NICE National Institute for Health and Care Excellence

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SLIDES FOR PUBLIC OBSERVERS

Risdiplam for treating spinal muscular atrophy [ID1631]

Lead team presentation

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Company: Roche

ACM 1: 11th May 2021

Key abbreviations

BSC	Best supportive care	MFM32	Motor Function Measure - 32 items
BSID-III	Bayley Scales of Infant and Toddler Development	NUS	Nusinersen
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders	NR	Not reported
EAMS	Early Access to Medicines Scheme	OS	Overall survival
EMA	European Medicines Agency	PAS	Patient Access Scheme
HINE-2	Hammersmith Infant Neurological Examination Module 2	PV	Permanent ventilation
HFMSE	Hammersmith Functional Motor Scale Expanded	QALY	Quality-adjusted life year
HRQoL	Health-related quality of life	RIS	Risdiplam
ICER	Incremental cost-effectiveness ratio	RULM	Revised Upper Limb Module
ITQOL-SF47	Infant and Toddler Quality of Life Questionnaire (47 item short form)	SE	Standard error
LY	Life years	SMA	Spinal muscular atrophy
MAA	Managed access agreement	SMAIS	SMA independence scale
MAIC	Matched adjusted indirect comparison	SMN	Survival motor neurone

Risdiplam (Evrysdi, Roche)

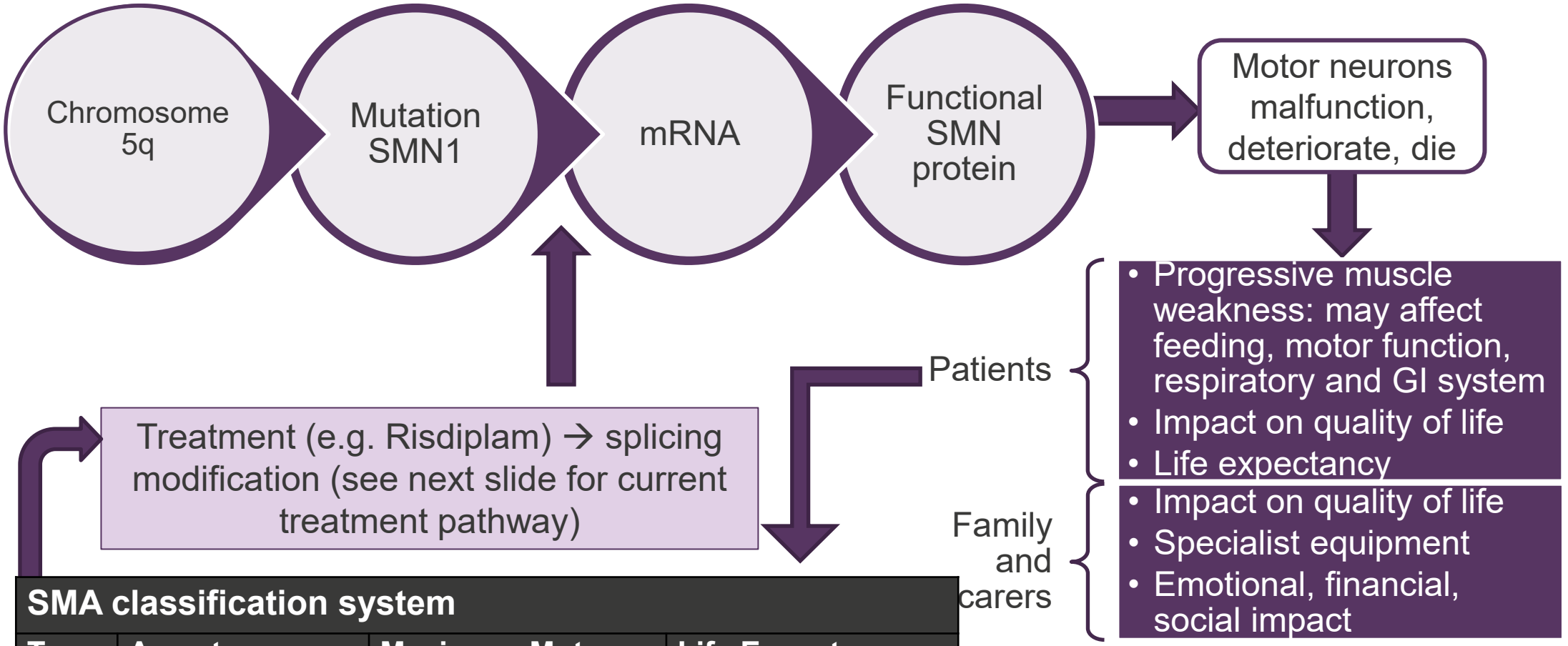
Covers pre-symptomatic SMA but no evidence for this group

Marketing authorisation	MA (EMA): Treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies
Mechanism of action	Risdiplam is a survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency.
Administration	Risdiplam is taken orally once a day using the re-usable oral syringe provided. The recommended once daily dose of risdiplam is determined by age and body weight. • 2 months to < 2 years of age: 0.20 mg/kg • ≥2 years of age (<20 kg): 0.25 mg/kg • ≥2 years of age (≥20 kg): 5 mg
Price	[redacted] per 60 mg/80 ml vial. Simple PAS discount approved (updated post TE). Annual list price: [redacted] (estimated by tech team, assumes 5 mg dosing based on ≥2 years of age [≥20 kg])

Spinal Muscular Atrophy (SMA)

- SMA is a genetic, progressive neuromuscular disease most commonly caused by mutations in the *SMN1* gene on chromosome 5q
  - *SMN1* gene encodes the “survival motor neurone” (SMN) protein
  - Lack of SMN protein causes the motor neurones to malfunction, deteriorate and eventually die
- Motor neurones control walking, crawling, arm movement, head and neck movement, swallowing and breathing
  - Causes muscle weakness and progressive loss of movement
- A heterogeneous condition, often grouped into 5 main types (0 to 4), based on age of onset of symptoms and level of motor function
- Some people can be diagnosed pre-symptomatically if they have a sibling with SMA – pre-natal screening is not routinely done in clinical practice in England
- Substantial effects on families and carers, including impact of caring for the patient, need for specialist equipment and ongoing emotional, financial and social impacts

Spinal Muscular Atrophy (SMA)



SMA classification system			
Type	**Age at symptom onset**	**Maximum Motor Function**	**Life Expectancy**
0*	Foetal	Nil	Days to weeks
1	< 6 months	Never sits	< 2 years (no PV)
2	6 to 18 months	Never walks	20 – 40 years
3	1.5 to 10 years	Walks, regression	As per general population
4*	>35 years	Slow decline	

