NICE National Institute for Health and Care Excellence

Slides for the public – redacted

Nusinersen for treating spinal muscular atrophy

Chair's presentation

2nd appraisal committee meeting
Committee C
Lead team: Kamal Balakrishnan, Andrea Manca, David Chandler
ERG: ScHARR
NICE technical team: Lulieth Torres, Thomas Strong
Company: Biogen
23 October 2018

Appraisal committee 2

Following consultation, the committee have received for consideration:

- Comments from consultees, clinicians, patients and carers
- The company has submitted:
  - Consultation comments on committee decision
  - Alternative model parameters to address concerns raised in the Appraisal Consultation Document
  - New confidential commercial proposal
  - Updated model structure, required to model the new commercial proposal
  - Proposal for a Managed Access Agreement

- No new clinical evidence incorporated into the model
- Note – due to the extensive modelling changes, ERG critique has focussed on assessing the new structural and parameter assumptions of updated model

[redacted]

Spinal muscular atrophy

Disease background

- SMA is a genetic, progressive neuromuscular disease most commonly caused by mutations in the *SMN1* on chromosome 5q
  - *SMN1* gene encodes the “survival motor neurone” (SMN) protein
  - The lack of SMN protein causes the motor neurones to malfunction, deteriorate and eventually die
- Long term degenerative condition causing muscle weakness, and results in gradually worsening physical disabilities and mobility loss.
- Estimated that ~100 people are born with SMA per year, and 1,200–2,500 children and adults currently living with SMA, in the UK
- SMN2 can compensate for the SMN1 deletion to some degree, the number of SMN2 gene copies is inversely related to the severity of SMA and can be used to predict the course of the disease

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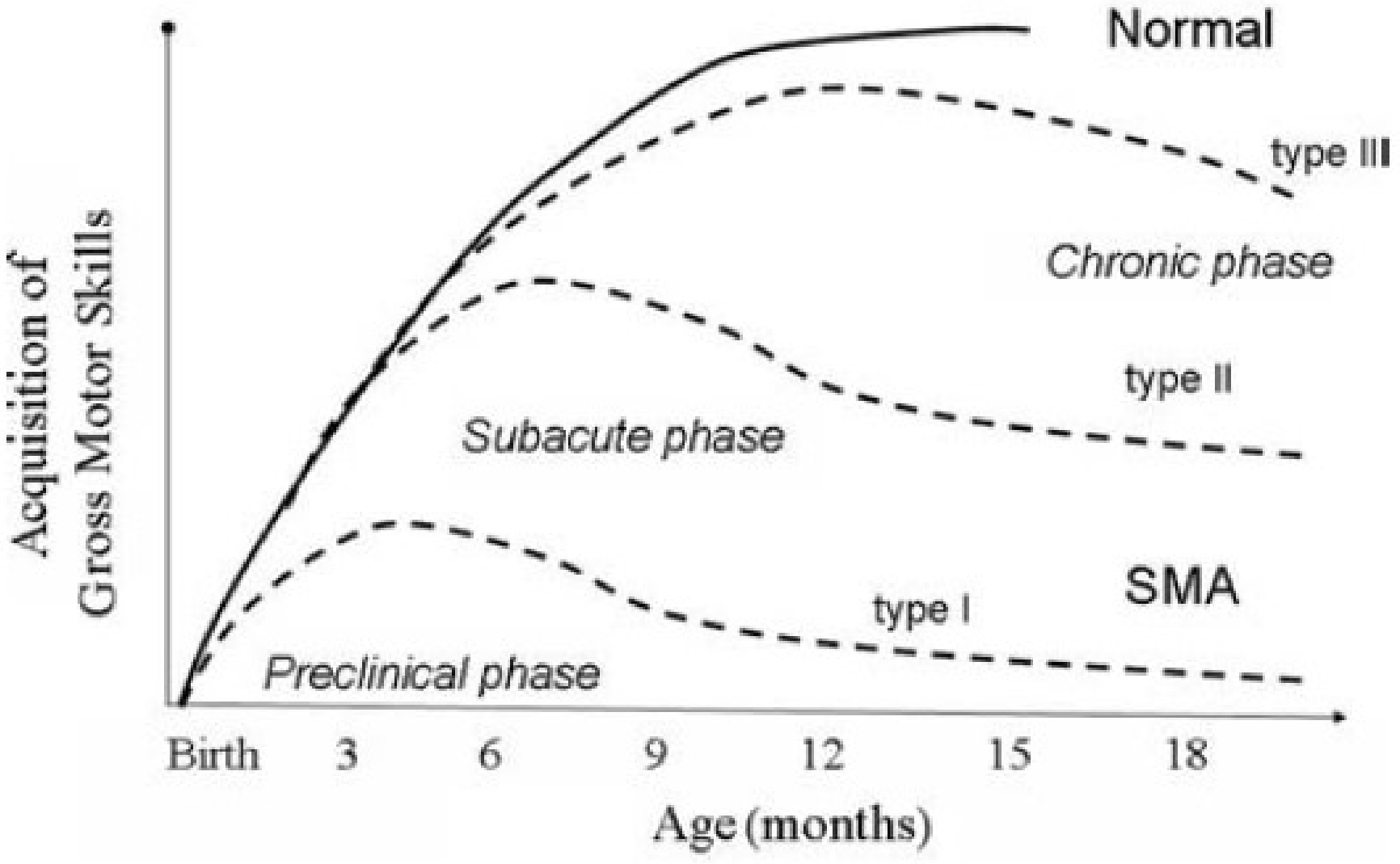
Symptoms and complications



Broad relationship between age and gross motor skills acquisition, depending on the different phenotype of SMA

Classification and subtypes of SMA

	Age of onset	Max. motor milestone	Motor ability and additional features	Survival
Type 0	Before birth	None	Severe hypotonia; unable to sit and roll	Respiratory insufficiency at birth: death within weeks
Type 1	2 weeks (Ia) 3 months (Ib) 6 months (Ic)	None	Severe hypotonia; unable to sit and roll	Death/ventilation by 2 years
Type 2	6–18 months	Sitting	Proximal weakness: unable to walk independently	Survival into adulthood (typically >25 years)
Type 3	<3 years (IIIa) >3 years (IIIb) >12 years (IIIc)	Walking	May lose ability to walk	Normal life span
Type 4	>30 years or 10–30 years	Normal	Mild motor impairment	Normal life span

- Type 1 SMA defined as **early onset** in the model
- Type 2 and 3 SMA defined as **later onset** in the model

Nusinersen (Spinraza, Biogen)

Marketing authorisation	"Nusinersen is indicated for the treatment of 5q SMA"
Mechanism of action	An antisense oligonucleotide, which stimulates the survival motor neurone (SMN)-2 gene to increase functional SMN protein levels.
Administration & dose	Intrathecal injection by lumbar puncture, 12 mg per administration 4 loading doses on days 0, 14, 28 and 63; maintenance dose once every 4 months.
List price	£75,000 per 12-mg vial ICERs include the proposed commercial arrangement. At list price the total annual treatment cost is **£450,000** for the first year and **£225,000** for subsequent years per patient.
Availability	Under the Expanded Access Programme (EAP), eligible children with type 1 SMA can receive nusinersen. The EAP will close to new patients on the 1st November 2018.

Source: Company submission. **Abbreviations:** SMA, spinal muscular atrophy; SMN, survival of motor neurone.

ACD: preliminary recommendation

Nusinersen is not recommended, within its marketing authorisation, for treating spinal muscular atrophy types 0 to 4.

- *Why the committee made the recommendation?*
  - Long-term benefits are highly uncertain
  - At list price the most plausible ICER's are likely to be between £400,000 and £600,000 per QALY but may be higher.
  - The committee also considered a range of other factors, including:
    - Rarity and severity of spinal muscular atrophy
    - Nature of population
    - Whether the cost effectiveness of nusinersen should be considered according to that for end-of-life treatments
    - Proposed commercial arrangement
  - Even taking these factors into account the cost of nusinersen is too high to be considered cost-effective

[redacted]

Recap of ACD committee's considerations

Clinical evidence (I)

Theme	Committee's conclusion
Nature of the condition	• The most severe types affect babies and young children.
	• SMA affects quality of life for patients, carers and families
	• SMA classifications are blurred and can be subjective
	• Currently there are no effective treatment options

Clinical evidence	• Evidence presented by the company was for SMA types 1 to 3, whilst marketing authorisation is for all types
	• Main clinical evidence from 2 RCTs:
	  • ENDEAR – type 1 SMA
	  • CHERISH – type 2 SMA and more severe type 3 SMA
	• 3 ongoing studies
	  • NURTURE – single-arm pre-symptomatic infants
	  • SHINE – extension of ENDEAR and CHERISH
	  • EMBRACE – for people not eligible for the RCTs

[redacted]

Recap of ACD committee's considerations

Clinical evidence (II)

Theme	Committee's conclusion
Randomised controlled trials	• Short follow-ups for both ENDEAR (13 months) and CHERISH (15 months)
	• Survival benefit of nusinersen is shown for early-onset SMA, however, other health benefits (respiratory function, time on ventilator and hospitalisations) are uncertain.
	• Nusinersen improves motor function for later-onset SMA • Survival benefit is unclear in the later-onset SMA
	• Nusinersen would likely provide long-term benefits, however the size and magnitude of these benefits is unknown.
	• Overall, evidence from the trials is uncertain but relevant for decision-making. Long-term benefits are associated with substantial uncertainty
Other trial evidence	• Ongoing-trials / real world evidence submitted as supportive evidence ▪ Not incorporated into company's economic models

Recap of ACD committee's considerations

Economic model

Theme	Committee's conclusion

Model structure	• 2 models received:
	  • Early-onset model: type 1 SMA
	  • Late-onset model: type 2 and 3 SMA
	• Based only on motor milestones (participating in activities, respiratory function, pain and physical impairment not included)
	• Consistent with the main outcomes of the clinical trials.
	• Relevant for decision-making.

Long-term benefit	• Nusinersen likely to improve long-term survival but adjustments assumed are implausibly large • Doesn't reflect clinical practice as nusinersen arm could not get worse and best supportive care arm could not get better. • The ERG considered its own preferred assumptions optimistic, as it was unable to make all the changes it wanted • Committee considered exploratory scenarios where 5% to 10% of people having nusinersen lose a milestone each cycle relevant
Utilities	• Utilities uncertain and quantifying carer-related disutilities extremely difficult. • Both company's and ERG's utilities had serious limitations

Recap of ACD committee's considerations

Other decision-making factors (I)

Theme	Committee's conclusion
Manage access arrangements	• Company's proposed MAA is vague and insufficient to be considered as an option for nusinersen. • A MAA could reduce risks to the NHS, once nusinersen has the potential to be cost-effective. • A MAA would require NHS England, patients, carers and clinicians to sign up to it.
Innovation	• Nusinersen is an innovative treatment and the first disease-modifying therapy for SMA • However, not presented with any data to show distinct and substantial benefits not captured in the analyses
Population includes children	• Committee acknowledged and considered the nature of the eligible population as part of its decision-making • No further considerations or adjustments were needed

[redacted]

Recap of ACD committee's considerations

Other decision-making factors (II)

Theme	Committee's conclusion
Uncaptured health-benefits	• There are important uncaptured health benefits, but it was unclear how this affects the cost-effectiveness estimates.
Rarity and severity of disease	• Nusinersen has a number of features that are commonly seen in the highly specialised technologies (HST) programme • Not an HST as the population is too large and SMA is not commissioned through a highly specialised service • Committee mindful of the need to consider if any adjustments must be made to account for rarity and severity of SMA
End of life criteria	• early-onset SMA could meet the end-of-life criteria, but later-onset SMA did not • Committee concluded it may be unreasonable to apply different levels at which nusinersen would be considered cost effective depending on the age of onset of SMA

Should committee's conclusion on end-of-life remain unchanged?

Recap of ACD committee's considerations

Preferred ICERs (list price)

Theme	Committee's conclusion
Company basecase	• The list price ICERs without carer disutility were **£407,605** and **£1,252,991** per QALY gained for early- and late-onset respectively • The list price ICER with carer disutility's was lower at **£402,361** and **£898,164** per QALY gained for early- and late-onset respectively
ERG preferred analysis	• Amended starting health state distributions, end-of-life costs and patient and carer utilities • Emphasised it considered transition probabilities and long-term survival optimistic, but could not address these in its analyses • The list price ICERs without carer disutility were **£421,303** and **£408,769** per QALY gained for early- and late-onset respectively • The list price ICER with carer disutility's was higher at **£631,583** and **£632,850** per QALY gained for early- and late-onset respectively
Committee preferred ICER	• Committee did not choose a preferred set of assumptions, due to the substantial uncertainty in the modelling • Exploratory scenarios where 5% to 10% of people having nusinersen lose a milestone each cycle relevant. This increases the ICER by up to £200,000 per QALY • Plausible ICER is very uncertain. At list price it may be in the range of £400,000 to £600,000 per QALY gained but may be higher.

ACD consultation responses: overview

- **Comments** received during consultation from:
  - Biogen
  - Clinical experts and patient groups:
    - BPNA, MD UK, SMA Reach, SMA support, SMA trust and TreatSMA.
  - Web comments:
    - 13x clinical; 25 x patient and carers
  - No comment response from Department of Health.

  - Total number of consultation responses 46.

