/2019/07/genetics-of-sma.pdf).
Diagnosis & Classification of SMA

A doctor may suspect SMA when a child is noticeably weak, hypotonic (floppy) or delayed in meeting developmental milestones. These may include, but are not limited to, inability to achieve head control, to rollover, sit independently, stand or walk. Given that SMA is a rare disease, and that its hallmark symptoms overlap with other neuromuscular diseases with similar presentation (i.e., metabolic myopathies such as Pompe, congenital myopathies, congenital myasthenic syndromes, among others), SMA is often misdiagnosed or all together missed and most parents undergo an arduous and prolonged diagnostic journey (Lin, Kalb, & Yeh, 2015, Qian et al., 2015; McGraw, 2017).

Diagnosing SMA

A physician may suspect a diagnosis of SMA when an infant or toddler displays one or more of the following clinical symptoms:

- Progressive muscle weakness (that is symmetrical, equally affecting both sides of the body) and is usually 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 when taking a breath ("pigeon chest") and rapid diaphragmic (belly) breathing (most severe types).
- Weak cry and cough (most severe types).
- Limited movement of limbs and trunk; antigravity movements (particularly lower limbs).
- Respiratory or swallowing difficulties/failure.
- 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.), due to the progressive nature of the disease.
- Alert (seemingly hyper alert) and normal cognition.


Confirmation of an SMA diagnosis may be done via genetic testing. A simple blood test is used to detect a homozygous deletion of the \( SMN1 \) gene /deletion of Exon 7, with or without deletion of Exon 8. The \( SMN1 \) gene will be present when DNA is prepared from individuals with 1 or 2 normal copies of \( SMN1 \). \( SMN1 \) will be absent when DNA is prepared from individuals with 5q-SMA.
A blood test is the only definitive way to confirm a diagnosis of SMA. Other methods to arrive at a diagnosis of SMA may include a muscle biopsy and electrophysiological studies such as electromyography (EMG), performing specific tests that correlate with disease progression and severity such as a compound muscle action potential (CMAP) or measures of motor unit count such as Motor Unit Number Estimation (MUNE). There are two types of SMN tests:

1. **Diagnostic Test**: One SMN test is used for the diagnosis of SMA of individuals showing muscular atrophy caused by degeneration of motor neurons.

2. **Carrier Test**: The second SMN test is used to determine carrier status, that is, 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.

Because about 95% of SMA patients possess DNA changes that can be detected with this test, namely homozygous deletion/gene conversion mutations, the SMN1 diagnostic test is said to have about 95% sensitivity (Lebebvre et al, 1995). This means that the current SMA diagnostic test can detect 95% of SMA patients who have 5q-SMA. The SMN diagnostic test is not informative for non-5q-SMA.

About 1 in 20 (5%) patients with 5q-SMA have rare point mutations that are not detected by the SMN tests described here (Lebebvre et al, 1995; Wirth et al, 1999). Most of these SMA individuals have one SMN1 gene in which SMN1 exon 7 is missing and a second SMN1 gene with a rare point mutation (Lebebvre et al, 1995; Wirth et al, 1999). One must identify SMN1 mutations in both genes to confirm that such an individual has 5q-SMA.

**Prenatal Testing**

Prenatal testing is used to determine if a fetus has inherited a genetic disorder such as SMA. One of two different tests may be used:

- **Amniocentesis**: In amniocentesis, the most common form of prenatal testing, a very fine needle is inserted into the woman’s abdomen 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).
The SMA Diagnostic Journey: The Patient & Parent Perspectives

Diagnostic delays are common in SMA. In some ways, this may be attributable to the incidence of the disease and the fact that up-until recently there was no treatment available to target the underlying cause of SMA. To further understand the diagnostic journey in SMA and address this issue, Cure SMA committed to further understanding and capturing the diagnostic experience of affected individuals and their families with SMA, given the limited literature on this topic (Qian et al., 2015, Cure SMA, 2015). Since 2014, Cure SMA has partnered with the community and research scientists to shed light on the experiences of individual and families with SMA and the diagnostic process. In March 2016, Cure SMA begun surveying newly diagnosed families, via a community-based survey, to capture information on the diagnostic journey including age of symptom presentation, timing of symptom onset vs. time to diagnosis, SMA type, physician that made that correct diagnosis, etc. (Belter et al., 2018). See a summary report below, from 2016.

Figure 3: Results of Cure SMA Newly Diagnosed Survey (2016-2019)

- Average age of diagnosis, mean (M)
  - Type I: 4.7 (3.8) months
  - Type II: 16.0 (8.8) months
  - Type III: 110.3 (116.6) months

- Questions
  - Physician information
  - Diagnosis information
  - Motor function, nourishment, breathing
  - Diagnostic journey

- 182 responses
  - Type I: 46.5%
  - Type II: 33.3%
  - Type III: 13.7%
  - Other/unknown: 6.6%

- Type of clinician making the correct dx
  - Pediatric neurologist – 61.8%
  - Genetics specialist/counselor – 19.7%
  - Adult neurologist – 2.7%
  - Pediatrician or family practitioner- 3.8%
  - Therapist – 0.6%
  - Neuromuscular specialist – 0.6%
  - Other – 10.8%
Cure SMA also partnered with the research community to further explore this phenomenon (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 with individuals with SMA; 64 parents.

Through this work, families reported substantial diagnostic delays which were attributed to many factors including:

1. Lack of awareness and knowledge about SMA;
2. The difficulty of distinguishing normal from abnormal development; and
3. The challenge of differential diagnosis.

