

Item 23b.a: Discussion – Limitations of evidence

**Comment on the appropriateness of outcome measurement, including aspects such as validity, feasibility, reliability, and responsiveness of measurement instruments, for each age groups or ranges**

Title	1a	Title
<b>Introduction</b>	3a	Rationale <i>Justification</i>
	3b	Rationale <i>Treatment effects</i>
<b>Methods</b>	5a	Eligibility criteria
	13d.a.	Synthesis methods
<b>Results</b>	17a	Study characteristics
<b>Discussion</b>	23b.a	Limitations

**Key elements for reporting this item:**

- ✓ • Whether the outcomes and outcome measurement instruments used were appropriate for included age groups/ranges, disease stage, subtype, or severity, in terms of their validity, reliability, responsiveness, and feasibility
- ✓ • If applicable, whether patient-reported outcomes were considered
- ✓ • If applicable, whether there were any translations or modifications to the OMI's used, and how this impacted data synthesis

**Example:**

✓ *“Our comprehensive subgroup analyses demonstrate that a modest improvement after nusinersen initiation is consistently observed in many adolescents and adults with a broad spectrum of [Spinal Muscular Atrophy] SMA, especially when the most sensitive scales are used for each sub-population (e.g., [Hammersmith Functional Motor Scale-Expanded] HFMSE for less severely affected, and [Revised Upper Limb Module] RULM for more severely affected)... Our study focused on motor function outcomes, which are the primary outcomes in many clinical trials for later-onset SMA [reference]. They are also the most frequently reported standardized outcomes in real-world studies of adolescents and adults. Despite the known limitations of ceiling and floor effects, motor function outcomes are generally suitable for the majority of adolescents and adults with Type II and III SMA, if appropriate scales are used based on patient characteristics (e.g., HFMSE for less severely affected patients and RULM for more severely affected patients). Other outcomes such as pulmonary or bulbar functions were often not consistently defined across studies and were not available in most large multicenter studies. Additionally, many scales and assessments that focus on non-motor outcomes were not validated for SMA, especially in adults. These outcomes may also hold greater significance for a selected group of patients in severe disease stages.”*

Hagenacker T, Maggi L, Coratti G, et al. Effectiveness of Nusinersen in Adolescents and Adults with Spinal Muscular Atrophy: Systematic Review and Meta-analysis. *Neurol Ther* 2024;13(5):1483–504. doi: 10.1007/s40120-024-00653-2 [published Online First: 20240902]