Single Technology Appraisal

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope**, **final stakeholder list** and **Call for evidence Documents** on the NICE website.

1. **Call for Additional Evidence document (CfE)** as issued to consultees and commentators

2. **Company response to the CfE**:
   a. Company response to EAG Clarification on CfE

3. **Consultee and commentator comments on the CfE consultation** from:
   a. Association of British Neurologists British Paediatric Neurology
   b. Clinical expert – Anne Marie Childs
      bi Clinical survey
   c. BPNA British Paediatric Neurology Association
   d. Duchenne UK
      di. Transcript Duchenne UK listening session
   e. Muscular Dystrophy UK and Action Duchenne
   f. British Paediatric Neurology Association (Muscle Interest Group)

4. **Expert personal perspectives** from:

   a. Dr Jon Hastie – Patient expert, nominated by Duchenne UK
   b. Fleur Chandler – Patient expert, nominated by Duchenne UK

5. **External Assessment Group critique of company response to the CfE**

Documents relating to the ScHARR carer utility study are marked confidential in their entirety, would have been fully redacted and so have not been shared.

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Call for additional evidence

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over

Committee discussion and call for additional evidence

The evaluation committee discussed this appraisal at its committee meeting in July 2025. It considered evidence submitted by ITF Pharma UK, a review of this submission by the external assessment group (EAG), and responses from stakeholders, including evidence submitted during the technical engagement. It also heard evidence and testimony raised by experts during the meeting. See the committee papers for full details of the evidence.

In its extensive discussion and deliberations, the committee took into account the nature of this rare, serious, progressive, fatal condition that begins in childhood, alongside the available evidence on clinical and cost effectiveness of givinostat. The committee was unable to reach a full conclusion, because it considered that more evidence is needed before it could make a fully informed decision. Therefore, the committee outlined additional information and analyses that it would need to determine whether givinostat should be recommended as an option in the NHS.

Stakeholder organisations and invited experts who are participating in the appraisal are invited to submit additional evidence to support the committee's decision making, as outlined in this document. You are encouraged to focus on the issues highlighted in the following sections. NICE will also consider any other points raised as appropriate. NICE is not able to accept comments from individuals, including people with Duchenne muscular dystrophy, family members or clinicians, unless they are

Issue date: August 2025

the invited experts. People are encouraged to contact participating organisations. Submission details and instructions are provided separately.

Duchenne muscular dystrophy

Duchenne muscular dystrophy is a rare, severe, and progressive genetic condition caused by mutations in the dystrophin gene, which is essential for maintaining muscle fibre integrity. Without dystrophin, muscles gradually weaken and degenerate. Because the gene is located on the X chromosome, the condition primarily affects boys and men, although in rare cases, girls may also be affected.

In the UK, around 100 people are born with Duchenne muscular dystrophy each year, and approximately 1,183 are currently living with the condition. Symptoms typically begin between ages 2 and 5, including delayed motor milestones, frequent falls, enlarged calf muscles, and Gower's sign. As the condition progresses, individuals lose the ability to walk, followed by loss of upper limb function, respiratory decline, and heart complications such as cardiomyopathy.

Most people with Duchenne muscular dystrophy require full-time support for daily activities including eating, dressing, and moving. Mobility aids such as wheelchairs become essential, and regular monitoring of the spine, heart, and breathing is needed. Scoliosis may develop and require surgery. Most people need ventilatory support in their teens or early twenties, including overnight non-invasive ventilation (a method of supporting breathing using a mask or mouthpiece, which helps maintain oxygen levels and reduce strain on weakened respiratory muscles) and cough assistance.

As dependence increases, families and carers play a central role in daily care. Duchenne muscular dystrophy is a fatal condition, and life expectancy is typically under 30 years.

Impact of the condition

Duchenne muscular dystrophy has a profound and wide-ranging impact on the lives of people with the condition and their families. The progressive loss of muscle

function, and associated loss of mobility and independence, leads to significant emotional, psychological, and physical strain. Support from carers is needed from the early stages of the disease. As the condition advances, full-time care is required. This has a substantial and sustained effect on carers. Siblings may also be affected emotionally, experiencing worry, guilt, or isolation, and their lives are often shaped by the needs and routines of the family member with Duchenne muscular dystrophy.

