SPINAL MUSCULAR ATROPHY

CHI Formulary Indication Review

مجلس الضمان الصحي
Council of Health Insurance

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- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
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Abbreviations

6MWT	Six-Minute Walk Test
ADL	Activities of Daily Living
BiPAP	Biphasic Positive Airway Pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CPAP	Continuous Positive Airway Pressure
DEXA	Dual Energy X-ray Absorptiometry Analysis
EK2	Egen Klassifikation Scale Version 2
FEV1	Forced Expiratory Volume In 1 Second
FVC	Forced Vital Capacity
HAS	Haute Autorité de Santé
HDAC	Histone Deacetylase Inhibitors
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE2	Hammersmith Infant Neurological Examination 2
IQWIG	Institute for Quality and Efficiency in Healthcare
MDT	Multidisciplinary Team
MLPA	Multiplex Ligation-dependent Probe Amplification
MRI	Magnetic Resonance Imaging
NGS	Next Generation Sequencing
NICE	National Institute for Health and Care Excellence
NIV	Non-Invasive Ventilation
PBAC	Pharmaceutical Benefits Advisory Committee
PHA	Phenylbutyrate
qPCR	quantitative Polymerase Chain Reaction

ROCK	Rho-Associated Protein Kinase
RSV	Respiratory Syncytial Virus
RULM	Revised Upper Limb Module
SAHA	Suberoylanilide Hydroxoic Acid
SARM	Selective Androgen Receptor Modulators
SMA	Spinal Muscular Atrophy
SMN	Survival Motor Neuron
TSA	Trichostatin
VPA	Valproic Acid
WHO	World Health Organization

Executive Summary

Spinal Muscular Atrophy (SMA) is a hereditary autosomal recessive disorder characterized by a wide range of manifestations. It is marked by progressive proximal muscle weakness, diminished muscle tone and atrophy. The above features stem from the destruction of alpha motor cells as a result of the degeneration of anterior horn cells in the spinal cord. Homozygous deletion at 5q13, the coding region for the survival motor neuron (SMN1) gene is responsible for 95% of cases of SMA. SMA is categorized into four primary subtypes based on the age of onset and disease severity (maximum motor function achieved)[1]; very weak infants unable to sit unsupported (Type 1), non-ambulant patients able to sit independently (Type 2), up to ambulant patients with childhood (Type 3) and adult onset SMA (Type 4)[2].

SMA is the second most common cause of autosomal recessive inherited related mortality with an estimated incidence of 1 in 6,000 to 11,000[1]. Type 1 SMA cases are the most frequent at a rate of 60%, with Type 2 occurring at a rate of 20% to 27% and Type 3 occurring at a rate of 12% to 20%[3]. As per Al Jumah et al, as of 2022, the birth incidence of SMA in the KSA was estimated to be 32 per 100,000 births and the total number of people living with SMA in KSA to be 2,265 of which 188 patients are Type 1, 1,213 patients are Type 2, and 864 patients are Type 3. The SMA carrier rate is reported to be at 2.6% in Saudi subjects and is slightly higher than the reported global frequency[4].

The clinical manifestations of SMA are a consequence of lower motor neuron loss and include muscle weakness and atrophy, hypotonia, decreased or absent reflexes (hypo- or areflexia) and twitching of muscle fibers[5]. SMA patients also suffer from respiratory, gastrointestinal, orthopedic complications that affect the quality of life and can potentially be life-threatening. For instance, patients may develop chest infections secondary to aspiration due to inadequate swallowing and muscle weakness. SMA patients are also prone to suffer from metabolic acidosis, especially during periods of illness or fasting[1].

This report compiles all clinical and economic evidence related to Spinal Muscular Atrophy according to the relevant sources. The ultimate objective of issuing SMA guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to SMA patients in Saudi Arabia**. The main focus of the review was on Saudi Arabian, North American, European and other international guidelines issued within the last five years. To elaborate, Saudi Arabian guidelines detailed the multidisciplinary approach to the management of SMA in the context of the COVID-19 Pandemic; however, only general measures were included in this review. North American guidelines drew focus on the classification of

SMA subtypes, diagnosis, and management of associated SMA complications namely respiratory, gastrointestinal, and orthopedic/musculoskeletal complications. European Guidelines emphasized the classification of SMA, approaches to SMA drug development, treatment objectives and the use of novel pharmacological agents. Lastly, international guidelines provided an update to the 2007 SMA Standards of Care, with a focus on orthopedic, nutritional, and respiratory management as well as immunizations for SMA patients.

Main recommendations issued by different health technology assessment (HTA) bodies on the use of the current medications in SMA were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

Regarding pharmacological therapy, focus was drawn on supportive care with the early involvement of pediatric palliative care specialists. These experts were mainly involved in the management of Types 0, 1, and 2 SMA. Novel therapies have emerged and have shown promising results when tackling the morbidity and mortality associated with Type 1 and Type 2 SMA. These include agents such as Nusinersen, Risdiplam, and Onasemnogene Abeparvovec-xioi; which were approved by the FDA in 2016, 2020, and 2019 respectively, and all three of which are newly SFDA registered. Early diagnosis and treatment of SMA can limit disease progression in children and adults, extending life expectancy and improving quality of life (QOL)[6].

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines and Strength of Agreement (SoA) reflecting specific drug class role in the management of Spinal Muscular Atrophy.

Major recommendations for suggested drug therapies are summarized in the table below:

For SFDA Registered Drugs:

Table 1. Recommendations for SFDA-Registered Drugs Used in the Management of Spinal Muscular Atrophy (SMA)

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Nusinersen	Treatment of spinal muscular atrophy (SMA) in	**1st line**	No Level of Evidence	**Positive Recommendation** from NICE[7], CADTH[8],

	pediatric and adult patients (Types 0 through 4)			HAS[9], IQWIG[10], PBAC[11].
Risdiplam	Treatment of spinal muscular atrophy (SMA) in pediatric and adult patients (Types 0 through 4)	**1st line**	No Level of Evidence	**Positive Recommendation** from NICE[12], CADTH[13], PBAC[14], HAS[15] (In the treatment of 5q spinal muscular atrophy in patients aged 2 months and older with a clinical diagnosis of SMA types 1, 2 and 3) and IQWIG[16] (For patients with 5q SMA, 2 months of age and older with SMA type 1) **Negative Recommendation** from HAS[15] (For patients with a clinical diagnosis of SMA type 4 and in pre-symptomatic patients) and IQWIG[16] (For patients with 5q SMA, 2 months of age and older with SMA type 2 and type 3 and for pre-symptomatic patients with 5q SMA, 2 months of age and older with 1 to 3 SMN2 gene

				copies and 4 SMN2 gene copies)
Onasemnogene Abeparvovec-xioi	Treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene (Types 0 through 3)	**Alternative Therapy**	No Level of Evidence	**Positive Recommendation** from NICE[17], CADTH[18], and HAS[19] (For patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1 and 2 or pre-symptomatic SMA, with up to 3 copies of the SMN2 gene) **Negative Recommendation** from HAS[19] (For patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 3) and IQWIG[20]. **Deferred Recommendation** from PBAC [21].

For Non-SFDA Registered Drugs:

To date, there are no new non-SFDA registered molecules for the management of Spinal Muscular Atrophy.

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

1.1.1 A Consensus Statement on Spinal Muscular Atrophy Management in Saudi Arabia in the Context of COVID-19 [2020]

The following guidelines do not provide a specified grade of evidence or level of recommendation.

Although the above guidelines were issued during the COVID-19 pandemic, they harbor general measures for the management of SMA. The recommendations issued include the following[22]:

Recommendations for Facility and Hospital Readiness for SMA Management:

- Pharmacological agents are fundamental in the management of SMA.
- Medication administration is highly prioritized in the SMA treatment plans.
- Ensuring early, prompt, and consistent SMA management, particularly when healthcare personnel are faced with a case of infantile-onset Type 1 SMA, allows for the best possible clinical and patient-based outcome.
- Due to the aggressive natural history and rapid progression of Type 1 SMA, it is of utmost importance to initiate treatment more urgently than other types of SMA.

Pharmacological Therapy:

- Multidisciplinary team (MDT) experts are to decide on the initiation of **individualized gene therapy** in SMA patients. Examples of gene therapy include the novel agent: Onasemnogene Abeparvovec-xioi; used as a treatment regimen in some SMA patients less than 2 years of age. The regimen consists of a single intravenous infusion followed by a few hours of observation in the hospital, then one month of oral corticosteroid therapy followed by 28 days of corticosteroid tapering.
- In stable patients, it is recommended that the initiation of gene therapy be delayed due to the risk of immune suppression by corticosteroids. As per Sack et al.[23], corticosteroids administered at the time of gene therapy lower the immune system response which subsequently allows the vector to deliver the promoter and transgene to target cells as intended.

- Upon gene therapy initiation in SMA patients, corticosteroids should not be discontinued or interrupted unless advised otherwise by the treating expert neurologist.
- Follow up visits include but are not limited to laboratory monitoring of liver function, troponin, and platelets.
- Patients on Nusinersen are recommended to adhere to a scheduled dosing time as it is a critical therapy for SMA patients to maintain a steady drug concentration in the cerebrospinal fluid.
- In case of a missed or delayed loading dose, Nusinersen should be given as soon as possible with an interval of at least 14 days between doses. It is also recommended that Nusinersen be given as soon as possible, and the following doses should be continued every 4 months as per the original dosing timeline.

The following figure describes the Nusinersen loading and maintenance dosing regimens:

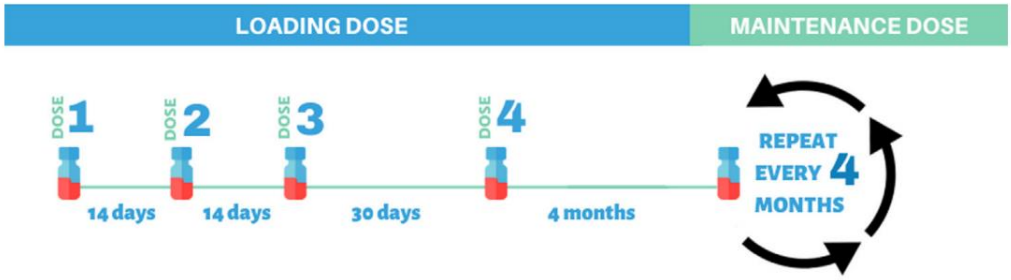


Figure 1. *Nusinersen Loading and Maintenance Dosing Regimen. Retrieved from Alghamdi F, Alshaikh N, Bamaga AK, et al. A consensus statement on spinal muscular atrophy management in saudi arabia in the context of COVID-19. Neurosciences. 2020;25(3):230-237. doi:10.17712/nsj.2020.3.20200083.*

<u>Recommendations for Multidisciplinary Team Approaches:</u>

- Regular physiotherapy is the cornerstone of SMA management.
- Assessments recorded within 3 months prior to the initiation of therapy can be considered as a baseline assessment.
- Regarding the frequency of assessments, a motor functional scale assessment should be conducted upon admission for intrathecal therapy every 4 months and one day prior to the injection.

1.2 North American Guidelines

1.2.1 Spinal Muscular Atrophy [2015]

The following review does not provide a specified grade of evidence or level of recommendation.

Physicians and professors from the Ohio State University Medical Center issued a review of current literature on the management of SMA in 2015. The recommendations are summarized below[24]:

Spinal Muscular Atrophy is categorized into four different subtypes; these are described in the following table:

Table 2. Spinal Muscular Atrophy Classification

Type	Age of Onset	Highest Function	Natural Age of Death	SMN2 # of Copies
0	Prenatal	Respiratory Support	< 1 month	1
1	0-6 months	Never sit	< 2 years	2
2	< 18 months	Never stand	> 2 years	3,4
3	> 18 months	Stand alone	Adult	–
3a	18 months – 3 years	Stand alone	Adult	3,4
3b	> 3 years	Stand alone	Adult	4
4	> 21 years	Stand alone	Adult	4 – 8

Diagnosis:

- The differential diagnosis of severe forms of SMA includes all other causes of hypotonic weakness in the infant.
- In patients with intermediate forms of the disease, the differential includes potential peripheral nervous system disorders as myopathy (Dystrophinopathies, limb girdle muscular dystrophy, metabolic myopathies, or inflammatory myopathies), neuropathy (inflammatory neuropathies), neuromuscular junction disorders (myasthenia gravis or congenital myasthenic syndromes), and other motor neuron disorders (non-5q form of SMA or late onset hexosaminidase A deficiency).
- In patients with adult-onset disease the differential overlaps with that of the intermediate forms of the disease but also includes later onset disorders such

as amyotrophic lateral sclerosis and Kennedy disease (X-linked spinobulbar muscular atrophy).