[redacted]

ACD consultation comments

Professional groups and clinicians (1)

Themes	Comment
SMA	• Very high unmet need • lack of consensus whether the boundaries between SMA types is blurred • SMN2 copy number can be predictive, but SMA type is better predictor
Clinical effectiveness	• Trials show a clear and very positive result • There is a greater benefit if nusinersen is started sooner • No mechanism to suggest nusinersen will become less effective in the long-term • Treated patients in each of the published studies continue to show improvement • Early Access Program and real world evidence shows sustained long-term improvement • In clinical practice – all patients on nusinersen have improved or stabilised in long-term • New developments mean that people who have scoliosis can continue treatment • The main outcomes of the trials may not adequately reflect the effectiveness of treatment. Very small improvements in motor milestones can have profound impact. • Drug should be made available based on clinical results, rather than on purely cost-effectiveness grounds • Wider, real world studies suggest lower uncertainty of long-term effectiveness. These should be considered further by committee • Further real world testing needed to fully understand long-term benefits

ACD consultation comments

Professional groups and clinicians (2)

Themes	Comment
NICE Process	• NICE process has been extremely lengthy. Decision needs to be made now • Consider the STA process insufficient in assessing this drug • Use of the QALY is inappropriate in assessing a rare disease • Discriminatory: Affluent people can move to Scotland • Strongly support development of a managed access agreement
Modelling and cost-effectiveness	• Recognise the very high cost of nusinersen • Full cost and impact of the worst health states substantially underestimated • Real world evidence should be incorporated into decision-making • Lack of consensus whether the company's assumptions are optimistic or pessimistic. Consensus that the ERG's assumptions are pessimistic • Long-term uncertainty is overestimated by committee, and lack of long-term data is not a barrier for other treatments

ACD consultation comments

Patient groups, patients and carers (1)

Themes	Comment
SMA	• Devastating diagnosis that destroys quality of life of the entire family • All SMA types need access to nusinersen • Young people with SMA require round-the-clock support from their families
Clinical effectiveness	• Benefits/outcomes measured in trials are a gross underestimate of life-changing nature of treatment • Even small changes in motor function can lead to life-changing improvements, e.g. being able to use a wheelchair joystick • Earlier treatment would lead to better outcomes • Real world evidence of effectiveness not fully appreciated by committee

[redacted]

ACD consultation comments

Patient groups, patients and carers (2)

Themes	Comment
NICE Process	• NICE process has been extremely lengthy. Decision needs to be made now • Should include all costs incurred, not just direct health costs • Negative decision would be immoral • Discriminatory: people with SMA have a right to life • Other countries with less money have already approved nusinersen
Modelling and cost-effectiveness	• Recognise very high cost of nusinersen • Substantial underestimate of direct healthcare costs incurred by families • Routinely spend this sort of money on other treatments, why not nusinersen? • Full cost and impact of the worst health states substantially underestimated • Long-term risk to NHS is low, as nusinersen could be used as a bridge to future treatments currently in development

[redacted]

ACD consultation comments

Company (1)

- "Disappointed committee unable to recommend nusinersen…committed to collaboratively finding solutions that address remaining uncertainties, mitigate risk to the NHS and ensure access to nusinersen managed appropriately without further delay"
- Description of SMA in the ACD does not fully reflect the condition, and there is concern that recommendation may imply unmet need is similar across subtypes
  - suggest noting life expectancy, maximal motor milestone achieved followed by constant decline, and that patients have normal intelligence so fully aware of condition
- Although a spectrum disorder, all patients recognised according to the main subtypes
- Early initiation of treatment may lead to greater improvements. Therefore important access to disease-modifying therapy as quickly as possible
- Short follow-up periods of RCTs due to extremely positive interim analyses and ethical considerations. SHINE study and other RWE studies provide longer term evidence
- The mechanism of action of nusinersen combined with the observed data to date, indicates that the effects of nusinersen can be sustained in the long-term

ACD consultation comments

Company (2)

- Number of factors contribute to large uncertainty in the estimates of cost-effectiveness:
  - Challenges of demonstrating long term benefits given the early termination, after positive interim findings of the pivotal trials
  - Sparse nature of additional data to aid the extrapolation of survival and their lack of alignment with standards of care in the UK.
  - Other uncertainties relate to the conceptual and practical issues surrounding the assessment of HRQoL and utilities in patient groups and quantifying the impact on carers
- The associated fear of losing abilities and independence imposes a major psychological burden on patients and carers
- Substantial burden on family carers, impacting on their quality of life. Unpaid caregiving is common and large proportion of caregivers give up work completely or go part-time
- More than one caregiver may be affected. Assuming multiple caregivers is consistent with other NICE evaluations (Ataluren for Duchenne Muscular Atrophy – HST3)
- Substantial impact for taking time out of work to attend appointments, emotional difficulties/distress and extra stress, challenging to help child be as independent as possible, and to fulfil their potential.

[redacted]

Additional Clinical evidence

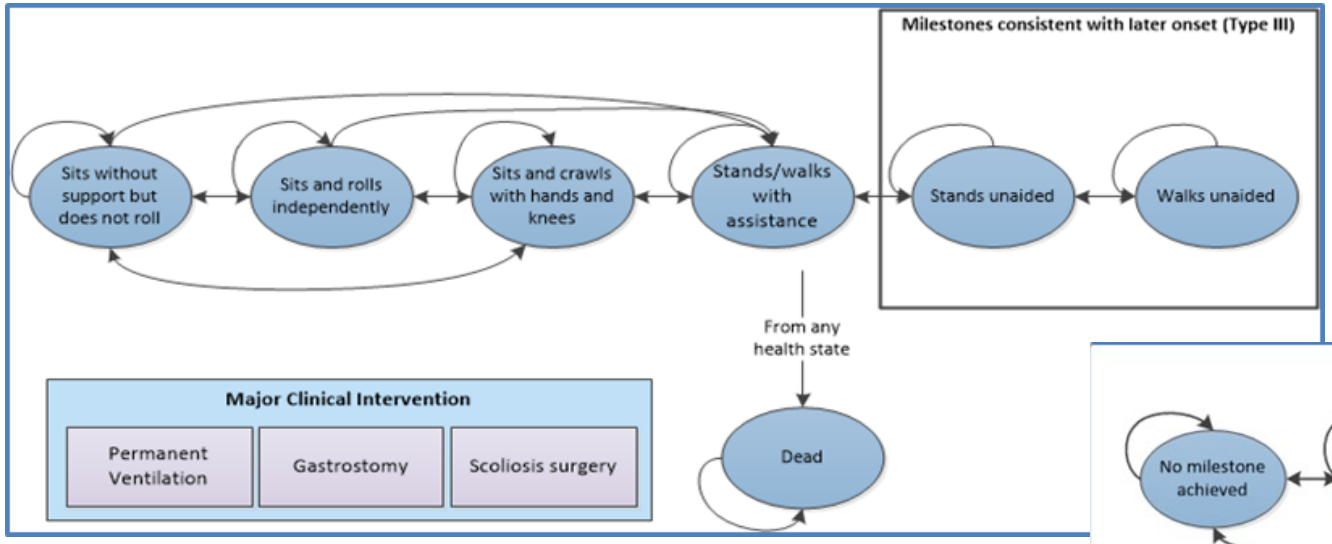
ERG's critique

- At consultation company submitted clinical evidence for the early-onset population from the ENDEAR RCT (n=122) and the SHINE extension study (n=146)
  - Majority of clinical data has been considered by committee previously
  - No new clinical data or real world evidence incorporated into company modelling
- There are only longer-term data (2 to 2.5 years) for a very small number of patients, and the time points across treatment arms are not comparable in the SHINE data.
- Data from SHINE indicate that a greater proportion of patients met HINE-2 and CHOP INTEND response criteria.
- Small number receiving nusinersen in SHINE achieved first response as late as day 818. This suggests it may take some patients time to respond to nusinersen.
- Data from SHINE suggests motor milestones were improved upon or maintained:
  - However, milestones achieved in the clinical trials are worse than at comparable time points predicted by the company's updated model

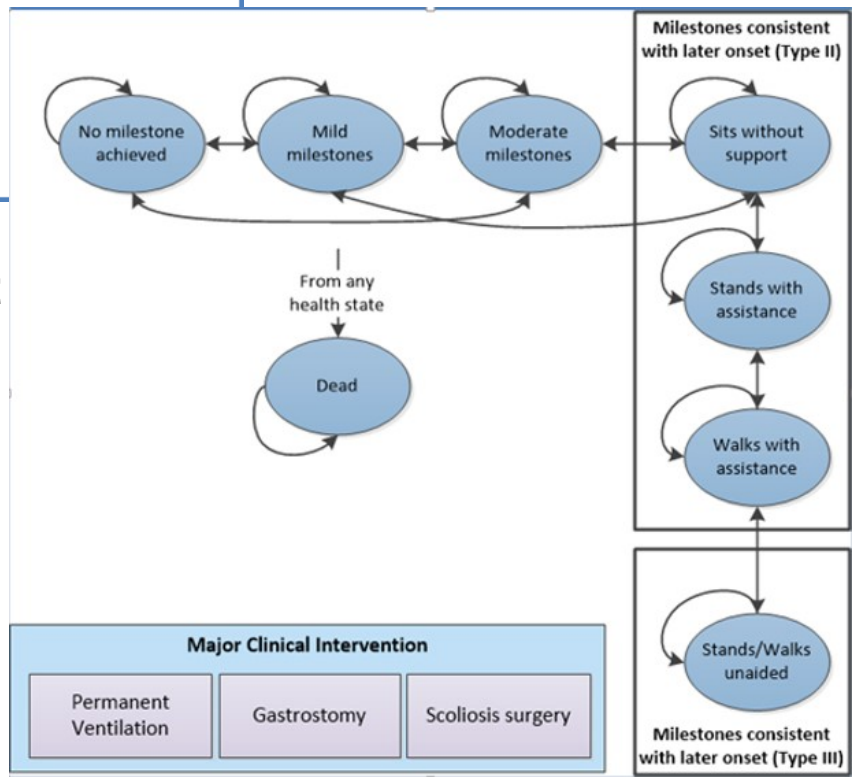
	Full head control	Sit independently	Stand unaided
Trial data up to 2 - 2.5 years	22%	15%	0%
Predicted by model at 26 months	Not comparable	47%	3.4%

Previous economic model structure

- ERG's concerns regarding model structures which focus only on motor milestones
- ERG considered model overly complex, and produced a simplified model for ACM1



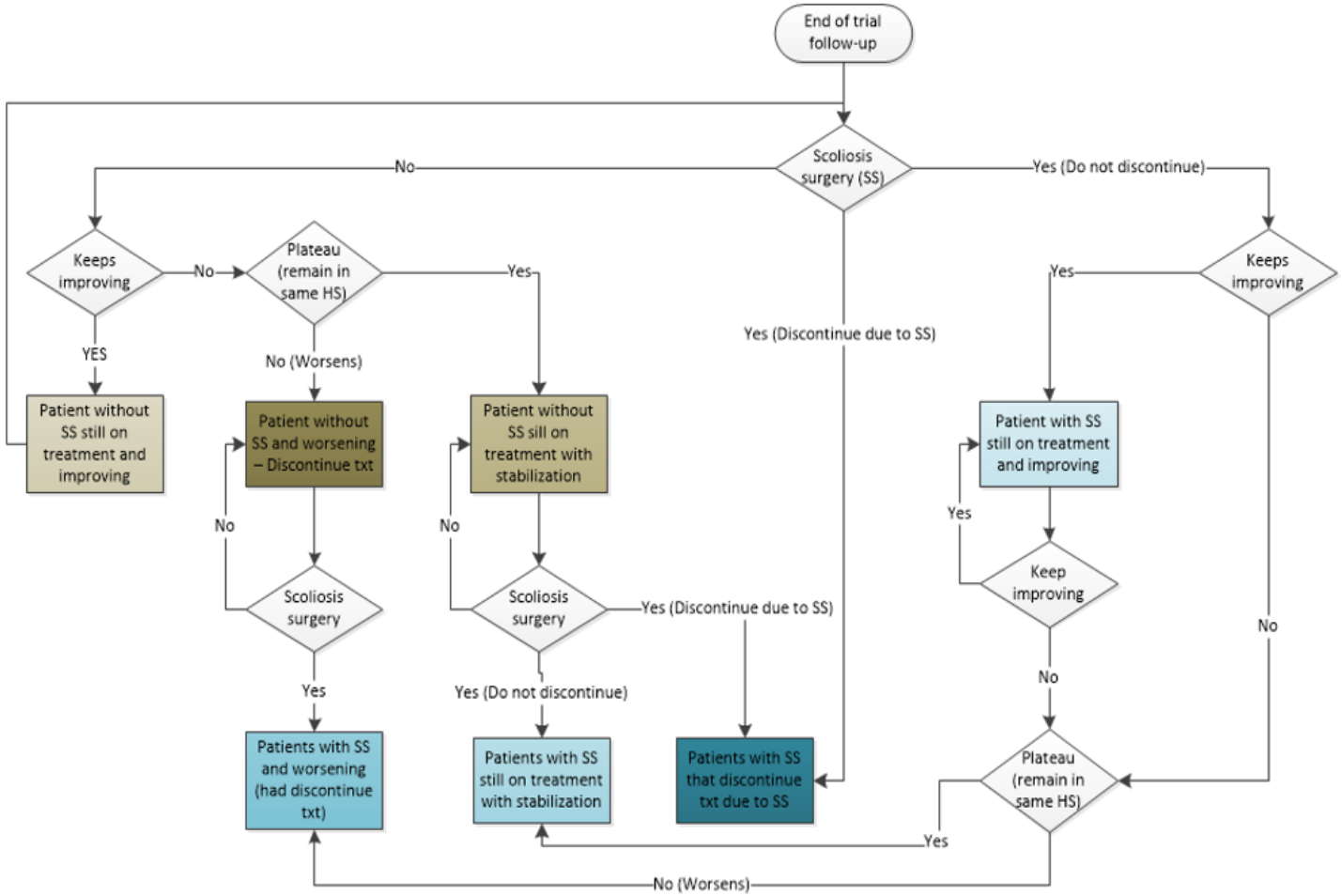
Model structure – **later onset**



Model structure – **early onset**

Model structures don't include improving and worsening patients separately, instead the respective transition matrices (improvement, worsening, plateau) were applied to patient proportions within each health state.