The patient and clinical experts highlighted that there is an unmet need for treatments that can slow disease progression. Maintaining the ability to move independently and using arms and hands for as long as possible is seen as essential for preserving independence, mental wellbeing, and participation in everyday life. One particularly important stage is known as the transfer stage, when a person can no longer walk but can still stand with support. A patient expert described how her 19-year-old son, who is still in the transfer stage, remains highly independent. He can work, travel, and with support, move independently. This level of independence has a profound impact on his quality of life and reduces the impact on carers.

The committee heard about the importance of delaying the loss of mobility and maintaining independence particularly during the teenage years. This is a time when most young people are gaining greater freedom, learning to drive, attending university, and spending more time with friends. While young people with Duchenne muscular dystrophy may be experiencing the opposite, increasing dependence. This contrast can be emotionally challenging and isolating. For some people with the condition, the loss of mobility can also be associated with experiences of bullying or social exclusion, further affecting mental health and self-esteem.

Delaying the loss of mobility can help preserve a sense of autonomy and self-worth and may allow young people to continue doing things that are important to them, such as attending university lectures, participating in social life and pursuing their interests. These aspects of independence are not only practical but are also deeply connected to emotional wellbeing, identity, and inclusion. Being able to maintain independence for longer can help people with Duchenne muscular dystrophy continue to engage in education, relationships, and other key parts of growing up.

The committee understood that Duchenne muscular dystrophy is a severe, progressive, and life-limiting condition that imposes a substantial and enduring impact on individuals, their families, and carers, affecting physical health, emotional wellbeing, and quality of life.

Company's positioning of givinostat

The company restricted the population in its submission to people 6 years and over who are ambulant at the start of treatment. This is consistent with the population in the EPIDYS trial and the open-label extension (OLE) study.

But givinostat is licensed for the treatment of Duchenne muscular dystrophy in people 6 years and over, regardless of whether they are ambulant at the start of treatment. The clinical experts noted that people who are non-ambulant may still benefit from treatment, and that restricting access based on ambulation status could exclude people who might otherwise experience important improvements. The patient experts thought that givinostat should be available to all people with Duchenne muscular dystrophy and that it would be unfair to deny this treatment to people who had already lost ambulation.

The company explained that at the time of submission, it only had evidence for the ambulant starting population so it could therefore only model the cost effectiveness of givinostat in this population. It noted that a trial, ULYSSES, was underway to assess givinostat in a non-ambulant starting population.

The committee acknowledged the broader licensed population and the views of clinical and patient experts. But it concluded that, while the appraisal scope includes the full marketing authorisation population, it could only consider this full population if sufficient evidence was submitted. On balance, the committee agreed that it was not possible to make recommendations beyond the narrower population for which the company had submitted evidence. So, the committee could only consider the ambulant starting population in its decision making.

Committee call for additional evidence

The committee recognised the high unmet need for effective treatments for Duchenne muscular dystrophy but because of high level of uncertainty in the evidence it was not able make a fully informed decision. The areas with most uncertainty were:

1. the estimation of givinostat treatment effect and its application in the model
2. the carer health-related quality-of-life modelling and assumptions
3. the patient health-related quality-of-life modelling and assumptions
4. the resource cost modelling and assumptions.

Therefore, the committee outlined the additional information and analyses that it would need to inform decision making.

Estimation of givinostat treatment effect and application in the model

- Explore alternatives to the company's acceleration factor-based approach (for example, applying the hazard ratios from the unanchored matching-adjusted indirect comparisons [MAIC] directly to the transitions); further justification that the relationship between outcomes would be the same between givinostat and established clinical management (ECM).
- Clarify whether the company's current approach modelled a treatment effect beyond loss of ambulation; clear explanation distinguishing between direct effects of ongoing givinostat treatment in non-ambulant patients and indirect (or knock-on) effects resulting from delaying disease progression during the ambulatory phase.
- If modelled, justify the magnitude of any post loss-of-ambulation treatment effect, and explore how uncertainty in longer-term treatment effects could otherwise be incorporated into decision making.
- Present updated economic modelling based on plausible, evidence-based and fully justified approaches to modelling the givinostat treatment effect.