SMA is a genetic, progressive neuromuscular disease

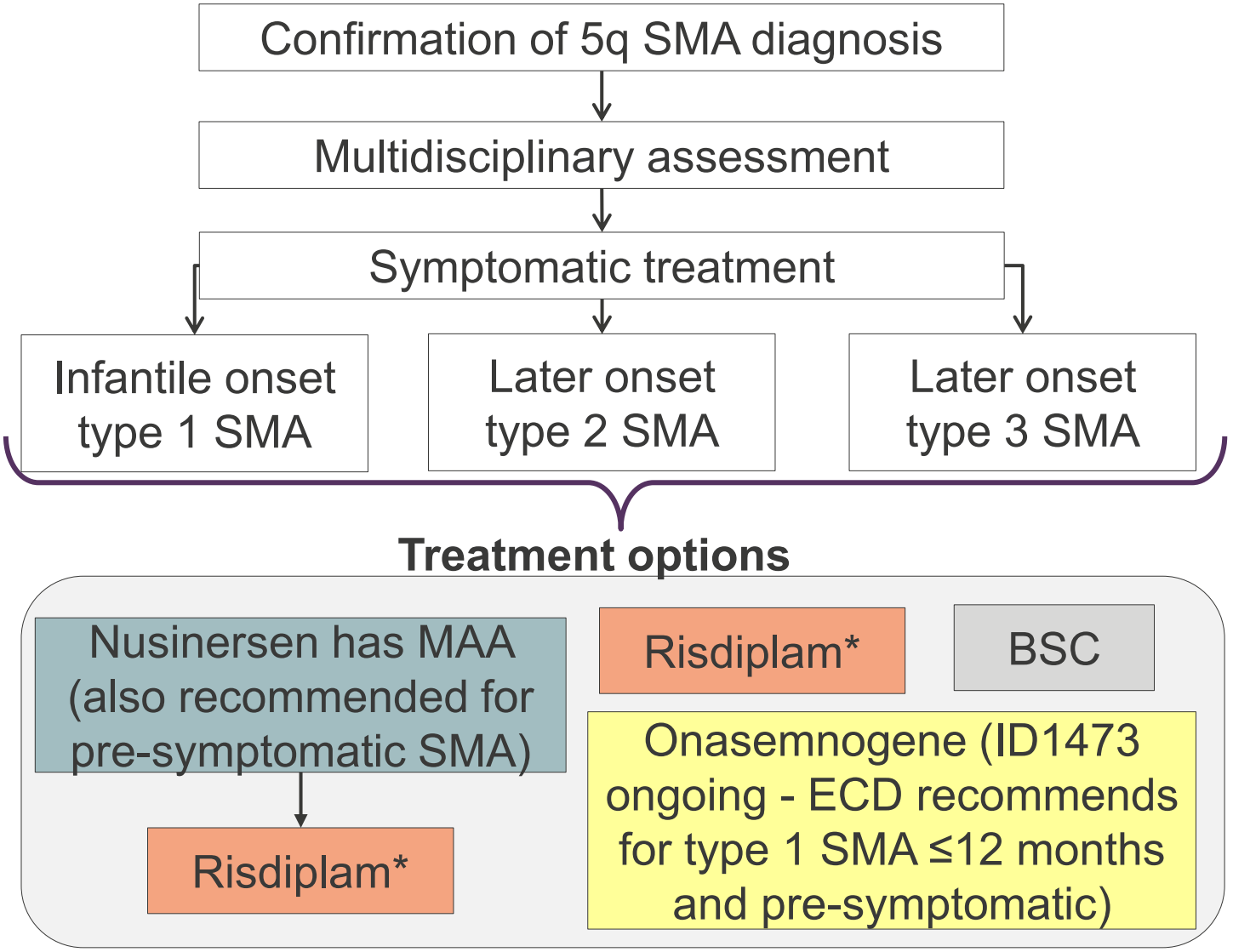
Current treatment pathway for SMA

*Risdiplam is currently available through EAMS (≥2 months, type 1 or 2 SMA for whom authorised treatments are not suitable)

Company

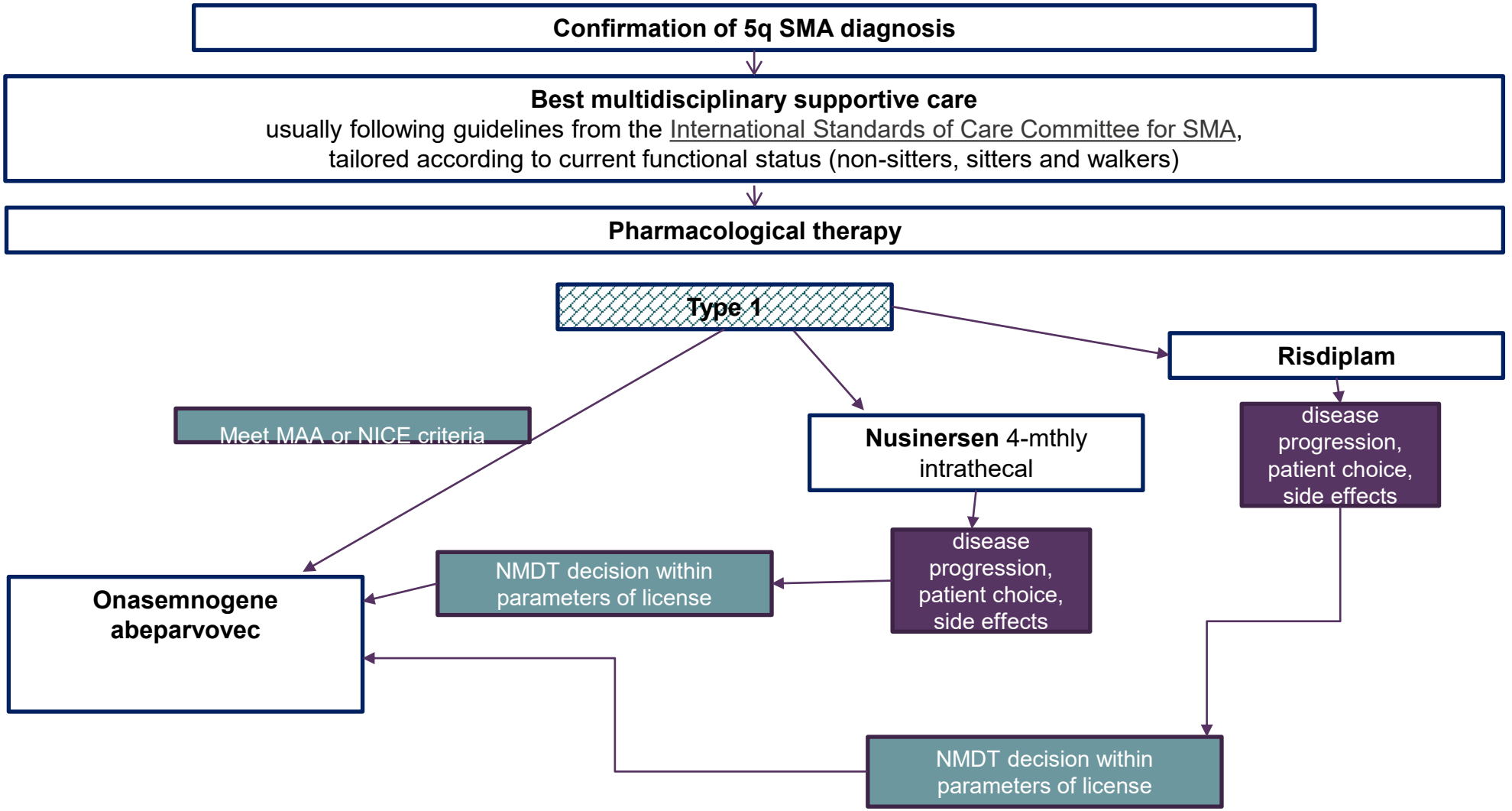
Position risdiplam after nusinersen or if it is not appropriate because:

- unmet need in this group
- current evidence shows earlier treatment is more beneficial
- no plausible biological reason why treatment benefit would differ after treatment with nusinersen. Both act on same SMN2 RNA



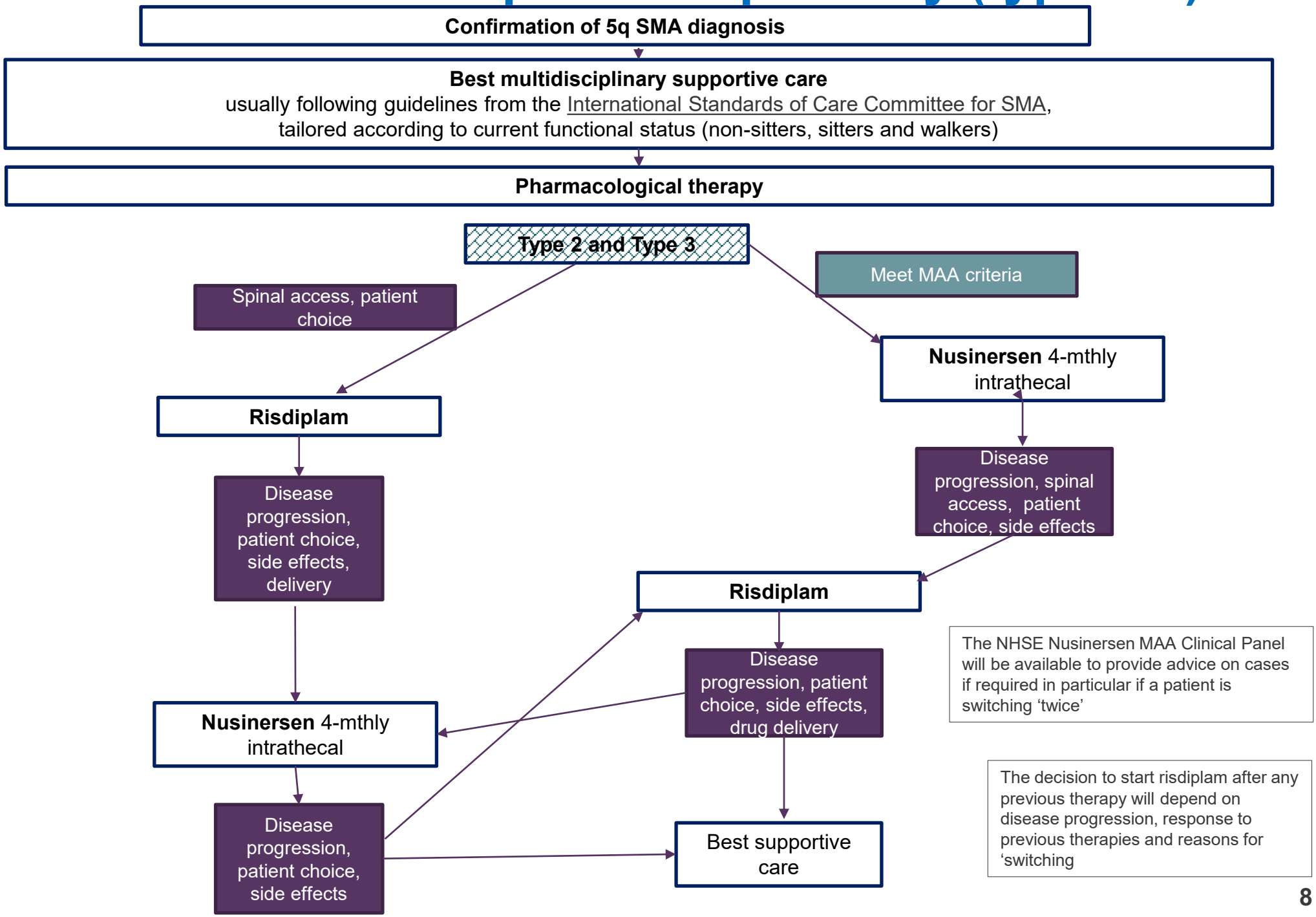
NICE Source: Based on figure 1 in company submission