Updated company economic model structure



HS, Health state; SS, scoliosis surgery; txt, treatment

Model tracks 7 different groups subgroups:

No scoliosis surgery

1. On treatment – improvers
2. On treatment – stable
3. Off treatment – worseners

Scoliosis surgery

4. Discontinue due to surgery
5. On treatment – improvers
6. On treatment – stable
7. Off treatment – worseners

Assume worseners discontinue treatment

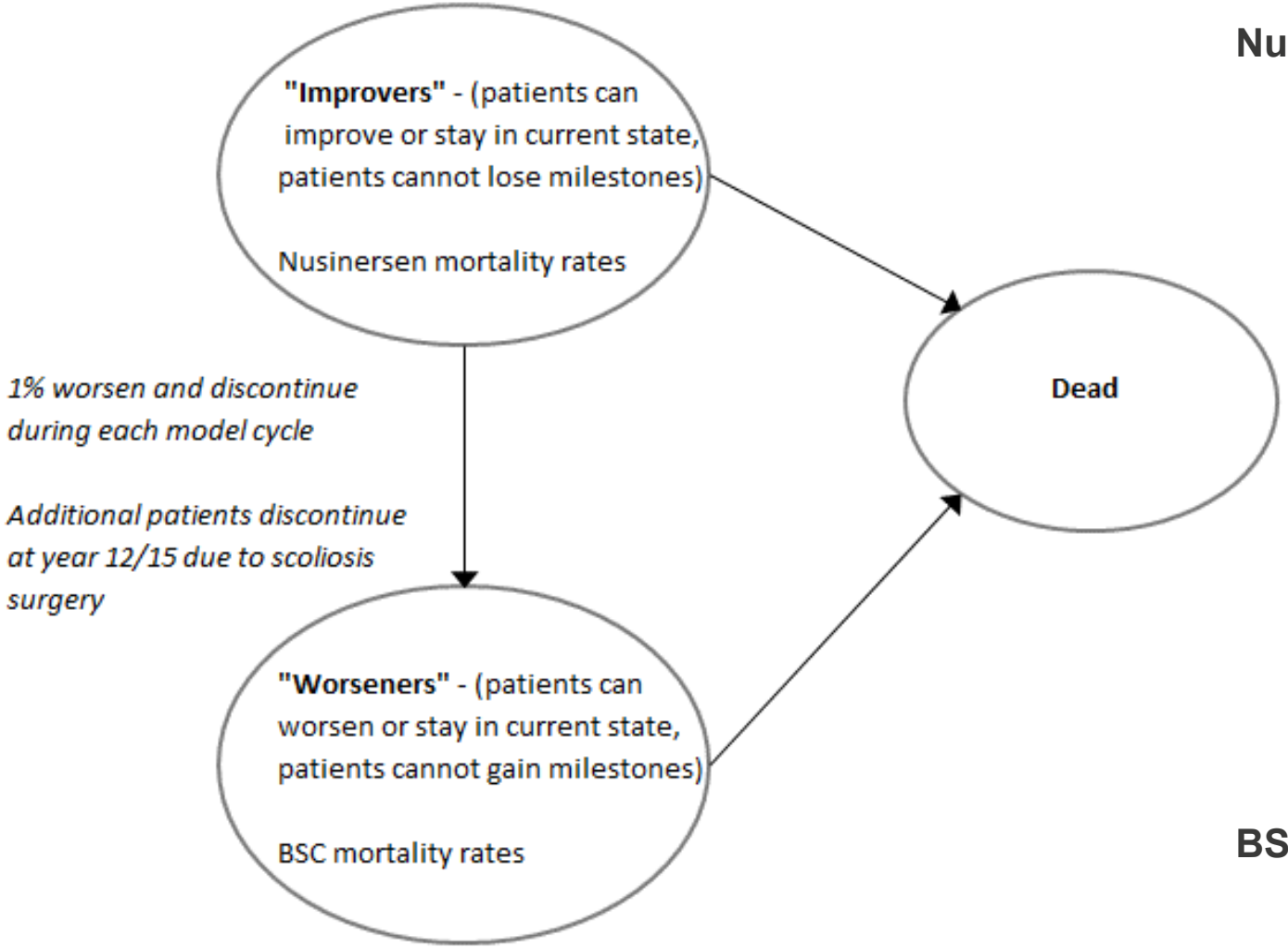
Company's rationale for new model structure:

- Addresses ERG's criticism that model is too complex
- Allows for incorporation of the proposed commercial offer – an outcome-based rebate scheme

[redacted]

Updated economic model structure

ERG simplified model description



Nusinersen group

- All nusinersen-treated patients begin extrapolation period as “improvers” – these patients cannot lose milestones
- 1% patients become “worseners” during each model cycle – these patients cannot gain milestones
- Additional patients discontinue at point of scoliosis surgery

BSC patients

- Are patients all assumed to be “worseners”

Updated economic model structure

ERG critique

- Both the updated and original model are complex, although in different ways.
  - Original model included extremely complex formulae. New model includes 7 sub-models, with discontinuation and mixing between them
- Complexity results in difficulties for the ERG in checking the models and in understanding the underlying logic
- The model could be substantially simplified, with removal of 5 sub-models
  - 2 sub models redundant: don't include any patients entering model
  - Removal of Scoliosis models. very minor impact for early-onset, higher discontinuation rate could be assumed instead for later-onset
- The ERG attempted to verify the new structural assumptions and:
  - Noted it produces similar, but not identical, ICERs. ERG do not have major concerns regarding discrepancy
  - broadly satisfied new models operate as expected

[redacted]

Transition probabilities

Company submission

Committee rationale ACM1	Company additional evidence
• Transition probabilities are very optimistic (nusinersen arm could not get worse but best supportive care arm could not get better) and Transition probabilities do not reflect clinical practice. • ERG's exploratory scenarios analyses in which 5% to 10% of people having nusinersen lose a milestone each cycle were more suitable for decision-making.	• Updated model allows people (estimated proportion) to improve, stabilise, discontinue due to worsening (according to scales e.g. CHOP-INTEND, HFSME),discontinue due to scoliosis or death. • 1% of improves assumed to worsen and discontinue treatment every cycle • Main assumption is that once a patient enters the worsening or the scoliosis treatment discontinuation group, that patient will never regain milestones. • The updated model includes 7 different groups, scoliosis incorporated. [redacted]

[redacted]

Transition probabilities
ERG critique

- Company assume 1% of 'improvers' move to 'worsener' state each cycle. No evidence to support this particular rate
- Model assumes that patients who worsen discontinue treatment immediately
  - ERG consider this more plausible than ACM1 assumption (no worsening)
  - Does not allow for people to temporarily worsen, and then recover
  - Does not reflect commercial proposal, [redacted] ERG unclear how this impacts the ICER
- Model assumes 'worseners' can never regain milestones. This does not reflect the clinical trials where some people in sham groups, particularly those with later onset, temporarily improved
- Model still more optimistic than observed clinical trial data (see slide 21)
  - Maximum proportion walking or standing unaided in updated model: 23.5% at ~4 years for early onset; 48.9% at ~7.5 years for later onset

Are the transition probabilities appropriate? Are they still optimistic?

Overall survival

ERG's critique

- Committee considered long-term survival was optimistic at ACM1
- Agree that the company's new approach is simpler and more transparent
- Company have not demonstrated that other extrapolations give implausible long-term predictions, nor has plausibility of company's approach been demonstrated
- New early-onset model assumes proportional hazards. Assuming proportional hazards then tapering mortality risk in one group using an HR, are not consistent approaches
- Late onset model assumes no long-term survival benefit for nusinersen
- Overall, ERG notes that the company's new survival assumptions in both models are more conservative than those employed in the original base case models.
- The long-term survival benefit for patients treated with nusinersen remains highly uncertain people with SMA.

	ACM1 model		ACM2 model	
	Nusinersen	Usual care	Nusinersen	Usual care
Early-onset life years (undiscounted)	13.01	3.87	4.02	2.32
late-onset life years (undiscounted)	41.71	36.45	36.35	36.35

Are the new long-term overall survival assumptions plausible?

Health–related quality of life
Company submission

Patient utilities

- Committee considered all utilities had serious limitations
- Company use ERG preferred patient utilities in updated company model, but explore using all approaches in scenario analyses

Care-giver utilities

- Committee considered trying to quantify caregiver disutility introduced uncertainty.
- Company consider substantial qualitative evidence to support inclusion of carer disutility
- Company previously based disutility around general mortality assumptions and assumed decrements between states. ERG preferred using unmodified *Bastida et al* evidence
- Company now assume:
  - 2 caregivers affected (compared to 1 caregiver at ACM1)
  - Best health state is associated with general population utility
  - Worst state is associated with mean caregiver utility in *Bastida et al*
  - equal difference in utility assumed between adjacent states

[redacted]

Health–related quality of life

ERG's critique

- The company's updated base case models apply patient utilities based on the vignette (Lloyd et al). The ERG noted that none of the available sources for patient utilities are ideal.
- The ERG does not necessarily consider the company's new caregiver disutility calculations are unreasonable, however they are mainly based on assumptions due to the lack of evidence.
  - Only available estimates which relate to SMA type from Bastida, but committee considered these lacked face validity (highest disutility in best health state)
  - The ERG clinical advisor estimates may have the greatest face validity, but are not utility estimates
- The company's original models included QALY impacts for a single caregiver; the company's updated models include QALY impacts for two caregivers, which means doubling the QALY losses assumed for carers.
- In the company's new later onset model, caregivers gain more incremental health from nusinersen than patients

[redacted]

Health state costs

Company submission – impact of health state costs

- Original costs were from cross-sectional SMA study (Bastida et al)
- Updated health state costs sourced from a RWE survey, 2017 from 9 paediatric neurology centres. Cited but described in original submission

SMA type	Updated RWE survey	Original model
SMA Type I	£77,968	[redacted]
SMA Type II	£55,185	[redacted]
SMA Type III	£20,229	[redacted]

- Early onset model: incremental costs are increased reflecting higher cost of managing type I SMA coupled with the critiqued highly optimistic survival and trajectory assumptions in the original model accruing additional management costs.
- Later onset model: costs are reduced as more patients achieve higher milestones which are associated with lower annual management costs.

[redacted]

Health state costs

ERG's critique

- The costs from the survey are considerably higher than the estimates from Bastida et al.
- Consultation comments received indicate that the costs of SMA have been substantially underestimated
- The RWE survey methods used have not been presented in detail.
- The use of costs from the RWE survey reduce the ICER in the later onset population, but increase the ICER in the early onset population.
- ERG's clinical advisor suggested that the RWE survey costs were more appropriate.
- The costs of care likely to be age-dependent (original ERG report). This is not accounted for in the company's models.

Are the new costs a better reflection of the burden of managing SMA?