Carer health-related quality-of-life modelling and assumptions

The committee acknowledged the sensitivity and critical importance of this issue for patients and families, and the substantial technical challenges associated with it. It also highlighted the substantial effect it had on the cost-effectiveness of givinostat. The committee recognised that it was important to ensure carer health-related quality of life was appropriately and robustly considered in decision making. The committee considered that it was not appropriate to assume that extending the life of someone with Duchenne muscular dystrophy would have no direct effect on carers' health-related quality of life. But, it also acknowledged that extending time in health states associated with a negative impact on carers' would extend that negative impact. The committee also highlighted important limitations and uncertainties in both the company's and EAG's approaches, including the number of carers, utility values and methodological approach.

The committee concluded that carer health-related quality of life needed to be captured appropriately, but neither the company's nor the EAG's approaches to quantify this had done so. It therefore concluded that further information and modelling was needed.

- Present updated economic modelling based on plausible, evidence-based and fully justified approaches to modelling effects on carer health-related quality of life, considering in particular:

  Approach to modelling (increments from midway, disutilities):
  - Comment on the rationale, implications and plausibility of each method, including the justification for using increments or disutilities compared to selected health states or general population values.
  - Ensure that the approach captures the increasing impact on carers as the condition progresses.
  - Explain why in the current model, the approaches produce different results if the numbers of carers are not equal in all health states (including in scenarios that do not model carers in state 9).

Utility source

- Clarify and justify how reported utility values were assigned to model health states. Justify the appropriateness of Landfeldt et al. (2017) versus Landfeldt et al. (2016a), and comment on the consistency in utility modelling between patient and carer utilities.
- Present analyses based on all sources of carer utilities.
- Explore different ways to differentiate between health states 7 and 8 for all possible sources.

Number of carers in ambulatory health states:

- Explore scenarios modelling between 1 and 2 carers in ambulatory states to better reflect the overall magnitude of effects on carer health-related quality of life (with 2 carers in the non-ambulatory health states).

Life-extension effect on carer health-related quality of life

- The committee was aware that modelling relating to the effects of life extension on carer health-related quality of life has a large impact on the ICER. The committee considered that it was unreasonable for the model to assume that there would be no negative effect of losing a child on health-related quality of life. But, it also considered that the company's approach and increment of -0.56 (implying a carer utility of 0) was not evidence based and may not be appropriate. It further acknowledged that extending time in health states with a negative effect on carers would extend that negative effect during that period.
- Therefore, explore and justify different approaches for modelling the effect of life extension on carers. This may include using different utilities for health state 9, and must take into account strengths and limitations of different methodological approaches for modelling life-extension effect on carer health-related quality of life.

Patient health-related quality-of-life modelling and assumptions

- Clarify and justify how reported utility values were assigned to model health states. Justify the appropriateness of Landfeldt et al. (2017) versus Landfeldt et

al. (2016b), and comment on the consistency in utility modelling between patient and carer utilities.
- Explore patient health-related quality of life informed by Crossnohere et al. (2021).
- Capture the increasing impact on patients as the condition progresses; explore different ways to differentiate between health states 7 and 8 for all possible sources (for example, by combining models 2 and 3 from Landfeldt et al. 2017).

Resource cost modelling and assumptions

- Further explore tertiary-care and medical-aid costs.
- Ensure scenarios differentiate between health states 7 and 8.

Equality

- Describe any further issues of equality that the committee should take into account in its decision making.

