Inclusion Criteria

- Diagnosis of spinal muscular atrophy (SMA) as defined by:
  - Homozygous SMN1 gene deletion or mutation
  - Compound heterozygous mutation (e.g., homozygous deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 [allele 2])
- Presymptomatic patients <6 months
  - 2 or 3 copies of the SMN2 gene
- Symptomatic patients
  - 2-4 copies of the SMN2 gene
  - Medically stable

Exclusion Criteria

- No genetically confirmed diagnosis of SMA
- 0-1 copies of the SMN2 gene
- 5 or more copies of the SMN2 gene
- Flaccid quadriplegia (Muscle strength 0/5 with possible exception of some finger movement)

Remarks: In order to optimize the success of treatment, the team recommends all patients be evaluated for malnutrition, active infection, laboratory abnormalities (platelets, PT, PTT, and urinalysis) history of hospitalization for surgery, history of bacterial meningitis (with subsequent neurologic disability), pulmonary events (within the past 2 months), severe brain or spinal cord injury or malformation other than spinal muscular atrophy (SMA), and presence of a cerebrospinal fluid (CSF) drainage shunt before initiation of treatment. Any clinical abnormalities should be corrected prior to the administration of nusinersen (Spinraza).

Background

Spinal muscular atrophy (SMA) is a genetic motor neuron disease (deletion or mutation of the Survival Motor Neuron 1 [SMN1] gene) characterized primarily by the degeneration of spinal cord motor neurons, resulting in progressive muscular atrophy and weakness. (23) SMA is the most common cause of genetic infant mortality and has an incidence of approximately 1 in 11,000 live births. (23) There are three main types of SMA, which are characterized by the age of onset of symptoms and maximum motor function obtained (Type I, Type II, Type III).

In this population, there is high morbidity and mortality related to hypoventilation, cough, poor airway clearance, lower respiratory tract infections, dysphagia, and failure to thrive. (6) Until recently, there have been no active treatments for SMA and the disease has been solely managed through multidisciplinary supportive care. However, in 2017 the Federal Drug Administration (FDA) approved the use of nusinersen (Spinraza), an antisense oligonucleotide, for the management of SMA. Nusinersen (Spinraza) works by stimulating the survival motor neuron (SMN2) gene, a paralogous gene, to increase production of survival motor neuron proteins. (6,7) Nusinersen (Spinraza) is delivered by intrathecal injection every few months and has been proven to show improvement in motor function in children with SMA. (6,8,7)

Despite the promising advantages of this treatment, there is an ethical component of administration due to the novelty of the drug, high cost, potential unknown long term effects, and treatment burden. Because of this, there is a clear need to define a criteria for eligibility and continuation of treatment. The purpose of this evidence summary is to critically appraise the literature for the use of nusinersen (Spinraza) in the management of SMA.

Critically Analyze the Evidence

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Type of Evidence</th>
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<tr>
<td>Strong</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
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<tr>
<td>Weak</td>
<td>Desirable effects closely balanced with undesirable effects</td>
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<tr>
<td>Quality</td>
<td>Type of Evidence</td>
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<tr>
<td>High</td>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
</tr>
<tr>
<td>Moderate</td>
<td>Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies</td>
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</tbody>
</table>
PICO Question 1: In children with symptomatic Type I SMA, does the use of nusinersen (Spinraza) improve or prevent decline of motor function?

Recommendation(s):
Weak recommendation with low quality evidence to administer nusinersen (Spinraza), in patients with symptomatic Type I SMA that have 2-3 copies of SMN2, and have some movement of their arms and/or legs. 

Remarks: Current studies have shown that nusinersen (Spinraza) may improve or prevent the decrease in motor function as measured by the appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIs]) after 12 months of therapy.

Consensus recommendation to continue nusinersen (Spinraza) in patients with symptomatic Type I SMA with at least a 2-3 point increase in CHOP-INTEND or no decrease in baseline function as measured by the appropriate motor function assessment tool (CHOP-INTEND and/or HINE-2) from pretreatment baseline after 12 months of therapy.

PICO Question 2: In children with symptomatic Type II SMA, does the use of nusinersen (Spinraza) improve or prevent decline of motor function?