- Molecular genetic testing is the standard tool for diagnosis of SMA and should be taken into consideration in any infant presenting with weakness or hypotonia.
- Other procedures for evaluation that have fallen out of practice include MRIs, muscle biopsy and electrodiagnostic testing.

Clinical Management:

1. **Pulmonary:**

- Respiratory failure is usually the ultimate cause of death in patients with Type 1 and Type 2 SMA.
- In patients with Type 1 SMA, early initiation of noninvasive ventilatory support has been associated with enhanced quality of life and survival.
- Patients usually tolerate bilevel positive airway pressure when it is applied with appropriate pressure settings and mask placement. It also does not affect hemodynamic balance and may improve daytime hypercapnic ventilatory drive.
- Patients with this extent of respiratory weakness also have a weak cough which subsequently increases the risk of aspiration and hypoxemia secondary to mucus plugging as well as an increased risk of recurrent pulmonary infections.
- Patients at risk for mucus plugging should be monitored with overnight oximetry during acute illnesses. Assisted airway clearance methods, such as manual suctioning, is recommended.
- Generally, during any acute illness and due to the risk of developing pneumonia and associated pulmonary complications, patients are to be started on antibiotics.
- In case the non-invasive support is insufficient, tracheostomy and permanent ventilatory support may be successfully initiated in SMA patients.
- Nocturnal hypoventilation is also managed using noninvasive ventilation.
- The management of respiratory function in other SMA types is also similar to that of Type 1.
- **Monitoring:** It is important to monitor respiratory muscle function and to conduct physical examinations and assessments of cough effectiveness

routinely. Forced vital capacity can also be routinely monitored in SMA children who are older than 5 years of age.

2. **Gastrointestinal and Nutritional:**

- Infants with Type 1 SMA often suffer from prolonged feeding times and instant fatigue. The reduction in feeding subsequently leads to a failure to thrive and aspiration.
- Complications also include gastroesophageal reflux, delayed gastric emptying and constipation. These complications are more commonly seen in patients who are less ambulant.
- **Management of aspiration associated with feeding and dysphagia:** Changing the food consistency to incorporate semisolid and thickened liquids is recommended.

  In SMA type 1 infants, early gastrostomy and laparoscopic Nissen fundoplication (if gastroesophageal reflux is present) are recommended and can be performed shortly after diagnosis in an attempt to maintain proper nutrition and to reduce the risk of infection as a result of aspiration.
- SMA patients are prone to malnutrition which may subsequently lead to decreased muscle mass and impaired function.
- Adequate supplementation of calcium and Vitamin D is recommended due to the tendency for decreased bone mineral density with advancing age.

3. **Orthopedic and Musculoskeletal Complications:**

- Contractures and scoliosis are common manifestations in non-ambulatory SMA patients.
- To preserve flexibility and prevent contractures, regular stretching and bracing programs are recommended.
- Manual and motorized wheelchairs may be incorporated into the management process in patients aged as early as 18 to 24 months of age.
- A standing frame or mobile stander with ankle-foot orthoses may be used in children who are able to bear weight and have trunk control.
- For scoliosis, spinal fusion and bracing are the treatments of choice subsequently preventing chest cage deformities and resulting respiratory restriction.

1.3 European Guidelines

1.3.1 Spinal Muscular Atrophy: Pathology, Diagnosis, Clinical Presentation, Therapeutic Strategies & Treatments [2020]

The following guidelines do not provide a specified grade of evidence or level of recommendation.

SMA Europe is a non-profit umbrella organization that consists of 23 SMA patients and research organizations from 22 countries across Europe. It has issued an extensive guideline on the management of SMA, the recommendations are detailed below[25]:

Diagnosing SMA:

- The initial clinical manifestations (Increasing difficulty with breast feeding, weight gain, ambulation) are detected by parents or close relatives.
- A diagnosis of SMA is suspected when an infant exhibits one or more of the following manifestations:
    - Proximal progressive muscle weakness
    - Rapid diaphragmatic breathing
    - Fluttering of the chest wall upon inhalation
    - Hypotonia with weak or absent reflexes
    - Fine tremor of the fingers
    - Fasciculations of the tongue
    - Weak cry
    - Cough
    - Limited movement of limbs and trunk particularly antigravity movements (lower limbs)
    - Floppy child
    - Respiratory difficulties
    - Delayed or missed milestones.
- Molecular testing is a definitive way of diagnosing SMA.

SMA Classification:

SMA Europe classifies SMA into four primary types and their respective subtypes:

Table 3. SMA Types & Subtypes

SMA Type	Age of Onset	Highest Motor Milestone	SMN2 Copy Number	Lifespan
IA	< 1 week	Never sits	1	< 1 month
IB	1 week – 3 months	Never sits	2,3	< 2 years
IC	3 – 6 months	Never sits	2,3	< 2 years
IIA	6 – 15 months	Sits independently. Loses the ability to sit	2,3,4	> 2 years
IIB	6 – 15 months	Sits independently. Maintains the ability to sit	2,3,4	> 2 years
IIIA	< 3 years	Walks independently	3,4	Adult
IIIB	> 3 years	Walks independently	3,4	Adult
IV	> 21 years	Walks independently	4,5	Adult

Therapeutic Approaches:

- The SMA drug pipeline identifies possible treatment targets:
    - SMN2 splicing modulation
    - Gene replacement therapy
    - Muscle targets
- The following table describes diverse strategies in therapeutic approaches:

Table 4. Approaches for SMA Drug Development

Therapeutic Approach	Examples
Upregulation of SMN protein	N/A
Increasing SMN2 Transcription	HDAC inhibitors (VPA,PHA, SAHA, TSA) Other: prolactin, HU, quinazoline/RG3039, lncRNA oligos
Correcting SMN2 splicing	Antisense oligonucleotides (ASO) Small molecules(PTKSMA1, RG7800,LMI070)
Stabilizing SMN Transcript	Celecoxib
Increasing translation to SMN Transcript	Indoprofene, Aminoglycosides
Stabilizing SMN protein	BIP 135

SMN Gene Therapy	scAAV9SMN, AVXS-101
Neuroprotection	Olesoxime, Gabapentin, Riluzol
Enhancement of Muscle	Myostatin inhibitors, albuterol, SARMs, exercise, fast troponin activators (Tirasemtiv and CK-2127107, TWEAK inhibitors)
Stem Cell Therapy	Embryonic stem cells derived neural stem cells, human embryonic stem cells derived MN progenitors (hMNPs)
Targeting modifiers	ROCK inhibitors (Fasudil)
Combined therapies	ASO or gene therapy in combination with muscle enhancers or neuroprotective

HDAC - histone deacetylase inhibitors, **VPA** - valproic acid, **PHA** - phenylbutyrate, **SAHA** - suberoylanilide hydroxoic acid, **TSA** - trichostatin, **SARM** - selective androgen receptor modulators, **TWEAK-TNF** - like weak inducer of apoptosis, **ROCK** - rho-associated protein kinase

Drug Treatment:

- Nusinersen, an antisense oligonucleotide, works by correcting the SMN2 gene splicing; it is given as an intrathecal injection, starting with a loading dose of 12 mg once every 14 days for 3 doses; then 12 mg as a single dose 30 days after the third dose, followed by maintenance dosing of 12 mg once every 4 months[26].
- Onasemnogene Abeparvovec (also known as AVXS-101), gene therapy, works by replacing the function of the missing or nonworking SMN1 gene with a new, working copy.
- Risdiplam is a survival of motor neuron 2 (SMN2) splicing modifier which is given as 5 mg orally once daily.

1.3.2 Delphi Consensus on Recommendations for the Treatment of Spinal Muscular Atrophy in Spain (RET-AME consensus) [2022]

The following guidelines do not provide a specified grade of evidence or level of recommendation, and provide a percentage (%) of consensus instead.

The RET-AME consensus recommendations provide a frame of reference for the appropriate use of disease-modifying treatments in patients with SMA, the recommendations are detailed below[27]:

Treatment Objectives:

- The following factors should be taken into consideration when setting treatment objectives for SMA patients:
    - Baseline functional status (walkers, sitters, or non-sitters)
    - Type of SMA
    - Current age
    - Disease course/phase: Asymptomatic phase, Symptom onset phase (onset), Chronic phase (stability), Decline phase (decline).
    - Presence of scoliosis, history of scoliosis surgery, or contractures. **(Reduced consensus: 77.8%)**
- Of note[28]:
    - Non-sitters: Patients who are unable to sit
    - Sitters: Patients who are able to sit but are not able to walk
    - Walkers: Patients who are able to walk
- The following efficacy variables are to be evaluated in all patients:
    - Motor function
    - Quality of life
    - Respiratory function
    - Bulbar function (Speech and swallowing) **(Reduced consensus: 77.8%)**
    - Reduction of hospital admissions **(Reduced consensus: 77.8%)**
    - Fatigability **(Reduced consensus: 72.2%)**

Tools for Evaluating Outcomes in Pediatric Patients:

- **For presymptomatic patients (diagnosed by screening tests)**: At least one motor function scale for SMA (CHOP INTEND) is recommended for patient assessment all while aligning with the WHO or HINE2 motor developmental milestones.
- Motor function should be measured using motor scales based on the patient's age and functional status:
    - < 24 months: CHOP INTEND
    - > 24 months (walkers): HFMSE + 6MWT
    - > 30 months (non-walkers): HFMSE + RULM

- Functional status should be evaluated using the EK2 scale in non-walkers older than 4 years.
- Quality of life is evaluated using the Pediatric Quality of Life Inventory (Neuromuscular Module) **(Reduced consensus 78%)**
- Respiratory function is evaluated using spirometry studies including FVC, FEV_1, FVC/FEV_1 ratio (%).

  Where required, capnography may be used to assess pulmonary function in infants.
- For bulbar function, there exists no consensus on the tools to be used for evaluation; however, it is recommended to be assessed routinely.

Management of Pediatric Patients with SMA:

- Neonatal screening is essential to be implemented to initiate treatment during the asymptomatic phase.
- It is of utmost importance that treatment be started as early as possible.
- For patients with type 0 and type 1A SMA, no consensus was established on disease-modifying therapy in these patients; therefore, individualized assessment by an expert committee is recommended.
- Ineligibility criteria for treatment includes: An unfavorable result of the risk-benefit analysis conducted by the responsible physician, very advanced clinical situations with minimal functional activity and need for support in ADLs (Irreversible and unlikely to benefit substantially from the drug used), patients requiring permanent ventilation (> 16 hours a day) considered to be irreversible, and off-label use unless justified by robust evidence.

Treatment Suspension:

- For pediatric patients, treatment suspension is considered with worsening scores of the motor scale selected for follow-up and/or loss of an acquired motor developmental milestone.
- The process of treatment suspension is as follows:
  - For patients with type 1B/1C SMA: Suspension is considered every 12 months.
  - For patients with type 2/3 SMA: Suspension is considered every 2 years.
- For adult patients, suspension is considered every 2 years.

1.4 International Guidelines

The following guidelines serve as a two-part update to the previous recommendations issued by the 2007 International Conference on the Standard of Care for SMA Consensus Statement.

1.4.1 Diagnosis and Management of Spinal Muscular Atrophy: Part 1: Recommendations for Diagnosis, Rehabilitation, Orthopedic and Nutritional Care [2018]

The following guidelines do not provide a specified grade of evidence or level of recommendation.

The SMA care group has issued the following recommendations on diagnosing and managing SMA with a focus on rehabilitation as well as orthopedic and nutritional care[29]:

SMA Diagnosis:

- Generally, clinical signs prompt the diagnosis of SMA.
- The SMA clinical manifestations include but are not limited to hypotonia, progressive symmetric and proximal weakness, bulbar muscle weakness and bell-shaped chest along with a paradoxical breathing pattern.
- Molecular genetic testing of SMN1/SMN2 is highly reliable and is the standard diagnostic tool for SMA.
- The gold standard of SMA genetic testing is a quantitative analysis of both SMN1 and SMN2 using multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next generation sequencing (NGS).
- The conduction of a PCR is a faster, more readily available and less expensive method to identify homozygous SMN1 deletions; however, it does not allow for quantification of SMN1 or SMN2 copy number.
- Of note, knowledge on SMN1 copies is relevant for identification of heterozygous deletions whereas SMN2 copies are important for prognosis and therapeutic approaches.
- A muscle biopsy is not necessary for SMA patients with a typical presentation.
- Electromyography is not necessary for patients with Type 1/Type 2 SMA; however, it could be helpful for more chronic forms of SMA with less prominent phenotypes.