Committee other considerations

The committee reached conclusions on some issues and preferred assumptions. It requested that analyses be presented using these conclusions and preferred assumptions. Specifically:

- use ECM based on treatment regimens used in EPIDYS as a comparator
- use the UK real-world dataset as a source for ECM data in the unanchored MAIC
- use the full givinostat population from EPIDYS and the OLE study (n=224) as a source of givinostat data for the unanchored MAIC
- use the reference-case discount rate of 3.5% for costs and health effects, throughout the model time horizon
- use the company's updated natural history model.

Single Technology Appraisal

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Call for additional evidence response form

Committee discussion and call for additional evidence

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In its extensive discussion and deliberations, the committee took into account the nature of this rare, serious, progressive, fatal condition that begins in childhood, alongside the available evidence on clinical and cost-effectiveness of givinostat. The committee was unable to reach a full conclusion, because it considered that more evidence is needed before it could make a fully informed decision. Therefore, the committee outlined additional information and analyses that it would need to determine whether givinostat should be recommended as an option in the NHS.

Stakeholder organisations and invited experts who are participating in the appraisal are invited to submit additional evidence to support the committee's decision making, as outlined in this document. You are encouraged to focus on the issues highlighted in the following sections. NICE will also consider any other points raised as appropriate. NICE is not able to accept comments from

individuals, including people with Duchenne muscular dystrophy, family members or clinicians, unless they are the invited experts.

People are encouraged to contact participating organisations. Submission details and instructions are provided separately.

About you

Table 1: About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	ITF Pharma UK (Company respondent)
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Committee call for additional evidence

Following the first Appraisal Committee Meeting (ACM), the Committee recognised the high unmet need for effective treatments for Duchenne muscular dystrophy (DMD), but it stated that because of high level of uncertainty in the evidence it was not able make a fully informed decision. The areas with most uncertainty were:

1. the estimation of givinostat treatment effect and its application in the model
2. the carer health-related quality of life (HRQoL) modelling and assumptions
3. the patient HRQoL modelling and assumptions
4. the resource cost modelling and assumptions.

The Committee outlined the additional information and analyses that it would need to inform decision making with respect to these topics; the Company has addressed each of these requests in the relevant Sections below. The Committee has reached conclusions on several issues and has also established preferred assumptions. They have requested that future analyses be presented using these updated assumptions, specifically:

1. use established clinical management (ECM) based on treatment regimens used in EPIDYS as a comparator
2. use the UK real-world dataset as a source for ECM data in the unanchored matching-adjusted indirect comparison (MAIC)
3. use the full givinostat population from EPIDYS and the open-label extension (OLE) study (n=224) as a source of givinostat data for the unanchored MAIC

4. use the reference-case discount rate of 3.5% for costs and health effects, throughout the model time horizon
5. use the company's updated natural history model (NHM).

The Company acknowledges the Committee's preferred assumptions and has updated its base case to include: (1) ECM based on treatment regimens used in EPIDYS as a comparator, (2) using the UK real-world dataset as a source for ECM data in the unanchored MAIC, (3) using the full givinostat population from EPIDYS and the OLE study (n=224) as a source of givinostat data for the unanchored MAIC, and (5) using the Company's updated NHM.

In response to the request to use the 3.5% reference-case discount rate (4), we have presented two base cases (see Section 5 for more detail). The Company's core rationale for a lower discount rate for health outcomes is that the benefits of givinostat extend over a patient's entire lifetime. For a child with a chronic progressive disease like DMD, the benefits of a treatment can accrue over many decades. A 3.5% discount rate heavily undervalues these future gains, as benefits are discounted more steeply over time. It is our understanding that the 1.5% discount rate is available to provide flexibility for technologies that provide sustained, long-term benefits in severe conditions. However, the strict application of the NICE criteria for non-reference discounting effectively excludes DMD and similar chronic paediatric conditions from this flexibility. Givinostat meets two of the three criteria, as it addresses a severely impairing condition and provides sustained benefits. However, it cannot meet the third criterion, which requires that a treatment restore patients to full or near-full health - a condition that is impossible to meet in the context of DMD. We believe that givinostat meets all the criteria it feasibly can, making a 1.5% discount rate for health outcomes appropriate and fair. Therefore, we have included two base cases for your review: (i) the Company-preferred base case applying a 1.5% discount rate to health outcomes, and (ii) a base case applying the 3.5% discount rate to health outcomes.