Cost-effectiveness results

Company base case – list price

Scenario	Incr. costs	Incr. QALYs (patient)	Incr. QALYs (patient + carer)	ICER (patient)	ICER (patient+carer)
Early-onset model					
ACM1 basecase	£2,187,311	5.37	5.44	£407,605	£402,361
ACM2 basecase	£940,146	1.05	1.37	£895,865	£684,389
Later-onset model					
ACM1 basecase	£2,964,442	2.37	3.30	£1,252,991	£898,164
ACM2 basecase	£1,869,905	4.74	10.74	£394,343	£174,106

Except for company's new caregiver assumptions, ERG believes company has presented ICERs which generally reflect a more appropriate and potentially unfavourable set of assumptions

[redacted]

Company exploratory analyses – early onset

List price

Scenario	ICER (patient)	ICER (patient+carer)
Updated model base case	£895,865	£684,389
Company exploratory analyses		
Slower usual care arm decline in CHOP-INTEND	£835,214	£621,804
120 months tapering period of the treatment effect	£808,890	£656,434
Later onset mortality adjustment applied (0.5)	£693,615	£626,825
2% of patients worsen and follow RWC matrix	£983,245	£789,476
1% of patients worsen and lose 1 milestone per cycle	£904,746	£694,673
No patients worsen (except discontinuation due to SS)	£815,847	£596,567
<= 12 weeks disease duration	£649,579	£459,996
> 12 weeks disease duration	£1,397,060	£1,419,462
Health state costs form Bastida et al. (2016)	£867,891	£663,018
ERG clinical advisors' patient utilities	£642,965	£526,256
PedsQL patient utilities	£738,433	£588,534
"Narrow range" caregiver utilities	£895,865	£826,349
[redacted]	[redacted]	[redacted]

[redacted]

Company exploratory analyses – Later onset

List price

Scenario	ICER (patient)	ICER (patient+carer)
Updated model base case	£394,343	£174,106
Company exploratory analyses		
Slower usual care arm decline in HFMSE	£380,476	£169,709
Type III mortality adjustment applied (0.5)	£385,233	£181,009
2% of patients worsen per cycle and follow RWC transition matrix	£397,590	£170,577
1% of patients worsen per cycle and lose 1 milestone per cycle	£474,009	£222,214
No patients worsen (except for discontinuation due to scoliosis surgery)	£400,359	£183,114
< 25 months disease duration	£336,836	£145,083
>= 25 months disease duration	£474,964	£226,870
Health state costs form Bastida et al. (2016)	£433,968	£191,601
ERG clinical advisors' patient utilities	£1,076,164	£241,722
PedsQL patient utilities	£2,112,435	£271,655
"Narrow range" caregiver utilities	£394,343	£228,742

[redacted]

Cost-effectiveness results

ERG critique

- In comparison with original early-onset model, key drivers are:
  - Less favourable mortality assumptions applied
  - Patient utilities from the vignette study (Lloyd et al)
  - Health state cost from real-world evidence (RWE) survey
- In comparison with original late-onset model, key drivers are:
  - the commercial access agreement
  - the use of the vignette study for patient utilities
  - New caregiver disutility and increase in number of caregivers
  - the use of the 2017 RWE survey to inform health state costs
- Given complexity of modelling, ERG explore sensitivity of alternative assumptions – but do not provide alternative base case

[redacted] *patient ICERs only, ** patient and caregiver ICERs

Cost-effectiveness results

ERG exploratory analyses

- Company have indicated they consider assumptions provided for ACM2 are pessimistic, and there are plausible scenarios where ICER is reduced
- ERG explored applying a simplified version of new commercial offer to company's original base case – considered optimistic by committee at ACM1
- Simplified commercial offer equivalent to [redacted] – therefore favouring nusinersen

Scenario	Incr. costs	Incr. QALYs (patient)	Incr. QALYs (patient + carer)	ICER (patient)	ICER (patient+carer)
Early-onset model					
ACM2 model + proposal	[redacted]	1.05	1.37	[redacted]	[redacted]
ACM1 model + proposal	[redacted]	5.37	5.44	[redacted]	[redacted]
Later-onset model					
ACM2 model + proposal	[redacted]	4.74	10.74	[redacted]	[redacted]
ACM1 model + proposal	[redacted]	2.37	3.30	[redacted]	[redacted]

Cost-effectiveness results

ERG exploratory analyses – carer disutility

- Committee previously concluded quantifying carer disutility introduced uncertainty and was extremely difficult
- Company consider assuming 2 carers is consistent with NICE evaluations (Ataluren for treating Duchenne muscular dystrophy – HST3)
- ERG noted that late onset model is driven by caregiver disutility and increase in number of caregivers

Scenario	Incr. QALYs: patients	Incr. QALYs: patients+carers	ICER (patient)	ICER (patient+carer)
Early-onset model				
Company basecase (2 carers)	1.05	1.37	[redacted]	[redacted]
Company basecase (1 carers)	1.05	1.21	[redacted]	[redacted]
Late-onset model				
Company basecase (2 carers)	4.74	10.74	[redacted]	[redacted]
Company basecase (1 carers)	4.74	7.74	[redacted]	[redacted]

Is it plausible that nusinersen gives greater benefit to carers than people with SMA?
Should carer disutility be incorporated using a quantitative approach?
Should 1 or 2 carers be assumed when calculating disutility?

Cost-effectiveness results

ERG exploratory analyses – short disease duration

- Company and consultation comments note that the early nusinersen starts, the better the clinical outcome
- Company consider it plausible that, following commissioning, all people will start treatment after a short disease duration

Scenario	ICER (patient)	ICER (patient+carer)
Early-onset model		
Updated model base case with commercial proposal	[redacted]	[redacted]
≤12 weeks disease duration	[redacted]	[redacted]
>12 weeks disease duration	[redacted]	[redacted]
Late-onset model		
Updated model base case with commercial proposal	[redacted]	[redacted]
<25 months disease duration	[redacted]	[redacted]
≥25 months disease duration	[redacted]	[redacted]

[redacted]

Cost-effectiveness results

ERG exploratory analyses – most favourable scenario

- Several changes have a favourable impact on the ICER for one population, but a negative impact on the other
- Company consider committee should assume [redacted]. ERG consider no justification for this assumption
- ERG present the most favourable scenario for both – even if inconsistent assumptions apply

Scenario	Incr. costs	Incr. QALYs (patient)	Incr. QALYs (patient + carer)	ICER (patient)	ICER (patient+carer)
Early-onset model; favourable scenario = ACM 1 model, <25 month disease duration subgroup					
ACM2 basecase	[redacted]	1.05	1.37	[redacted]	[redacted]
Most favourable scenario	[redacted]	7.72	7.81	[redacted]	[redacted]
Late-onset model; favourable scenario = doubled nusinersen improvement rate, <25 month disease duration subgroup					
ACM2 basecase	[redacted]	4.74	10.74	[redacted]	[redacted]
Most favourable scenario	[redacted]	7.22	16.78	[redacted]	[redacted]

Innovation and equalities

Innovation

- Company states that it is likely that the innovative benefits of nusinersen will help to alleviate several clinical aspects that were not captured in the nusinersen clinical trials. Areas to include: swallowing, speech and forms of communication, weight over/under gain, cough assist, pain, contracture management / contracture stretching, fracture frequency and management, constipation, psychological impact, impact on siblings and family, frequency of infections and scoliosis.

Equalities

- No potential equality issues were identified during the scoping process
- Patients with SMA have a range of disabilities
- Company and patient groups consider that nusinersen should be considered for all ages and disabilities
- The population for which nusinersen is indicated includes children and adolescents

Any further considerations committee should be mindful of in its decision-making?

Managed Access Arrangement
Proposal

[redacted]

MAA – proposed eligibility criteria

Motor milestone must be met as follows:

Pre-symptomatic:
- Sibling history of non-sitters or sitters
- Intrathecal injection must be technically feasible
- No permanent ventilation

Non-sitters (type 1) must fulfil all of the following:
- Symptom onset <6 months
- Intrathecal injection must be technically feasible
- No permanent ventilation

Sitters (type 2) must fulfil all of the following:
- Symptom onset >6 months and <18 months
- Must not have severe contractures which in the opinion of the clinician
- Must not have received spinal fusion surgery following a diagnosis of scoliosis
- Intrathecal injection must be technically feasible
- No permanent ventilation

Ambulatory (type IIIa) must fulfil all of the following:
- Symptom onset > 18 months and < 3 years of age
- Must still be ambulant (WHO definition of standing with assistance)
- Intrathecal injection must be technically feasible
- No permanent ventilation

[redacted] No permanent ventilation: (≥16 hours/day for 21 consecutive days)/ tracheostomy requirement at baseline

MAA – Proposed data collection and stopping rule

- Proposal period of 5 year term.
- Assessment points: at 12 months after initiation of therapy and at every 2 month +/- window either side.
- Outcomes determined by patient motor milestones at initiation of therapy (non-sitters; sitters; ambulatory) in the following order: survival, respiratory events, motor function, scoliosis surgery, Quality of life (options for discussion)
- If treatment is stopped: data collection will continue as part of a separate group.

Proposed stopping rule	
Respiratory event	**Motor milestones**
Advanced ventilatory support not caused by reversible infection / tracheostomy where further treatment is deemed futile	HINE: Worsening in symptoms 2 consecutive measures of decline of: >2 on horizontal kick or 1 on other HINE scores excluding voluntary grasp CHOP INTEND: 2 consecutive measures decline of: >4 points on the scale RHS: 2 consecutive measures decline of: >3 points on the RHS scale

HINE, Hammersmith Infant Neurological Exam; CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; RHS: Revised Hammersmith Scale

Would the MAA proposals manage and address the key uncertainties?

Key issues for consideration

- Has the committee heard anything in consultation to change its preliminary recommendation?
- Which model structure is more appropriate for decision-making?
- Are there any uncaptured benefits of nusinersen that have not previously been considered by committee in its decision-making?
- What assumptions and inputs does the committee consider to be most plausible regarding:
  - Transition probabilities
  - Long-term benefit
  - Patient and carer utilities
  - Resource costs
- Could nusinersen plausibly be cost-effective?
- Would the MAA proposals manage and address the key uncertainties?

[redacted]

NICE National Institute for Health and Care Excellence

Slides for public handouts - redacted

Nusinersen for treating spinal muscular atrophy

Chair's presentation

3rd appraisal committee meeting

Committee C

Lead team: Kamal Balakrishnan, Andrea Manca, David Chandler

ERG: ScHARR

NICE technical team: Heather Stegenga, Thomas Strong, Eli Gajraj

Company: Biogen

6 March 2019

History of the appraisal

European Medicines Agency (EMA) approves nusinersen '*for the treatment of 5q Spinal Muscular Atrophy*'

2nd Appraisal Committee Meeting:
- consultation comments discussed
- updated commercial proposal and new economic model

not recommended

1st Appraisal Committee Meeting:
not recommended

Further discussions with company

3rd Appraisal Committee Meeting: updated commercial proposal and updated economic model

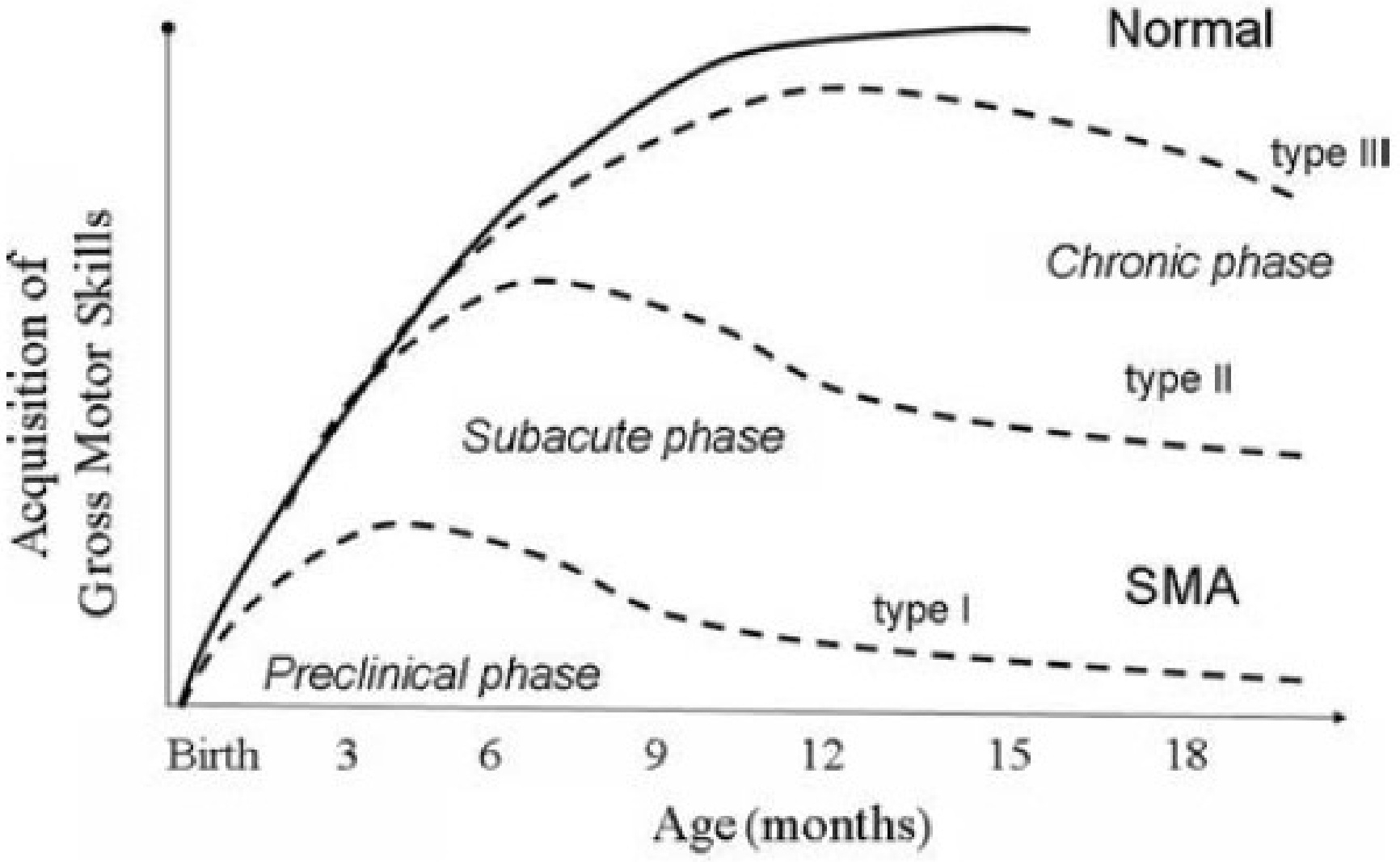
[redacted]