- The following figure describes the diagnostic process of SMA as per the SMA Care Group:

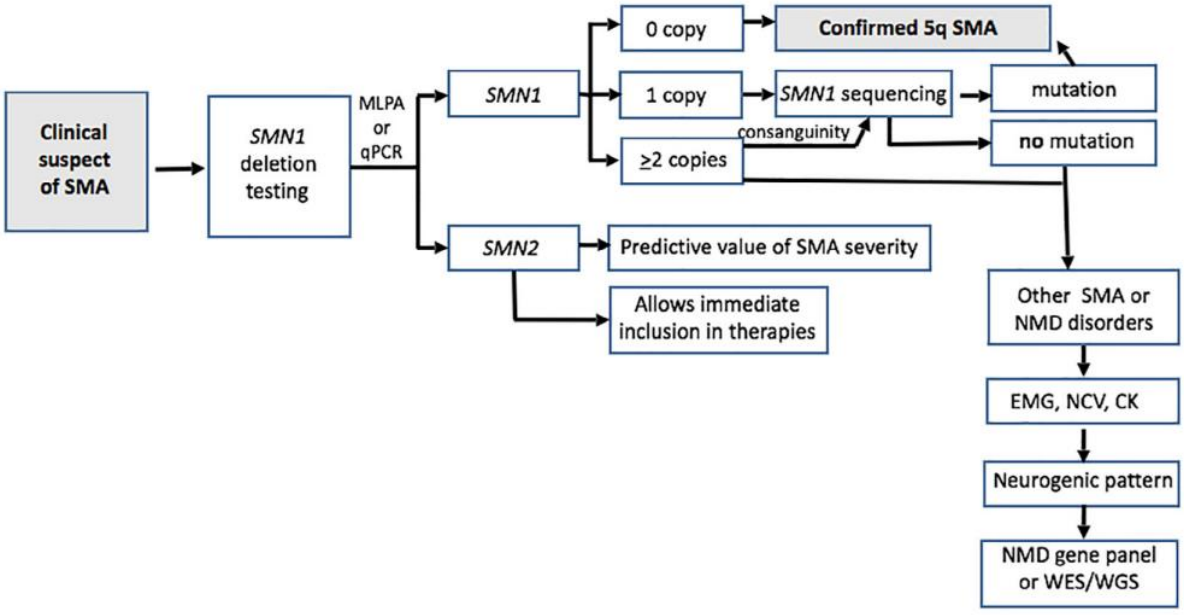


Figure 2. *Diagnostic Algorithm for Spinal Muscular Atrophy. Retrieved from SMA Care Group 2018 Guidelines.*

SMA: spinal muscular atrophy; **SMN1**: survival motor neuronon 1; **SMN2**: survival motor neuron 2; **NMD**: neuromuscular disorders; **EMG**: electromyography; **NCV**: nerve conduction velocity; **CK**: creatine kinase levels; **WES**: whole exom sequencing; **WGS**: whole genome sequencing

<u>Primary Rehabilitation Goals for Non-Sitters, Sitters, and Walkers:</u>

- **For Non-Sitters:** Optimization of function, minimization of impairment, and optimizing tolerance to various positions.
- **For Sitters:** Prevention of contractures and scoliosis, and maintenance, restoration or promotion of function and mobility.
- **For Walkers:** Maintenance, restoration or promotion of function, mobility, adequate joint range, and improvement of balance and endurance.

The following table details the rehabilitation assessment, intervention and care considerations for non-sitters, sitters, and walkers/ambulant patients.

Table 5. Rehabilitation Assessment and Intervention. Adapted from SMA Care Group 2018 Guidelines.

	Assessment	Intervention	Care Considerations
Non-Sitters	Postural control Scoliosis Hip dislocation Sitting tolerance Chest deformities	***Positioning and Bracing*** Daily use of seating systems, postural and positioning supports, thoracic bracing and cervical bracing for head support. Static thoracic bracing should have incorporated modifications for respiratory support including abdominal cutouts.	To be effective, orthoses should be applied for more than 60 minutes to overnight. Session duration for effective stretching and range of motion depends on specific patient needs, joints, and rehabilitation aims.
	Contractures (ROM, goniometry)	***Stretching*** Daily use of orthoses for upper lower limb orthoses for stretching and to promote function and range of motion. Static orthoses Knee immobilizers and hand splints are recommended for positioning and stretching. AFOs and KAFOs can be used for stretching and positioning. TLSOs are used for positioning. Supported standing.	The minimal frequency for stretching and range of motion is 3–5 times per week. The minimal frequency for bracing to be effective is 5 times per week.
	Muscle weakness (Antigravity movements) Functional	***Promote function and mobility*** Use of seating and mobility systems	Recommend toys with switches, light weight rattles, Bath equipment, adapted beds, upper extremity

	scales (CHOP INTEND) Motor development (HINE)	Mobile arm supports to assist upper extremity function.	assistive devices, as well as hoists (lifts), Environmental controls, and eye tracking devices for computers and communication, Strollers with recline and the ability to lay flat, power wheelchairs should have recline/tilt, adapted seating systems.
Sitters	Postural control Foot and chest deformities Scoliosis and pelvic obliquity Hip dislocation	***Positioning and Bracing*** Thoracic bracing is recommended for posture and to promote function. Cervical bracing is often used for head support for safety and transportation.	Orthoses should be worn for more than 60 minutes to overnight. The minimal frequency for bracing: 5 times/week.
	Contractures (ROM, goniometry)	***Stretching*** Orthoses are used for the upper and lower limbs to promote function and ROM Regular stretching for segments known to be at risk for contractures: hip, knee and ankle, wrist and hand. Knee immobilizers, KAFOs, and AFOs are recommended for positioning and standing. RGOs and KAFOs can be used for supported ambulation.	Minimal frequency for stretching and ROM: 5–7 times/week When stretching or performing joint mobilization ensure joint segments are aligned throughout the treatment. Supported standing should be up to 60 minutes and minimal frequency is 3–5 times/week, optimal 5–7 times/week.

		TLSOs and hand splints are used for positioning.	
	Functional scales (HFMSE, RULM, MFM) Muscle weakness (Strength tests)	***Promote function and mobility*** Use of seating and mobility systems. Use of gait training devices and mobility devices to promote supported ambulation Mobile arm supports to assist upper extremity function.	Exercise can have an effect on function, strength, ROM, endurance, ADLs, participation, and balance Recommend swimming, hippotherapy, and wheelchair sports. All sitters should have electric/power wheelchairs with custom postural support and seating systems The option to tilt and/or recline and a seat elevator is sometimes necessary in weaker patients. Lightweight manual wheelchairs or power assist wheels are ideal to promote self-propulsion in stronger patients.
Ambulant	Mobility Timed tests Measure of endurance (6MWT) Falls Functional scales (HFMSE, RULM) Muscle weakness (Strength tests)	***Promote function and mobility***	Recommend aerobic and general conditioning exercise for SMA walkers. Options include: Swimming, walking, cycling, yoga, hippotherapy, rowing, elliptical/cross-trainers. Exercise program should be designed and monitored by a

			physical or occupational therapist, familiar with SMA. Optimal duration for aerobic exercise: at least 30 minutes
	Contractures (ROM, goniometry)	***Stretching***	Minimal frequency: 2–3 times/week, optimal: 3–5 Maintain flexibility through active assisted stretching and include the use of orthoses according to specific needs.
	Postural Control Scoliosis Hip Dislocation	***Positioning and Bracing***	Recommend some form of balance exercise. Lower limb orthoses are used for posture and function at the ankle and knee, Thoracic bracing may be used to promote posture in sitting.

ROM, range of motion; **CHOP INTEND**, Children Hospital of Philadelphia InfantTest of Neuromuscular Disorders; **HINE**, Hammersmith Infant Neurological Examination; **AFOs**, ankle foot orthosis; **KAFOs**, knee ankle foot orthosis; **TLSOs**, thoraco lumbo sacral orthosis; **HFMSE**, Hammersmith Function Motor Scale Expanded; **RULM**, Revised Upper Limb Module; **MFM**, Motor Function measure; **6MWT**, 6-minute walk test; **ADL**, activities of daily living; **SMA**, spinal muscular atrophy.

Orthopedic Management:

The following figure details the management of spinal deformity:

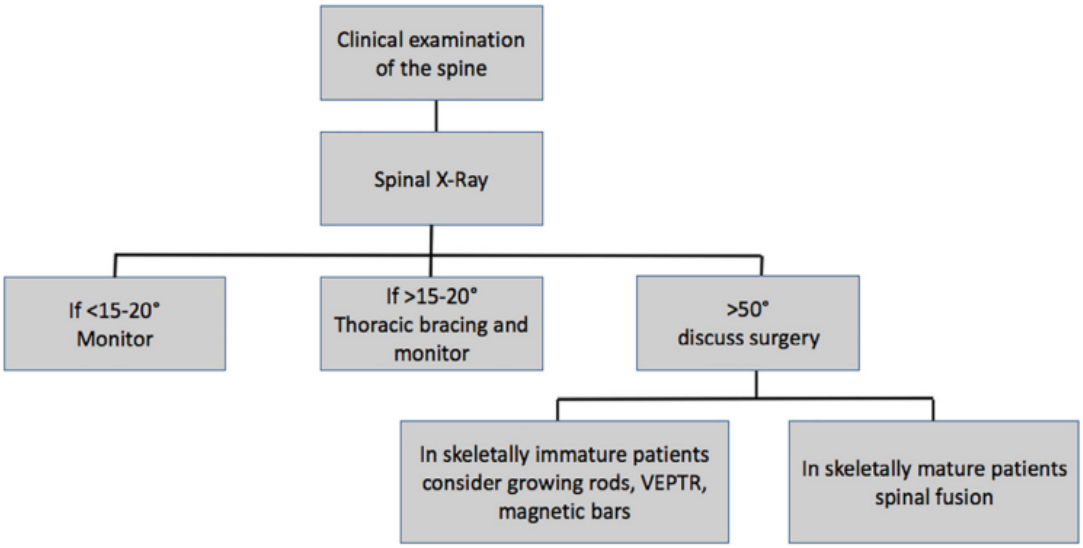


Figure 3. *Spinal Deformity Management. Retrieved from SMA Care Group 2018 Guidelines.*

- Unless they have stable respiratory and nutritional function, spinal deformity management in non-sitters is seldom an option due to their limited survival.
- Patients with type 1/type 2 SMA with scoliosis >20° should be monitored every 6 months until skeletal maturity and yearly after skeletal maturity.
- Spinal orthoses is recommended to support the hypotonic trunk and treat scoliosis >20°, especially in a child with significant growth remaining.
- There is no evidence that favors the use of one brace over the other, as both rigid and soft spinal thoracolumbar orthoses were recommended.
- Surgical treatment of spine deformity should be delayed until after the age of 4 years.
- Conversion of growth-friendly instrumentation to definitive posterior spine fusion should be decided on a case-by-case basis depending on several factors such as skeletal maturity and spine growth remaining.
- Rib- or spine-based growth friendly instrumentation systems are not recommended for use in children with hypotonic scoliosis. This is attributed to poor efficacy in ameliorating parasol rib deformity or increasing thoracic volume.
- In the case of unilateral and bilateral hip instability, only patients with significant pain should be surgically managed.
- Patients with contractures of the upper or lower extremities that cause pain or impair function are considered for surgical management.
- Fragility fractures are prominent among children with type 1 and type 2 SMA.

For non-ambulatory patients: Closed treatment with cast immobilization is generally recommended; but prolonged cast immobilization (>4 weeks) that aggravates muscle wasting and disuse osteoporosis should be avoided.

For non-ambulatory patients with hip fractures and for ambulatory patients with long bone fractures of the lower extremities: Surgical stabilization using intramedullary rods or bridging fracture plates are recommended.

Bone Health:

- Yearly Dual energy x-ray absorptiometry analysis (DEXA) is recommended in SMA patients to monitor bone density.
- Calcium and Vitamin D intake are of utmost importance for the amelioration of bone health.
- Vitamin D blood levels and intake should be monitored at least annually, and supplements should be given in the presence of low levels of Vitamin D or in case the patient is subject to osteopenia.
- Bisphosphonates may be considered in the case of frequent fractures.

Nutritional Management:

This also involves management of swallowing dysfunction and dysphagia, weight control and gastrointestinal dysfunction.

Table 6 details the nutritional assessments, interventions, and care considerations for SMA patients:

Table 6. Nutritional Assessment and Intervention. Adapted from SMA Care Group 2018 Guidelines.

