# Spinal muscular atrophy (SMA): Development of natural history models for disease subtypes

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## Introduction

- Spinal muscular atrophy (SMA) is a rare, severe, progressive, inherited neuromuscular disease resulting in loss of muscle function, paralysis and premature death.[1]
- The disease spectrum is defined by age of onset and highest achieved motor milestone.[1]
- The absence of a standard natural history model for use in Health Technology Assessment (HTA) appraisal submissions is one of the biggest challenges in assessing cost effectiveness of pharmaceutical interventions in SMA.[2]
- The natural progression of SMA can be assessed by several age- and ability-appropriate motor function scales, (Table 1), which can inform natural history models.
- The aim of the current project was to develop robust natural history disease models to inform the cost-effectiveness assessment of innovative, disease-modifying treatments in this indication for the following populations:
  - SMA infantile onset (Type 1);
  - SMA late onset (Type 2/3).

## Methods

- The following sources of evidence were used to inform the natural history of disease models:
  - a *de novo* systematic review (SR) was conducted which identified published economic evaluations of SMA;
  - a review through MEDLINE®, MEDLINE® In-Process, Embase, and The Cochrane Library, was conducted on 29th August 2019;
  - interviews with clinicians were conducted to: (i) review current disease management guidelines to define relevant model health states and appropriate functional scales to assess transition through these health states; (ii) identify appropriate disease-related, treatment-independent adverse events (TIAEs).
- Based on the evidence collected, disease health states for both Type 1 and Type 2/3 SMA were defined.

**Table 1: Assessment scales in SMA**

| Assessment scales | Age of patient | | | |
|---|---|---|---|---|
| | <6 months | 6–18 months | 1.5–10 years | >35 years |
| CHOP-INTEND[3,4] | 1–38 months | | Can be used in less severe patients, but is designed to assess severe Type 1 patients | |
| BSID-III[5] | 1–42 months | | | |
| HINE-2[6,7] | 2–24 months | | | |
| 6MWT[8,9] | | | Ambulatory patients aged from 3 years | |
| HFMSE[10,11] | | | Types 2/3 aged from 24 months | |
| RULM[12,13] | | | From 2.5 years | |
| MFM[14,15,16] | | | MFM20: 2–7 years/MFM32: 6–60 years | |

## Results

### Systematic review

- A total of nine publications reporting eight unique economic evaluations covering both Type 1 and Types 2/3 subtypes of SMA were identified from the SR, confirming the paucity of published economic models in this indication.
  - HTA submissions, n=3 (CADTH,[17] NICE,[18] and ICER[19]);
  - Published cost-utility analyses, n=6 publications (full publications, n=2;[20,21] abstracts, n=4[22-25]) covering five unique analyses.
- Limitations reported by the five unique economic evaluations were related to a lack of long-term effectiveness and safety data, the restricted generalisability of results, and a requirement for assumptions concerning survival, costs, utilities, and whether the motor milestone function was sustained over a lifetime.[20-23]
  - Feedback from clinicians highlighted the importance of considering the full breadth of the natural history of the disease (i.e. progression, stabilization, and regression for disease modifying therapies).
  - Additionally, existing models for Type 1[19,20] and Type 2/3[19] SMA highlight progression and worsening within simplified health states. Hence, they do not differentiate between "with support" and "without support" and do not contain a transfer (standing) health state.

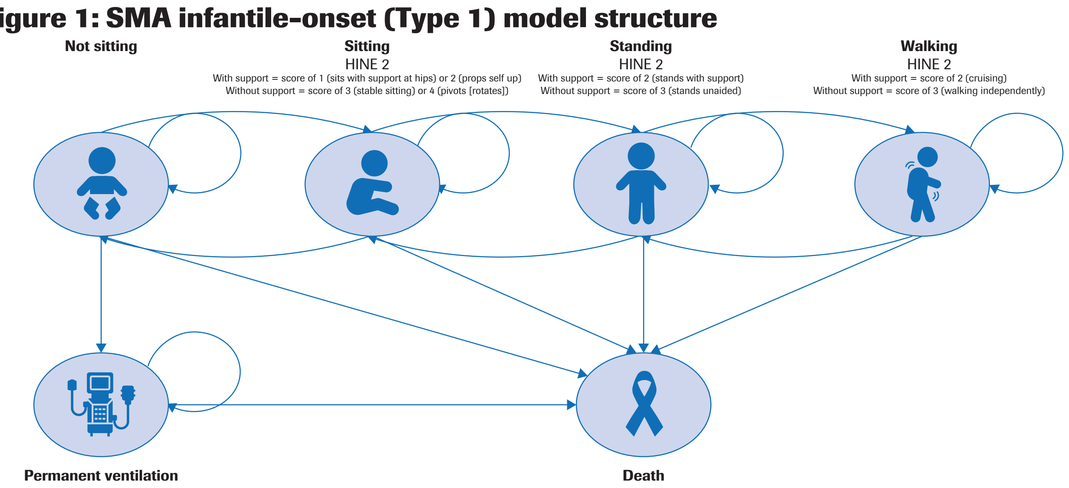
### Proposed model structures

#### *SMA infantile onset (Type 1) model structure*

- The proposed infantile-onset (Type 1) Markov model includes four motor milestones: "not sitting", "sitting", "standing", and "walking", together with "permanent ventilation" and "death" health states (Figure 1).
- Clinical data were obtained from FIREFISH, an open-label trial in infants aged 1–7 months with Type 1 SMA[26,27] FIREFISH considered several motor function scales, including HINE-2, BSID-III, and CHOP-INTEND.
- Based on internal and external clinical expertise (data not shown), the HINE-2 scale was selected as the broadest scale for capturing motor function for patients with Type 1 SMA.
- *Mortality rate:* Patients can die from any health state; mortality rate was based on a review of Type 1 survival data (data not shown, abstract forthcoming) and Type 2 survival data.[28]