NHSE&I slide - SMA potential pathway (type 1)



The NHSE Nusinersen MAA Clinical Panel will be available to provide advice on cases if required
NMDT = national MDT of gene therapy centres

NHSE&I slide - SMA potential pathway (type 2/3)



NHSE&I slide - Issues to note

- There may be patients currently not accessing any therapy who would benefit from risdiplam
- A lack of response to one treatment does not necessarily mean that the next treatment will fail if they have different mechanisms of action
- The clinical ‘consent’ discussion about side effects, pros and cons of this drug can be considerable
- If there were an MAA there would be significant complexity around establishing starting criteria
- Lack of long term evidence of effectiveness

Patient and carer perspectives (1)

Based on submissions from: TreatSMA, SMAUK-MDUK, patient experts who contributed testimonies, the survey participants, the clinical experts who responded as individuals and as part of SMA REACH UK, and the expert input from NHSE and commissioning.

5q SMA types

- Classification “The classifications were never meant as a way to make decisions about who should/should not have access to treatment.”
- Spectrum “For children and adults, the severity of the condition…both within and between ‘Types’ - each child and adult is affected differently.”

Natural history

- Clinical perspectives v. PROMs
- Children “extensive knowledge of natural history of SMA in paediatric population”
- Adults “…no validated study of natural history in SMA Adult patients and therefore there is no suitable base line.”

Patient and carer perspectives (2)

Impact on patients and others

- Spectrum “Spinal Muscular Atrophy is a devastating… condition.” “…the most significant concerns are respiratory, swallowing functions, scoliosis, hip displacement, subluxation of shoulders, chronic pain , contractures and depression.” “My employment means a lot to me, to a large extent it is the only independence that I really have, but should I lose the ability to use a mouse or even press a mouse button it would be gone overnight.”

- Family and network of carers “… living with the reality of SMA is emotionally, mentally, financially and physically exhausting.” “Many families are broken apart by the condition. Even when strong relationships come across SMA it grinds these down.” “we [shouldn’t] see the caregiver only as someone who sees themselves as ‘burdened’.”

Patient and carer perspectives (3)

Treatment options

- Nusinersen
- Risdiplam
  - Experience “As someone not able to receive nusinersen, risdiplam has a major impact on my quality-of-life.”
  - Outcomes “Our relationship has become more son and mother rather than son and carer.”
  - Improvements and importance of stable disease “We need to move away from the constant expectation of improvements - stability of the condition is just as important as improvement.” “We…asked…if stopping progression of SMA would be a satisfactory outcome and 124 out of 141 (88%) strongly agree that it would be.”

Other experts (clinical, NHSE and commissioning)

Clinical expert

- Spectrum of disease severity and progressive nature of SMA mean the clinically significant effects of treatment will be different at different ages:
  - Type 1: stabilisation in motor function, in particular maintaining effective respiratory and bulbar function improves overall survival considerably
  - Later onset: more likely to see stabilisation and more subtle improvements in motor skills - but maintaining upper limb strength to independently transfer, operate controls has a considerable impact on independence and in turn meaningful participation in society with less need for carer support and medical interventions

NHS England and commissioning expert

- No national NHSE clinical commissioning policies for SMA

Summary of main clinical evidence

Type 1 SMA

FIREFISH (part 2)

Infants with Type 1 SMA with 2 copies of SMN2, not previously treated, not receiving chronic ventilation, age 1-7 months.

Risdiplam (41)

Type 2/3 SMA

SUNFISH (part 2)

Children and young adults with Type 2/3 SMA, not previously treated, non-ambulatory, age 2-25 years.

Risdiplam (120)

Placebo (60)

Company

Upper age limit of 25 years to represent patients who would have risdiplam in practice while extending limit beyond childhood

Tech team

There are infants with type 1 SMA >7 months old but this group are not included in FIREFISH

ERG

- No UK sites. ERG's clinical expert suggest trial populations representative of patients with SMA in England. Eligibility criteria reasonable but SUNFISH excluded ambulant Type 3 patients, (accounts for small proportion of patients with SMA)
- Both studies excluded patients with previous treatment, this is inconsistent with company's proposed positioning

Note: Part 1 was exploratory dose-finding, Part 2 was used to examine the efficacy and safety of the selected dose of risdiplam in each study. Different patients were recruited to Parts 1 and 2 for each study

Summary of outcomes in clinical evidence

Outcome	Measure	Summary	FIREFISH	SUNFISH
Motor function	BSID-III	Motor milestones including static positioning, dynamic movement, quality of movement, balance & motor planning	✓	✗
	HINE-2	8 developmental motor milestones*	✓	✗
	CHOP-INTEND	16 item to assess both active and elicited reflexive movement	✓	✗
	MFM32	Assesses 3 domains**	✗	✓
	RULM	Upper limb function	✗	✓
	HFMSE	Functional abilities†	✗	✓
Survival	OS & PV	Proportion alive & alive without PV	✓	✗
Nutrition		Able to feed orally and swallow	✓	✗
Healthcare use		Hospitalisations per patient year	✓	✗
Patient/caregiver reported		ITQOL-SF47 in FIREFISH SMAIS in SUNFISH	✓	✓

Green = primary endpoint; Blue = fine motor skills *head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking; **D1 (standing and transfers), D2 (axial and proximal motor function), and D3 (distal motor function). † standing, transfers, ambulation, & proximal & axial function.

Summary of trial results – type 2/3 SMA

- Higher scores for all motor function measures indicate improvement
- SUNFISH measured least squares mean change from baseline and p-values were adjusted to account for multiple testing
- Patient expert highlight the importance of stable disease (i.e. no worsening)

Outcome	SUNFISH results (least squares mean change from baseline to month 12)			
	Risdiplam n=120 (SE)	Placebo n=60 (SE)	Difference, risdiplam minus placebo (95% CI)	p-value
Primary endpoint				
MFM-32 total Score	1.36 (0.38)	–0.19 (0.52)	1.55 (0.30 to 2.81)	0.02*, 0.02**
Secondary endpoints				
HFMSE total Score	0.95 (0.33)	0.37 (0.46)	0.58 (–0.53 to 1.69)	0.39*, 0.30**
RULM total Score	1.61 (0.31)	0.02 (0.43)	1.59 (0.55 to 2.62)	0.05*, 0.00**
MFM32 D3 score	[redacted]	[redacted]	[redacted]	[redacted]
Caregiver-reported SMAIS score	1.65 (0.50)	–0.91 (0.67)	2.55 (0.93 to 4.17)	0.39*, 0.00**
Patient-reported SMAIS total score	1.04 (0.65)	–0.40 (0.86)	1.45 (–0.68 to 3.57)	0.18
Data source: Table 12 in ERG report; * adjusted; **unadjusted				