The lack of awareness and knowledge among primary care physicians (PCPs), and even 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 the “lack of sensitivity” from physicians when communicating the diagnosis (a potentially fatal and devastating disease) to them. This work further explored families’ attitudes toward New Born Screening as well as the psychosocial impact of living with SMA, and characterized the impact on the following:

1. Confronting premature death
2. Making difficult treatment choices
3. Fearing the loss of functional ability
4. Coming to terms with lost expectations
5. Loss of sleep and stress
6. Stigma
7. Limitations on social activities
8. Independence
9. Uncertainty and helplessness
10. Family finances
The results of this study reiterated what anyone caring for families with SMA would already know: that the effects of managing and coping with SMA are significant and multifaceted. Both individuals living with SMA and family members are affected in physical, psychosocial, emotional, financial and practical ways. SMA was recently recommended to be added to the list of conditions, tested for at birth, on the recommended uniform screening panel (RUSP). This was an important step toward shortening the diagnostic journey in SMA and ensuring that all children with this disease are treated shortly after birth to ensure the best outcome and improved quality of life. However, it might take anywhere from 3-5 years for newborn screening for SMA to be implemented across all 50 states. For a review of the “Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening”, please see Glascock et al., 2018.

Now more than ever- as new therapies are 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 early 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 and clinical studies which have shown that early introduction to 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.

To promote reduction of diagnostic delays, Cure SMA has launched SMArt Moves, 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 the SMArt Moves effort are resources dedicated to health care professionals that detail current diagnostic criteria, educational resources, and the latest treatment options and protocols. In addition, parents also have access to an easy-to-use website that encourages parents 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 improve their understanding of the early signs of motor delays, watch instructional videos, and download a helpful checklist, including the hallmark signs of SMA to share with their doctor and help address their concerns. Learn more at www.curesma.org/smartmoves/ or follow us on Twitter at @SMArtMovesHCP and on Facebook at @SMArtMovesHCP.
Classification of Spinal Muscular Atrophy

No two people with SMA have identical experiences. Even among those with the same type, the progression of the disease can differ. The number of copies of the SMN2 gene varies in the population. The number of SMN2 gene copies a person possesses has been shown to modify SMA disease severity: the severity of SMA in people living with the disease broadly correlates with the number of SMN2 gene copies (see Table 1).

More copies of SMN2 = less severe phenotype

Every person living with SMA has at least one copy of the SMN2 gene, since some amount of SMN protein is required for every type of cell in the human body to survive.

There are four primary types of SMA: type I, II, III, and IV. The type of SMA is 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.

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)

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

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 trouble 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 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 after 3 months of age), or IC (usually has 2 or 3 copies) (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 difficulty swallowing, or eating difficulties due to muscle fatigue which may ensue when chewing meals. With treatment and improved standard of care, survival in 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 (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. It has recently been reported with prenatal onset, 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.

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

Table 2: Non-5q-Forms of SMA
Clinical Presentation

The clinical presentation, age of onset, degree of symptoms and rate of progression varies greatly across SMA types and between patients. Differences are generally based on the number of copies of the SMN2 backup gene. A high-level overview of changes that may occur in patients as a result of each type of the disease is provided below (Lefebvre et al., 1995, Wirth, 2002, Wang et al., 2007, D’Amico et al, 2011, Wadman et al., 2017).

In SMA, muscle weakness can cause several complications ranging from respiratory complications, musculoskeletal, nutritional, etc. (see Disease Management section below).

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 the joints/joints lock in place due to lack of motion), which limit the range of motion in a joint
- Bone fractures (Osteoporosis is common in type Is, IIs due to lack of weight bearing)
- Hip dislocation
- Spinal deformities, such as scoliosis, lordosis, and kyphosis


Scoliosis is an abnormal bending 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. Scoliosis often results in twisting of the chest and 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.

Musculoskeletal issues can cause pain, as well as difficulty sitting, standing, or performing normal daily activities.

Below is a high-level overview of the clinical presentation typically found across the disease spectrum. As the disease progresses, patients experience similar symptoms across systems, SMA types (e.g., similar orthopedic, respiratory and even nutritional complications are experienced, as the degree of muscle weakness increases and level of function decreases).
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, 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, Krosschell et al., 2013, Krosschell 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 present early on or rapidly with 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, by definition, fail to gain independent sitting, and as a rule do not achieve motor skills beyond those which are present at the time of diagnosis. This observation is important to remember when considering the effect of enhanced standard of care and/or the therapeutic effect of a drug intervention.

Oral-motor dysfunction

- If not already present at the time of diagnosis in type IB, oral-motor dysfunction (weak suck) typically evolves within the next few months (median age 8 months in one study, approximately 3 months prior to the median age of when initiation of more aggressive breathing support is required). 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 feeding with nasogastric tube or gastrostomy tube placement is an option available to support infants with these limitations.

Respiratory insufficiency

- If respiratory insufficiency is not already present at the time of diagnosis in type IB, such typically evolves after feeding compromise is present, but 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 for these symptoms includes nasal and oral suctioning, chest percussion to loosen airway secretions, cough assist devices to increase lung expansion and to mobilize secretions, and ventilation support – non-invasive and invasive techniques.

SMA Type II

In contrast to the majority of patients with severe generalized weakness with respiratory failure in the neonatal period (i.e., SMA type I), SMA type II patients, before treatment was available, typically survive to age 25, and many patients live much longer due to improved and more aggressive supportive care. Children with SMA type II usually do not have swallowing problems, but this can vary
from child to child. Some children may have difficulty eating enough food by mouth to maintain their weight and grow (some experience fatigue while eating), and a feeding tube may become necessary if the family decides this is best.