In addition as detailed in Section 2, new interim data have become available from an ongoing study led by the University of Sheffield for Duchenne UK: "*Health-related quality of life (HRQoL) impacts on Duchenne parent-carers: A qualitative survey*."[1] These interim findings offer additional evidence on caregiver burden in DMD, including EQ-5D-5L values (mapped to EQ-5D-3L) reported by UK caregivers aligning with health states from the Project HERCULES cost-effectiveness model (CEM), and the number of caregivers involved.[2] It should be noted that these results are provisional and confidential, as the quality assurance process and full analysis are ongoing. However, they have been provided to the Company at this stage to support this appraisal. The Company updated base case includes the new health state EQ-5D utility data for caregivers and incorporates the new information on the number of caregivers.

Table 1 presents the step-change from the Company base case presented in the technical engagement (TE) to the updated Company base case. Note: the starting incremental cost-effectiveness ratio (ICER) of £[redacted] reflects the 1.5% discount rate for health outcomes applied across the whole time horizon and was presented in Table 8 in the TE response form. Whereas the starting ICER of £[redacted] reflects the 3.5% discount rate for health outcomes applied across the whole time horizon and has not been presented previously. **The updated Company base case reflects an ICER of £[redacted] when using the 1.5% discount rate and £[redacted] when using the 3.5% discount rate.**

Table 1: Step change in the Company updated base case ICERs

	Base case 1: 1.5% discount rate (outcomes), 3.5% discount rate (costs)		Base case 2: 3.5% discount rate (outcomes), 3.5% discount rate (costs)	
	ICER step change	**% change each step**	**ICER step change**	**% change each step**
Original Company base case	[redacted]	NA	[redacted]	NA
Use ECM based on treatment regimens used in EPIDYS as a comparator	No change – already in Company base case			
Use the UK real-world dataset as a source for ECM data in the unanchored MAIC	No change – already in Company base case			
Use the full givinostat population from EPIDYS and the OLE study (n=224) as a source of givinostat data for the unanchored MAIC	[redacted]	-1.7%	[redacted]	-1.7%
Use the company's updated natural history model	No change – already in Company base case			
Source of caregiver utilities (University of Sheffield and Project HERCULES new interim data)[1]	[redacted]	-6.3%	[redacted]	-3.6%
Number of caregivers (University of Sheffield and Project HERCULES new interim data)[1]	[redacted]	-26.6%	[redacted]	-22.8%
Updated Company base case	[redacted]	**-26.6%**	[redacted]	**-22.8%**

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; NA, not applicable; OLE, open-label extension; UK, United Kingdom.

1 Estimation of givinostat treatment effect and application in the model

Note: The estimation of givinostat's treatment effect and its application within the model have been detailed extensively in the Company Submission (CS), response to Clarification Questions (CQs), and in response to the TE. This response begins by summarising the previously submitted evidence, with references to where further detail can be found. It also aims to clarify the overall approach before addressing each of the specific requests outlined in the Call for Evidence documentation.

As a randomised controlled trial in a population starting as ambulant, EPIDYS offers robust evidence of givinostat's early clinical benefit by directly comparing outcomes over an 18-month randomisation period against a placebo group.[3,4] While EPIDYS provides valuable evidence on short-term outcomes, its randomised follow-up period is limited relative to the disease course of DMD, primarily due to ethical constraints around prolonged use of placebo (for more detail see response to Key Issues 4, 5 and 6 in the TE response). Therefore, these data alone cannot inform long-term outcomes required in CEM, such as loss of ambulation (LOA), initiation of non-invasive ventilation (NIV), or decline in forced vital capacity (FVC).