## Results (cont.)

**Figure 1: SMA infantile-onset (Type 1) model structure**

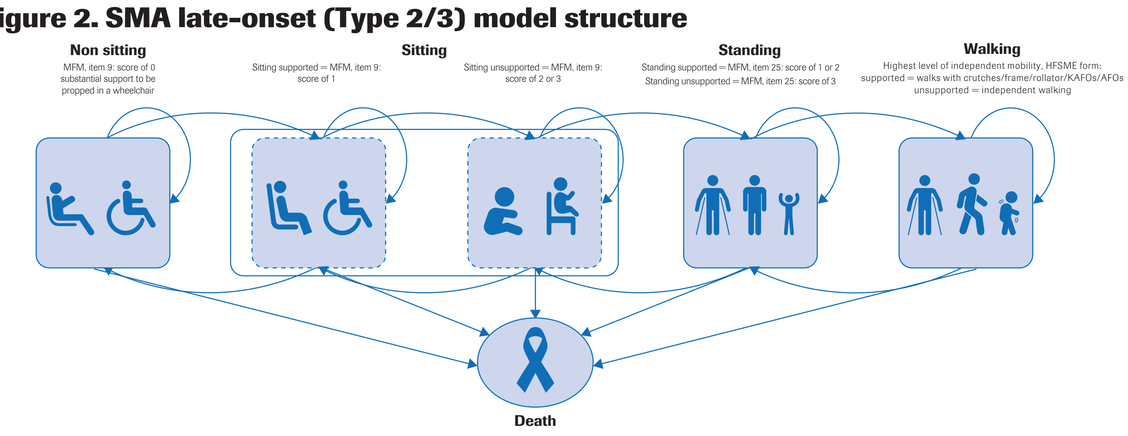



*Arrows indicate "permissible patients transitions."

#### *SMA late-onset (Type 2/3) model structure*

- The late-onset (Type 2/3) Markov model was identical to that for infantile onset, apart from the splitting of "sitting" into two distinct states, "supported" and "not supported," and the removal of the "permanent ventilation" health state (Figure 2).
- Clinical data were obtained from SUNFISH, a randomized, placebo-controlled trial in children and young adults (2–25 years) with Types 2 and 3 SMA.[29] SUNFISH considered several motor function scales, including MFM32, RULM, and HFMSE.
- Based on internal and external clinical expertise (data not shown), the MFM32 scale was selected as the best option for capturing motor function for patients with Types 2 and 3 SMA.[30]
- *Mortality rate:* Patients can die from any health state, mortality rate for SMA Type 2 was based on a review of Type 2 survival data.[28] Whereas, mortality rate for SMA Type 3 was based on country specific life tables.[31]

**Figure 2. SMA late-onset (Type 2/3) model structure**




*Arrows indicate "permissible patients transitions". AFO, ankle-foot orthosis; KAFO, knee-ankle-foot orthosis.

#### *Structure common to both models*

- "Sitting (for Type 1)", "standing" and "walking" included sub-health states for "with support" and "without support" to account for potential differences in QoL and cost.
- TIAEs (e.g. scoliosis, respiratory tract infections, sleep apnea, contractures, noninvasive ventilation, feeding support, eye monitoring, intrathecal injection, etc.) were incorporated in the model (independent of the health state) by attaching the relevant cost and disutility.
- Treatment-related AEs (especially those requiring hospitalization) were included in the model by attaching the AE management cost against each AE.
- Patients can transition to a "death" health state from any of the other health states.
- The newly defined transfer health state ("standing") represented an important preliminary health state. A prolonged standing ability can reduce scoliosis, decelerate contracture progression, and improve posture and respiratory function[32,33] which diminishes the reliance on caregivers (increasing caregiver QoL and reducing costs).

## Conclusions

- Natural history models for Type 1 and Type 2/3 SMA were created from a literature review, clinician interviews, and reflections on disease severity and current disease management.
  - Models include appropriate health states across disease subtypes which affect lifetime costs, survival, and QoL.
- These models will help standardize economic decision models in SMA that can be easily adapted by pharmaceutical manufacturers for use in HTA appraisal submissions.

## Abbreviations

6MWT, 6-minute Walk Test; AE, adverse event; BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CADTH, Canadian Agency for Drugs and Technologies in Health; CHOP-INTEND, Children's Hospital of Philadelphia Infant test of Neuromuscular Disorders; HFMSE, Expanded Hammersmith Functional Motor Scale; HINE-2, Hammersmith Infant Neurological Examination, Module 2; HTA, Health Technology Assessments; ICER, Institute for Clinical and Economic Review; MFM20, 20-item Motor Function Measure; MFM32, 32-item Motor Function Measure; NICE, National institute for Health and Care Excellence; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SR, systematic review; TIAE, treatment-independent adverse events; QoL, quality of life.

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