**Respiratory Function**

- Children with SMA type 2 may also develop weakness of the muscles used for breathing and experience difficulty coughing. Some of these children may require equipment to help them breathe easier at night.

**Musculoskeletal Function**

- Weakness also leads to contractures (shortening and hardening of muscles, tendons, or other tissue, often leading to deformity and rigidity of joints). Stretching and bracing are often prescribed to preserve flexibility and prevent contractures. Problems with the spine (scoliosis) and hips (displacement) that may lead to further loss of function. Severe curvature of the spine (scoliosis) can be treated with a brace and in many instances surgery. Bones become weak (porous) and may break easily, and a variety of therapeutic supports are available to help position children and adults with SMA type II comfortably.

- Children and adults with SMA Type II most often develop severe scoliosis that is often corrected via orthopedic surgery (rod placement, including VEPTR surgery, and more commonly used now, growing rods or MAGEC rods) and would often undergo a spinal fusion. Adults with SMA type II often develop contractures, and extremely limited mobility with disease progression necessitating the aid of caregivers or adaptive technology to perform all activities of daily living (Haaker and Fujak, 2013, Finkel et al., 2017, Cruz et al., 2018).

**SMA Type III**

Type III SMA is associated with onset between ages 18 months through adulthood. By definition, standing or walking without support is achieved, although many patients lose these abilities later with disease progression. An abnormal gait is characteristic of this phenotype; this typically develops when those affected tries to compensate for weakness (particularly of the hips and thighs). With the help of supportive devices, many can continue to walk despite severe weakness. Affected individuals may have difficulty walking, running, and climbing stairs as they get older; some will lose the ability to walk independently in childhood, while others may remain ambulatory into adolescence or adulthood. Problems with the spine (scoliosis) may develop at various rates and ages. Swallowing and coughing difficulties, along with breathing difficulty at night, may occur but do so much less commonly and later in the disease course than in SMA type II. Children and adults with SMA type III are at risk of becoming overweight, as they are not usually able to be extremely physically active. 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 treated with a brace and in some instances surgery. As in SMA type II, bones become weak and may break easily, and a variety of
therapeutic supports are available to help position individuals with SMA type III 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.

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 the child’s inability to smile due to near complete muscle paralysis. SMA spares the diaphragm but affects the intercostal muscles (muscles between the ribs). With disease progression, noninvasive ventilation (NIV) can be initiated at night in children with sleep-disordered breathing and later on during the day if daytime hypercapnia becomes an issue.

The burden of SMA for those affected and their families, is tremendous. Apart from the physical effects, the uncertainty that often comes with an SMA diagnosis, the burden of a disease that typically affect multiple systems and require ongoing monitoring, can take a powerful emotional toll on families (Cruz et al., 2018, Cure SMA, 2015, Qian et al., 2015, McGraw, 2017).

Disease Management and Current Treatments

The landscape of disease management and treatment for SMA has changed rapidly since the 2000s and continues to evolve. While approaches vary depending upon individual needs and treatment options, disease management typically involves a combination of interventions focused on preserving key functions important to daily living (such as breathing, swallowing, and movement), palliative care, and – if appropriate and available – drug treatment for SMA. At the time this toolkit was last, there are currently, two FDA-approved treatment options available for SMA and several experimental therapeutics are currently being explored, including approaches to combination therapies. As studies of these approaches move forward, the treatment landscape for SMA as a result the disease phenotype will continue to change.

Standard of Care

An international, multidisciplinary SMA working group developed the initial standard of care guidelines for SMA. This included a detailed review of the pertinent literature and used 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, dieticians, and physical, occupational and speech therapists, and with psychosocial support for the patient and the parents/caregivers (Wang, 2007, Wang et al., 2007, Finkel et al., 2017; Mercuri et al., 2017). Palliative care begins at the time of diagnosis and emphasizes quality of life and comfort measures. This guideline has also been endorsed uniformly by pharmaceutical companies as the basis for specifying that there is an expectation for a certain degree of supportive care for participants in a clinical trial. This is often listed as an inclusion criterion. It has not been made a requirement, however, in most instances, and still allows for parental autonomy of choice during participation in a clinical trial).
The standard of care guidelines was recently updated (Finkel et al., 2017; Mercuri et al., 2017). This included more patient input and allowed for comments from pharmaceutical representatives than was included in the initial 2007 effort. In February 2016, working groups were convened to address nine topics: diagnosis, pulmonary, acute care, nutrition, orthopedics, physical and occupational therapy (PT/OT), medication, ethics and non-CNS organ system involvement. Recently published, Glascock et al. (2018), outlines standard of care for SMA of varying SMN2 copy number.

Infants and children with SMA type I and II, will 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. Standards of care are available (Wang et al., 2007, Finkel et al., 2017; Mercuri et al., 2017) but type, level, and quality of care can vary greatly, not only by country but by region. Much of the infants’ care takes place at home, with parents/care givers taking responsibility for aspects of care such as those described below.

