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Using Expert Consensus to Expand Access in Rare Disease Populations: Generating Evidence for Permanently Ventilated Individuals Living With Spinal Muscular Atrophy

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BACKGROUND

- Spinal muscular atrophy (SMA) is a rare, inherited disorder characterised by progressive musculoskeletal, respiratory, and bulbar dysfunction, leading to early mortality.
- In England, disease-modifying therapies (DMTs), including nusinersen and risdiplam (*SMN2*-targeted therapies) and onasemnogene abeparvovec (*SMN1* replacement therapy), have significantly improved outcomes for people living with SMA, and are available either routinely or under Managed Access Agreements (MAAs)[1].
- People living with SMA who require permanent ventilation (PV; defined as tracheostomy or ventilatory support for at least 16 hours per day for 21 consecutive days without acute reversible infection) are excluded from DMTs under the current MAA criteria. Treatment requires case-by-case review by an NHS England National Clinical Panel[2,3,4].
  - Fewer than 20 individuals with SMA who require PV (SMA-PV) currently have access to *SMN2*-targeted therapies in the UK through compassionate medicine use schemes.
- In order to lift access restrictions for patients with SMA-PV, there is a need to understand what clinical benefit DMTs may offer to this cohort, and how this benefit may be evaluated in clinical practice.

THE HTA CHALLENGE

Measuring benefit

- Benefit in SMA-PV is hard to measure with standard scales (e.g. BSID-III[5], HINE-2[6], CHOP-INTEND[7], MFM-32[8], RULM[7], HFMSE[9]).
- Current assessment often relies on subjective observations which do not align with MAA criteria.
- Patients report that standardised scores do not reflect improvement in quality-of-life (QoL)[10]. E.g. a 'small' change in a score can mean a huge functional impact, such as operating a wheelchair.
- Clinically significant response to treatment is undefined, which led to no plausible cost-effectiveness data for this group in the initial NICE appraisal (TA755).

Evolving clinical practice

- Advances in therapy have led parents and physicians to be more willing to prolong life with PV[4].
- Clinicians report observations of improvements in QoL or slowing of deterioration for patients with SMA-PV.
- Clinical experts believe that remaining on PV does not preclude a relatively good QoL.

2024 survey findings

A survey of 5 UK neuromuscular experts managing patients with SMA-PV on risdiplam via a compassionate use scheme found:

- Clinical benefits across motor, respiratory and bulbar function were realised in these patients[11].
- Potential for reduced hospital admissions, more energy and maintained employment for patients (where applicable)[11].
- All specialists recommended a DMT for patients with SMA-PV.

Next steps

- Results from the survey suggests clinical benefit, but the small sample size highlights the need for further evidence as well as collecting data in a more robust manner. However, there is a lack of validated criteria to quantify benefits in patients with SMA-PV.
- A Delphi consensus process may help address these evidence gaps.