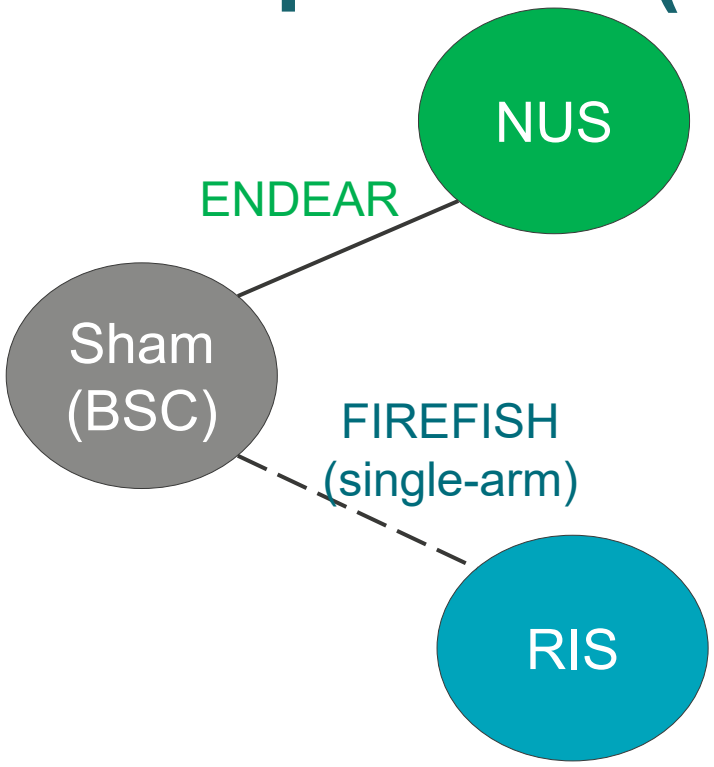
Summary of trial results – type 1 SMA

Outcomes were assessed against a pre-defined performance criterion, which was based on natural history data for Type 1 SMA.

Outcome at month 12	FIREFISH results	
	Risdiplam n=41 Number and proportion (90% CI) of patients	Performance criterion
Primary endpoint		
Sitting without support for at least 5 seconds (BSID-III)	12/41, 29.3% (17.8 to 43.1%)	5%
Secondary endpoints		
Able to support weight or stand with support[b] as assessed by the HINE-2	9/41, 22.0% (12.0 to 35.2%)	N/A
Able to bounce while assessing the walking item of the HINE-2	1/41, 2.4% (0.1 to 11.1%)	N/A
Alive without permanent ventilation	35/41, 85.4% (73.4 to 92.2%)	42%
Alive	38/41, 92.7% (82.2 to 97.1%)	60%

[b] Includes 7 patients (17.1%) who could support weight and 2 patients (4.9%) who could stand without support. Data source: Table 14 in ERG report

Type 1 SMA matched adjusted indirect comparison (MAIC)



Baseline characteristic	Pre-matching		Post matching
	Nusinersen & BSC (ENDEAR)	Risdiplam (pooled FIREFISH)	Risdiplam (FIREFISH matched to ENDEAR)
Sample size / ESS	121	58	[redacted]
Mean age at first dose	169 days	[redacted]	[redacted]
Female gender	55%	57%	[redacted]
Mean age at symptom onset	60 days	[redacted]	[redacted]
Mean disease duration at screening	94 days	[redacted]	[redacted]
Mean age at diagnosis	14.3 weeks	[redacted]	[redacted]
Mean score on CHOP-INTEND	27.24	[redacted]	[redacted]
Mean HINE-2 score	1.37	[redacted]	[redacted]
Patients with ventilatory support	22%	[redacted]	[redacted]

Abbreviations:
- BSC, best supportive care;
- NUS, nusinersen; RIS, risdiplam;
- ESS, effective sample size

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Type 1 SMA - MAIC results

It is not clear whether other variables that were not available in the ENDEAR and FIREFISH studies might also be relevant covariates

After TE, both the company and ERG use MAIC in their base case (see issue 2)

Outcome	Unadjusted	MAIC	Updated MAIC
Ventilation-free survival	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]
Sitting with and without support*	[redacted]	[redacted]	Not updated in clarification response
Standing with support and unaided	[redacted]	[redacted]	

Note: MAIC includes matching on age at 1st dose, symptom duration, baseline CHOP-INTEND score. Updated MAIC at clarification also matched for sex, age at symptom onset, HINE-2 score, ulnar nerve CMAP amplitude, proportion with feeding tube / unable to swallow and proportion on ventilation at baseline.

* ORs calculated using half-cell correction

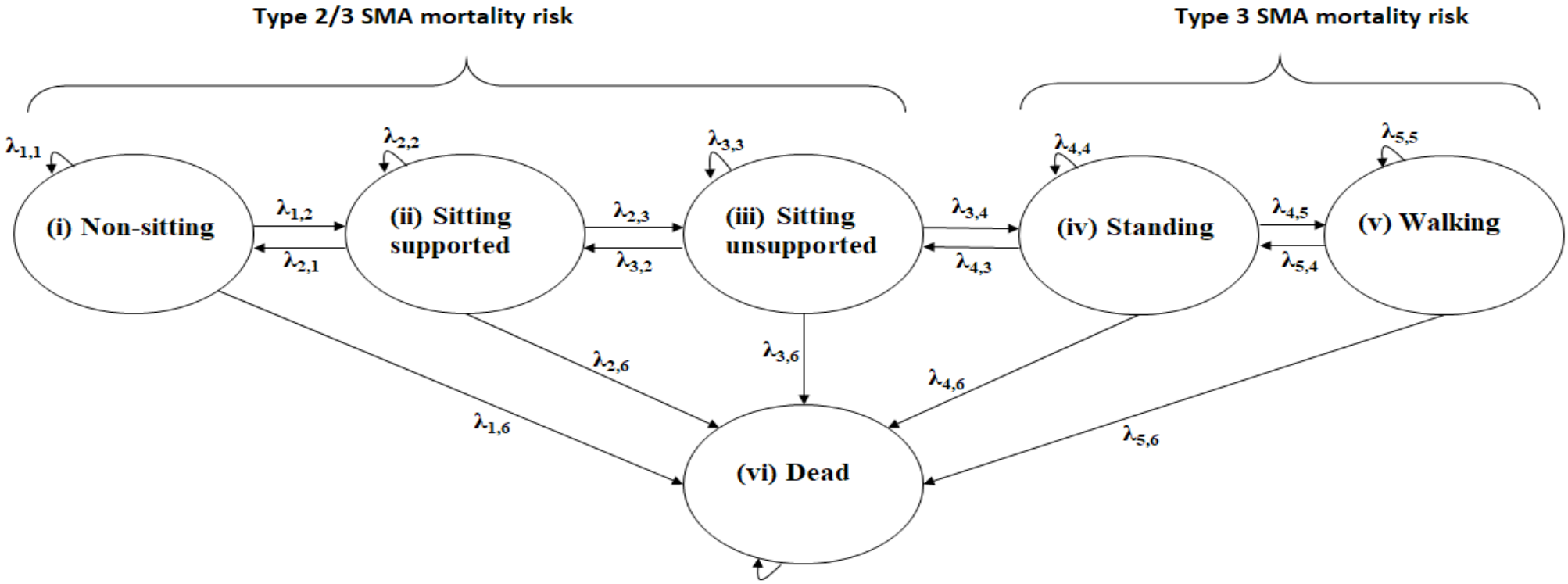
Model background for type 2/3 SMA

- State transition approach
- Efficacy informed by SUNFISH
- Health states defined according to MFM32 apart from walking (based on HFMSE)

Model health state	Instrument	Criteria for model health state
(1) Non-sitting	MFM32	Patients have a score of 0 in item 9 of the MFM32 (maintain seated position). Trunk support required, substantial support to be propped in a wheelchair.
(2) Sitting supported	MFM32	Patients have a score of 1 in item 9 of the MFM32 (maintain seated position). Upper limb support required.
(3) Sitting unsupported	MFM32	Patients have a score of 2 or 3 in item 9 of the MFM32 (maintain seated position). No upper limb support required.
(4) Standing	MFM32	Patients have a score of 1, 2 or 3 in item 25 of the MFM32 (maintain standing position).
(5) Walking	HFMSE	HFSME form, highest level of independent mobility. Supported = 'walks with crutches/ frame/ rollator/ KAFOs/AFOs' or unsupported = 'independent walking'.