Respiratory Care

Breathing problems are the most common cause of illness for children with SMA. In healthy individuals, the muscles between the ribs—called 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, which compromises this normal breathing rhythm. This can result in:

- Weak and underdeveloped lungs
- Ribcage deformities
- A weak cough
- Severe risk from 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 (mainly relatives) usually learn to assist coughing when needed, through use of a cough-assist device and these other means:

- Chest physiotherapy to maintain comfort and to loosen mucus from the lungs
- Suction to remove secretions
- Medication to reduce secretions
- Pain relief to reduce any distress caused by breathlessness
- NIV with mechanical ventilation to increase comfort, in the management of acute infection or to correct night-time hypoventilation
Invasive ventilation in some regions

**Orthopedic Care**

Many times, the musculoskeletal team will prescribe activities that can be done at the therapist's office, or with the child and parents at home—oftentimes both. These may include:

- Daily exercises, can comprise of 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, if bone density is compromised. Vitamin D is a recommended supplement which use is recommended as a preventative measure to protect bone health
- Bracing of the spine for sitting support
- Surgery (from growing rods, or MAGEC rods for support, to spinal fusion (maximally invasive)

For more on this you may visit the Cure SMA website: [http://curesma.pub30.convio.net/support-care/living-with-SMA/medical-issues/orthopedics/](http://curesma.pub30.convio.net/support-care/living-with-SMA/medical-issues/orthopedics/)

**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). Nutrition is also critical to fostering:

- **Improved Growth**: Gaining weight while growing in height is essential to good health. Having enough energy (calories) and protein helps keep the body growing by supporting 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/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 children with SMA to decline in both strength and ability to move.

Most patients with SMA experience various gastrointestinal and nutrition-related complications that make the nutritional management a critical component in the care of SMA patients. For instance, most patients with SMA, particularly those with type I and II, have an abnormal body composition and experience difficulties with feeding, chewing 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). Additionally, problems with constipation, distention, gastroesophageal reflux (GERD), malnutrition (may be due to problems with fatigue while eating, difficulty opening mouth, a byproduct of bulbar dysfunction) and low or high blood sugar have
been reported. Swallowing studies are typically performed in SMA type I and II to ensure that no aspiration is taking place during feeds.

It is recommended that the dietary intake of patients with SMA be monitored periodically in consultation with a dietician experienced in management of patients with neuromuscular disorders or SMA specifically (Wang, 2007, Swoboda et al., 2007).

Management is associated with:

- Nasogastric (NG) tube
- Nasojejunal (NJ) tube
- Gastrostomy (G) tube (with or without fundoplication)

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.

**Physical (PT) and Aquatic Therapy**

Physical therapy is recommended to help 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).

- Passive exercises to enable movement and help circulation/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/increased mobility and prevent contractures

The goal of supportive care is to enable children to enjoy a good quality of life at home with their family for as long as possible, with a minimum of hospital admissions. However, keeping up with the recommended standards of care takes a considerable amount of effort, time and financial strain on parents/care givers (Cruz et al., 2018; Cure SMA, 2015; Qian, 2015).
Drug Treatments: Approved and Experimental

Approved Drug Treatments:

There are currently two FDA-approved treatments for SMA that treat the underlying cause of the disease through distinct mechanisms, to enhance the production and availability of \textit{SMN} protein throughout the body.

\textbf{NUSINERSEN (SPINRAZA\textsuperscript{TM})}

Nusinersen (Spinraza), is an antisense oligonucleotide that works by correcting the \textit{SMN2} transcript splicing, thereby improving functional \textit{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). For more on Spinraza, you may click here.

\textbf{ZOLGENSMA (onasemnogene abeparvovec-xioi)}

Approved by the FDA in May 2019, Zolgensma is an \textit{SMN}-enhancing therapy that works by replacing the missing or mutated \textit{SMN1} gene. Zolgensma is given via intravenous infusion. A virus, AAV9, carries the replacement gene into the body. This virus “infects” the cells with the new DNA. Zolgensma is a type of treatment that is often called gene therapy or gene replacement therapy. FDA-approved for infants with all types of SMA under 2 years of age. 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.

In addition, there are several care/supportive care options available for issues including palliative care, pulmonary care, and nutritional support, among others. For more information on SMA care and on handling medical issues, you may refer to the Cure SMA site, handling medical issues to learn more.

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 a diversity of approaches, we maximize our chances for success. If one drug candidate or one approach fails, we have others to take its place.

The Cure SMA drug pipeline identifies four possible treatment targets:

- Replacement or correction of the faulty \textit{SMN1} gene
- Modulation of the low functioning \textit{SMN2} “back-up gene”
- Neuroprotection of the motor neurons affected by loss of \textit{SMN} protein
• Muscle protection to prevent or restore the loss of muscle function in SMA

_Therapeutic Programs and Strategies in SMA_

Cure SMA’s research model funds drug programs at all stages of development. Our basic research program studies the biology and causes of SMA, often revealing new and more effective ways of making drugs. These basic research ideas are then converted into practical drug candidates through drug discovery. Finally, those drug candidates move through the clinical trial process (see Table 3).

The SMA Pipeline, above, depicts the pre-clinical drug discovery (basic research) and clinical development programs in SMA (as of October 2019, from CureSMA.org website). 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. Since 1984, Cure SMA has granted $80 million in basic research, including over $20 million in drug discovery grants, converting basic research seed ideas into candidates that can be tested in the next stage of research: clinical trials.
Table 3: Cure SMA Drug Pipeline

Therapeutic Approaches

The strength, including its breadth and depth, of the Cure SMA’s drug discovery program is that it attacks SMA from multiple angles. This gives SMA patients and their families great reason for hope. We know that if one approach fails, we have several others we can pursue.