Following the randomised study, an OLE is collecting longer-term data; however, this study is single-arm, with all patients receiving givinostat.[5] As a result, the OLE lacks a comparator group, limiting its ability to assess relative treatment effectiveness over the long term. Nevertheless, the OLE provides one of the longest follow-ups of treatment for DMD with a mean follow-up of 1,204.2 days (standard deviation [SD] ±446.3; median 1,179.0 [range 99 to 2,259] days) at December 2023 data cut-off (DCO).[5] This has allowed us to observe a median LOA of 17.25 years (95% CI: 15.40–NE) when including all givinostat-treated patients (i.e., the Company's updated base case, aligning with the Committee's preferences, see CS Section B.2.8.4, and TE response to Key Issue 3 for more detail).[5] No events have yet been observed for the NIV and FVC<1L endpoints.

To estimate the relative effectiveness of givinostat compared with ECM for informing the lifetime CEM, UK real-world data (reflecting a national dataset comprising the leading adult DMD centre and two other leading UK centres, capturing outcomes for N=209 patients) are used as an external control arm.[6,7] These data provide key information on LOA, NIV, and FVC endpoints, which have been validated as representative of current UK clinical practice by clinicians and during the first Committee meeting for this appraisal (see Section B.3.12.2 of the CS and Committee papers pages 520, 547 and 550). The median ages observed in the UK real-world data are 12.28 years for LOA, 18.46 years for NIV, and 23.86 years for FVC <1L, also aligning closely with published literature.[6,8–13] In the EAG report (page 67, Section 3.4.2.2), the EAG "acknowledge the relevance of a UK data source, particularly to inform the natural history baseline". Use of a historical control arm to assess relative efficacy is aligned with that taken in the ataluren NICE submission and is aligned with numerous NICE appraisals in rare diseases.[14–17]

For the LOA endpoint, this approach allows use of the observed data for givinostat and matches these data in an indirect treatment comparison (ITC) to the UK real-world data based on the variable "age at start of corticosteroids (CS)".

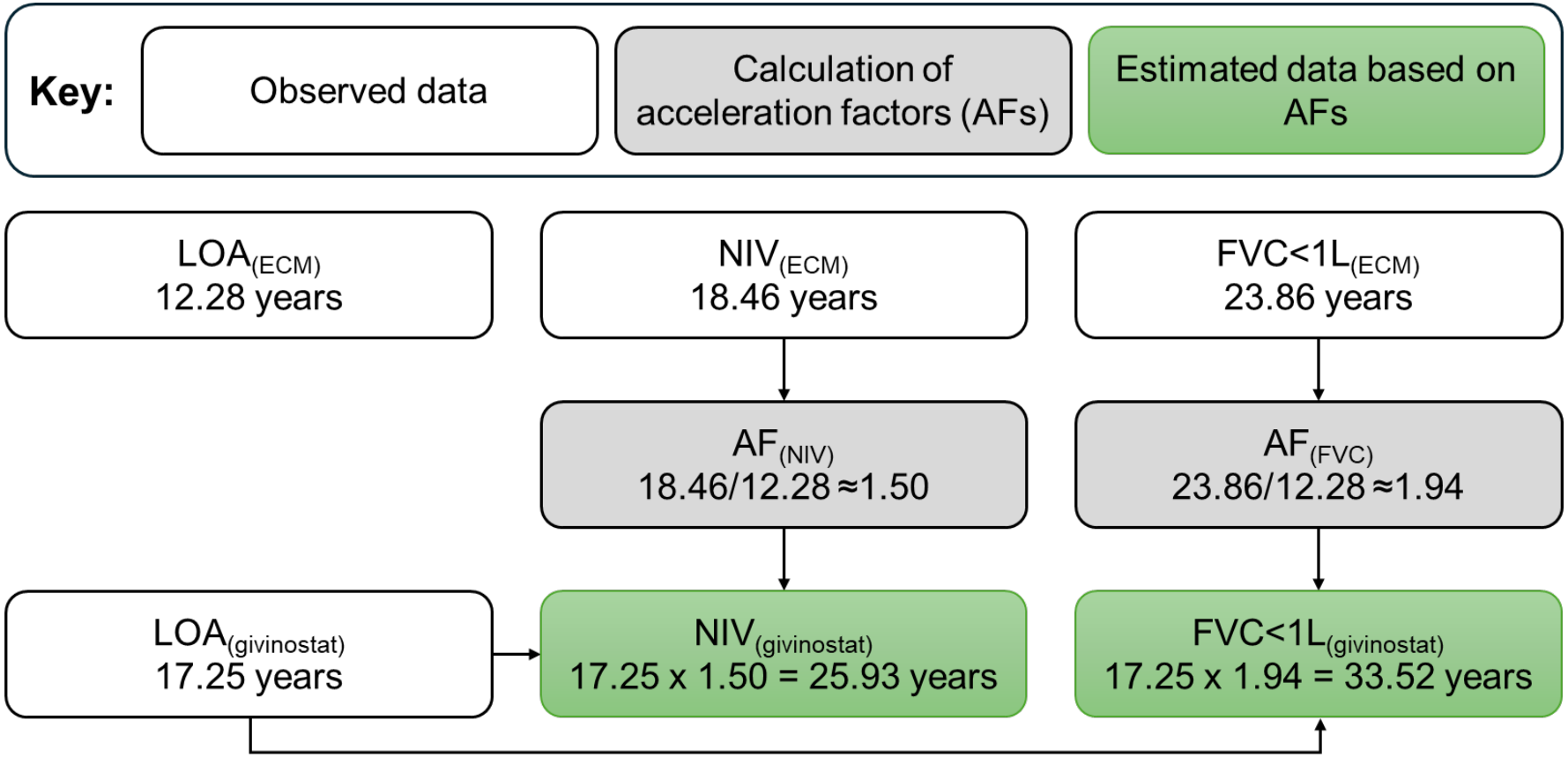
Acceleration factor calculation based on real-world data