	Assessment	Intervention	Care Considerations
Non-Sitters	Video Fluoroscopic Swallow Study shortly after diagnosis and when suggested by clinical signs suggestive of dysphagia (weak suck, fatigue, humid voice, pneumonias) Difficulties with feeding (pocketing,	If swallow study is passed, consider referral to specialist for feeding therapy/modification. For failure of a swallow study or for growth failure, for proactive care, place nasojejunal tube until a gastric tube can be placed	Determine appropriate calorie needs based on growth. Standardized growth charts are a good tool to track growth trends, but optimally, should be used with other body composition measurement tools

	jaw contractures, increased mealtimes) Nutritional analysis of food records/feeding regimen Longitudinal anthropometrics Acute care monitoring 25 Hydroxy-vitamin D labs and Body Composition and Bone density Constipation	with Nissen fundoplication. A dietitian should adjust caloric, fluid, macronutrient, micronutrient intake and timing of feeds. Nutrition labs may be indicated. Minimize fasting during acute care to less than 6 hours. Provide adequate fluid intake during illness. Monitor electrolyte levels and correct as needed. Monitor glucose levels to correct hypo/hyperglycemia. Provide adequate calcium and vitamin D intake for bone health. Adequate hydration. Use of bowel regulation medications.	to assess appropriate growth. For optimal care, recommend evaluation by a dietitian every 3–6 months for younger children and annually for older children/adults. Evaluation is especially important for those on specialized diets.
Sitters	Assessment of symptoms of dysphagia/aspiration /Difficulties with feeding Video Fluoroscopic Swallow Study if suggested by clinical signs suggestive of dysphagia. Nutritional analysis of food records/feeding	If safe to swallow, refer to specialist for feeding therapy/modification. If failed swallow or interventions are not sufficient place nasofeeding tube as indicated prior to placement of a long term Gastric feeding tube.	At minimum, recommend evaluation by a dietitian shortly after diagnosis and for concerns of under/over nutrition. For optimal care, recommend evaluation by a dietitian every 3–6 months for younger children and

	regimen Longitudinal anthropometrics (height, weight, OFC) Nutrition labs may be indicated. Acute care monitoring Glucose metabolism labs 25 Hydroxy-vitamin D labs and Body Composition and Bone density (DXA) Constipation	For growth failure, provide supplemental nutrition products. Referral to dietitian for increasing calories with nutrient dense foods. Adjust caloric, fluid, macronutrient, and micronutrient intake based on growth and intake. Limit calorie intake in overweight individuals and maximize nutrient intake. Minimize fasting during acute care. Appropriate fasting time depends on prior nutritional status and nature of acute event. Provide adequate fluid intake during illness. Monitor electrolyte levels and correct as needed. Monitor glucose levels to correct hypo/hyperglycemia. Indicated for individuals with increased body fat or other prediabetic symptoms. Adequate calcium, vitamin D intake. Diets rich in fiber are recommended to promote gastric motility and reduce constipation.	annually for older children/adults. Evaluation is especially important for those on specialized diets.

		Adequate fluid is needed with increased fiber intakes. Bowel regulation medication may be indicated.	
Ambulant	See dietitian for concerns of over/under nutrition Nutritional analysis/monitoring if underweight or overweight Longitudinal anthropometrics (height, weight, OFC). Glucose metabolism labs 25 Hydroxy-vitamin D labs	Provide macro/micronutrient intakes based on guidelines for a healthy sedentary individual. Limit calories as indicated to prevent obesity. Minimize fasting during acute care Indicated for individuals with increased body fat or other prediabetic symptoms Provide adequate calcium, vitamin D intakes for bone health if needed	

1.4.2 Diagnosis and Management of Spinal Muscular Atrophy: Part 2: Pulmonary and Acute Care; Medications, Supplements, and Immunizations; Other Organ Systems; and Ethics [2018]

The following guidelines do not provide a specified grade of evidence or level of recommendation.

The SMA Care Group has issued the recommendations below:

Pulmonary Management:

- The severity of loss of muscle function dictates the impact of SMA on the patient's respiratory function.
- Medical management for non-sitters, sitters, and walkers:

Non-Sitters:

- If asthma is suspected, nebulized bronchodilators should be available.
- Caution should be exercised when treating SMA patients with Glycopyrrolate for hypersalivation. (Dosage adjustment is of utmost importance to attain the proper effect, and to avoid over drying of secretions, which may contribute to the development of mucus plugs.)
- During RSV season, Palivizumab should be given through the first 24 months of life, and influenza vaccination should be administered annually after 6 months of age.

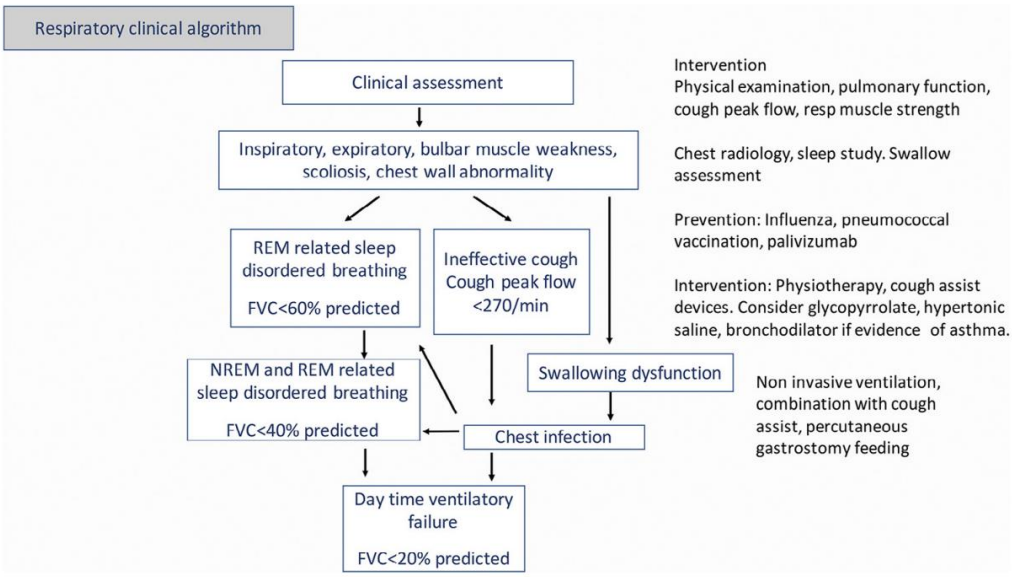
Sitters:

- If asthma is suspected, nebulized bronchodilators should be available.
- Annual influenza and pneumococcal immunizations should be administered.

Walkers:

- Prior to empiric oxygen supplementation, it is important to optimize the use of bilevel positive airway pressure (NIV) respiratory support.
- Oxygen supplementation should not be provided empirically in the absence of NIV or without monitoring CO2 gas exchange.
- Oxygen supplementation should be weaned to minimal provision prior to extubation.

The figure below depicts the respiratory clinical algorithm:



REM: rapid eye movements; **NREM**, non-REM; **FVC**: forced vital capacity

Figure 4. *Respiratory Clinical Algorithm. Retrieved from SMA Care Group 2018 Guidelines.*

The table below details the pulmonary assessment, interventions, and care considerations for SMA patients:

Table 7. Pulmonary Assessment, Intervention and Management Recommendations. Adapted from SMA Care Group 2018 Guidelines.

	Assessment	Intervention	Care Considerations
Non-Sitters	Physical examination Assessment of hypoventilation (End tidal CO2) Sleep study or pneumograms in all symptomatic patients or to determine if a patient needs to initiate NIV Clinical assessment of gastroesophageal reflux	Support airway clearance Oral suctioning Physiotherapy/respiratory therapy should be implemented immediately: Manual chest therapy Cough insufflator/exsufflator Support ventilation with bilevel NIV in symptomatic patients. Nebulized bronchodilators in patients with asthma or a positive bronchodilator response Customary immunizations, palivizumab through 24 months, influenza vaccination annually after 6 months of age	Assessments should be performed at least every 3 months initially, then every 6 months Supporting airway clearance with oronasal suctioning, physiotherapy/respiratory therapy and cough assist is critical to all non-sitters with ineffective cough. Ventilation should be started in all symptomatic patients. Some experts recommend using it before documented respiratory failure to palliate dyspnea. This should be judged on individual basis. NIV should be initiated in observing the patient clinically for adequate gas exchange or during a sleep study. NIV interfaces should be fitted by skilled

			physiotherapists selecting two interfaces with different skin contact points. Mucolytics should not be used long-term
Sitters	Physical examination Spirometry (when possible depending on age and cooperation) Sleep study or pneumograms in all patients with even minimal suspicion of symptoms of nocturnal hypoventilation Assessment of gastroesophageal reflux	Support airway clearance Physiotherapy/respiratory therapy should be implemented immediately: Manual chest physiotherapy Cough insufflator/exsufflator. Support ventilation with bilevel NIV in symptomatic patients. Nebulized bronchodilators in patients with suspicion of asthma Customary immunizations, annual influenza, and pneumococcal vaccination.	Assessments should be performed every 6 months Supporting airway clearance is critical to all patients with ineffective cough. Ventilation should be started in all symptomatic patients. Some experts recommend using it during acute respiratory illnesses to facilitate discharge. NIV should be initiated during a sleep study or observing the patient clinically for adequate gas exchange. NIV interfaces should be fitted by skilled physiotherapists selecting two interfaces to alternate skin contact points. Mucolytics should not be used long-term
Ambulant	Clinical examination with review of cough effectiveness and detailed search for	Supportive care when needed. Customary immunizations,	Evidence of weak cough or recurrent infections or suspicion of nocturnal

	signs of nocturnal hypoventilation.	annual influenza, and pneumococcal vaccination	hypoventilation should prompt referral to a pneumologist

Pharmacological Therapy:

- Nusinersen, an antisense oligonucleotide, received recent approval by both the US FDA and the EMA for the treatment of all SMA types.
- Nusinersen is intrathecally administered; therefore, there is a required institutional infrastructure to provide administration and post-procedural monitoring in a reliable way.
- Despite immobilization of many patients with SMA, prophylactic anticoagulation is not deemed necessary in the absence of additional risk factors.

1.5 Systematic Reviews & Meta Analyses

The table below tackles a systematic review and meta-analyses issued in **2021** and **2022** for Spinal Muscular Atrophy.

Table 8. Systematic Review and Meta-Analysis for Spinal Muscular Atrophy

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Erdos et al. (2022)[30]	*"Mid- and long-term (at least 12 months) follow-up of patients with spinal muscular atrophy (SMA) treated with Nusinersen, Onasemnogene Abeparvovec, Risdiplam or combination therapies: A systematic*	The systematic review aimed to assess mid- and long-term (at least 12 months) real-world study data from all types of spinal muscular atrophy (SMA) patients treated with any of the	Outcomes were grouped into four main categories: mortality and treatment discontinuation, motor endpoints, quality of life endpoints (respiratory and nutritional support, caregiver, or	Nusinersen, Onasemnogene Abeparvovec and combination therapies improved motor endpoints in SMA type 1 patients. SMA type 2 to type 4 patients treated with Nusinersen showed stabilization or small improvements in motor endpoints with some deterioration observed. Quality of life endpoints, such as respiratory and

		review of real-world study data"	approved drugs or combination therapies.	self-evaluation) and any safety endpoints.	nutritional support were poorly reported on. Drug-related adverse events occurred rarely in all types of SMA patients with all assessed drugs. Mid- and long-term studies on Risdiplam could not be identified.
2	Ribero et al. (2022)[31]	*"How does Risdiplam compare with other treatments for Types 1–3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison"*	The study aims to investigate the efficacy and safety of treatments for Type 1 through Type 3 SMA. Types 0 and 4 SMA were not included in the search as these were not included in the Risdiplam clinical trials.	Outcomes include motor function, safety, survival outcomes, and achievement of motor milestones.	In Type 1 SMA, studies of Risdiplam and Nusinersen included similar populations. Indirect comparison results found improved survival and motor function with Risdiplam versus Nusinersen. Comparison with Onasemnogene Abeparvovec in Type 1 SMA and with Nusinersen in Types 2/3 SMA was challenging due to substantial differences in study populations; no concrete conclusions could be drawn from the indirect comparison analyses. Indirect comparisons support Risdiplam as a superior alternative to Nusinersen in Type 1 SMA.
3	Dangouloff et al. (2021)[32]	*"Systematic literature review of the economic burden of spinal*	Given the increasing importance of economic considerations in healthcare	Cost (Annual cost of care) and outcomes (in Quality Adjusted Life	The average annual cost of SMA1 was similar according to the different studies, ranging from $75,047 to $196,429 per year.

		muscular atrophy and economic evaluations of treatments"	decision-making, the review summarizes the studies assessing the cost of SMA and economic evaluations of treatments.	Years and Cost Effectiveness)	The yearly costs for later-onset forms, namely SMA2, SMA3, and SMA4, which were usually pooled in estimates of healthcare costs, were more variable, ranging from $27,157 to $82,474. The evaluations of cost-effectiveness of treatment compared Nusinersen treatment against standard of care (n=3), two treatments (Nusinersen and Onasemnogene Abeparvovec) against each other and no drug treatment (n=1), Nusinersen versus Onasemnogene Abeparvovec (n=1), and standard of care versus Nusinersen with and without newborn screening (n=1). The incremental cost-effectiveness ratio (ICER) of Nusinersen compared to standard of care in SMA1 ranged from $210,095 to $1,150,455 per quality-adjusted life years (QALY) gained and that for Onasemnogene Abeparvovec ranged from $32,464 to $251,403. For pre-symptomatic patients, the ICER value ranged from $206,409 to $735,519. The ICERs for

					later-onset forms of SMA (2, 3 and 4) were more diverse ranging from $275,943 to $8,438,049. This review confirms the substantial cost burden of standard of care for SMA patients and the high-cost effectiveness ratios of the approved drugs at the current price when delivered in post-symptomatic patients. Since few studies have been conducted so far, there is a need for further prospective and independent economic studies in pre- and post-symptomatic patients.