Researchers have identified four different therapeutic approaches that show promise in treating SMA:

- **Neuroprotection** of the motor neurons affected by loss of *SMN* protein. Aimed to protect against neuronal injury or degradation
- **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
    - Antisense Oligonucleotides (ASOs) or small molecules (Genentech/Roche and Novartis); Ex. Spinraza (Biogen)
- **Replacement or correction** of the faulty SMN1 gene. Gene Therapy replaces the missing SMN1 gene via a viral vector
  - Ex. AVXS-101/Zolgensma (AveXis)
- **Muscle protection/enhancement** to prevent or restore the loss of muscle/motor function in SMA
  - Ex. CK2127107 (Cytokinetics)
  - Ex. SRK – 015 (Myostatin Inhibitor), (Scholar Rock)
- **Combinations of the above** i.e. Spinraza + a muscle enhancer
  - e.g. Spinraza + a muscle enhancer

For an overview of these therapeutic approaches you may visit: [https://www.curesma.org/therapeutic-approaches/](https://www.curesma.org/therapeutic-approaches/).


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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 Cilical 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.

To help support coordinators that are new to SMA clinical trials, Cure SMA has developed the Best Practices for Clinical Research Coordinators in SMA (click here to access the toolkits). This provides strategies and recommendations to help CRCs effectively mitigate and anticipate challenges that can arise when coordinating SMA clinical trials and includes an overview of recommended trainings for coordinators, links to additional helpful resources, and general templates for key coordinator activities.
The information is drawn from a 2018 literature survey and a series of interviews of experienced SMA trial coordinators.

**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.

Please refer to the Best Practices for Physical Therapists and Clinical Evaluators (CEs) in SMA for a comprehensive discussion of key challenges PTs/clinical evaluators in SMA may encounter when assessing patients with SMA and learn productive ways to navigate these challenges (click here to access the toolkits). Developed by Cure SMA and two lead physical therapists who work extensively in SMA, this addresses steps to take before participating in a trial, clinical evaluation of study participants, and considerations related to assessments and patient Evaluation (SOC, supportive care, and multidisciplinary care) and much more.

**Clinical Outcome Measures in SMA**

Functional measures in SMA allow us to assess the impact of SMA and possible response to treatment. Outcome measures commonly used in evaluation of SMA patients, both in clinic and in clinical trials include, but are not limited to:

**Motor Function Scales:**

- Children’s Hospital of Philadelphia (CHOP-INTEND), developed to evaluate weak infants with SMA (Pediatric Neuromuscular Clinical Research Network (PNCR) Natural history studies, nusinersen, AveXis 101, Firefish, [SMA type I trials])
- Test of Infant Performance Screening Items (TIMP)/TIMPSI (NeuroNEXT), [SMA type I trials]
- Bayley Scales of Infant Development (AveXis 101, Nurture, [SMA type I trials])
- Motor Function Measure (MFM) (Sunfish, Jewelfish [SMA type II/III trials]
- Hammersmith Functional Motor Scale, Modified Hammersmith Functional Motor Scale, Hammersmith Functional Motor Scale Expanded (HFMSE), developed to evaluate children with SMA type II and III (ages, 2 and older, ambulatory and non-ambulatory)
- Upper Limb Module or Revised Upper Limb Module, developed to evaluate upper limb function/arm function, particularly in weak type IIs.
Six-Minute Walk Test – shown to be a reliable and valid functional assessment in ambulatory patients with SMA (Dunaway Young, 2016, Montes, 2010)

Hand-Held Dynamometry – to capture muscle strength in various muscle groups (nusinersen, Cytokinetics, etc.)

**Scales of Motor Development:**

- Hammersmith Infant Neurological Examination (HINE) – developed to assess motor development and infants under 2 years with SMA. (nusinersen trials)

- WHO Motor Milestones (Scale of development) (Nurture trial), to capture milestone achievement in the first year of life.

**Electrophysiological measures**

- Used to capture disease progression; motor unit number estimation (MUNE) and output activity (CMAP) [nusinersen trials, NeuroNEXT, Natural History of SMA, PNCR]

**Pulmonary Outcome Measures**

- Assessment of pulmonary function may include a pulse oximeter, to measure blood oxygen levels, various SMA trials, measures of respiratory rate, pulmonary function tests,

A significantly more comprehensive review of motor function outcomes used clinically and in clinical trials in SMA is presented in the Best Practices for Physical Therapists and Clinical Evaluators (CEs) in SMA (click here to access the toolkits).

**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
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 very important that investigators adhere to sponsor, IRB, and/or applicable regulatory body requests, including requests for additional documentation, Section 8 of this ICH Guideline provides a helpful baseline for understanding 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 an especially critical role in ensuring that key information about subjects is captured, and substantiating the integrity of trial data. They include original documents related to the trial, medical treatment, and subject history. More specifically, 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 will take place throughout the clinical trial process, and are an important part of ensuring that, in accordance with ICH GCP E6, 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 at any point, prompt action will be needed to address these. Corrective actions may involve staff training, or creation of new SOPs, tools and, templates. Prior to implementation, all potential corrective actions should be tested 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 (first come first enrolled) (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, but the rarity of SMA means patients are often geographically dispersed. As a result, it may become more difficult to connect with patients and recruit them 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 (IRDIRC), 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 (c) or (d) of this section [not included here], in seeking informed consent the following information shall be provided to each subject:

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; and
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.

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; and
6) The approximate number of subjects involved in the study (U.S. Department of Health & Human Services (HHS), 2009).

It can be difficult for some to ensure that all requirements have 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).