Recommendation(s):
Weak recommendation with low quality evidence to administer nusinersen (Spinraza) in patients with symptomatic Type II SMA that have 2-4 copies of SMN2.

Consensus recommendation to continue nusinersen (Spinraza) in patients with symptomatic Type II SMA as long as there is no decrease in baseline function as measured by appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIs]) after 12 months of therapy.

Remarks: Current studies have shown that nusinersen (Spinraza) may improve or prevent the decrease in motor function as measured by appropriate motor function assessment tool. Additional outcome measures such as PedsQL and physician manual motor and core testing should also be taken into consideration when determining continuation of treatment. Each patient case must be reviewed by an interdisciplinary team before clinical recommendations should be made on whether to continue or discontinue treatment.

PICO Question 3: In children with symptomatic Type III SMA, does the use of nusinersen (Spinraza) improve or prevent decline of motor function?

Recommendation(s):
Weak recommendation with low quality evidence to administer nusinersen (Spinraza) in patients with symptomatic Type III SMA.

Consensus recommendation to continue nusinersen (Spinraza) in patients with symptomatic Type III SMA as long as there is no decrease in baseline function as measured by appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIs]) after 12 months of therapy.

Remarks: Current studies have shown that nusinersen (Spinraza) may improve or prevent the decrease in motor function as measured by appropriate motor function assessment tool. The team also recommends continued research in this area to further understand long term treatment costs and effects.

PICO Question 4: In children with presymptomatic SMA, does the use of nusinersen (Spinraza) improve or prevent decline of motor function?

Recommendation(s):
Weak recommendation with low quality evidence to administer nusinersen (Spinraza), in patients with presymptomatic Type I SMA that have 2-4 copies of SMN2, and have some movement of their arms and/or legs.

Consensus recommendation to continue nusinersen (Spinraza) in patients with presymptomatic Type I SMA that have 2-3 copies of SMN2, and have some movement of their arms and/or legs.

Remarks: Current studies have shown that nusinersen (Spinraza) may improve or prevent the decrease in motor function as measured by the appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIs]) after 12 months of therapy.

PICO Question 5: In children with symptomatic Type II SMA, does the use of nusinersen (Spinraza) improve or prevent decline of motor function?

Recommendation(s):
Weak recommendation with low quality evidence to administer nusinersen (Spinraza) in patients with symptomatic Type II SMA that have 2-4 copies of SMN2.

Consensus recommendation to continue nusinersen (Spinraza) in patients with symptomatic Type II SMA as long as there is no decrease in baseline function as measured by appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIs]) after 12 months of therapy.

Remarks: Current studies have shown that nusinersen (Spinraza) may improve or prevent the decrease in motor function as measured by appropriate motor function assessment tool. Additional outcome measures such as PedsQL and physician manual motor and core testing should also be taken into consideration when determining continuation of treatment. Each patient case must be reviewed by an interdisciplinary team before clinical recommendations should be made on whether to continue or discontinue treatment.

PICO Question 6: In children with symptomatic Type III SMA, does the use of nusinersen (Spinraza) improve or prevent decline of motor function?

Recommendation(s):
Weak recommendation with low quality evidence to administer nusinersen (Spinraza) in patients with symptomatic Type III SMA that have 2-3 copies of SMN2, and have some movement of their arms and/or legs.

Consensus recommendation to continue nusinersen (Spinraza) in patients with symptomatic Type III SMA as long as there is no decrease in baseline function as measured by appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIs]) after 12 months of therapy.

Remarks: Current studies have shown that nusinersen (Spinraza) may improve or prevent the decrease in motor function as measured by appropriate motor function assessment tool. Additional outcome measures such as PedsQL and physician manual motor and core testing should also be taken into consideration when determining continuation of treatment. Each patient case must be reviewed by an interdisciplinary team before clinical recommendations should be made on whether to continue or discontinue treatment.

PICO Question 7: In children with presymptomatic SMA, does the use of nusinersen (Spinraza) improve or prevent decline of motor function?

Recommendation(s):
Weak recommendation with low quality evidence to administer nusinersen (Spinraza) in patients with presymptomatic Type I SMA that have 2-4 copies of SMN2, and have some movement of their arms and/or legs.