Section 2.0 Drug Therapy

2.1 Survival Motor Neuron-2 (SMN2)-Directed Antisense Oligonucleotide

2.1.1 Nusinersen

Information on Nusinersen is detailed in the table below[26,33]:

Table 9. Drug Therapy with Nusinersen

SCIENTIFIC NAME NUSINERSEN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	G12
Drug Class	Antisense Oligonucleotide
Drug Sub-class	SMN2-Directed Antisense Oligonucleotide
ATC Code	M09AX07
Pharmacological Class (ASHP)	Antisense Oligonucleotide
DRUG INFORMATION	
Dosage Form	Solution
Route of Administration	Intrathecal
Dose (Adult) [DDD]*	**Loading Dose:** 12 mg once every 14 days for 3 doses; then 12 mg as a single dose 30 days after the third dose, followed by maintenance dosing. **Maintenance Dose:** 12 mg once every 4 months.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Loading Dose:** 12 mg once every 14 days for 3 doses; then 12 mg once 30 days after the third dose. **Maintenance Dose:** 12 mg once every 4 months.

Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, MD, PE
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	This medication must be prescribed by or in consultation with a physician who specializes in treatment of spinal muscular atrophy.
PA (Prior Authorization)	Nusinersen should be given to presymptomatic patients or those with Type 1,2 or 3 SMA initiated with 4 loading doses; the first three loading doses should be administered at 14-day intervals; the 4th loading dose should be administered 30 days after the 3rd dose; a maintenance dose should be administered once every 4 months thereafter. This medication is to be prescribed by a physician specialized in the treatment of spinal muscular atrophy. At baseline and prior to each dose, a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing are to be obtained. + Check other PEs (MD, PE)
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Nusinersen is given as follows: **Loading Dose:** 12 mg once every 14 days for 3 doses; then 12 mg as a single dose 30 days after the third dose, followed by maintenance dosing. **Maintenance Dose:** 12 mg once every 4 months.
SAFETY	

Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Headache, constipation, vomiting, proteinuria, and lower respiratory tract infections. **Most serious:** Thrombocytopenia, coagulation abnormalities, renal toxicity, upper and lower respiratory infections.
Drug Interactions*	No interactions of Risk Level A or greater identified.
Special Population	N/A
Pregnancy	Adverse events have been observed in some animal reproduction studies.
Lactation	It is not known if Nusinersen is present in breast milk. According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should take into account the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Known or suspected hypersensitivity to Nusinersen or any component of the formulation.
Monitoring Requirements	Platelet count, coagulation tests (prothrombin time; activated partial thromboplastin time), and quantitative spot urine protein testing (preferably first morning urine) at baseline, prior to each dose, and as clinically indicated (eg, repeat testing if urinary protein concentration >0.2 g/L).
Precautions	**Hematologic effects:** Coagulation abnormalities and thrombocytopenia (including acute severe thrombocytopenia) have been observed with some antisense oligonucleotides; increased risk of bleeding complications may occur.

	Renal toxicity: Renal toxicity, including potentially fatal glomerulonephritis, has been observed with some antisense oligonucleotides. For urinary protein concentration >0.2 g/L, consider repeat testing and further evaluation.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Spinal Muscular Atrophy treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Nusinersen.**

Table 10. Nusinersen HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Nusinersen	NICE[7]	July 24, 2019: **Conditional Positive Recommendation** Nusinersen should be recommended as an option for treating pre-symptomatic and types 1, 2 and 3 SMA, for the duration of and within the conditions set out in the managed access agreement, when the company provides Nusinersen with the confidential commercial terms agreed with NHS England. The committee acknowledged that the cost-effectiveness estimates it had been presented with were above the range normally considered cost effective by NICE. The committee concluded that Nusinersen had demonstrated the potential to be cost effective, based on assumptions it considered clinically plausible and acceptable.
	CADTH[8]	February 20, 2019: **Conditional Positive Recommendation** The CADTH Canadian Drug Expert Committee recommends that Nusinersen be reimbursed for the

		treatment of 5q spinal muscular atrophy (SMA), if the following conditions are met: **Conditions for Reimbursement** **Initiation Criteria** 1. Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote. 2. Patients who: 2.1. are pre-symptomatic with two or three copies of SMN2, or 2.2. have had disease duration of less than six months, two copies of SMN2, and symptom onset after the first week after birth and on or before seven months of age, or 2.3. are 12 years of age or younger with symptom onset after six months of age, and never achieved the ability to walk independently. 3. Patient is not currently requiring permanent invasive ventilation. **Administration Criteria** 1. A baseline assessment using an age-appropriate scale (the Hammersmith Infant Neurological Examination [HINE] Section 2, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP INTEND], or Hammersmith Functional Motor Scale-Expanded [HFMSE]) must be completed prior to initiation of Nusinersen treatment. 2. Patient must be under the care of a specialist with experience in the diagnosis and management of SMA. **Renewal Criteria** 1. Treatment should be discontinued if, prior to the fifth dose or any subsequent dose of Nusinersen: 1.1. there is no demonstrated achievement or maintenance of motor milestone function (as assessed using age-appropriate scales: the HINE Section 2, CHOP INTEND, or HFMSE) since treatment initiation in patients who were pre-symptomatic at the time of treatment initiation; or 1.2. there is no demonstrated maintenance of motor milestone function (as assessed using age-

		appropriate scales: the HINE Section 2, CHOP INTEND, or HFMSE) since treatment initiation in patients who were symptomatic at the time of treatment initiation; or 1.3. permanent invasive ventilation is required. **Pricing Condition** 1. Reduction in price.
	HAS[9]	September 2, 2020: **Positive Recommendation** Favorable opinion for reimbursement in pre-symptomatic infants and children with genetically diagnosed 5q spinal muscular atrophy and having 2 to 3 copies of the SMN2 gene.
	IQWIG[10]	February 25, 2021: **Positive Recommendation** There exists an indication of major added benefit for patients with 5q SMA and early onset of disease (infantile form, SMA type 1) and a hint of a non-quantifiable added benefit for pre-symptomatic patients with 5q SMA. The added benefit; however, was not proven for patients with 5q SMA and later onset of disease (SMA type 2, type 3 and type 4).
	PBAC[11]	July 2020: **Positive Recommendation** The PBAC recommended the addition of pre-symptomatic initiation to the current listing of Nusinersen to include the pre-symptomatic initiation of treatment of patients genetically diagnosed with SMA, who have an SMN2 copy number of ≤ 2. The PBAC considered that pre-symptomatic initiation of treatment with Nusinersen would provide an additional benefit for some patients compared with initiation upon development of symptoms. The PBAC noted there was remaining uncertainty regarding the cost-effectiveness of presymptomatic initiation of nusinersen due to the uncertain magnitude of incremental benefit compared to symptomatic treatment. However, the PBAC was satisfied that extension of the current listing would be adequately cost-effective if the conditions specified in the existing

		Deed of Agreement were also applied to the extended listing.

CONCLUSION STATEMENT- Nusinersen

Nusinersen is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. It is initiated with 4 loading doses; the first three loading doses should be administered at 14-day intervals; the 4th loading dose should be administered 30 days after the 3rd dose followed by a maintenance dose administered once every 4 months thereafter. Nusinersen is administered intrathecally. Prior to administration, 5ml of cerebrospinal fluid is to be removed. Its use is backed by several HTA bodies such as NICE, CADTH, HAS, IQWIG and PBAC. The use of Nusinersen is limited by the heightened risks of respiratory tract infections, thrombocytopenia, coagulation abnormalities and renal toxicity.

2.2 Survival Motor Neuron 2 (SMN2) Splicing Modifier

2.2.1 Risdiplam

Information on Risdiplam is detailed in the table below:[26,33]

Table 11. Drug Therapy with Risdiplam

SCIENTIFIC NAME RISDIPLAM	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	G12
Drug Class	Survival of Motor Neuron 2 (SMN2)-Directed RNA Splicing Modifier
Drug Sub-class	N/A
ATC Code	M09AX10
Pharmacological Class (ASHP)	Survival of Motor Neuron 2 (SMN2)-Directed RNA Splicing Modifier
DRUG INFORMATION	
Dosage Form	Solution Reconstituted
Route of Administration	Oral

Dose (Adult) [DDD]*	5mg once daily
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Infants < 2 months: Oral: 0.15 mg/kg/dose once daily. Infants ≥ 2 months and Children <2 years: Oral: 0.2 mg/kg/dose once daily. Children ≥ 2 years and Adolescents: < 20 kg: Oral: 0.25 mg/kg/dose once daily. ≥ 20 kg: Oral: 5 mg once daily.
Maximum Daily Dose Pediatrics*	5 mg/day
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, MD, PE
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	This medication must be prescribed by or in consultation with a physician who specializes in treatment of spinal muscular atrophy.
PA (Prior Authorization)	Risdiplam should be given to patients 2 months and older with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 SMN2 copies. In adults, it is given as 5 mg orally once daily. In infants and children, the dosing schedule is as follows: For infants <2 months: 0.15 mg/kg/dose once daily. For infants ≥2 months and children <2 years: 0.2 mg/kg/dose once daily. For children ≥2 years and adolescents: <20 kg: 0.25 mg/kg/dose once daily and for those who are ≥20 kg: 5 mg once daily for as long as it is prescribed by the physician – a specialist in the management of Spinal Muscular Atrophy. + Check other PEs (MD, PE)

QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	**For adults:** Risdiplam is given as 5 mg orally once daily. **For infants and children:** Infants <2 months: 0.15 mg/kg/dose once daily. Infants ≥2 months and Children <2 years: 0.2 mg/kg/dose once daily. Children ≥2 years and Adolescents: <20 kg: 0.25 mg/kg/dose once daily. ≥20 kg: 5 mg once daily.
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Fever, skin rash, diarrhea. **Most serious:** Respiratory tract infections, urinary tract infections, arthralgia.
Drug Interactions*	No Category X interactions. **Category D:** Dofetilide Flecainide Lamivudine Metformin Pramipexole Procainamide
Special Population	N/A
Pregnancy	Based on data from animal reproduction studies, in utero exposure to Risdiplam may cause fetal harm.
Lactation	According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	Hypersensitivity to Risdiplam or any component of the formulation.

Monitoring Requirements	It is important to monitor the respiratory status in neonates and infants and to monitor for any signs of urinary tract infection.
Precautions	Benzyl alcohol and derivatives: Avoid or use dosage forms containing benzyl alcohol derivative with caution in neonates. Large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity in neonates; the "gasping syndrome" consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (including convulsions, intracranial hemorrhage), hypotension, and cardiovascular collapse; some data suggest that benzoate displaces bilirubin from protein binding sites.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Spinal Muscular Atrophy treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Risdiplam.**

Table 12. Risdiplam HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Risdiplam	NICE[12]	**Conditional Positive Recommendation** – December 16, 2021 Risdiplam is recommended as an option for treating 5q spinal muscular atrophy (SMA) in people 2 months and older with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 SMN2 copies. It is recommended only if the conditions of the managed access agreement are followed. The

		committee acknowledged that the cost-effectiveness estimates were above the range NICE normally considers cost effective. It reiterated that an updated model structure should be provided when the guidance is reviewed as part of the agreed managed access agreement.
	CADTH[13]	**Conditional Positive Recommendation** – August 26, 2021 CADTH recommends that Evrysdi should be reimbursed by public drug plans for the treatment of spinal muscular atrophy (SMA) in patients aged 2 months and older, if certain conditions are met: The patient is under the care of a specialist with experience in the diagnosis and management of SMA, it is not used in combination with nusinersen or Onasemnogene Abeparvovec, and the price is reduced.
	HAS[15]	**Positive Recommendation** – September 30, 2021 Favorable opinion for reimbursement in the treatment of 5q spinal muscular atrophy in patients aged 2 months and older with a clinical diagnosis of SMA types 1, 2 and 3. **Negative Recommendation** – September 30, 2021 Opinion against reimbursement in SMA patients with a clinical diagnosis of SMA type 4 and in pre-symptomatic patients.
	IQWIG[16]	**Positive Recommendation** – July 29, 2021 Hint of non-quantifiable added benefit for patients with 5q SMA, 2 months of age and older with SMA type 1. **Negative Recommendation** – July 29, 2021 Added benefit is not proven for patients with 5q SMA, 2 months of age and older with SMA type 2 and type 3. Added benefit is also not proven in pre-symptomatic patients with 5q SMA, 2 months of age and older with 1 to 3 SMN2 gene copies and 4 SMN2 gene copies.
	PBAC[14]	**Conditional Positive Recommendation** – March 2021

		The PBAC recommended the listing of Risdiplam (Evrysdi®) for patients with Spinal Muscular Atrophy (SMA) Types 1, 2 or 3a who are aged 18 years or under at treatment initiation, on the basis that it should be available only under special arrangements. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of Risdiplam would be acceptable if it were cost-minimized against nusinersen.