* 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.
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 (Steinhilber, 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 (Steinhilber, 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


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.


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 (GCP) 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.

**Duel 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 (Glascock 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.

<table>
<thead>
<tr>
<th>Title</th>
<th>Tools, Templates, &amp; SOPs (hyperlinks to external resources)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event (AE) reporting</td>
<td>Adverse Event Log</td>
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<tr>
<td></td>
<td>Adverse Events Record Template</td>
</tr>
<tr>
<td></td>
<td>Safety assessment and reporting SOP</td>
</tr>
<tr>
<td>Audit / Quality Control</td>
<td>File Review Checklist</td>
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<td></td>
<td>Regulatory File Review Checklist</td>
</tr>
<tr>
<td></td>
<td>Routine Self Audit SOP</td>
</tr>
<tr>
<td>Case Report Form</td>
<td>Case Report Form Template (Generic)</td>
</tr>
<tr>
<td>Activities for study close out</td>
<td>Study Close Out and Early Termination Checklist</td>
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<tr>
<td></td>
<td>Site Close Out SOP</td>
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<tr>
<td>Communication documents*</td>
<td>Communication Log</td>
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<td></td>
<td>Meeting Minutes</td>
</tr>
<tr>
<td>Title</td>
<td>Tools, Templates, &amp; SOPs (hyperlinks to external resources)</td>
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<tr>
<td>Concomitant Medications</td>
<td>Concomitant Medications Log</td>
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<td>*Maintaining accurate, well-documented medication logs is an especially important part of recordkeeping.</td>
</tr>
<tr>
<td>Drug accountability and storage</td>
<td>Pharmacy Accountability Form</td>
</tr>
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<td></td>
<td>Managing Investigational Drug SOP</td>
</tr>
<tr>
<td>IND Safety Report</td>
<td>IND Safety Report Log</td>
</tr>
<tr>
<td>Informed consent process</td>
<td>Informed Consent Template</td>
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<td></td>
<td>Informed Consent Checklist</td>
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<td>Informed Consent Version Tracker</td>
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<td>Informed Consent SOP</td>
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<tr>
<td>Training Log</td>
<td>Research Staff Training Log</td>
</tr>
<tr>
<td>Protocol Deviation</td>
<td>Protocol Deviation Log</td>
</tr>
<tr>
<td>Regulatory Binder</td>
<td>Regulatory Binder Instructions</td>
</tr>
<tr>
<td>Screening &amp; Enrollment</td>
<td>Recruitment and Enrollment SOP</td>
</tr>
<tr>
<td></td>
<td>Subject Screening Log</td>
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<td>Subject Identification Log</td>
</tr>
<tr>
<td>Site Initiation</td>
<td>Site Initiation SOP</td>
</tr>
<tr>
<td>Staff Training and Study Handover</td>
<td>Staff Training and Study Handover SOP</td>
</tr>
<tr>
<td>Standard Operating Procedures (SOPs)</td>
<td>SOP for Preparing SOPs</td>
</tr>
<tr>
<td></td>
<td>SOP Template</td>
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<td></td>
<td>SOP Management</td>
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<td></td>
<td>SOP Log</td>
</tr>
</tbody>
</table>
### 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**

<table>
<thead>
<tr>
<th>8.2.1</th>
<th>Title of Document</th>
<th>Purpose</th>
<th>Located in Files of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INVESTIGATOR’S BROCHURE</td>
<td>To document that relevant and current scientific information about the investigational product has been provided to the investigator</td>
<td>Investigator: X, Sponsor: X</td>
</tr>
</tbody>
</table>

| 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 | Investigator: X, Sponsor: X |

<table>
<thead>
<tr>
<th>8.2.3</th>
<th>INFORMATION GIVEN TO TRIAL SUBJECT</th>
<th>To document the informed consent</th>
<th>Investigator: X, Sponsor: X</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- INFORMED CONSENT FORM (including all applicable translations)</td>
<td>To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent</td>
<td>Investigator: X, Sponsor: X</td>
</tr>
<tr>
<td></td>
<td>- ANY OTHER WRITTEN INFORMATION</td>
<td>To document that recruitment measures are appropriate and not coercive</td>
<td>Investigator: X</td>
</tr>
</tbody>
</table>