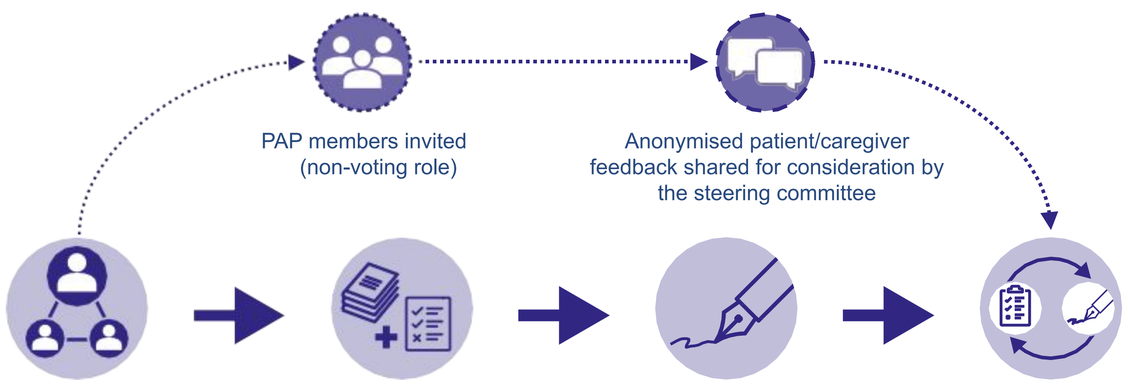
OBJECTIVE

To develop statements that outline the clinical benefits associated with DMT use in people with SMA-PV, and to provide best practice recommendations regarding their use through an anonymised evidence-based consensus process to support access to DMTs for this patient subgroup.

METHODS

A modified Delphi consensus process was conducted, informed by a targeted literature review (TLR) and clinical expertise (**Figure 1**).

Figure 1. The modified Delphi consensus process



[a]Non-voting PAP members had the opportunity to review each statement and provide anonymous feedback for consideration by the steering committee. This activity was run in parallel to the consensus process.
PAP, patient advisory panel; TLR, targeted literature review.

Recruitment

- A UK-based multi-disciplinary expert panel comprising neurologists, respiratory consultants and physiotherapists with experience in managing individuals with SMA or SMA-PV was recruited (N=19; UK SMA Delphi panel): 1 non-voting chair (Mariacristina Scoto*), 3 steering committee members (Elaine Chan,† Chiara Marini-Bettolo*, Anita Simonds†) and 15 panel members (Giovanni Baranello,* Anne-Marie Childs,* Lisa Edel,‡ Chris Edwards,† Marjorie Illingworth,* Richa Kulshrestha,* Min Ong,* Rishi Pabary,† Matt Parton,* Sithara Ramdas,* Saam Sedehizadeh,* Hui-Leng Tan,† Stuart Wilkinson,† Tracey Willis*, Elizabeth Wraige*). Specialties: *neurology; †respiratory medicine; ‡physiotherapy.
- A non-voting patient advisory panel (PAP) was recruited to run in parallel to the Delphi panel, in order to capture the patient voice. This included patients with SMA-PV, caregivers of patients with SMA-PV and reps from patient advisory groups (N=5).

METHODS - CONTINUED

Consensus process

After statement development, Delphi panel and steering committee members (excluding the Chair) anonymously rated their agreement using a 6-point Likert scale over a maximum of 3 voting rounds

Participants who disagreed had the chance to suggest revisions. Patient Advisory Panel (PAP) members also reviewed and provided anonymous feedback for the steering committee's consideration.

Statements failing to reach the predefined consensus threshold (≥ 75% agreement [somewhat agree, agree, strongly agree]) were revised using clinical and patient feedback, then included in the next round. A statement was finalised upon reaching consensus in any of the 3 rounds.

Throughout the process, members received a summary of the TLR and articles identified.

RESULTS

The TLR identified 58 articles reporting clinical and real-world outcomes relating to DMT use in individuals with SMA-PV.

Overall, 22 draft statements were developed using evidence identified by the TLR and expert clinical insights captured in the questionnaire.

Voting was completed in 2 rounds, with all 18 voting panel members participating in both.

21/22 statements (95.5%) achieved consensus in Round 1.

The final statement, revised following PAP feedback, achieved consensus in Round 2.

The final 22 statements that met consensus are presented in Table 1.

Overall, 20/22 statements (90.9%) achieved > 90% agreement.