Spinal muscular atrophy

Disease background

- SMA is a genetic, progressive neuromuscular disease most commonly caused by mutations in the *SMN1* on chromosome 5q
  - *SMN1* gene encodes the “survival motor neurone” (SMN) protein
  - The lack of SMN protein causes the motor neurones to malfunction, deteriorate and eventually die
- Long-term degenerative condition causing muscle weakness, results in gradually worsening physical disabilities and mobility loss.
- Estimated that ~100 people are born with SMA per year, and 1,200–2,500 children and adults are currently living with SMA, in the UK
- SMN2 can compensate for the SMN1 deletion to some degree, the number of SMN2 gene copies is inversely related to the severity of SMA and can be used to predict the course of the disease

Symptoms and complications



Broad relationship between age and gross motor skills acquisition, depending on the different phenotype of SMA

Classification and subtypes of SMA

	Age of onset	Max. motor milestone	Motor ability and additional features	Survival
Type 0	Before birth	None	Severe hypotonia; unable to sit and roll	Respiratory insufficiency at birth: death within weeks
Type 1	2 weeks (Ia) 3 months (Ib) 6 months (Ic)	None	Severe hypotonia; unable to sit and roll	Death/ventilation by 2 years
Type 2	6–18 months	Sitting	Proximal weakness: unable to walk independently	Survival into adulthood (typically >25 years)
Type 3	<3 years (IIIa) >3 years (IIIb) >12 years (IIIc)	Walking	May lose ability to walk	Normal life span
Type 4	>30 years or 10–30 years	Normal	Mild motor impairment	Normal life span

- Type 1 SMA defined as **early onset** in the model
- Type 2 and 3 SMA defined as **later onset** in the model

Nusinersen (Spinraza, Biogen)

Marketing authorisation	"Nusinersen is indicated for the treatment of 5q SMA"
Mechanism of action	An antisense oligonucleotide, which stimulates the survival motor neurone (SMN)-2 gene to increase functional SMN protein levels.
Administration & dose	Intrathecal injection by lumbar puncture, 12 mg per administration 4 loading doses on days 0, 14, 28 and 63; maintenance dose once every 4 months.
List price	£75,000 per 12-mg vial At list price the total annual treatment cost is **£450,000** for the first year and **£225,000** for subsequent years per patient.
Availability	Under the Expanded Access Programme (EAP), eligible children with type 1 SMA can receive nusinersen. The EAP closed to new patients in November 2018

Source: Company submission. **Abbreviations:** SMA, spinal muscular atrophy; SMN, survival of motor neurone.

[redacted]

Draft recommendation

Nusinersen is not recommended

- *Why the committee made the recommendation?*
  - Long-term benefits are highly uncertain
  - Committee did not choose a preferred set of assumptions, due to the substantial uncertainty in the modelling
  - At list price the most plausible ICER's are likely to be several hundred thousand pounds per QALY
  - The committee also considered a range of other factors, including:
    - Rarity and severity of spinal muscular atrophy
    - Nature of population
    - Whether the cost effectiveness of nusinersen should be considered according to that for end-of-life treatments
    - Proposed commercial arrangement
  - Even taking these factors into account the cost of nusinersen is too high to be considered cost-effective

[redacted]

Committee considerations: Clinical evidence (1/2)

Theme	Committee's conclusion
Nature of the condition	• The most severe types affect babies and young children. • SMA affects quality of life for patients, carers and families • SMA classifications are blurred and can be subjective • Currently there are no effective treatment options

Clinical evidence	• Evidence presented by the company was for SMA types 1 to 3, whilst marketing authorisation is for all types
	• Main clinical evidence from 2 RCTs:
	  • ENDEAR – type 1 SMA
	  • CHERISH – type 2 SMA and more severe type 3 SMA
	• 3 ongoing studies
	  • NURTURE – single-arm pre-symptomatic infants
	  • SHINE – extension of ENDEAR and CHERISH
	  • EMBRACE – for people not eligible for the RCTs

[redacted]

Committee considerations: Clinical evidence (2/2)

Theme	Committee's conclusion
Randomised controlled trials	• Short follow-ups for both ENDEAR (13 months) and CHERISH (15 months)
	• Survival benefit of nusinersen is shown for early-onset SMA, however, other health benefits (respiratory function, time on ventilator and hospitalisations) are uncertain.
	• Nusinersen improves motor function for later-onset SMA • Survival benefit is unclear for later-onset SMA
	• Nusinersen would likely provide long-term benefits, however the size and magnitude of these benefits is unknown.
	• Overall, evidence from the trials is uncertain but relevant for decision-making. Long-term benefits are associated with substantial uncertainty
Other trial evidence	• Ongoing-trials / real world evidence submitted as supportive evidence • Previously not incorporated into company's economic models

[redacted]

Committee considerations: Economic model

Theme	Committee's conclusion

Model structure	• 2 models received:
	  • Early-onset model: type 1 SMA
	  • Late-onset model: type 2 and 3 SMA
	• Based only on motor milestones (participating in activities, respiratory function, pain and physical impairment not included)
	• Consistent with the main outcomes of the clinical trials.
	• Relevant for decision-making.

Long-term benefit	• Nusinersen likely to improve long-term survival but adjustments assumed are implausibly large • Doesn't reflect clinical practice as nusinersen arm could not get worse and best supportive care arm could not get better.
Utilities	• Utilities uncertain and quantifying carer-related disutilities extremely difficult. • Both company's and ERG's utilities had serious limitations • Committee agreed SMA can affect multiple members of an extended family

[redacted]

Committee considerations: Other factors (1/2)

Theme	Committee's conclusion
Managed access arrangements	• A MAA could reduce risks to the NHS, but could only be considered once nusinersen has the potential to be cost-effective. • A MAA would require NHS England, patients, carers and clinicians to sign up to it.
Innovation	• Nusinersen is an innovative treatment and the first disease-modifying therapy for SMA • However, not presented with any data to show distinct and substantial benefits not captured in the analyses
Early-onset SMA includes children	• Committee acknowledged and considered the nature of the eligible population as part of its decision-making • No further considerations or adjustments were needed

[redacted]

Committee considerations: Other factors (2/2)

Theme	Committee's conclusion
Uncaptured health-benefits	• There are important uncaptured health benefits, but it was unclear how this affects the cost-effectiveness estimates.
Rarity and severity of disease	• Nusinersen for early-onset SMA has a number of features that are commonly seen in highly specialised technologies (HST) • Not an HST as population is too large and SMA is not commissioned through a highly specialised service • Committee mindful of need to consider if any adjustments must be made to account for rarity and severity of early-onset SMA
End of life criteria	• Early-onset SMA could meet the end-of-life criteria, but later-onset SMA did not • Committee concluded it may be unreasonable to apply different levels at which nusinersen would be considered cost effective depending on the age of onset of SMA

[redacted]

New since December ACM2

- Updated commercial offer ([redacted])
- Further clinical evidence included in early-onset model
  - month 13-26 data from SHINE now included
  - incorporated into early-onset model
- Clinical validation performed
- New model structure (including plateau sub-model)
- Amended model parameters. Key changes are:
  - transition probabilities; survival; health state costs; patient and caregiver utilities
- Additional evidence on natural history of early onset SMA, early access programme (EAP) data, and NURTURE study.

[redacted]

Additional evidence
Early onset – natural history

- Abstract submitted by clinical adviser (Alanizi et al).
- Retrospective analysis of **clinical care** and **survival** of infants with genetically confirmed SMA1
  - at GOSH
  - between 2007 to 2017
  - 64 children identified
    - 65% [41] SMA type 1B
    - 36% [23] SMA type 1C

[redacted]

Additional evidence
Early onset – natural history

- Change in non-invasive ventilation (NIV) over time
  - 2007-2011 - **18.5%** (5/27)
  - 2012-2017 - **81.8%** (36/44)

- 77% (14/18), age 6-111 months are on NIV.
- 61% (11/18) using cough assist

- Median survival - 11 months
  - SMA type 1C - 21 months
  - SMA type1B – 4 months
  - Children using NIV lived longer than those who did not (14 vs. 8 months)

Additional evidence
Early onset – early access programme (EAP)

- Presented at BPNA Annual Scientific Meeting, January 2019 (Scoto et al).
- Experience in UK and Ireland with EAP
  - SMA Type 1
  - March 2017 – October 2018
  - 95 infants
    - Median age at starting treatment – 11.5 months (range 1.5 months to 9.5 years)
    - Median age at symptom onset – 2.6 months

[redacted]

Additional evidence
Early onset – early access programme (EAP)

- Results (maximum 788 days / ~2 years' follow-up):
  - 56% **motor function improvement,** 37% stabilization, ?7% worsen
  - 15% acquired **major milestones** (i.e. sitting without support)
  - 60% had degree of **respiratory response** (maintenance) and 10% improvement
  - 3 **withdrew**, mainly from worsening of respiratory status and parental decision to avoid further hospital attendance.
  - 9 **died** after being enrolled for causes not related to the drug.
  - Mean age survival of those treated at age < 7 months: 24.5 months (range 9-28 months, mostly on nocturnal NIV support only, few not needing respiratory support)*
- Patients treated earlier showed better response

[redacted]

* Survival data difficult to interpret without information about exposure time and censoring.

Additional evidence
Early onset – NURTURE trial

- Single-arm, phase 2 trial
- 25 infants with pre-symptomatic SMA (likely to develop type 1 & 2)

- Treated with nusinersen
  - Median age at first dose 22 days (range 3 – 42 days)

- At interim analysis (May 2018)
  - Median age - 26 months (14.0–34.3)
  - Median time on study - 27 months (15.1–35.5)
  - All alive and none required permanent ventilation

[redacted]

Additional evidence
NURTURE trial – interim analysis, May 2018

Required respiratory intervention	2 SMN2 copies (n=15)	3 SM0N2 copies (n=10)	Total N=25
≥6 hours/day continuously for ≥7 days or tracheostomy (primary endpoint)	27% (4)	0	16% (4)
≥6 hours/day continuously for ≥1 or <7 days or tracheostomy	0	0	0
≥16 hours/day continuously for >21 days (permanent ventilation) in the absence of an acute reversible event or tracheostomy	0	0	0

Note: For the primary endpoint, respiratory intervention was defined as invasive or noninvasive ventilation for ≥6 hours/day continuously for ≥7 days or tracheostomy.

Additional evidence
Early onset – NURTURE trial – motor milestones (HINE-2)

- Pre-symptomatic patients treated with SMA gain motor milestones not expected for patients with this disease.

Motor milestone	Expected age of attainment*	Proportion of those attaining at expected age (or older) of expected	
		3 SNM2 copies	2 SNM2 copies
Full head control	5 months	100% (10/10)	100% (15/15)
Independent sitting	7 months	100% (10/10)	93% (14/15)
Stands with support	8 months	100% (10/10)	87% (13/15)
Walking with support	11 months	100% (10/10)	80% (12/15)
Standing unaided	12 months	90% (9/10)	47% (7/15)
Independent walking	15 months	100% (9/9)	54% (7/13)

[redacted]

* Haataja L, et al. J Pediatr. 1999;135(2 pt 1):153-161.

Additional evidence
Early onset – NURTURE trial

- Improvements in total motor milestone scores (HINE-2) in infants with **pre-symptomatic** SMA compared with symptomatic infants in other trials (such as ENDEAR).*
- All infants continue to make progress throughout the study with no evidence of sustained regression.

* NB: evidence included in the economic model is based on **symptomatic** patients from ENDEAR and SHINE. We do not have economic modelling to assess cost-effectiveness of non-symptomatic patients (which may need to include screening).

Cost-effectiveness results – Early onset

Company base case – list price

- Note: Numerous changes to model structure/logic and assumptions used for each meeting. Key changes described in further slides.