Abbreviations: AFO, Ankle-foot orthosis; KAFO, Knee-ankle-foot-orthosis

Model structure for SMA type 2/3



- Patients enter the model according to the baseline distribution in SUNFISH (non-Asian subgroup). No patients enter the model as non-sitters
- During first 2-years, both risdiplam and BSC-treated patients can remain in their current state, improve or worsen by one milestone. But transitions to standing and walking are not permitted for BSC-treated patients.
- After 2 years, transitions to worse health states, for risdiplam-treated patients are reduced by [redacted] indefinitely. BSC-treated patients can only remain in their current state or transition to the next worst state during each cycle; improvements are not permitted.
- Mortality rate is conditional on health state

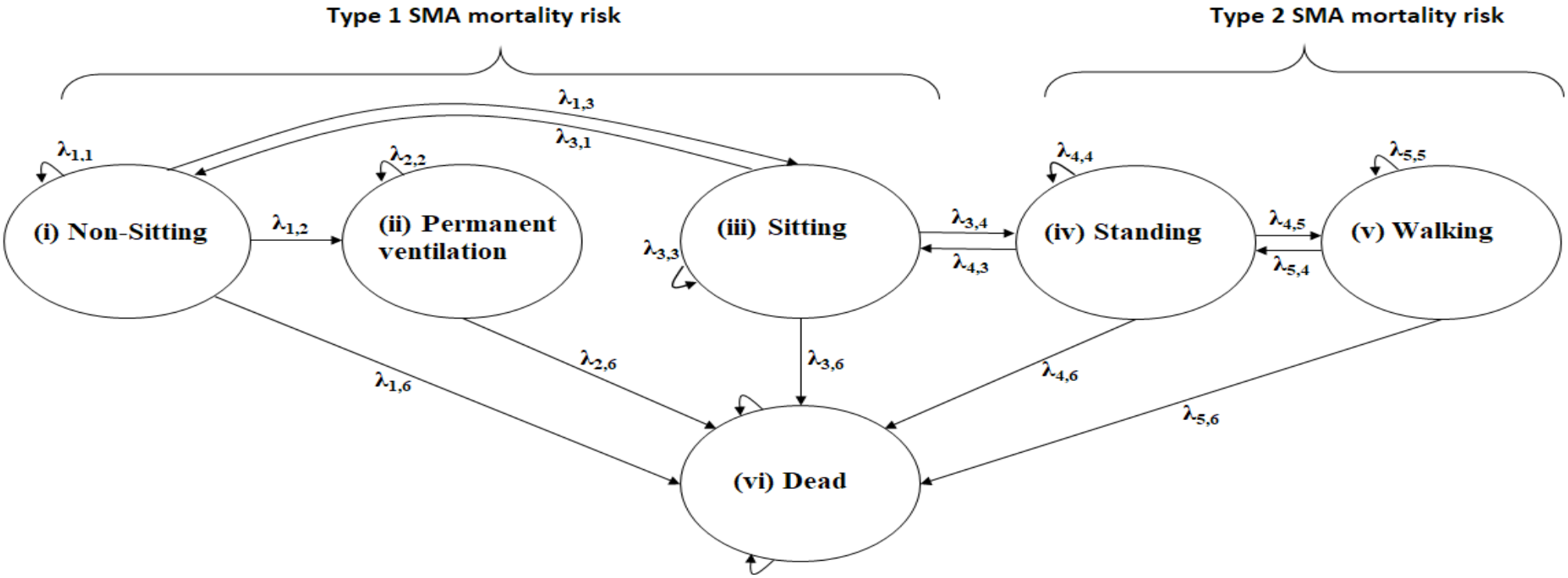
Model background for type 1 SMA

- State transition approach
- Efficacy informed by MAIC
- Health states defined according to HINE-2 scoring and permanent ventilation

Model health state	Criteria for model health state
(1) Non-sitting	Patients cannot sit, stand or walk.
(2) Permanent ventilation	More than 16 hours of non-invasive ventilation such as BiPAP per day or intubation for more than 21 consecutive days in the absence of, or following the resolution of, an acute reversible event of tracheostomy.
(3) Sitting	Patients have a score of 1, 2, 3 or 4 in sitting ability in HINE-2 motor function group. Supported corresponds to scores 1 (sits with support at hips) or 2 (props self up), whilst unsupported corresponds to scores 3 (stable sitting) or 4 (pivots and rotates).
(4) Standing	Patients have a score of 2 or 3 in standing ability in HINE-2 motor function group. Supported corresponds to score 2 (stands with support), whilst unsupported corresponds to score 3 (stands unaided).
(5) Walking	Patients have a score of 2 or 3 in walking ability in HINE-2 motor function group. Supported corresponds to score 2 (cruising), whilst unsupported corresponds to scores 3 (walking independently).

Abbreviations: BiPAP, Bilevel Positive Airway Pressure

Model structure for SMA type 1



- In line with FIREFISH, [redacted].
- During the first 2-year period, BSC and risdiplam-treated patients can remain in their current state, improve or worsen by 1 milestone. Non-sitters may proceed to permanent ventilation (PV); these patients are assumed to never return to the other motor milestone states. Transitions to walking are not permitted in any cycle for BSC-treated patients
- After 2 years, risdiplam-treated patients are assumed to never transition to worse health states (including PV) indefinitely, whilst all BSC-treated patients are assumed to remain stable or worsen (patients never improve).
- Mortality rate is conditional on health state (use OS data from MAIC for non-sitters)

Model alignment with TA588 – after TE

Model feature	TA588 (final model)	Risdiplam	ERG
Structure	Based on gross motor milestones (no PV state)	Similar approach but PV included	Broadly similar
Mortality risk	Conditional on patient's current motor milestone		Broadly similar but TA588 included tapering of treatment effect on OS in worse states
Long-term benefit	Nusinersen arm: all plateau & no additional motor milestone gains	Risdiplam: add treatment plateau	Broadly similar (after TE, see backup slide for model trace)
Stopping rules	Include based on loss of motor milestones	Include time-based rule	Different approach assumed (Issue 5)
Patient utilities	Non-preference based values		Broadly similar (after TE)
Caregiver utilities	Incremental QALY losses compared plus bereavement	Incremental QALY gains compared, no bereavement	Inconsistent (Issue 4)
Number of caregivers	3 (later-onset: 3 in worst state, 2 otherwise)	2.2	Inconsistent (Issue 4)
Health state costs	Based on Biogen RWE study		Generally consistent

Issues resolved after technical engagement

Issue	Summary	Stakeholder responses	Technical team consideration	Included in base case?
1	No evidence for pre-symptomatic, Type 0, 4, or previously treated SMA patients	Company reiterate no evidence but suggest earlier treatment is more beneficial	CHMP: SMA Type 1, 2 or 3 or with 1 to 4 SMN2 copies. Unknown clinical & cost effectiveness for previously treated and presymptomatic	Company **x** ERG **x**
2	No direct comparative evidence for type 1 SMA	Company use unanchored MAIC	Prefer unanchored MAIC to unadjusted analyses (slide 13)	Company ✓ ERG ✓
3,6,7	No evidence for long-term benefits	Company add treatment plateau	No long-term evidence but plateau is consistent with TA588	Company ✓ ERG ✓
8	Patient utility values not consistent with TA588	Company use non-preference-based utility in line with TA588	Reasonable to accept ERG preference and this is in line with TA588.	Company ✓ ERG ✓
9	Modelling should be aligned with TA588	Company align modelling as much as possible	There are some differences (see issues 4 & 5) but modelling is broadly in line with TA588	Company ✓ ERG ✓

Key Issues

Model driver | Unknown impact | Small impact

Issue	Company revised base case	Technical team	Question for committee
Caregiver utility (4)	No change but include scenario using ERG approach	There is substantial uncertainty and both the ERG's and company's approach are limited	How should caregiver utility be included in the model? How many caregivers should be included for patients who cannot sit?
Stopping rule (5)	Includes time-based rule	The new stopping rule is not evidence based and differs to TA588	Is the company's time-based stopping rule appropriate?
Fine motor skills (10)	Includes utility gain for fine motor skills	It is appropriate to capture fine motor skills in HRQoL, but the values are not evidence based	Should a utility gain for fine motor skills be modelled?
EOL (11)		Is EOL met for type 1 and type 2/3 SMA?	