CONCLUSION STATEMENT- Risdiplam

Risdiplam is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. It is given as 5 mg once daily for adults. For infants and children, the following regimen is followed: For infants <2 months: 0.15 mg/kg/dose once daily. For infants ≥2 months and Children <2 years: 0.2 mg/kg/dose once daily. For children ≥2 years and Adolescents: <20 kg: 0.25 mg/kg/dose once daily and ≥20 kg: 5 mg once daily. Its use is backed up by several HTA bodies namely NICE, CADTH, PBAC; other HTA bodies favor the reimbursement of Risdiplam in specific cases and reject its reimbursement in others; these HTA bodies include IQWIG and HAS. The use of Risdiplam is limited by the elevated risk of respiratory tract infections, urinary tract infections and arthralgia.

2.3 Adeno-Associated Virus Vector-Based Gene Therapy

2.3.1 Onasemnogene Abeparvovec-xioi

The following table describes the characteristics of Onasemnogene Abeparvovec-xioi[26,33]:

Table 13. Drug Therapy with Onasemnogene Abeparvovec-xioi

SCIENTIFIC NAME ONASEMNOGENE ABEPARVOVEC-XIOI	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	G12

<table>
<tr><td>Drug Class</td><td>Gene Therapy</td></tr>
<tr><td>Drug Sub-class</td><td>Adeno-Associated Virus Vector-Based Gene Therapy</td></tr>
<tr><td>ATC Code</td><td>M09AX09</td></tr>
<tr><td>Pharmacological Class (ASHP)</td><td>Adeno-Associated Virus Vector-Based Gene Therapy</td></tr>
<tr><td colspan="2">DRUG INFORMATION</td></tr>
<tr><td>Dosage Form</td><td>Suspension for Injection</td></tr>
<tr><td>Route of Administration</td><td>Intravenous Use</td></tr>
<tr><td>Dose (Adult) [DDD]*</td><td>N/A</td></tr>
<tr><td>Maximum Daily Dose Adults*</td><td>N/A</td></tr>
<tr><td>Dose (pediatrics)</td><td>In infants and children less than 2 years of age: IV infusion: 1.1 × 10^{14} vector genomes/kg as a single dose.
Dose volume is based on weight range:
<table>
<tr><th>Weight range (kg)</th><th>Dose Volume (mL)</th></tr>
<tr><td>2.6 to 3 kg</td><td>16.5 mL</td></tr>
<tr><td>3.1 to 3.5 kg</td><td>19.3 mL</td></tr>
<tr><td>3.6 to 4 kg</td><td>22 mL</td></tr>
<tr><td>4.1 to 4.5 kg</td><td>24.8 mL</td></tr>
<tr><td>4.6 to 5 kg</td><td>27.5 mL</td></tr>
<tr><td>5.1 to 5.5 kg</td><td>30.3 mL</td></tr>
<tr><td>5.6 to 6 kg</td><td>33 mL</td></tr>
<tr><td>6.1 to 6.5 kg</td><td>35.8 mL</td></tr>
<tr><td>6.6 to 7 kg</td><td>38.5 mL</td></tr>
<tr><td>7.1 to 7.5 kg</td><td>41.3 mL</td></tr>
<tr><td>7.6 to 8 kg</td><td>44 mL</td></tr>
<tr><td>8.1 to 8.5 kg</td><td>46.8 mL</td></tr>
<tr><td>8.6 to 9 kg</td><td>49.5 mL</td></tr>
<tr><td>9.1 to 9.5 kg</td><td>52.3 mL</td></tr>
<tr><td>9.6 to 10 kg</td><td>55 mL</td></tr>
<tr><td>10.1 to 10.5 kg</td><td>57.8 mL</td></tr>
<tr><td>10.6 to 11 kg</td><td>60.5 mL</td></tr>
<tr><td>11.1 to 11.5 kg</td><td>63.3 mL</td></tr>
</table></td></tr>
</table>

	11.6 to 12 kg	66 mL
	12.1 to 12.5 kg	68.8 mL
	12.6 to 13 kg	71.5 mL
	13.1 to 13.5 kg	74.3 mL
	13.6 to 14 kg	77 mL
	14.1 to 14.5 kg	79.8 mL
	14.6 to 15 kg	82.5 mL
	15.1 to 15.5 kg	85.3 mL
	15.6 to 16 kg	88 mL
	16.1 to 16.5 kg	90.8 mL
	16.6 to 17 kg	93.5 mL
	17.1 to 17.5 kg	96.3 mL
	17.6 to 18 kg	99 mL
	18.1 to 18.5 kg	101.8 mL
	18.6 to 19 kg	104.5 mL
	19.1 to 19.5 kg	107.3 mL
	19.6 to 20 kg	110 mL
	20.1 to 20.5 kg	112.8 mL
	20.6 to 21 kg	115.5 mL
Maximum Daily Dose Pediatrics*	N/A	
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling. Patients with preexisting hepatic impairment may be at increased risk for hepatotoxicity; risk vs benefit should be assessed.	
Prescribing edits*	AGE, CU, MD, PA, PE	
AGE (Age Edit)	Onasemnogene Abeparvovec-xioi is not approved for patients older than 2 years of age.	
CU (Concurrent Use Edit)	One day prior to the infusion, patients are to be initiated on oral corticosteroids (Prednisolone 1 mg/kg/day or equivalent) and continue for ≥30 days;	

	IV corticosteroids may be used in case oral therapy is not tolerated.
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	This medication must be prescribed by or in consultation with a physician who specializes in treatment of spinal muscular atrophy.
PA (Prior Authorization)	Onasemnogene Abeparvovec-xioi is indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene or a clinical diagnosis of SMA Type 1 or 2 or pre-symptomatic SMA, with up to 3 copies of the SMN2 gene. The recommended dosage is 1.1×10^{14} vector genomes (vg) per kg of body weight. It is given as a single infusion. Patients should be clinically stable in overall baseline health status prior to administration due to increased risk of systemic immune responses. Therapy should be postponed until resolution of any infection. One day prior to infusion, oral corticosteroids (Prednisolone 1 mg/kg/day or equivalent) are to be administered and continued for ≥30 days; IV corticosteroids may be used if oral therapy is not tolerated. Baseline labs (SCr, CBC [platelets, Hb]), troponin I, presence of anti-AAV9 antibodies, and liver function are to be assessed. + Check other PEs (AGE, CU, MD, PE)
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	This medication is given as an IV infusion at a dose of 1.1×10^{14} vector

	genomes/kg as a single dose with a weight-based dose volume.
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** The most common adverse reactions (incidence ≥ 5%) were elevated aminotransferases and vomiting. **Most serious**: Post marketing studies have shown thrombocytopenia, acute hepatic failure, and acute hepatotoxicity.
Drug Interactions*	No interactions of Risk Level A or greater identified.
Special Population	N/A
Pregnancy	Onasemnogene Abeparvovec is not approved for use in patients of reproductive age.
Lactation	Onasemnogene Abeparvovec is not approved for use in patients of reproductive age.
Contraindications	Hypersensitivity to Onasemnogene Abeparvovec or any component of the formulation.
Monitoring Requirements	**Baseline:** Liver function (clinical exam, AST, ALT, total bilirubin, and PT), CBC (Hb, platelet count), SCr, troponin-I, and anti-AAV9 antibody test. **First month after treatment:** Liver function (clinical exam, AST, ALT, total bilirubin, and PT), platelets, and troponin-I (check weekly); signs and symptoms of thrombotic microangiopathy (eg, hypertension, bruising, decreased urine output, seizures). **Second and third month after treatment:** Liver function (clinical exam, AST, ALT, total bilirubin, and PT) every other week until AST/ALT are <2 × ULN, PT is normal, total bilirubin is normal,

	and clinical exam is normal; platelet count every other week until counts return to baseline, and troponin-I monthly until troponin-I level returns to baseline; signs and symptoms of thrombotic microangiopathy (eg, hypertension, bruising, decreased urine output, seizures).
Precautions	**Cardiac effects:** Increases in troponin-I levels have been observed, but clinical significance is unknown; cardiac toxicity was observed in animal studies. Consider cardiology consultation in patients with troponin elevations accompanied by cyanosis, heart rate changes, respiratory distress, or tachypnea. **Hepatotoxicity:** Acute serious liver injury and acute liver failure, including fatalities, as well as elevated transaminases have been reported and may be immune mediated in nature; concomitant systemic corticosteroids therapy should be continued for ≥28 days after dose. Patients with preexisting hepatic impairment or acute hepatic viral illness may be at increased risk for hepatotoxicity; use with caution. **Thrombocytopenia:** Transient decreases in platelet counts have been observed, typically within the first 2 weeks after the infusion. **Thrombotic microangiopathy:** Cases of thrombotic microangiopathy (TMA), including acute kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia, have been reported within the first 2 weeks after therapy; may be life-threatening or fatal. Concurrent immune system activation

	(eg, infections, vaccinations) was present in some cases. Monitor patients closely and further evaluate patients for hemolytic anemia and renal impairment if signs occur in the presence of thrombocytopenia. Consult a pediatric hematologist and/or nephrologist immediately if clinical symptoms or laboratory findings are consistent with TMA. **Infection:** Underlying active infection (acute or chronic) can lead to increased risk of serious systemic immune response, resulting in a more severe clinical course of the infection. Patients should be clinically stable in overall baseline health (eg, hydration and nutritional status, absence of infection) prior to infusion. Postpone therapy in patients with concurrent infection until the infection has resolved; risk of serious systemic immune response may occur. **Vaccines:** Vaccination schedule may need to be adjusted due to corticosteroid administration before and after Onasemnogene Abeparvovec infusion. Update seasonal influenza and respiratory syncytial virus vaccines prior to Onasemnogene Abeparvovec infusion.
Black Box Warning	**Serious liver injury and acute liver failure:** Cases of acute liver failure with fatal outcomes have been reported. Acute serious liver injury and elevated aminotransferases can occur with Onasemnogene Abeparvovec. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing.

	Administer systemic corticosteroid to all patients before and after Onasemnogene Abeparvovec infusion. Continue to monitor liver function for at least 3 months after infusion and at other times as clinically indicated.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Spinal Muscular Atrophy treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Onasemnogene Abeparvovec-xioi.**

Table 14. Onasemnogene Abeparvovec-xioi HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Onasemnogene Abeparvovec-xioi	NICE[17]	**Positive Recommendation** – April 19, 2023 Onasemnogene Abeparvovec is recommended as an option for treating presymptomatic 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies aged 12 months and under. It is only recommended if the company provides it according to the commercial arrangement.
	CADTH[18]	**Conditional Positive Recommendation** - March 26, 2021 The CADTH Canadian Drug Expert Committee recommends that Onasemnogene Abeparvovec be reimbursed for the treatment of pediatric patients with 5q spinal muscular atrophy with biallelic mutations in the survival motor neuron 1 gene, only if the following conditions are met. **Conditions for Reimbursement** **Initiation criteria**

		1. Genetic documentation of 5q spinal muscular atrophy with biallelic mutations in the survival motor neuron 1 gene. 2. Patients who are: 2.1. symptomatic or pre-symptomatic with one to three copies of the survival motor neuron 2 gene 2.2. 180 days of age or younger 2.3. not currently requiring permanent feeding or ventilatory support (either invasive or non-invasive). **Prescribing conditions** 1. Patient must be under the care of a specialist with experience in the diagnosis and management of spinal muscular atrophy. 2. Reimbursement is limited to one lifetime administration of Onasemnogene Abeparvovec. **Pricing conditions** 1. A reduction in price.
	HAS[19]	**Positive Recommendation** – December 18, 2020 Favorable opinion for reimbursement in the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1 and 2 or pre-symptomatic SMA, with up to 3 copies of the *SMN2* gene. **Negative Recommendation** – December 18, 2020 Unfavorable opinion for reimbursement in the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 3.
	IQWIG[20]	**Negative Recommendation** – August 12, 2021 In its dossier, the company did not present any suitable data on the comparison of Onasemnogene Abeparvovec with Nusinersen in patients with SMA type 1. This resulted in no hint of an added benefit of Onasemnogene Abeparvovec in comparison with the ACT nusinersen; an added benefit is therefore not proven.