Consensus recommendation to continue nusinersen (Spinraza) in patients with presymptomatic Type I SMA as long as there is no decrease in baseline function as measured by appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIs]) after 12 months of therapy.

Remarks: Current studies have shown that nusinersen (Spinraza) may improve or prevent the decrease in motor function as measured by appropriate motor function assessment tool. Additional outcome measures such as PedsQL and physician manual motor and core testing should also be taken into consideration when determining continuation of treatment. Each patient case must be reviewed by an interdisciplinary team before clinical recommendations should be made on whether to continue or discontinue treatment.

PICO Question 8: In children with symptomatic Type II SMA, does the use of nusinersen (Spinraza) improve or prevent decline of motor function?

Recommendation(s):
Weak recommendation with low quality evidence to administer nusinersen (Spinraza) in patients with symptomatic Type II SMA that have 2-4 copies of SMN2.

Consensus recommendation to continue nusinersen (Spinraza) in patients with symptomatic Type II SMA as long as there is no decrease in baseline function as measured by appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIs]) after 12 months of therapy.

Remarks: Current studies have shown that nusinersen (Spinraza) may improve or prevent the decrease in motor function as measured by appropriate motor function assessment tool. Additional outcome measures such as PedsQL and physician manual motor and core testing should also be taken into consideration when determining continuation of treatment. Each patient case must be reviewed by an interdisciplinary team before clinical recommendations should be made on whether to continue or discontinue treatment.

PICO Question 9: In children with symptomatic Type III SMA, does the use of nusinersen (Spinraza) improve or prevent decline of motor function?

Recommendation(s):
Weak recommendation with low quality evidence to administer nusinersen (Spinraza) in patients with symptomatic Type III SMA that have 2-3 copies of SMN2, and have some movement of their arms and/or legs.

Consensus recommendation to continue nusinersen (Spinraza) in patients with symptomatic Type III SMA as long as there is no decrease in baseline function as measured by appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIs]) after 12 months of therapy.

Remarks: Current studies have shown that nusinersen (Spinraza) may improve or prevent the decrease in motor function as measured by appropriate motor function assessment tool. Additional outcome measures such as PedsQL and physician manual motor and core testing should also be taken into consideration when determining continuation of treatment. Each patient case must be reviewed by an interdisciplinary team before clinical recommendations should be made on whether to continue or discontinue treatment.

PICO Question 10: In children with presymptomatic SMA, does the use of nusinersen (Spinraza) improve or prevent decline of motor function?

Recommendation(s):
Weak recommendation with low quality evidence to administer nusinersen (Spinraza) in patients with presymptomatic Type I SMA that have 2-4 copies of SMN2, and have some movement of their arms and/or legs.

Consensus recommendation to continue nusinersen (Spinraza) in patients with presymptomatic Type I SMA as long as there is no decrease in baseline function as measured by appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIs]) after 12 months of therapy.

Remarks: Current studies have shown that nusinersen (Spinraza) may improve or prevent the decrease in motor function as measured by appropriate motor function assessment tool. Additional outcome measures such as PedsQL and physician manual motor and core testing should also be taken into consideration when determining continuation of treatment. Each patient case must be reviewed by an interdisciplinary team before clinical recommendations should be made on whether to continue or discontinue treatment.
**Recommendation:** Consensus recommendation to not administer nusinersen (Spinraza) in patients with presymptomatic SMA that have a genetic diagnosis of 5q SMA and greater than 3 copies of the SMN2 gene.

**Remarks:** Currently, there is not enough evidence to support or refute a recommendation to administer nusinersen (Spinraza) in presymptomatic SMA patients. The team recommends that the risks, benefits, treatment burden, and the patient’s values and preferences be discussed and taken into consideration when deciding on the clinical management of SMA. The team also recommends continued research in this area to further understand the long term treatment costs and effects.

**PICO Question 5:** In children with SMA, does the use of nusinersen (Spinraza) improve quality of life?

**Remarks:** Currently, there is not enough evidence to support or refute a recommendation to administer nusinersen (Spinraza) to improve quality of life in children with SMA. The team recommends that the risks, benefits, treatment burden, and the patient’s values and preferences be discussed and taken into consideration when deciding on the clinical management of SMA. The team also recommends continued research in this area to further understand the long term treatment costs and effects.