Other considerations for recommendations:

- Company position risdiplam after nusinersen but there is no evidence after prior treatment. Also, there is no evidence for pre-symptomatic group, which is included in MA
- Trial evidence restricts age of patients (type 1: 1-7 months but, some are diagnosed late and some of those 7-12 months could have similar benefit. Type 2: 2-25 years) and FIREFISH also excluded those on chronic ventilation

Issue 4. Caregiver QALY gains - summary

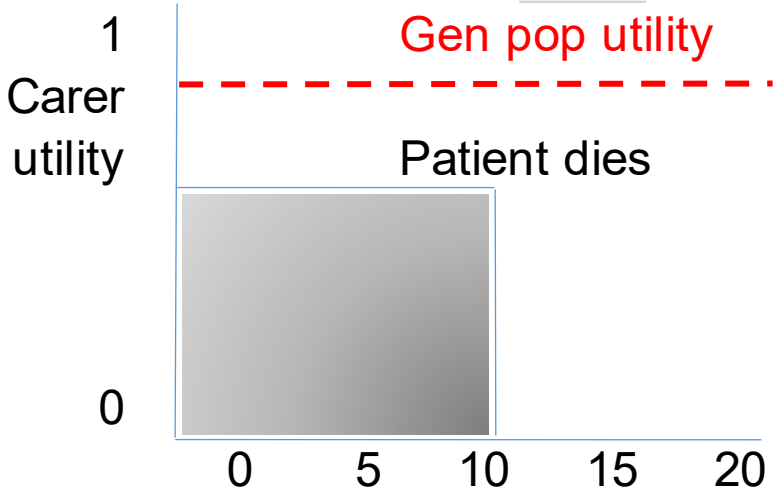
Background	In TA588 the committee concluded that carer utilities are important and should be included in decision-making, but noted that quantifying these impacts is very difficult

	Approach	Company comments	ERG comments
Company base case	Additive approach: • caregiver utility value linked to patients' disease status – increases linearly with each milestone up to standing • utility values only counted while SMA patient is alive and assume 2.2 carers per patient.	No change in revised base case. Extension to life is not penalised because additional life years are gained by the carer whilst the patient is still alive.	Approach assumes that the carer utility is zero (equivalent to being dead) when the patient dies → artificially inflates net QALY gains
ERG preferred (Company scenario)	Caregiver disutility approach (TA588)- carer disutility linked to patient health status whilst alive: • estimate caregiver QALY losses (decrement from general pop utility) • apply while the patient with SMA is alive ERG prefer 3 carers for type 2/3 patients who cannot sit (company scenario: 2.2)	Risdiplam is penalised if it is considered life-extending because it may result in greater carer QALY losses compared to current treatment. Also assumes there is no negative impact on carer HRQoL when patient dies	Consistent with TA588 and assumes caregivers will continue to accrue health gains after the SMA patient has died. New scenario to include impact of bereavement

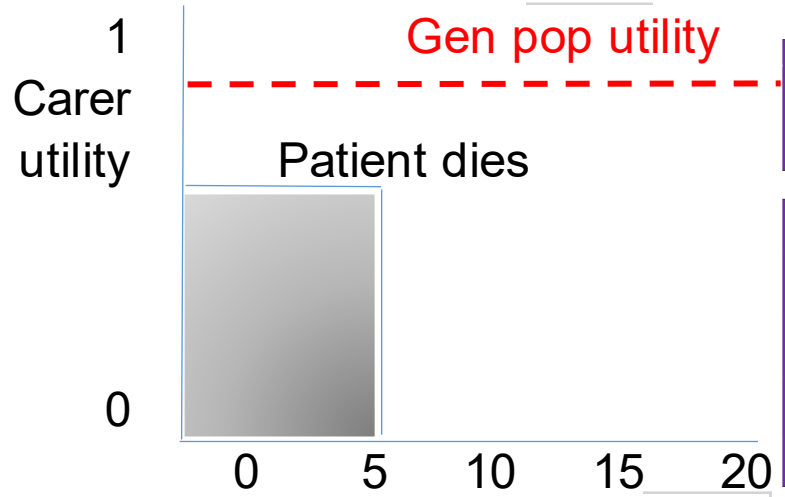
Issue 4. Caregiver QALY gains – conceptual illustration

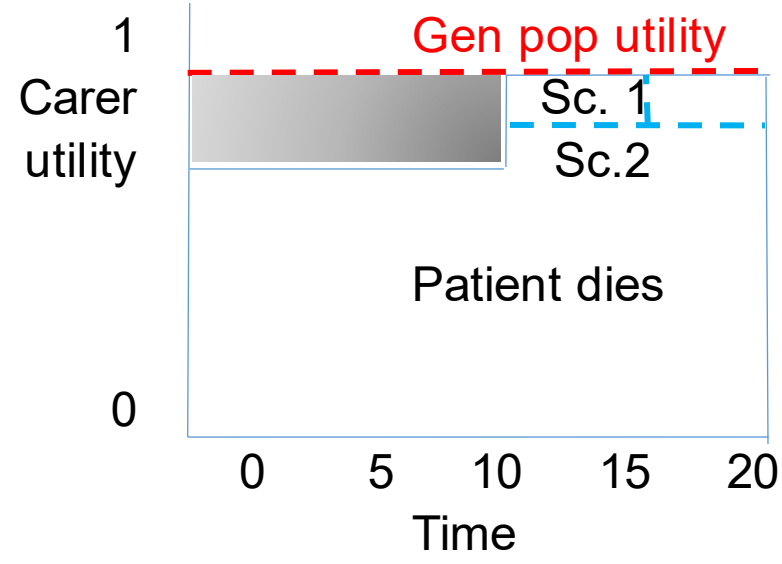
- Patient A is treated with RIS & survives 10 yrs, patient B treated with BSC & survives 5 yrs
- Each patient has 1 carer and general population utility is 0.80. Both patients spent entire survival time in a health state associated with caregiver disutility of 0.20 (caregiver utility 0.60)

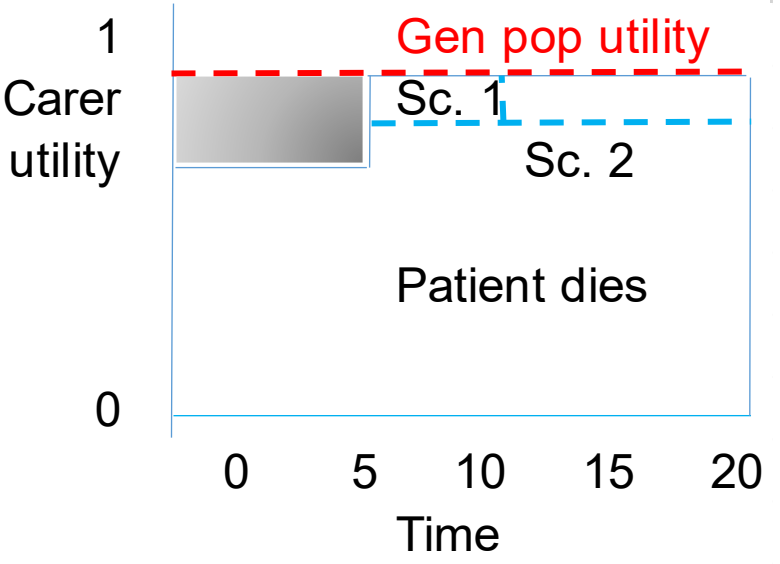
Patient A (RIS)



Patient B (BSC)