Model	Costs	QALYS (patient)	QALYs (carer)	Incr. costs	Incr. QALYS (patient)	Incr. QALYS (patient+ carer)	ICER (patient)	ICER (patient + carer)
ACM1; List price								
Nusi	£2,258,362	7.86	-0.25	£2,186,822	5.37	5.44	**£407,605**	**£402,361**
BSC	£71,540	2.49	-0.32					
ACM2; List price								
Nusi	£1,116,254	0.57	-1.54	£940,146	1.05	1.37	**£895,865**	**£684,389**
BSC	£176,108	-0.48	-1.86					
ACM3; List price								
Nusi	£2,200,847	2.64	-4.48	£1,897,211	2.64	0.76	**£718,184**	**£2,482,192**
BSC	£303,635	0.00	-2.61					

[redacted]

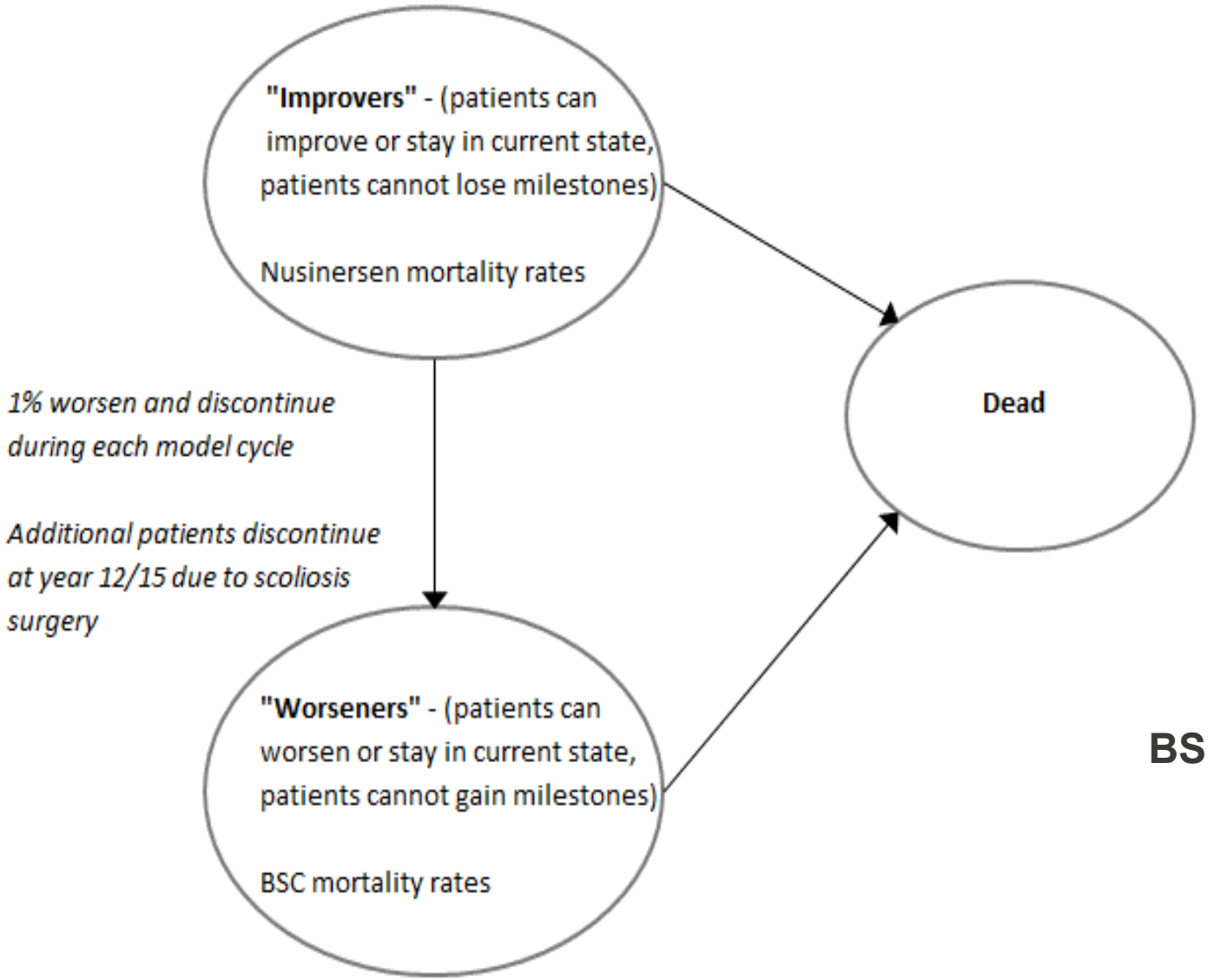
Cost-effectiveness results – Late onset

Company base case – list price

- Note: Numerous changes to model structure/logic and assumptions used for each meeting. Key changes described in further slides.

Model	Costs	QALYS (patient)	QALYs (carer)	Incr. costs	Incr. QALYS (patient)	Incr. QALYS (patient + carer)	ICER (patient)	ICER (patient + carer)
ACM1; List price								
Nusi	£3,148,754	16.88	-1.22	£2,964,442	2.37	3.30	**£1,252,991**	**£898,164**
BSC	£184,312	14.52	-2.16					
ACM2; List price								
Nusi	£2,943,909	5.83	-9.39	£1,869,905	4.74	10.74	**£394,343**	**£174,106**
BSC	£1,074,004	1.09	-15.38					
ACM3; List price								
Nusi	£4,125,556	8.75	-9.02	£1,922,784	2.56	5.94	**£750,709**	**£323,663**
BSC	£2,202,772	6.19	-12.40					

ACM2 economic model logic



Nusinersen group

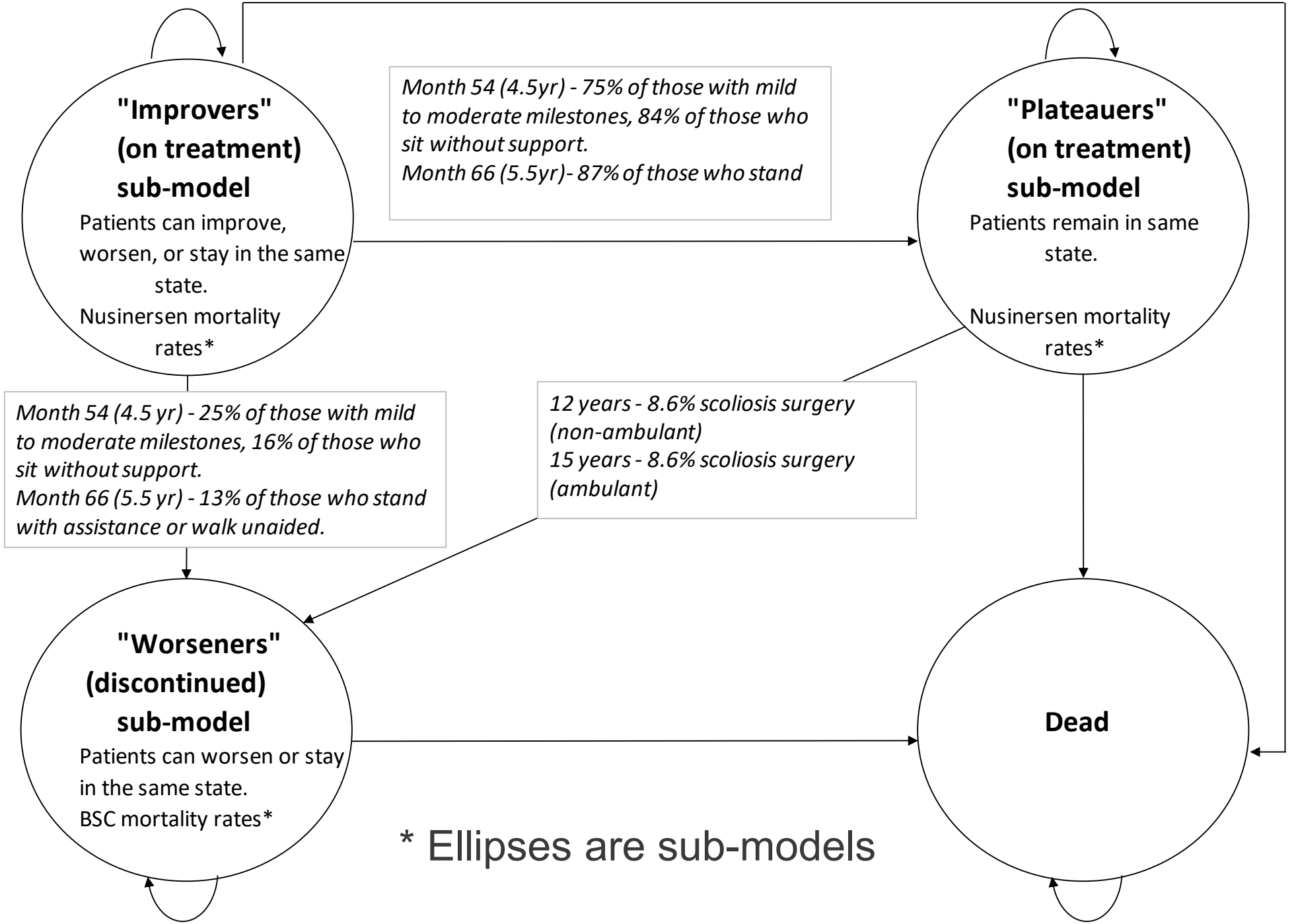
- All nusinersen-treated patients begin extrapolation period as “improvers” – these patients cannot lose milestones
- 1% patients become “worseners” during each model cycle – these patients cannot gain milestones
- Additional patients discontinue at point of scoliosis surgery

BSC patients

- Are patients all assumed to be “worseners”

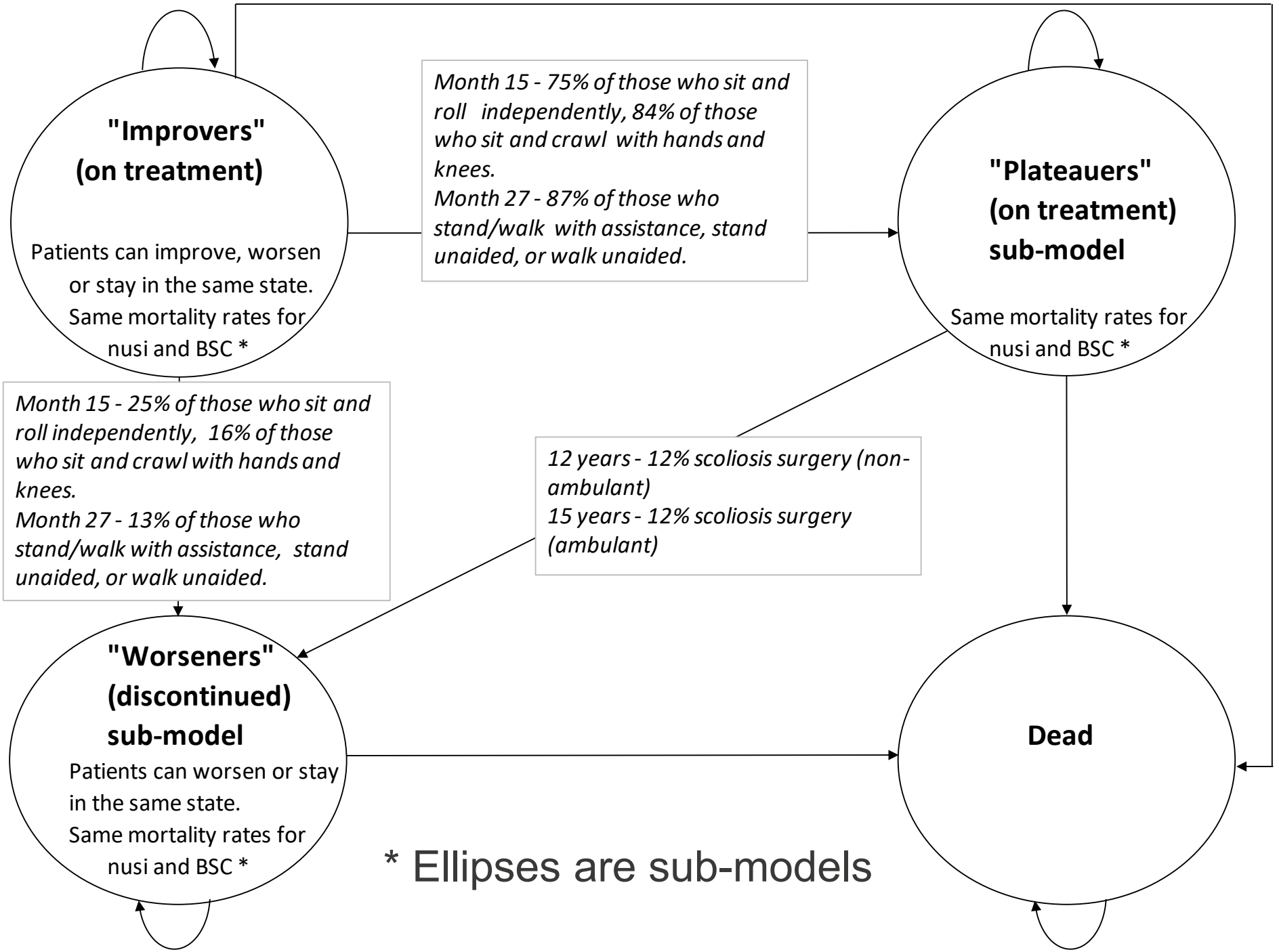
[redacted]

ACM3 economic model logic – early onset



* Ellipses are sub-models

ACM3 economic model logic – late onset



* Ellipses are sub-models

Model structure

ERG critique

- ERG broadly satisfied with structural amendments. ‘plateauer’ sub-model a more conservative assumption and better reflects clinical practice. However:
- ‘Improvers’ can only move sub-model at 2 timepoints:
  - Time-points informed by clinical opinion: 54 and 66 months for early onset, 15 and 27 months for later onset
  - ERG’s clinical advisor agree with the clinical advice concerning time-points
  - Proportion moving to ‘plateauers’ or ‘worseners’ sub-model for each health state informed by percentage of patients worsening at their last assessment
- ‘Improvers’ can repeatedly worsen but still be classed as improver and remain on treatment
- ‘Plateauers’ can no longer lose milestones, unless due to scoliosis surgery
- Model does not / cannot implement the proposed discontinuation rule: [redacted]

[redacted]

New ‘plateauers’ assumption

ERG critique

- ‘Plateauer’ sub-model a more conservative assumption and better reflects clinical practice. However:
- ‘Plateauers’ assumptions are a key driver of the model.
- ‘Plateauers’ can no longer lose milestones, unless due to scoliosis surgery
  - ERG consider it more reasonable to assume some people would worsen
- Impact of ‘plateauer’ assumptions highly dependent on other assumptions. For example in the **later-onset model**:
  - If ‘plateauers’ worsen and remain on treatment, ICER increases as people remain incurring treatment costs, increase management costs and lose health benefits
  - If ‘plateauers’ discontinued treatment, ICER decreases as decrease in treatment costs is greater than the increase in management costs and health benefits
  - Highly dependent on management costs assumptions, particularly type I SMA costs and whether those with late-onset SMA lose the ability to sit without support