**PICO Question 6:** In children with SMA, which of the following tools is best to measure motor function:
- Hammersmith Functional Motor Scale (HFMS),
- Hammersmith Functional Motor Scale Expanded (HFMSE),
- Modified Hammersmith Functional Motor Scale (MHFMS),
- Hammersmith Infant Neurological Examination Section 2 (HINE-2),
- Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND),
- Motor Function Measure (MFM),
- Gross Motor Function Measure (GMFM),
- Upper Limb Module (ULM),
- Revised Upper Limb Module (RULM),
- 6 Minute Walk Test (6MWT),
- Timed Up and Go (TUG)?

**Recommendation:** Strong recommendation with very low quality evidence to use the following motor function tools, dependent on the patient’s level of motor function and achieved milestones, to assess improvement, stability, or decline of motor function: Hammersmith Functional Motor Scale Expanded (HFMSE), Hammersmith Infant Neurological Examination Section (HINE-2), Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), and Revised Upper Limb Module (RULM) for the weak Type IIs and IIs, and physician manual motor testing when assessing motor function.

**Critical Points of Evidence**

**Evidence Supports**
- Administer nusinersen (Spinraza), in patients with symptomatic Type I SMA that have 2-3 copies of SMN2, and have some movement of their arms and/or legs. (6,7) – Weak recommendation, low quality evidence
- Administer nusinersen (Spinraza) in patients with symptomatic Type II SMA that have 2-4 copies of SMN2. (3) – Weak recommendation, low quality evidence
- Administer nusinersen (Spinraza) in patients with symptomatic Type III SMA. (3) – Weak recommendation, low quality evidence

**Evidence Lacking/Inconclusive**
- Continue nusinersen (Spinraza) in patients with symptomatic Type I SMA with at least a 2-3 point increase in CHOP-INTEND score or 2-3 point increase in HFMSE score from pretreatment baseline after 12 months of therapy. – Consensus recommendation
- Continue nusinersen (Spinraza) in patients with symptomatic Type II SMA as long as there is no decrease in baseline function as measured by appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIs]) after 12 months of therapy. – Consensus recommendation
- Continue nusinersen (Spinraza) in patients with symptomatic Type III SMA as long as there is no decrease in baseline function as measured by appropriate motor function assessment tool (HFMSE, CHOP-INTEND, Revised Upper Limb Module [for the weak Type IIIs]) after 12 months of therapy. – Consensus recommendation
- Do not administer nusinersen (Spinraza) in patients with presymptomatic SMA that have a genetic diagnosis of 5q SMA and greater than 3 copies of the SMN2 gene. – Consensus recommendation

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

**Remarks:** Unpublished studies were identified and reviewed but not taken into consideration when making recommendations, as the studies were not currently deemed methodologically rigorous enough for inclusion.
References


Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children’s Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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No relevant financial or intellectual conflicts to report.

Development Process
This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing External Guidelines
   - Washington State Health Care Authority: Nusinersen (Spinraza) Clinical Policy
3. Literature Review of Relevant Evidence
   - Searched: PubMed, Cochrane
4. Critically Analyze the Evidence
   - 1 randomized controlled trial, and 22 nonrandomized studies
5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a nusinersen (Spinraza) evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence
Published clinical guidelines were evaluated for this review using the AGREE II criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence in support of or against specific interventions and identifies where evidence is lacking/inconclusive. The following categories describe how research findings provide support for treatment interventions.

“Evidence Supports” provides evidence to support an intervention
“Evidence Against” provides evidence against an intervention.
“Evidence Lacking/Inconclusive” indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn from the evidence.

The GRADE criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

<table>
<thead>
<tr>
<th>Recommendation</th>
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<td>STRONG</td>
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</tr>
<tr>
<td>Low</td>
<td>Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence</td>
</tr>
<tr>
<td>Very Low</td>
<td>Evidence for at least 1 critical outcome from unystematic clinical observations or very indirect evidence</td>
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</table>

Recommendations
Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in nusinersen (Spinraza) treatment for children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process
Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children’s Hospital. Content Expert Teams are involved with every review and update.

Disclaimer
Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient’s family, to make the ultimate judgment regarding care.

Version History
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