	PBAC[21]	**Recommendation is deferred** – November 2020 The PBAC deferred making a decision on the request for PBS listing of Onasemnogene Abeparvovec (ONA) in patients less than 2 years of age with confirmed Type I SMA (based on genotype and phenotype) to allow the TGA to confirm the indication for the therapy and work to be progressed on a Decision Support Analysis. However, the PBAC had a number of concerns with the current subsidy proposal for ONA. Most importantly, the PBAC did not accept the submission's claim that ONA is superior in terms of effectiveness and safety compared to NUSI (Nusinersen). Overall, having considered all the available evidence, the PBAC concluded that, on balance ONA would likely deliver similar clinical outcomes to NUSI in matched patients.

CONCLUSION STATEMENT- Onasemnogene Abeparvovec-xioi

Onasemnogene Abeparvovec-xioi is indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene. The recommended dosage is 1.1×10^{14} vector genomes (vg) per kg of body weight. Patients should be clinically stable in overall baseline health status prior to administration due to increased risk of systemic immune responses. Therapy should be postponed until resolution of any infection. One day prior to infusion, oral corticosteroids (Prednisolone 1 mg/kg/day or equivalent) are to be administered and continued for ≥30 days; IV corticosteroids may be used if oral therapy is not tolerated. Baseline labs are to be assessed (SCr, CBC [platelets, Hb]), troponin I, for presence of anti-AAV9 antibodies, as well as liver function. Its use is backed by several HTA bodies such as NICE and CADTH. HAS backed the use of Onasemnogene Abeparvovec conditionally. Its use is limited by the increased risk of hepatotoxicity and liver failure.

2.4 Other Drugs

To date, there are no new non-SFDA registered molecules for the management of Spinal Muscular Atrophy.

Section 3.0 Key Recommendations Synthesis

The guidelines mentioned in Section 1.0 do not provide a specified grade of evidence or level of recommendation.

Diagnosis:

Molecular genetic testing is the standard tool for diagnosis of SMA and should be taken into consideration in any infant presenting with weakness or hypotonia.

SMA Classification:

SMA Europe classifies SMA into four primary types and their respective subtypes:

SMA Type	Age of Onset	Highest Motor Milestone	SMN2 Copy Number	Lifespan
IA	< 1 week	Never sits	1	< 1 month
IB	1 week – 3 months	Never sits	2,3	< 2 years
IC	3 – 6 months	Never sits	2,3	< 2 years
IIA	6 – 15 months	Sits independently. Loses the ability to sit	2,3,4	> 2 years
IIB	6 – 15 months	Sits independently. Maintains the ability to sit	2,3,4	> 2 years
IIIA	< 3 years	Walks independently	3,4	Adult
IIIB	> 3 years	Walks independently	3,4	Adult
IV	> 21 years	Walks independently	4,5	Adult

Prevention and Management of Disease Progression:

Pulmonary:

- In patients with Type 1 SMA, early initiation of noninvasive ventilatory support has been associated with enhanced quality of life and survival.
- In case the non-invasive support is insufficient, tracheostomy and permanent ventilatory support may be successfully initiated in SMA patients.
- The management of respiratory function in other SMA types is also similar to that of Type 1.
- Medical management for non-sitters, sitters and walkers:

- **Non-Sitters:**
    - If asthma is suspected, nebulized bronchodilators should be available.
    - Caution should be exercised when treating SMA patients with Glycopyrrolate for hypersalivation. (Dosage adjustment is of utmost importance to attain the proper effect, and to avoid over drying of secretions, which may contribute to the development of mucus plugs.)
    - During RSV season, Palivizumab should be given through the first 24 months of life, and influenza vaccination should be administered annually after 6 months of age.
- **Sitters:**
    - If asthma is suspected, nebulized bronchodilators should be available.
    - Annual influenza and pneumococcal immunizations should be administered.
- **Walkers:**
    - Prior to empiric oxygen supplementation, it is important to optimize the use of bilevel positive airway pressure (NIV) respiratory support.
    - Oxygen supplementation should not be provided empirically in the absence of NIV or without monitoring CO2 gas exchange.
    - Oxygen supplementation should be weaned to minimal provision prior to extubation.

Gastrointestinal and Nutritional:

- **Management of aspiration associated with feeding and dysphagia:** Changing the food consistency to incorporate semisolid and thickened liquids is recommended.
- In SMA type 1 infants, early gastrostomy and laparoscopic Nissen fundoplication (if gastroesophageal reflux is present) are recommended and can be performed shortly after diagnosis in an attempt to maintain proper nutrition and to reduce the risk of infection as a result of aspiration.
- Adequate supplementation of calcium and Vitamin D is recommended due to the tendency for decreased bone mineral density with advancing age.
- Bisphosphonates may be considered in the case of frequent fractures.
- Yearly Dual energy x-ray absorptiometry analysis (DEXA) is recommended in SMA patients to monitor bone density.

Orthopedic and Musculoskeletal:

- Manual and motorized wheelchairs may be incorporated into the management process in patients aged as early as 18 to 24 months of age.
- A standing frame or mobile stander with ankle-foot orthoses may be used in children who are able to bear weight and have trunk control.
- For scoliosis, spinal fusion and bracing are the treatments of choice subsequently preventing chest cage deformities and resulting respiratory restriction.
- Spinal orthoses is recommended to support the hypotonic trunk and treat scoliosis >20°, especially in a child with significant growth remaining.
- Surgical treatment of spine deformity should be delayed until after the age of 4 years.
- In the case of a unilateral and bilateral hip instability, only patients with significant pain should be surgically managed.
- Patients with contractures of the upper or lower extremities that cause pain or impair function are considered for surgical management.

Pharmacological Management:

- Nusinersen is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. It is initiated with 4 loading doses; the first three loading doses should be administered at 14-day intervals; the 4th loading dose should be administered 30 days after the 3rd dose followed by a maintenance dose administered once every 4 months thereafter.
- MDT experts are to decide on the initiation of individualized gene therapy in SMA patients.
- Onasemnogene Abeparvovec-xioi is indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene. The recommended dosage is 1.1×10^{14} vector genomes (vg) per kg of body weight.
    - Patients should be clinically stable in overall baseline health status prior to administration due to increased risk of systemic immune responses. Therapy should be postponed until resolution of any infection.
    - One day prior to infusion, oral corticosteroids (Prednisolone 1 mg/kg/day or equivalent) are to be administered and continued for ≥30 days; IV corticosteroids may be used if oral therapy is not tolerated.

- Risdiplam is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. It is given as 5 mg once daily for adults. For infants and children, the following regimen is followed: For infants <2 months: 0.15 mg/kg/dose once daily. For infants ≥2 months and Children <2 years: 0.2 mg/kg/dose once daily. For children ≥2 years and Adolescents: <20 kg: 0.25 mg/kg/dose once daily and ≥20 kg: 5 mg once daily.
- Follow up visits include but are not limited to laboratory monitoring of liver function, troponin and platelets.
- Regular physiotherapy is the cornerstone of SMA management.

Treatment Suspension:

- For pediatric patients, treatment suspension is considered with worsening scores of the motor scale selected for follow-up and/or loss of an acquired motor developmental milestone.
- The process of treatment suspension is as follows:
- For patients with type 1B/1C SMA: Suspension is considered every 12 months.
- For patients with type 2/3 SMA: Suspension is considered every 2 years.
- For adult patients, suspension is considered every 2 years.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Spinal Muscular Atrophy.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

Query	Sort By	Filters	Search Details	Results
((Muscular Atrophy, Spinal[MeSH Terms]) OR (Atrophy, Spinal Muscular[Title/Abstract])) OR (Spinal Amyotrophy[Title/Abstract])) OR (Amyotrophies, Spinal[Title/Abstract])) OR (Amyotrophy, Spinal[Title/Abstract])) OR (Spinal Amyotrophies[Title/Abstract])) OR (Spinal Muscular Atrophy[Title/Abstract])) OR (Distal Spinal Muscular Atrophy[Title/Abstract])) OR (Spinal Muscular Atrophy, Distal[Title/Abstract])) OR (Hereditary Motor Neuronopathy[Title/Abstract])) OR (Hereditary Motor Neuronopathies[Title/Abstract])) OR (Motor Neuronopathies, Hereditary[Title/Abstract])) OR (Motor Neuronopathy, Hereditary[Title/Abstract])) OR (Neuronopathies, Hereditary Motor[Title/Abstract])) OR (Neuronopathy, Hereditary Motor[Title/Abstract])) OR (Scapuloperoneal Form of Spinal Muscular Atrophy[Title/Abstract])) OR (Spinal Muscular Atrophy, Scapuloperoneal Form[Title/Abstract])) OR (Spinal Muscular Atrophy, Scapuloperoneal[Title/Abstract])) OR (Amyotrophy, Neurogenic Scapuloperoneal, New		Guideline, in the last 5 years	("muscular atrophy, spinal"[MeSH Terms] OR "atrophy spinal muscular"[Title/Abstract] OR "spinal amyotrophy"[Title/Abstract] OR (("muscular atrophy"[MeSH Terms] OR ("Muscular"[All Fields] AND "Atrophy"[All Fields]) OR "muscular atrophy"[All Fields] OR "Amyotrophies"[All Fields] OR "Amyotrophy"[All Fields]) AND "Spinal"[Title/Abstract]) OR (("muscular atrophy"[MeSH Terms] OR ("Muscular"[All Fields] AND "Atrophy"[All Fields]) OR "muscular atrophy"[All Fields] OR "Amyotrophies"[All Fields] OR "Amyotrophy"[All Fields]) AND "Spinal"[Title/Abstract]) OR "spinal amyotrophies"[Title/Abstract] OR "spinal muscular atrophy"[Title/Abstract] OR "distal spinal muscular atrophy"[Title/Abstract] OR "spinal muscular atrophy distal"[Title/Abstract] OR "hereditary motor neuronopathy"[Title/Abstract] OR "hereditary motor neuronopathies"[Title/Abstract] OR ((("Motor"[All Fields] OR "motor s"[All Fields] OR "motoric"[All Fields] OR "motorically"[All Fields] OR "motorics"[All Fields] OR "motoring"[All Fields] OR "motorisation"[All Fields] OR "motorised"[All Fields] OR	2

England Type[Title/Abstract])) OR (Scapuloperoneal Spinal Muscular Atrophy[Title/Abstract])) OR (Oculopharyngeal Spinal Muscular Atrophy[Title/Abstract])) OR (Spinal Muscular Atrophy, Oculopharyngeal[Title/Abstract])) OR (Progressive Muscular Atrophy[Title/Abstract])) OR (Atrophies, Progressive Muscular[Title/Abstract])) OR (Atrophy, Progressive Muscular[Title/Abstract])) OR (Muscular Atrophies, Progressive[Title/Abstract])) OR (Muscular Atrophy, Progressive[Title/Abstract])) OR (Progressive Muscular Atrophies[Title/Abstract])) OR (Progressive Myelopathic Muscular Atrophy[Title/Abstract])) OR (Myelopathic Muscular Atrophy, Progressive[Title/Abstract])) OR (Progressive Proximal Myelopathic Muscular Atrophy[Title/Abstract])) OR (Proximal Myelopathic Muscular Atrophy, Progressive[Title/Abstract])) OR (Bulbospinal Neuronopathy[Title/Abstract])) OR (Bulbospinal Neuronopathies[Title/Abstract])) OR (Neuronopathies, Bulbospinal[Title/Abstract])) OR (Neuronopathy, Bulbospinal[Title/Abstract])) OR (Myelopathic Muscular Atrophy[Title/Abstract])) OR (Atrophy, Myelopathic Muscular[Title/Abstract])) OR (Muscular Atrophy, Myelopathic[Title/Abstract])) OR (Adult-Onset Spinal Muscular			"motorization"[All Fields] OR "motorized"[All Fields] OR "motors"[All Fields]) AND ("Neuronopathies"[All Fields] OR "Neuronopathy"[All Fields])) AND "Hereditary"[Title/Abstract]) OR ((("Motor"[All Fields] OR "motor s"[All Fields] OR "motoric"[All Fields] OR "motorically"[All Fields] OR "motorics"[All Fields] OR "motoring"[All Fields] OR "motorisation"[All Fields] OR "motorised"[All Fields] OR "motorization"[All Fields] OR "motorized"[All Fields] OR "motors"[All Fields]) AND ("Neuronopathies"[All Fields] OR "Neuronopathy"[All Fields])) AND "Hereditary"[Title/Abstract]) OR (("Neuronopathies"[All Fields] OR "Neuronopathy"[All Fields]) AND "hereditary motor"[Title/Abstract]) OR (("Neuronopathies"[All Fields] OR "Neuronopathy"[All Fields]) AND "hereditary motor"[Title/Abstract]) OR (("Scapuloperoneal"[All Fields] AND "Form"[All Fields]) AND "spinal muscular atrophy"[Title/Abstract]) OR (("muscular atrophy, spinal"[MeSH Terms] OR ("Muscular"[All Fields] AND "Atrophy"[All Fields] AND "Spinal"[All Fields]) OR "spinal muscular atrophy"[All Fields] OR ("Spinal"[All Fields] AND "Muscular"[All Fields] AND "Atrophy"[All Fields])) AND "scapuloperoneal form"[Title/Abstract]) OR "spinal muscular atrophy scapuloperoneal"[Title/Abstr	