[redacted]

New ‘plateauers’ assumption

Sensitivity of the ICER

	ICER (patient)	ICER (patient+carer)
Early onset model; List price		
ACM3 company base case	£718,184	£2,482,192
Increase in ages for improvement plateau	£674,434	£1,730,278
1% of plateauers worsen each cycle and stay on treatment	£743,318	£3,006,575
5% of plateauers worsen each cycle and stay on treatment	£834,572	£8,723,757
1% of plateauers worsen each cycle and discontinue	£733,268	£2,941,617
5% of plateauers worsen each cycle and discontinue	£825,762	Nusinersen Dominated
Later onset model; List price		
ACM3 company base case	£750,709	£323,663
Increase in ages for improvement plateau	£463,155	£230,379
1% of plateauers worsen each cycle and stay on treatment	£1,018,162	£432,744
5% of plateauers worsen each cycle and stay on treatment	£2,756,894	£1,139,919
1% of plateauers worsen each cycle and discontinue	£716,819	£303,648
5% of plateauers worsen each cycle and discontinue	£562,655	£237,886

Transition probabilities

Key changes and considerations

ACM 1	• Nusinersen arm could not get worse and BSC arm could not get better
	• Improvement and worsening rate based on trial data
	• Committee conclude:
	  • assumptions very optimistic and didn't reflect clinical practice
	  • preferred scenario where 5-10% of nusinersen arm lose milestone each cycle

ACM 2	• 1% of 'improvers' assumed to worsen and discontinue treatment every cycle • Does not allow for people to temporarily worsen, and then recover and 'worseners' can never regain milestones • Committee considered model was still very optimistic compared to trial data
ACM 3	• Further follow-up data to inform early-onset model (SHINE) • Slower rate of improvement for early-onset based on later half of trial data (from 13-26 months) • Improvers can temporarily worsen based on weighted average from trial data • Patients can plateau (cannot improve or worsen – but remain on treatment) • Those sitting without support can lose ability to sit independently.

Transition probabilities

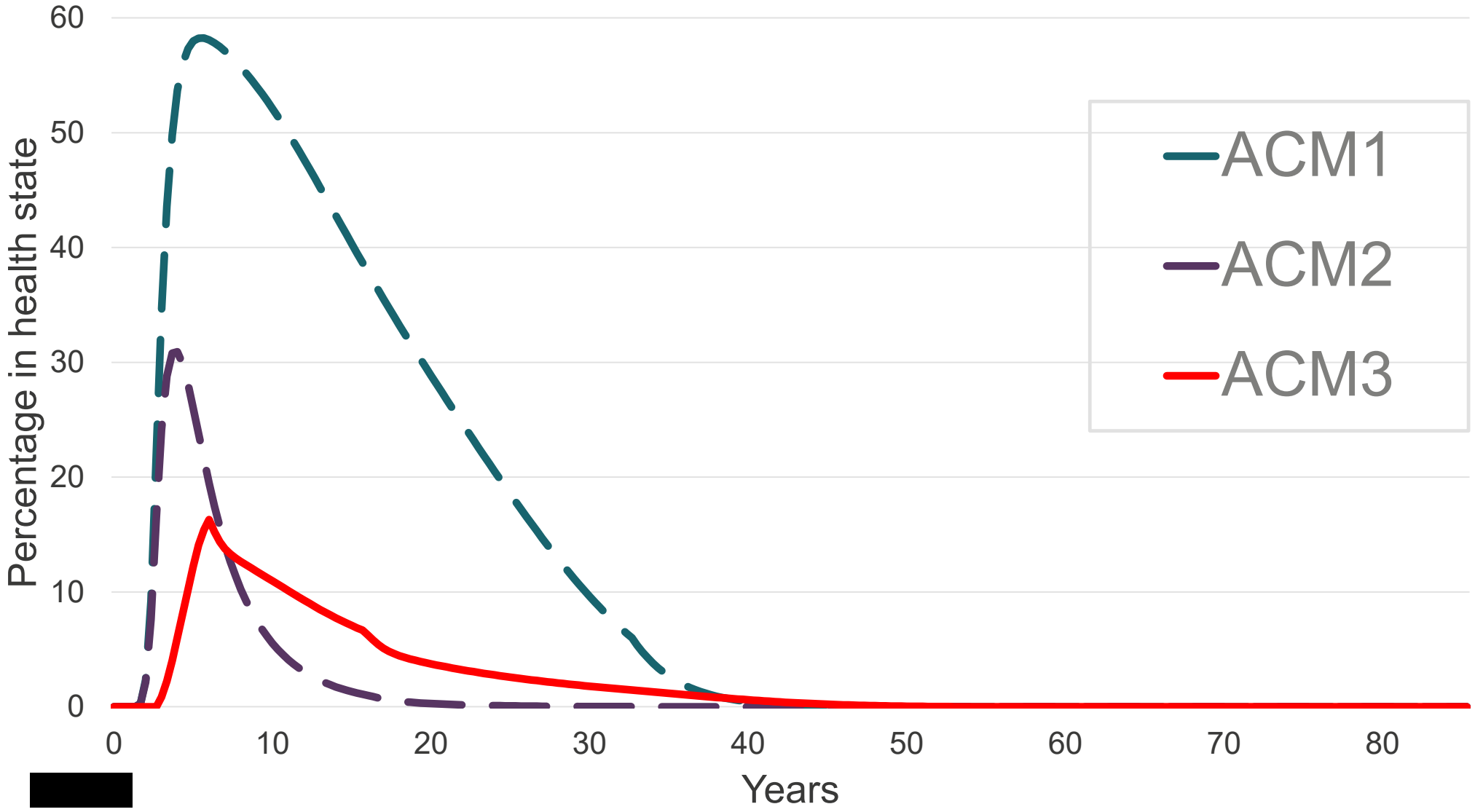
ERG critique

- **Early onset model:**
  - [redacted] probability of worsening while receiving nusinersen reasonable
  - Inclusion of month 13-26 SHINE data for longer term data in nusinersen group reasonable but limited after 22 month (n=34, with further attrition at later dates)
  - Slower rate of improvement used is reasonable
  - Considerable uncertainty regarding patients reaching walking unaided. [redacted]
  - ERG's advisor stated that the proportion of patients reaching the two best health states in the current early onset model was probably reasonable
- **Later-onset model:**
  - [redacted] probability of worsening while receiving nusinersen reasonable
  - Clinical advisor suggests losing the ability to sit may be reasonable. Suggest 85-90% would lose ability. This assumption is key driver for ICER

[redacted]

Transition probabilities: early-onset models

*Probability of walking with assistance or standing/walking unaided – **Company's Basecase***



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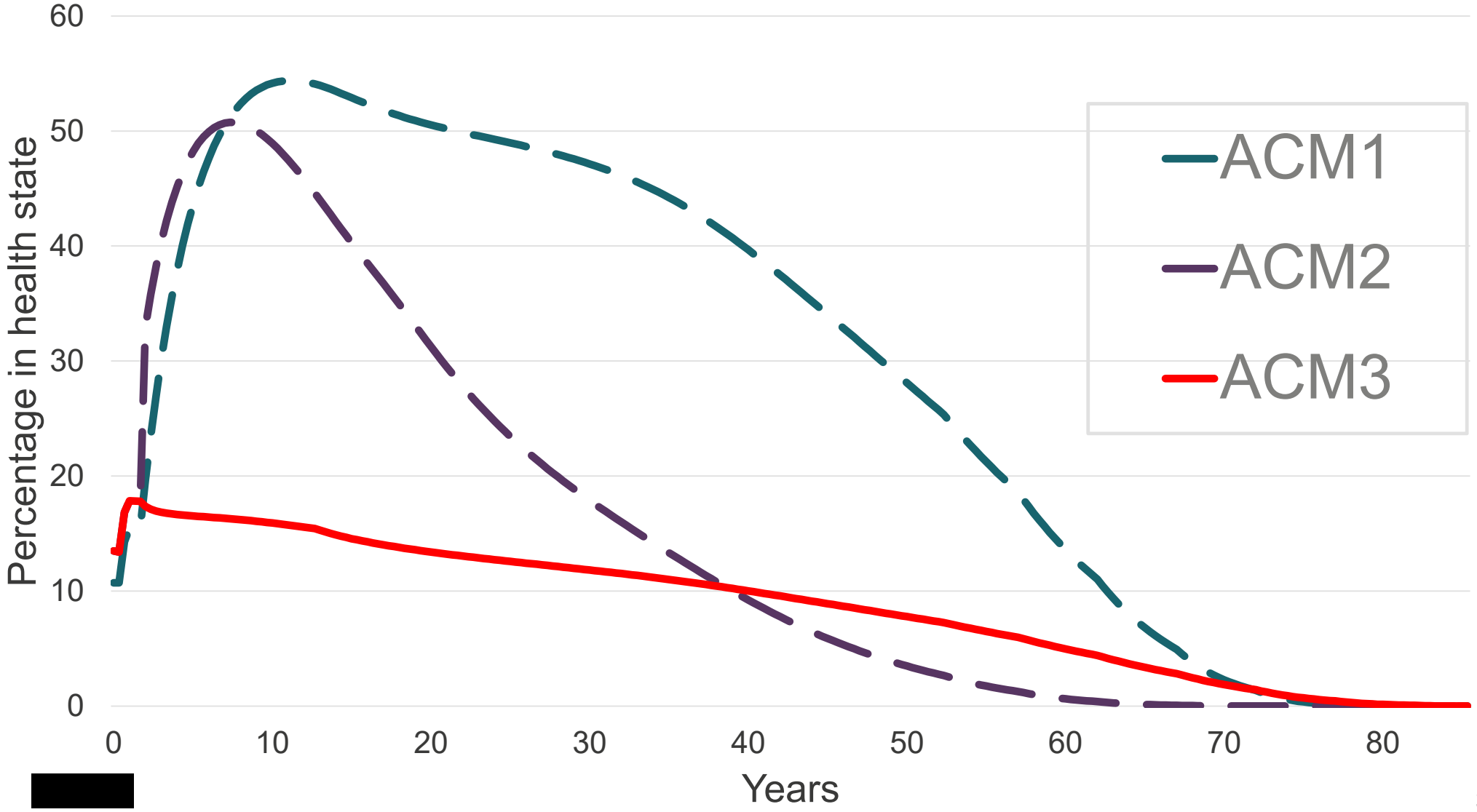
Transition probabilities: late-onset models

*Probability of walking with assistance or standing/walking unaided – **Company's Basecase***



[redacted]

Transition probabilities
Sensitivity of the ICER: early onset model

Early onset model; List price	ICER (patient)	ICER (patient+carer)
ACM3 company base case	£718,184	£2,482,192
Exploratory analyses		
Slower usual care arm decline	£669,977	£1,978,163
Proportion who can worsen and subsequently improve doubled	£815,343	£8,525,240
Proportion who can worsen and subsequently improve halved	£673,475	£1,770,266
Discontinuation based on last observed assessment	£709,106	£2,176,309
Proportion who discontinue per cycle doubled	£740,938	£3,325,249
No patients reach milestone of walking unaided	£741,592	£ 3,200,750
All scoliosis surgery undertaken 24 months earlier	£721,508	£2,569,323

Transition probabilities
Sensitivity of the ICER: later onset model

Late onset model; List price	ICER (patient)	ICER (patient+carer)
ACM3 company base case	£750,709	£323,663
Exploratory analyses		
Slower usual care arm decline	£762,278	£329,352
Proportion who can worsen and subsequently improve doubled	£782,226	£332,601
Proportion who can worsen and subsequently improve halved	£735,546	£319,263
Discontinuation based on last observed assessment	£775,629	£333,830
Proportion who discontinue per cycle doubled	£693,656	£302,035
Patients do not lose ability to sit without support	£1,423,083	£757,520
Proportion of patients who lose ability to sit set equal to 85%	£795,264	£349,195
All scoliosis surgery undertaken 24 months earlier	£746,345	£321,893

[redacted]

Survival

Key changes and considerations

- Committee previously considered modelled long-term overall survival benefit is based on optimistic assumptions and is highly uncertain
- Updated overall survival extrapolations more conservative

	ACM 1	ACM 2	ACM 3
Early-onset	•Piecewise function using ENDEAR + external data •Nusinersen mortality adjusted (90% of improved, 10% worst)	•Weibull fitted to both arms with ENDEAR •Tapered HR over 60 months for nusinersen arm	•Weibull fitted to ENDEAR and SHINE for nusinersen arm •Tapered HR over 120* months for nusinersen arm •Nusinersen mortality adjusted (75% of improved, 25% worst)

- Note: Late-onset model ICER is not sensitive to changes in survival assumptions

[redacted]