Table 1. Final agreed consensus statements

	Statement	Level of agreement, n/N (%)
Overarching statements regarding DMT use in patients with SMA-PV		
1	Access to SMN2-targeted therapy should be modified to incorporate a trial period of at least six months to determine treatment benefit in patients with SMA-PV, irrespective of prior experience with SMN1 replacement therapy	17/18 (94.4)
2	PV alone should not preclude the use of DMTs in patients with SMA-PV	18/18 (100.0)
3	Ideally, access to DMTs for patients with SMA-PV should not be limited by treatment cost alone. However, decisions regarding ongoing access should be based on a resource-benefit analysis conducted in consultation with an expert clinical panel	17/18 (94.4)
Considerations before initiating DMTs in patients with SMA-PV		
4	Candidacy for DMT in patients with SMA-PV should be determined in accordance with local/regional guidelines and in consultation with an expert clinical panel. Patient age and disease stage; extent of disease progression (i.e., the degree of motor, respiratory or bulbar dysfunction); concurrent illness; mode of ventilatory support; level of ventilator dependency; potential to wean from PV; DMT route of administration; and anticipated long-term clinical outcomes should all be considered	18/18 (100.0)
5	The decision to initiate DMTs in patients with SMA-PV should be agreed with the patient, where possible, or their caregivers. Additionally, it is important to agree on realistic, individualised treatment goals with predefined timepoints to guide future treatment decisions, including palliative or supportive care	18/18 (100.0)
6	To optimise clinical outcomes in patients with SMA-PV, respiratory (e.g., ventilatory support, secretion management and antimicrobial prophylaxis) nutritional (e.g., weight management, gastronomy and supplementation) and orthopaedic supportive care should be prioritised, and comorbidities that may be associated with respiratory deterioration (e.g., aspiration or gastroesophageal reflux disease) should be managed	18/18 (100.0)
Considerations following treatment with SMN1 replacement therapy or during SMN2-targeted therapy in patients with SMA-PV		
7	Following SMN1 replacement therapy or during SMN2-targeted therapy, patients with SMA-PV should continue to be managed in accordance with international standards of care, with an emphasis on optimising respiratory, bulbar and musculoskeletal function, in order to maintain the highest perceived QoL possible	18/18 (100.0)
8	Following SMN1 replacement therapy or during SMN2-targeted therapy, patients with SMA-PV should be reviewed biannually by the MDT. For adult patients, reviews may be reduced to a minimum of once a year if respiratory and bulbar functions have stabilised	18/18 (100.0)
9	The decision to continue SMN2-targeted therapy in patients with SMA-PV should be made on an individualised basis within the MDT and in consultation with an expert clinical panel, where needed. Factors may include any reportable evidence of stabilisation or improvement in respiratory, bulbar or motor function, or ventilation needs; lack of treatment-related side effects; reduction in hospitalisations; patient- and/or caregiver-perceived QoL; and patient or caregiver consent for continued treatment	17/18 (94.4)
10	Supportive or palliative care should continue to be offered to patients with SMA-PV when SMN2-targeted therapy is discontinued, as there are no other approved treatments available and the use of off-label treatment is not recommended. Discussions regarding this change should be conducted sensitively and in careful consideration of the patient's or caregivers' preference	18/18 (100.0)
11	Candidacy for switching SMN2-targeted therapy should be determined on an individualised basis, by the MDT and in consultation with an expert clinical panel. If approved, a trial period of at least six months should be initiated following switching treatment	16/18 (88.9)
Defining clinical benefit in patients with SMA-PV treated with DMTs		
12	The clinical benefit associated with DMT use in patients with SMA-PV should be determined through practical, validated clinical outcomes, observations and patient- and caregiver-reported outcomes	18/18 (100.0)
13	Patient- and caregiver-perceived changes in functional ability, where possible validated by the care team, should be considered when assessing the effectiveness of DMT use in patients with SMA-PV	17/18 (94.4)
14	As the functional changes observed in patients with SMA-PV treated with DMTs may be subtle, it is advised that caregivers and family members record or diarize any perceived changes which may be shared with the MDT	18/18 (100.0)
Monitoring functional changes following treatment with SMN1 replacement therapy or during SMN2-targeted therapy in patients with SMA-PV		
15	In patients with SMA-PV, the choice of motor assessment measure should be accurate enough to capture the patient's level of functional ability at presentation, as well as any changes following treatment with DMTs	17/18 (94.4)
16	Polysomnography, cardiorespiratory polygraphy and carbon dioxide monitoring should be considered when assessing respiratory function in patients with SMA-PV. Breathing studies (maximal inspiratory pressure, maximal expiratory pressure and sniff nasal inspiratory pressure) and spirometry may also be considered, where appropriate	16/18 (88.9)
17	In patients with SMA-PV whose motor function is too severely impaired to detect measurable changes through standard assessments following treatment with DMTs, it is advisable to investigate subtle changes in fine motor function. Examples may include changes in eye movement, facial expression and finger dexterity (e.g., the ability to gesture or interact with touchscreens, switches or communication aids)	18/18 (100.0)
18	Indicators of improved respiratory function in patients with SMA-PV treated with DMTs may include increased hours off ventilation, improved cough or speech strength, and reduced frequency of respiratory tract infections, hospitalisations related to exacerbation or need for suctioning or antibiotics	18/18 (100.0)
Monitoring changes in QoL following treatment with SMN1 replacement therapy or during SMN2-targeted therapy in patients with SMA-PV		
19	Employing a combination of direct clinical observations, discussions with the patient and/or caregivers and PROMs (e.g., SMA-QoL, SRI, PedsQL, or SF-36 or SF-12 in adult patients) is recommended to generate a comprehensive understanding of QoL in patients with SMA-PV treated with DMTs	18/18 (100.0)
20	Additional indicators of improved QoL may include increased social interaction and/ or school engagement, and reduced hospitalisations, infections or need for secretion management	18/18 (100.0)
Additional considerations and considerations for future research		
21	Research priorities should include the harmonisation of QoL data and patient- and/or caregiver-reported outcome measures, and their integration with clinician-reported data in national registries for patients with SMA-PV treated with DMTs. Additional endpoints may include the impact of DMTs on healthcare resource use and caregiver burden	18/18 (100.0)
22	To quantify the subtle changes associated with DMT use in patients with SMA-PV, a validated functional assessment tool which employs remote video recording and biometric data (e.g., from wearable devices) should be considered	17/18 (94.4)