<p>|  | ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used) | To document that recruitment measures are appropriate and not coercive | Investigator: X |</p>
<table>
<thead>
<tr>
<th>Title of Document</th>
<th>Purpose</th>
<th>Located in Files of:</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Investigator</td>
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<tr>
<td>8.2.4 FINANCIAL ASPECTS OF THE TRIAL</td>
<td>To document the financial agreement between the investigator/institution and the sponsor for the trial</td>
<td>X</td>
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<tr>
<td>8.2.5 INSURANCE STATEMENT (where required)</td>
<td>To document that compensation to subject(s) for trial-related injury will be available</td>
<td>X</td>
</tr>
<tr>
<td>8.2.6 SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.:</td>
<td>To document agreements</td>
<td>X</td>
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<tr>
<td>- investigator/institution and sponsor</td>
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<tr>
<td>- investigator/institution and CRO</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>- sponsor and CRO</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>- investigator/institution and authority(ies) (where required)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>8.2.7 DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</td>
<td>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)</td>
<td>X</td>
</tr>
<tr>
<td>- protocol and any amendments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CRF (if applicable)</td>
<td></td>
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<tr>
<td>- informed consent form(s)</td>
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<tr>
<td>- any other written information to be provided to the subject(s)</td>
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<tr>
<td>- advertisement for subject recruitment</td>
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<td>Title of Document</td>
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<td>Investigator</td>
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<td>- subject compensation (if any)</td>
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<td>- any other documents given approval/ favorable opinion</td>
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<tr>
<td>8.2.8 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION</td>
<td>To document that the IRB/IEC is constituted in agreement with GCP</td>
<td>X</td>
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<tr>
<td>8.2.9 REGULATORY AUTHORITY(IES) AUTHORIZATION/APPROVAL/ NOTIFICATION OF PROTOCOL</td>
<td>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)</td>
<td>(where required)</td>
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<td>(where required)</td>
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<tr>
<td>8.2.10 CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)</td>
<td>To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects</td>
<td>X</td>
</tr>
<tr>
<td>8.2.11 NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL</td>
<td>To document normal values and/or ranges of the tests</td>
<td>X</td>
</tr>
<tr>
<td>8.2.12 MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS</td>
<td>To document competence of facility to perform required test(s), and support reliability of results</td>
<td>(where required)</td>
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<td>Title of Document</td>
<td>Purpose</td>
<td>Located in Files of:</td>
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<tr>
<td>- established quality control and/or external quality assessment or</td>
<td>To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects</td>
<td>X</td>
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<tr>
<td>- other validation (where required)</td>
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<tr>
<td>8.2.13 SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)</td>
<td>To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects</td>
<td>X</td>
</tr>
<tr>
<td>8.2.14 INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED</td>
<td>To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials</td>
<td>X</td>
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<tr>
<td>MATERIALS (if not included in protocol or Investigator’s Brochure)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>8.2.15 SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS</td>
<td>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</td>
<td>X</td>
</tr>
<tr>
<td>8.2.16 CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED</td>
<td>To document identity, purity, and strength of investigational product(s) to be used in the trial</td>
<td>X</td>
</tr>
<tr>
<td>8.2.17 DECODING PROCEDURES FOR BLINDED TRIALS</td>
<td>To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for (3rd party if applicable)</td>
<td>X</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Title of Document</th>
<th>Purpose</th>
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<tr>
<td></td>
<td>the remaining subjects' treatment</td>
<td>Investigator Sponsor</td>
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<tr>
<td>8.2.18 MASTER RANDOMISATION LIST</td>
<td>To document method for randomization of trial population</td>
<td>X</td>
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<td>(3rd party if applicable)</td>
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<tr>
<td>8.2.19 PRE-TRIAL MONITORING REPORT</td>
<td>To document that the site is suitable for the trial (may be combined with 8.2.20)</td>
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<tr>
<td>8.2.20 TRIAL INITIATION MONITORING REPORT</td>
<td>To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)</td>
<td>X                    X</td>
</tr>
</tbody>
</table>
**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.