Atrophy[Title/Abstract])) OR (Adult Onset Spinal Muscular Atrophy[Title/Abstract])) OR (Muscular Atrophy, Adult Spinal[Title/Abstract])) OR (Adult Spinal Muscular Atrophy[Title/Abstract])			act] OR ((("muscular atrophy"[MeSH Terms] OR ("Muscular"[All Fields] AND "Atrophy"[All Fields]) OR "muscular atrophy"[All Fields] OR "Amyotrophies"[All Fields] OR "Amyotrophy"[All Fields]) AND ("neurogenic"[All Fields] OR "neurogenically"[All Fields] OR "neurogenics"[All Fields]) AND "Scapuloperoneal"[All Fields] AND ("new england"[MeSH Terms] OR ("new"[All Fields] AND "england"[All Fields]) OR "new england"[All Fields])) AND "Type"[Title/Abstract]) OR "scapuloperoneal spinal muscular atrophy"[Title/Abstract] OR ("Oculopharyngeal"[All Fields] AND "spinal muscular atrophy"[Title/Abstract]) OR (("muscular atrophy, spinal"[MeSH Terms] OR ("Muscular"[All Fields] AND "Atrophy"[All Fields] AND "Spinal"[All Fields]) OR "spinal muscular atrophy"[All Fields] OR ("Spinal"[All Fields] AND "Muscular"[All Fields] AND "Atrophy"[All Fields])) AND "Oculopharyngeal"[Title/Abstract]) OR "progressive muscular atrophy"[Title/Abstract] OR (("atrophie"[All Fields] OR "Atrophy"[MeSH Terms] OR "Atrophy"[All Fields] OR "atrophied"[All Fields] OR "Atrophies"[All Fields] OR "atrophying"[All Fields]) AND "progressive muscular"[Title/Abstract]) OR (("atrophie"[All Fields] OR "Atrophy"[MeSH Terms] OR "Atrophy"[All Fields] OR	

			"atrophied"[All Fields] OR "Atrophies"[All Fields] OR "atrophying"[All Fields]) AND "progressive muscular"[Title/Abstract]) OR (("muscular atrophy"[MeSH Terms] OR ("Muscular"[All Fields] AND "Atrophy"[All Fields]) OR "muscular atrophy"[All Fields] OR ("Muscular"[All Fields] AND "Atrophies"[All Fields]) OR "muscular atrophies"[All Fields]) AND "Progressive"[Title/Abstract]) OR "muscular atrophy progressive"[Title/Abstract] OR "progressive muscular atrophies"[Title/Abstract] OR "progressive myelopathic muscular atrophy"[Title/Abstract] OR ("Myelopathic"[All Fields] AND "muscular atrophy progressive"[Title/Abstract]) OR "progressive proximal myelopathic muscular atrophy"[Title/Abstract] OR ((("Proximal"[All Fields] OR "proximalization"[All Fields] OR "proximalize"[All Fields] OR "proximalized"[All Fields] OR "proximalizes"[All Fields] OR "proximalizing"[All Fields] OR "proximally"[All Fields] OR "proximals"[All Fields]) AND "Myelopathic"[All Fields]) AND "muscular atrophy progressive"[Title/Abstract]) OR "bulbospinal neuronopathy"[Title/Abstract] OR ("Bulbospinal"[All Fields] AND "Neuronopathies"[Title/Abstract]) OR (("Neuronopathies"[All Fields] OR "Neuronopathy"[All Fields]) AND "Bulbospinal"[Title/Abstract])	

			OR (("Neuronopathies"[All Fields] OR "Neuronopathy"[All Fields]) AND "Bulbospinal"[Title/Abstract]) OR "myelopathic muscular atrophy"[Title/Abstract] OR (("atrophie"[All Fields] OR "Atrophy"[MeSH Terms] OR "Atrophy"[All Fields] OR "atrophied"[All Fields] OR "Atrophies"[All Fields] OR "atrophying"[All Fields]) AND "myelopathic muscular"[Title/Abstract]) OR (("muscular atrophy"[MeSH Terms] OR ("Muscular"[All Fields] AND "Atrophy"[All Fields]) OR "muscular atrophy"[All Fields]) AND "Myelopathic"[Title/Abstract]) OR "adult onset spinal muscular atrophy"[Title/Abstract] OR "adult onset spinal muscular atrophy"[Title/Abstract] OR (("muscular atrophy"[MeSH Terms] OR ("Muscular"[All Fields] AND "Atrophy"[All Fields]) OR "muscular atrophy"[All Fields]) AND "adult spinal"[Title/Abstract]) OR "adult spinal muscular atrophy"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix C. Treatment Algorithm

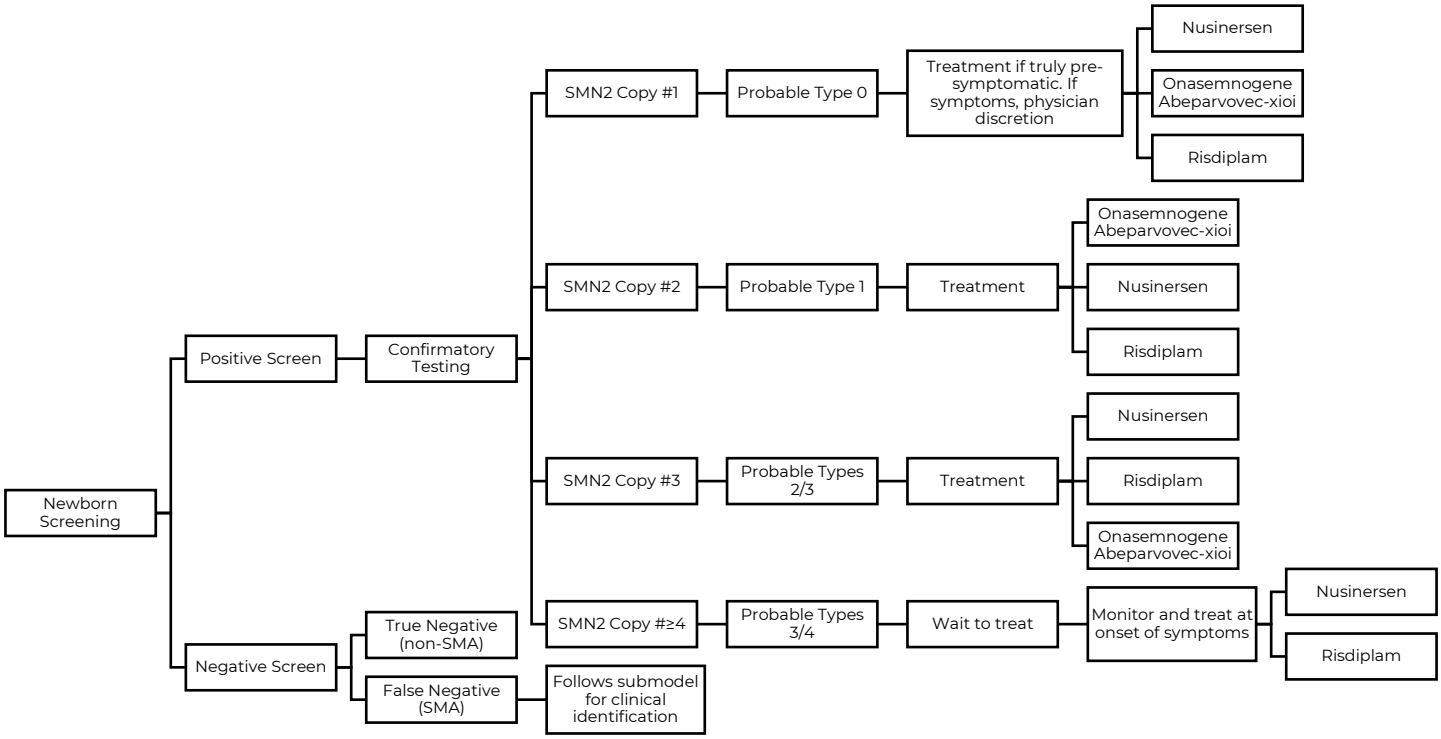

Figure 5. *Treatment Algorithm for the Management of Spinal Muscular Atrophy*

The following treatment algorithm is adapted from **"Decision-Making and Challenges Within the Evolving Treatment Algorithm In Spinal Muscular Atrophy: A Clinical Perspective"**[34] and describes the management of potential complications in SMA:

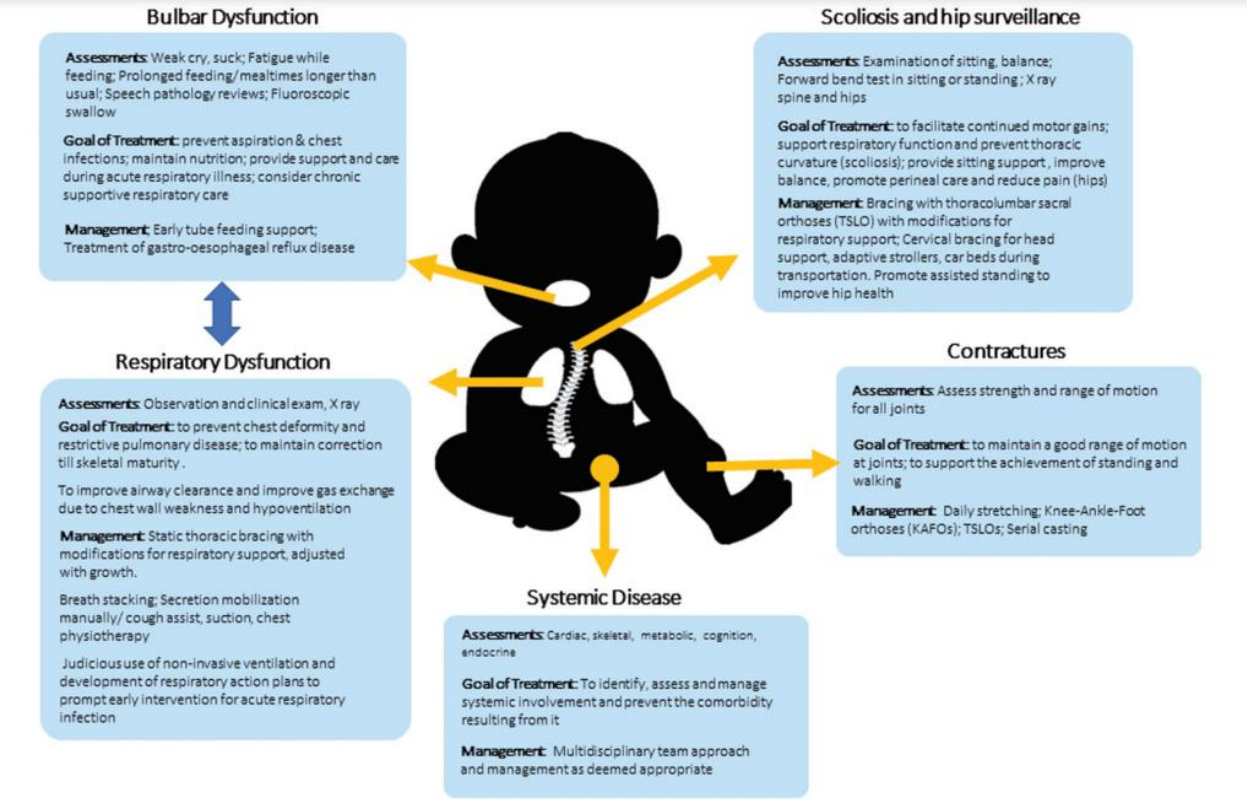

Figure 6. *Management of Potential Spinal Muscular Atrophy Complications*