* Corrected after meeting

Survival

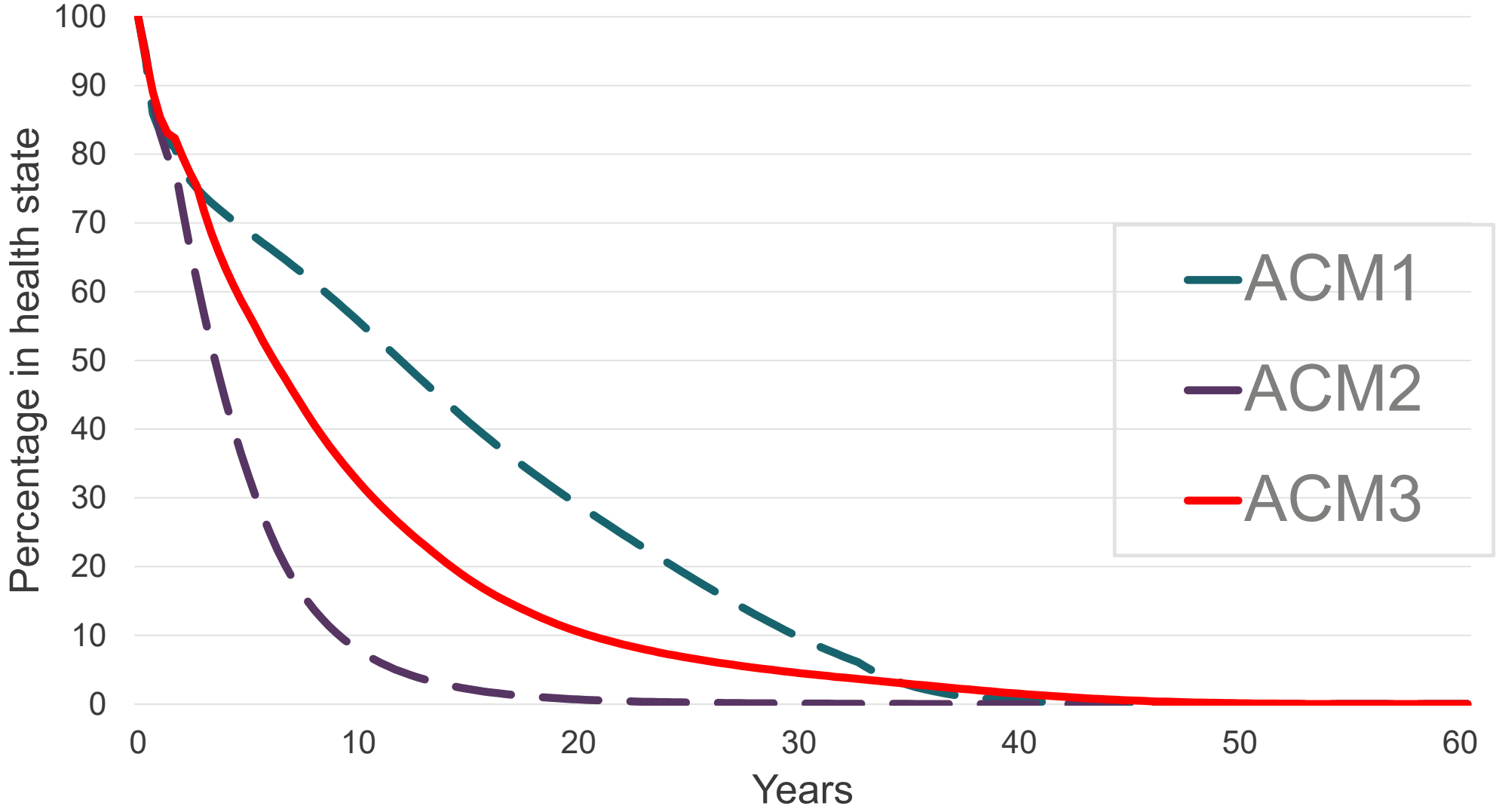
ERG critique

- Survival estimates may be clinically plausible, but associated with considerable uncertainty
  - Wide range of mortality adjustments elicited from clinical experts: **0.50 to 1.00**
- ERG concerns over methodology:
  - Proportion of mortality risk from 2 separate survival functions unconventional
  - Tapering HR inconsistent with proportional hazards assumption
  - Change in duration of HR tapering unsupported (60 to 120 months).

Early onset model; List price	ICER (patient)	ICER (patient+carer)
ACM3 company base case	£718,184	£2,482,192
Exploratory analyses		
Later onset mortality adjustment applied (0.5)	£619,276	£61,974,968
Later onset mortality adjustment applied (1)	£798,441	£2,779,726
Overall survival HR and mortality adjustment factor removed	£1,066,629	£2,059,464

Survival: early-onset models

Company's Basecases



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Healthcare costs

Key changes and considerations

ACM 1	• Costs were from cross-sectional SMA study *Bastida et al*
ACM 2	• Updated health state costs sourced from a RWE survey, 2017 from 9 paediatric neurology centres. Cited but not described in original submission • RWE survey substantially reduced the ICER in the later onset population, but increased the ICER in the early onset population • Committee heard at ACM2/consultation that costs likely to be underestimated, and there are substantial costs borne by patients and their families
ACM 3	• GOSH and Newcastle values from RWE survey only, based on clinical advice • Clinical advice to company is type I costs underestimated, so costs doubled

SMA type	ACM1: *Bastida et al*	ACM2: Updated RWE survey	ACM3: GOSH/Newcastle only and type I cost doubled
SMA Type I	[redacted]	£77,968	£148,214
SMA Type II	[redacted]	£55,185	£68,322
SMA Type III	[redacted]	£20,229	£21,765

Healthcare costs

ERG critique

- Use of company RWE survey is appropriate
- ERG clinical experts believe type I cost may still be underestimated
- Key driver of ACM3 later onset model

	ICER (patient)	ICER (patient+carer)
Early onset model; List price		
ACM3 company base case	£718,184	£2,482,192
All disease management costs halved	£655,150	£2,264,336
All disease management costs doubled	£844,250	£2,917,904
SMA 1 cost x 4 of RWE survey	£747,646	£2,584,019
SMA 1 costs x 1.5 of RWE survey	£710,818	£2,456,735
Later onset model; List price		
ACM3 company base case	£750,709	£323,663
All disease management costs halved	£838,462	£361,497
All disease management costs doubled	£575,203	£247,995
SMA 1 cost x 4 of RWE survey	£477,312	£205,790
SMA 1 cost x 1.5 of RWE survey	£819,058	£353,131

Health–related quality of life

Key changes and considerations

ACM 1	• Company used PedsQL data (CHERISH) mapped to EQ-5D for utilities • ERG presented alternatives: EQ-5D vignette and clinical advisor estimates • Committee considered all patient utilities had serious limitations • Caregiver disutility included (1 caregiver assumed) • Committee conclude quantifying caregiver disutility introduced uncertainty
ACM 2	• Company used ERG's EQ-5D vignette study • 2 caregivers assumed • Carers gained more incremental health from nusinersen than patients • Committee agreed SMA can affect multiple members of an extended family
ACM 3	• Company use new clinical experts estimates (not preference-based) • 3 caregivers assumed for early-onset model • 2 caregivers + 3 caregivers in worst health state assumed for late-onset

Health–related quality of life: patient utilities

Milestones	ACM1 PedsQL->EQ-5D	ACM2 EQ-5D vignette	ACM3 Company clinical expert
Early-onset model			
None	[redacted]	-0.240	-0.020
Mild	[redacted]	-0.120	0.100
Moderate	[redacted]	-0.170	0.200
Sits with support	[redacted]	-0.040	0.400
Stands assistance	[redacted]	0.040	0.650
Walks with aid	[redacted]	0.520	0.750
Stand/wlks unaided	[redacted]	0.710	0.850
Later-onset model			
Sits without support	[redacted]	0.040	0.400
Sits and rolls	[redacted]	0.040	0.450
Sits and crawls	[redacted]	0.100	0.500
Stands/walks with aid	[redacted]	0.390	0.700
Stands unaided	[redacted]	0.720	0.850
Walks unaided	[redacted]	0.720	0.850

Health–related quality of life: patient utilities

ERG critique

- Issues with face validity of preference-based utility estimates for SMA so use of clinical opinion reasonable.
- Concerns:
  - values not based on formal elicitation
  - defined only by motor function
  - may vary by clinician
  - may not reflect people with SMA or their carers.
- Later onset model:
  - ERG clinical adviser suggest might be reasonable to distinguish HRQoL between some health states (states i, ii, iii) on basis of correlation with other markers of disease but this may not apply as patients age.
  - Utility for patients who lose ability to sit (0.2) is reasonable.

[redacted]

Health–related quality of life: carer utilities

Milestones	ACM1 Bastida + linked to patient utility	ACM2 Bastida + linked to general population utility	ACM3 Bastida + linked to general population utility
Early-onset model			
None	0.832	0.484	0.484
Mild	0.850	0.556	0.556
Moderate	0.850	0.628	0.628
Sits with support	0.878	0.700	0.700
Stands assistance	0.905	0.771	0.771
Walks with aid	0.905	0.843	0.843
Stand/wlks unaided	0.905	0.915	0.915
Later-onset model			
Sits without support	0.797	0.484	0.700
Sits and rolls	0.815	0.592	0.743
Sits and crawls	0.843	0.700	0.786
Stands/wlks with aid	0.870	0.807	0.807
Stands unaided	0.870	0.915	0.915
Walks unaided	0.941	0.915	0.915

Health–related quality of life – Carer utilities

ERG critique

- Estimates of caregiver burden based on assumptions not evidence.
- For early onset, caregiver burden for patients with significantly improved motor milestones may be less – not reflected in model (may lower ICER).
- For later onset, assumption that those who lose ability to sit will require additional caregiver support is appropriate.
- Caregiver utilities and number of caregivers explored in sensitivity analyses.

[redacted]

Utilities: early onset

Early onset model; List price	Incr QALYS (patient)	Incr QALYS (patient+ carer)	ICER (patient)	ICER (patient+carer)
ACM3 company base case	2.64	0.76	£718,184	£2,482,192
Exploratory analyses				
ERG clinical advisors' patient utilities	2.99	1.11	£634,232	£1,703,059
HRQoL for sits without support set equal to 0.50	2.81	0.93	£676,051	£2,042,291
'Narrow range' caregiver utilities	2.64	1.08	£718,184	£1,761,063
Number of caregivers changed to 1	2.64	2.01	£718,184	£941,126
Number of caregivers required for patients in health states consistent with Type 2/3 SMA set equal to 2	2.64	1.34	£718,184	£1,409,705

[redacted]

Utilities: later onset

Late onset model; List price	Incr QALYS (patient)	Incr QALYS (patient +carer)	ICER (patient)	ICER (patient+carer)
ACM3 company base case	2.56	5.94	£750,709	£323,663
Exploratory analyses				
ERG clinical advisors' patient utilities	2.04	5.42	£942,142	£354,739
'Narrow range' caregiver utilities	2.56	4.61	£750,709	£416,836
Number of caregivers changed to 1	2.56	4.89	£750,709	£392,735
Use of caregiver utilities from the company's post-ACD model	2.56	5.88	£750,709	£327,125

Key drivers of the ICER

- Both models are sensitive to:
  - Assumptions concerning the new ‘plateauer’ sub-model, including time at which the plateau is applied and whether people will worsen plateaued
  - Caregiver assumptions
- The early-onset model is also sensitive to:
  - Expected overall survival gain
  - Proportion who are expected to temporarily worsen whilst having nusinersen
- The late-onset model is also sensitive to:
  - The expected proportion who would lose the ability to sit without support
  - Transition probabilities
  - Increased healthcare costs, particularly SMA type I
- Note: many key drivers are **not** independent of one another. E.g. increased SMA type I healthcare costs is a key driver **only** if people are assumed to lose ability to sit

[redacted]

Key issues for consideration

- Is the new model structure suitable for decision-making?
- What assumptions and inputs does the committee consider to be most plausible regarding:
  - Transition probabilities
  - Survival
  - Resource costs
  - Patient and carer utilities
- Could further data collection resolve uncertainties?
- Any other benefits that have not been incorporated into the ICER?
- What is the most plausible ICER for early onset SMA?
- What is the most plausible ICER for late onset SMA?
  - Could this be considered plausibly cost-effective?

[redacted]

Proposed managed access agreement (MAA)*
Patient eligibility

- Subset of authorised SMA population
  - Infantile onset (type 1)
  - Later onset (types 2 & 3)
- In addition to fulfilling criteria of marketing authorisation, additional criteria for the following subgroups developed with clinical input organised by NICE
  - Pre-symptomatic
  - Non-sitters (type1)
  - Sitters (type 2)
  - Ambulatory (type 3)
- Further discussion required for older children and young adults

[redacted]

** These criteria were drawn up as a result of meetings involving NICE, NHSE, clinicians and patients. They were sent to committee in October 2018.*

Proposed Managed Access Agreement (MAA)*
Outcomes and stopping rules

Outcomes	Proposed stopping rule
Survival	All stop due to mortality.
Respiratory - Incidence, length and type of ventilation - LRTI, pneumonia and pneumonia-like illness – rates, severity and duration	Advanced ventilatory support not caused by reversible infection / tracheostomy where further treatment is deemed futile.
Motor function - Non-sitters - HINE (infants), RHS, CHOP INTEND, RULM - Sitters and ambulatory - RHS, RULM	Worsening in symptoms two (2)* consecutive measures of decline of: > 2 on horizontal kick or 1 on other HINE scores excluding voluntary grasp >4 points on the CHOP INTEND scale >3 points on the RHS scale * in order to allow for confirmation of worsening and not a 'off' assessment day
Scoliosis	Inability to administer nusinersen by intrathecal administration as a consequence of spinal fusion surgery.

* These criteria were drawn up as a result of meetings involving NICE, NHSE, clinicians and patients.