Company's additive approach

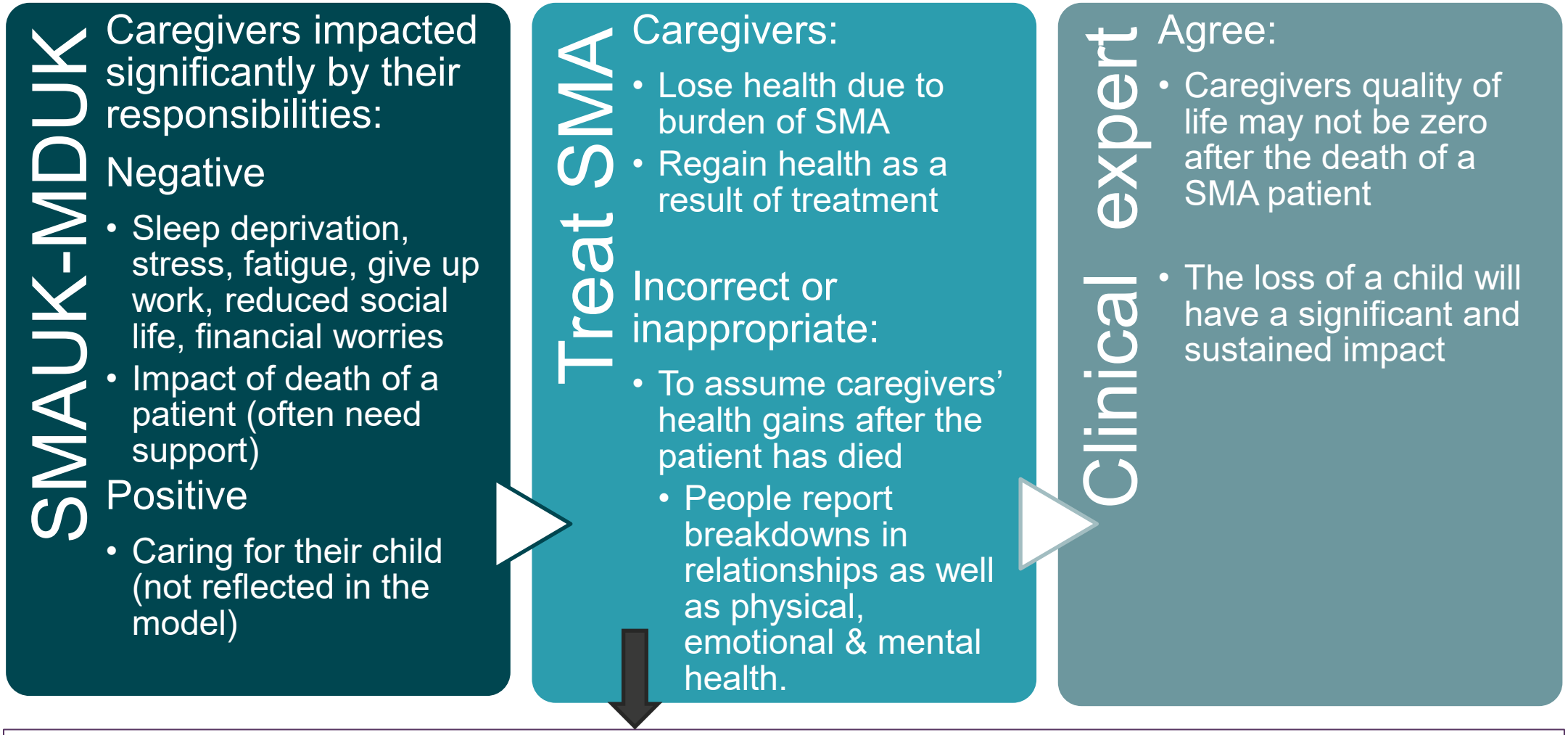
Carer QALY
Patient A: 0.60 x 10 = 6;
Patient B: 0.60 x 5 = 3;
incremental QALY gained = 6-3 = 3

ERG's disutility approach

Carer QALY
Patient A: -0.20 x 10 = -2;
Patient B: -0.20 x 5 = -1;
incremental QALY gained = -1

Sc=scenarios → additional bereavement QALY loss

Issue 4. Caregiver QALY gains – TE responses



"A child who has lost ability to self transfer becomes a burden on the caregivers back as they must now do the lifting. Equally, as the ability is reinstated the caregivers back gets in a better health."

Issue 4. Caregiver QALY gains – after TE

Company

- Approach taken has larger impact on cost-effectiveness for type 1 SMA
  - Patients already have low utility and adding additional caregiver decrement results in negative net utility.
  - Therefore after death of the patient, the caregiver utility decrement is removed and the utility for that patient improves from a negative value to 0.
  - Given that survival is lower in the BSC arm, this decrement is removed more frequently and quickly, resulting in a lower incremental QALY difference between risdiplam and BSC overall.
- **Even with 100% discount the ICER is still high → ERG approach lacks face validity**

ERG

- Neither the company nor the ERG approach is ideal but excluding subsequent health gains for caregivers (company approach) after an SMA patient has died implies a normative position that society places value on the HRQoL of caregivers of surviving SMA patients, but not bereaved caregivers – this may not be reasonable
- **High ICERs with 100% discount is driven by several factors** (extension of patient survival, imperfect utility in surviving SMA patients, and high disease management costs). Also applies when excluding caregiver impacts.

Issue 4. ERG comments

ERG	Not aware of precedent for company's preferred additive approach and this would deviate considerably from previous appraisals:

TA217 Alzheimer's disease

- Only example found of additive approach.
- Proposed but not used for decision making

TA588 Nusinersen for SMA

- Cttee included caregiver disutility (bereavement QALY loss) in decision-making but considered it was very difficult to estimate size of disutility.

ongoing ID1473 Onasemnogene for type 1 SMA

- Did not include caregiver utility in either company or ERG base case.
- ERG scenario: including caregiver disutility ↑ ICER significantly because caregiver burden is ↓ in the short run but longer survival increases amount of caregiving needed over a lifetime.
- Cttee recognised complex considerations for caregiver quality of life & considered qualitatively rather than quantitatively

Issue 4. ERG's new scenario analysis

ERG's new scenarios

New scenario analyses that include impact of bereavement on caregiver (both assume SMA patient has 2.2 caregivers):

1. Fixed 'lump sum' QALY loss applied to new deaths in each model cycle. Assumes: (i) a disutility of -0.04 for bereaved caregivers based on Song et al (2010) (ii) 20-year duration of disutility → arbitrary.
2. Lifetime caregiver disutility (-0.04) applied when SMA patients have died. Applied for max time horizon → arbitrary.

- Scenarios have larger impact for type 1

Limitations of ERG's new scenarios

- Scenario analyses are illustrative and use arbitrary assumptions.
- Also limited because company models do not include caregiver ageing or survival.
- Valuing caregiver bereavement is not in NICE methods guide or included in majority of NICE appraisals for other conditions

How should carer utility values be included in the model?
How many caregivers should be included for patients who cannot sit?

Issue 5. Stopping rule

Background

The MAA for TA588 (nusinersen) includes stopping criteria based on repeated loss of motor function, ventilation requirement, ambulation and scoliosis

ERG

- ERG's clinical advisor: progression to permanent ventilation, AEs & repeated loss of motor function may be useful stopping criteria.
- Company's stopping rule may be reasonable but not based on empirical evidence.

TE responses

Association of British Neurologists, SMA reach and SMAUK-MDUK agree stopping criteria should be used. Treatment should be continued if disease is stable

Company

- **Revised base case includes stopping rule** where patients can be treated for a max of 50 years for type 1 or 30 years for type 2/3
- Input from 2 NHS clinicians suggest milestone based stopping rules and those used in TA588 are limited and put patients and their family under immense pressure to achieve outcomes to continue treatment
- Company suggest time-based stopping rule may be more appropriate and easy to implement in NHS
- No data but expect over a long treatment duration of 30 or 50 years patients are likely to have built up both respiratory and skeletal musculature through years of restored SMN protein production

Is the company's time-based stopping rule appropriate?

Issue 10. Fine motor skills

Background

ERG's scenario with utility gains of 0.05 and 0.10 for non-sitting and sitting states were taken from Thokala (2020) to reflect potential benefits for patients gaining fine motor skills.

ERG

Fine motor skills are relevant but there is uncertainty around (1) how many patients treated with risdiplam would accrue gains, (2) duration of gains, (3) impact on patient and caregiver HRQoL. Values from Thokala (2020) are based on assumptions not evidence. Long-term evidence from FIREFISH & SUNFISH may help to resolve this.

TE responses

Association of British Neurologists: further data on the effect of risdiplam on fine motor skills will help understanding of its benefits.

Company

- **Revised base case includes ERG's suggested additional utility gains for fine motor skills**
  - 0.05 and 0.10 for risdiplam-treated patients in the non-sitting and sitting states, respectively
- Company note these values are assumptions and not evidence-based but SUNFISH showed clinically meaningful improvement in upper limb function (RULM total score) after 12 months and SMAIS which focuses on upper limb activities such as writing, dressing and washing
- Company suggest values used are conservative and do not fully capture impact that upper limb function will bring to patients and caregivers

Should a utility gain for fine motor skills be included in model?