[a]Defined as ≥ 75% agreement.
DMT, disease-modifying therapy; MDT, multidisciplinary team; PedsQL, Paediatric Quality of Life Inventory; PROM, patient-reported outcome measure; PV, permanent ventilation; QoL, quality of life; SF-36 or -12, Short Form 36- or 12-item Health Survey; SMA, spinal muscular atrophy; SMA-PV, spinal muscular atrophy with permanent ventilation; SRI, Severe Respiratory Insufficiency Questionnaire.

CONCLUSIONS

- Patients with SMA-PV are currently excluded from DMTs under MAA criteria due to limited clinical and cost-effectiveness data. This study supports access to DMTs for SMA-PV as TA588 and TA755 are reviewed (NICE ID6195).
- Since quantitative data is scarce for this subgroup, a Delphi consensus process was used. This method provides pragmatic, acceptable qualitative data for HTA.
- A UK expert panel maintained high participation and endorsed the resulting statements. These statements define clinical benefit and response for SMA-PV, where standardised tools fail.
- Statements 12-14 reached 94.4% consensus, defining clinical response through: observations, patient/caregiver reported outcomes (PROs), and perceived functional changes (recorded by caregivers due to subtle changes).
- For monitoring, 88.9% agreed that other methods are appropriate, including measuring subtle functional changes, selecting tailored motor assessments, and tracking respiratory function. QoL measurement should use a combinative approach: clinical observations, patient/caregiver discussions, PROMs, social interaction, and tracking reduced hospitalisations/infections.
- We hope that, by presenting this compelling data within ID6195, it supports the need to avoid inequity of care with the SMA patient population, and work towards reducing barriers to accessing DMTs for those living with SMA-PV. We hope these insights will expand DMT access, guide commissioning, and improve outcomes for the SMA-PV group.

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DISCLOSURES

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