<table>
<thead>
<tr>
<th></th>
<th>Title of Document</th>
<th>Purpose</th>
<th>Located in Files of:</th>
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<tbody>
<tr>
<td>8.3.1</td>
<td>INVESTIGATOR’S BROCHURE UPDATES</td>
<td>To document that investigator is informed in a timely manner of relevant information as it becomes available</td>
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<tr>
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<td>Sponsor</td>
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<tr>
<td>8.3.2</td>
<td>ANY REVISION TO:</td>
<td>To document revisions of these trial related documents that take effect during trial</td>
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<tr>
<td></td>
<td>- protocol/amendment(s) and CRF</td>
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<td>- informed consent form</td>
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<td>- any other written information provided to subjects</td>
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<td>- advertisement for subject recruitment</td>
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<tr>
<td>8.3.3</td>
<td>DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</td>
<td>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).</td>
<td>Investigator</td>
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<td>- protocol amendment(s)</td>
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<td>- revision(s) of:</td>
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<td>- informed consent form</td>
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<td>- any other written information to be provided to the subject</td>
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<td>- advertisement for subject recruitment (if used)</td>
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<td>- any other documents given approval/favorable opinion</td>
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<td>- continuing review of trial (where required)</td>
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<tr>
<td>8.3.4</td>
<td>REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:</td>
<td>To document compliance with applicable regulatory requirements</td>
<td>Investigator</td>
</tr>
<tr>
<td></td>
<td>- protocol amendment(s) and other documents</td>
<td></td>
<td>X (where required)</td>
</tr>
<tr>
<td>8.3.5</td>
<td>CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)</td>
<td>(see 8.2.10)</td>
<td>Investigator</td>
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<td></td>
<td>Title of Document</td>
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<tr>
<td>8.3.6</td>
<td>UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL</td>
<td>To document normal values and ranges that are revised during the trial (see 8.2.11)</td>
<td>X</td>
</tr>
<tr>
<td>8.3.7</td>
<td>UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS</td>
<td>To document that tests remain adequate throughout the trial period (see 8.2.12)</td>
<td>X (where required)</td>
</tr>
<tr>
<td>8.3.8</td>
<td>DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT</td>
<td>(see 8.2.15.)</td>
<td>X</td>
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<tr>
<td>8.3.9</td>
<td>CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS</td>
<td>(see 8.2.16)</td>
<td>X</td>
</tr>
<tr>
<td>8.3.10</td>
<td>MONITORING VISIT REPORTS</td>
<td>To document site visits by, and findings of, the monitor</td>
<td>X</td>
</tr>
</tbody>
</table>
| **8.3.11** | **RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS**  
- letters  
- meeting notes  
- notes of telephone calls | **Purpose** | **Located in Files of:**  
| **Investigator** | **Sponsor** |
| --- | --- | --- | --- |
| To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting  
- 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. | X | X |
| **8.3.12** | **SIGNED INFORMED CONSENT FORMS** | **Purpose** | **Located in Files of:**  
<p>| <strong>Investigator</strong> | <strong>Sponsor</strong> |
| 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) | X |</p>
<table>
<thead>
<tr>
<th>Title of Document</th>
<th>Purpose</th>
<th>Located in Files of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.3.13 SOURCE DOCUMENTS</td>
<td>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.</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>NOTE: See note in 8.3.11</td>
<td></td>
</tr>
<tr>
<td>8.3.14 SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)</td>
<td>To document that the investigator or authorized member of the investigator’s staff confirms the observations recorded</td>
<td>X (copy)</td>
</tr>
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<td></td>
<td>X (original)</td>
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</tr>
<tr>
<td>8.3.15 DOCUMENTATION OF CRF CORRECTIONS</td>
<td>To document all changes/additions or corrections made to CRF after initial data were recorded</td>
<td>X (copy)</td>
</tr>
<tr>
<td></td>
<td>X (original)</td>
<td></td>
</tr>
<tr>
<td>8.3.16 NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS</td>
<td>Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11</td>
<td>X</td>
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<tr>
<td></td>
<td>Title of Document</td>
<td>Purpose</td>
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</tr>
<tr>
<td>8.3.17</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>8.3.18</td>
<td>NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION</td>
<td>Notification by sponsor to investigators of safety information in accordance with 5.16.2</td>
</tr>
<tr>
<td>8.3.19</td>
<td>INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)</td>
<td>Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3</td>
</tr>
<tr>
<td>8.3.20</td>
<td>SUBJECT SCREENING LOG</td>
<td>To document identification of subjects who entered pre-trial screening</td>
</tr>
<tr>
<td>Title of Document</td>
<td>Purpose</td>
<td>Located in Files of:</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>8.3.21 SUBJECT IDENTIFICATION CODE LIST</td>
<td>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</td>
<td>X</td>
</tr>
<tr>
<td>8.3.22 SUBJECT ENROLLMENT LOG</td>
<td>To document chronological enrollment of subjects by trial number</td>
<td>X</td>
</tr>
<tr>
<td>8.3.23 INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE</td>
<td>To document that investigational product(s) have been used according to the protocol</td>
<td>X  X</td>
</tr>
<tr>
<td>8.3.24 SIGNATURE SHEET</td>
<td>To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs</td>
<td>X  X</td>
</tr>
<tr>
<td>8.3.25 RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)</td>
<td>To document location and identification of retained samples if assays need to be repeated</td>
<td>X  X</td>
</tr>
</tbody>
</table>
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:

<table>
<thead>
<tr>
<th>Title of Document</th>
<th>Purpose</th>
<th>Located in Files of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.4 .1 INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE</td>
<td>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</td>
<td>Investigator: X, Sponsor: X</td>
</tr>
<tr>
<td>8.4 .2 DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION</td>
<td>To document destruction of unused investigational products by sponsor or at site</td>
<td>Investigator: X, Sponsor: X (if destroyed at site)</td>
</tr>
<tr>
<td>8.4 .3 COMPLETED SUBJECT IDENTIFICATION CODE LIST</td>
<td>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</td>
<td>Investigator: X</td>
</tr>
<tr>
<td>8.4 .4 AUDIT CERTIFICATE (if available)</td>
<td>To document that audit was performed</td>
<td>Investigator: X</td>
</tr>
<tr>
<td>8.4 .5 FINAL TRIAL CLOSE-OUT MONITORING REPORT</td>
<td>To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files</td>
<td>Investigator: X</td>
</tr>
<tr>
<td>8.4 .6 TREATMENT ALLOCATION AND DECODING DOCUMENTATION</td>
<td>Returned to sponsor to document any decoding that may have occurred</td>
<td>Investigator: X</td>
</tr>
<tr>
<td>Title of Document</td>
<td>Purpose</td>
<td>Located in Files of:</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>8.4.7 FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)</td>
<td>To document completion of the trial</td>
<td>X</td>
</tr>
<tr>
<td>8.4.8 CLINICAL STUDY REPORT</td>
<td>To document results and interpretation of trial</td>
<td>X (if applicable)</td>
</tr>
</tbody>
</table>

(ICH, 2016)
Appendix C: Relevant Certifications for Key Members of the Research Team

<table>
<thead>
<tr>
<th>Certification</th>
<th>Relevant For</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association of Clinical Research Professionals Clinical Research Certification for PIs (Certified Principal Investigator)</td>
<td>PIs</td>
</tr>
<tr>
<td>Association of Clinical Research Professionals Clinical Research Coordinator Certification</td>
<td>CRCs</td>
</tr>
<tr>
<td>Society of Clinical Research Associates Clinical Research Certification</td>
<td>CRCs</td>
</tr>
</tbody>
</table>

**External Resources Related to Training**

**CITI Program**: Offers a wide range of key trainings for those involved in clinical research.

**Global Health Network**: Includes a variety of free training opportunities, including short courses and modular courses. Certificate is provided upon completion of each course.

**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.

**HHS.gov** *(HHS, 2018)*: Provides a comprehensive overview of HIPAA and confidentiality issues.

**An Individual’s Right to Access and Obtain Their Health Information Under HIPAA** *(McGraw et al., 2017)*: FREE CME that reviews patient rights related to HIPAA