Company's new scenario analyses – after TE

Background

- NICE reference case specifies 3.5% discount rate should be used but a 1.5% may be used instead when:
  - treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives;
  - if it is highly likely that there will be long-term benefits (normally sustained for at least 30 years); and
  - if the treatment does not commit the NHS to substantial irrecoverable costs
- 3.5% discount rate used in TA588

Company

Include 2 new scenario analyses:

1. lower costs for risdiplam after [redacted] when generics may be available
2. 1.5% discount rate instead of 3.5%

Technical team

Company's new scenario analyses are not appropriate because:

1. **including a lower cost of risdiplam in [redacted] when it loses exclusivity is based on an estimate** (no agreements in place around future pricing) → committee can't consider in decision-making
2. **company do not provide rationale to support using 1.5% discount rate in relation to the current methods guide** (only reference methods update but this is still in progress)

- Results of these analyses are not shown

Additional areas of uncertainty

Additional areas of uncertainty that committee need to be aware of but where there isn't a decision to be made

Issue	Why issue is important	Impact on ICER
Limited evidence base	• For type 1 SMA there is no direct evidence comparing risdiplam vs. BSC • Current evidence is limited but, ongoing trials RAINBOWFISH and JEWELFISH include pre-symptomatic and previously treated patients respectively (currently no evidence for these subgroups) • Long term effectiveness is uncertain because SUNFISH and FIREFISH studies are ongoing and we currently only have access to 12 month follow up data. It's also noted that 24 month data from SUNFISH will not be comparative because the placebo controlled period ended after 12 months	Unknown
Other outcomes	Models do not adequately reflect benefits of risdiplam that have a significant effect on patient and caregiver quality of life, such as improved bulbar function and feeding/swallowing, reductions in hospitalisations and improved upper limb function	Unknown (scenarios with fine motor skill utility gain)

End of life considerations

Company suggest EOL applies to patients with type 1 SMA and although criteria unlikely to be met for type 2/3 decision modifiers should be taken into account “to recognise that SMA is a severe and rare condition, with a broad impact on patients, many of whom are children and people with disabilities, and their carers”

EOL criteria	Type 1 SMA	
	Company	ERG
Life expectancy < 24 months	• Criterion was met in TA588; natural history studies for type 1 show mean or median age of death or PV is < 24 months. • Natural history studies in infantile-onset SMA show that 50% of infants, who only have two copies of SMN2 gene will die or require permanent non-invasive ventilation support by 10.5 months	• Without respiratory support, mean survival for BSC-treated patients reported in natural history studies is less than 2 years • Company’s revised base case (using MAIC) shows mean survival duration of 4.88 years in BSC arm
Life extension ≥ 3 months	• In FIREFISH 92.7% of patients (90% CI: 82.2%, 97.1%) were still alive at 12 months. • Type 1 model predicts mean survival gain 7.29 years	Company’s LY gains are optimistic but likely that risdiplam will extend mean OS by more than 3 months (model predictions highly uncertain)

Other considerations

Equality issues

- Patient/professional submissions:
  - Age and mobility; arbitrary disease categorisations (tend to exclude adults and type 3 patients)
  - Under-recognised barriers of socioeconomic and minoritised groups where available evidence does not capture the “diverse ethnicity among the 40 young people with SMA under my care”
- Company: topic has several features commonly seen in the HST programme, so, decision modifiers & flexibility in NICE’s decision making should be taken into account

Innovation

- Risdiplam is the first oral disease-modifying treatment available for SMA and can be administered at home
- Risdiplam rapidly increases functional SMN protein levels and is the only disease modifying therapy that can be initiated within hours of diagnosis

Other

- Consider whether any adjustments to committee’s normal considerations are needed to take into account the rarity and severity of the disease.

Summary of base case assumptions

Model input	Company	ERG
Caregiver utility	• Use additive approach (utility values only counted while SMA patient is alive) • Assume 2.2 caregivers	• Prefer to value caregiver disutility while patient is alive, possibly include impact of bereavement (ERG's new scenario). • Assume 3 caregivers for type 2/3 if patient is unable to sit (Scenario type 2/3: 2.2 caregivers)
Stopping rule	Include max of 50 years treatment for type 1 or 30 years for type 2/3. Gradual loss of benefit but no impact on OS.	Excluded from preferred base case as not based on empirical evidence. Scenarios included.
HRQoL gains for fine motor skills	Include additional utility gains in non-sitting and sitting states	Excluded from preferred base case due to uncertainty but scenario included

Company cost effectiveness results – after TE

Type 2/3 SMA – includes updated PAS

Deterministic results from ERG critique of company TE (table 2) and includes undiscounted LYGs

Option	LYGs	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
Company's updated base case						
Risdiplam	48.57	11.57	39.49	[redacted]	-	-
BSC	43.77	5.98	33.25	[redacted]	-	-
Incremental	4.79	5.59	6.23	[redacted]	[redacted]	[redacted]
Company's updated base case + ERG-preferred caregiver disutility approach						
Risdiplam	48.57	11.57	-4.22	[redacted]	-	-
BSC	43.77	5.98	-7.67	[redacted]	-	-
Incremental	4.79	5.59	3.46	[redacted]	[redacted]	[redacted]

Company cost effectiveness results – after TE

Type 1 SMA – includes updated PAS

Deterministic results from ERG critique of company TE (table 3) and includes undiscounted LYGs

Option	LYGs	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
Company's updated base case						
Risdiplam	21.90	5.11	18.43	[redacted]	-	-
BSC	4.88	0.02	3.56	[redacted]	-	-
Incremental	17.03	5.09	14.88	[redacted]	[redacted]	[redacted]
Company's updated base case + ERG-preferred caregiver disutility approach						
Risdiplam	21.90	5.11	-6.76	[redacted]	-	-
BSC	4.88	0.02	-3.14	[redacted]	-	-
Incremental	17.03	5.09	-3.61	[redacted]	[redacted]	[redacted]

ERG cost effectiveness results – type 2/3

ERG preferred: caregiver disutility approach, 3 caregivers if unable to sit and excludes stopping rule and utility gain from fine motor skills

Technology	Incremental				ICER (patient)	ICER (patient & carer)
	Costs (£)	LYGs	Patient QALYs	Carer QALY		
ERG-preferred						
BSC	-	-	-		-	
Risdiplam	[redacted]	6.53	5.44	6.45	[redacted]	[redacted]
Scenario analyses						
1. Add fine motor skills utility gain	[redacted]	6.53	6.40	6.45	[redacted]	[redacted]
2. Use 2.2 caregivers*	[redacted]	6.53	5.44	4.19	[redacted]	[redacted]
3. Add company's stopping rule	[redacted]	4.83	4.53	5.39	[redacted]	[redacted]
4. Cumulative impact of 1 to 3	[redacted]	4.83	5.62	3.48	[redacted]	[redacted]
5. Add bereavement 'lump sum' QALY loss	[redacted]	6.53	5.44	6.55	[redacted]	[redacted]
6. Add indefinite bereavement related disutility	[redacted]	6.53	5.44	6.59	[redacted]	[redacted]
Note: all analyses are deterministic and include updated PAS. *type 2/3 only						

NICE

ERG cost effectiveness results – type 1

ERG preferred : caregiver disutility approach, 2.2 caregivers and excludes stopping rule and utility gain from fine motor skills

Technology	Incremental				ICER (patient)	ICER (patient & carer)
	Costs (£)	LYGs	Patient QALYs	Carer QALYs		
ERG-preferred						
BSC	-	-	-		-	
Risdiplam	[redacted]	16.80	4.75	-3.54	[redacted]	[redacted]
Scenario analyses						
1. Add fine motor skills utility gain	[redacted]	16.80	5.17	-3.54	[redacted]	[redacted]
2. Add company's stopping rule	[redacted]	17.11	4.70	-3.61	[redacted]	[redacted]
3. Cumulative impact of 1 to 2	[redacted]	17.11	5.13	-3.61	[redacted]	[redacted]
4. Add bereavement 'lump sum' QALY loss	[redacted]	16.80	4.75	-2.98	[redacted]	[redacted]
5. Add indefinite bereavement related disutility	[redacted]	16.80	4.75	-2.73	[redacted]	[redacted]
Note: all analyses are deterministic and include updated PAS						

Key Issues

Model driver | Unknown impact | Small impact

Issue	Company revised base case	Tech team	Question for committee
Caregiver utility (4)	No change but include scenario using ERG approach	There is substantial uncertainty and both the ERG's and company's approach are limited	How should caregiver utility be included in the model? How many caregivers should be included for patients who cannot sit?
Stopping rule (5)	Includes time-based rule	The new stopping rule is not evidence based and differs to TA588	Is the company's time-based stopping rule appropriate?
Fine motor skills (10)	Includes utility gain for fine motor skills	It is appropriate to capture fine motor skills in HRQoL, but the values are not evidence based	Should a utility gain for fine motor skills be included?
EOL (11)	Is EOL met for type 1 and type 2/3 SMA?		

Other considerations for recommendations:

- Company position risdiplam after nusinersen but there is no evidence after prior treatment. Also, there is no evidence for pre-symptomatic group
- Trial evidence restricts age of patients (type 1: 1-7 months but, some are diagnosed late and some of those 7-12 months could have similar benefit. Type 2: 2-25 years) and FIREFISH also excluded those on chronic ventilation

Back up slides

Treatment plateau – model trace Type 2/3

Treatment plateau – model trace Type 1