For the NIV and FVC <1L endpoints, data are not yet available in the givinostat dataset. To address this gap, the relationship between age at LOA and age at NIV initiation or FVC <1L is assumed to be the same as observed in the ECM data. For example, if the age at NIV is 1.50x the age at LOA for patients receiving ECM, then age at NIV is also assumed to be 1.50x the age at LOA for patients receiving givinostat. Using this assumption, acceleration factors (AFs) were calculated based on the observed data for ECM. The AFs were then applied to the givinostat LOA data to estimate the corresponding NIV and FVC <1L outcomes. Figure 1 illustrates how AFs are used to estimate givinostat endpoints from available data. Note: while the figure highlights the process for

median outcomes, in the analyses the AFs are applied to the entire Kaplan-Meier curve for LOA. This results in time-shifted curves, with the givinostat LOA curve scaled by factors of 1.50 and 1.94 to estimate the corresponding NIV and FVC<1L Kaplan-Meier data, respectively.

The AF-adjusted data were then used in the ITCs and, as with the LOA endpoint, were matched to the UK real-world data based on the variable “age at start of CS”. Section B.2.8.2 of the CS, Section B.3 of the Response to CQs, and TE response to Key Issue 11 provide more information on the approach to the ITCs.

Figure 1: How AFs are calculated and applied based on the observed data from the UK real-world study and EPIDYS/OLE



Notes: the givinostat data from EPIDYS/OLE reflect all patients i.e., the Company's updated base case, aligning with the Committee's preferences

Sources: EPIDYS publication: Mercuri et al. 2024;[3,4] DoF (Study 51 Clinical Study Report; Dec 2023 DCO);[5] UK real-world data: Pietrusz et al. (unpublished slide deck)[6] and Pietrusz et al. 2023.[7]

Abbreviations: AF, acceleration factor; DoF, data on file; ECM, established clinical management; FVC, forced vital capacity; LOA, loss of ambulation; NIV, non-invasive ventilation; OLE, open-label extension.

This approach assumes that NIV and FVC<1L occur at proportionally consistent intervals after LOA, regardless of treatment. In other words, disease progression follows the same relative timing and trajectory; givinostat only affects the timing indirectly through its impact on LOA. This assumption requires a clinically plausible rationale that time to later milestones (e.g., NIV or FVC decline) would scale proportionally with LOA. This evidence has been provided in Section B.2.8.2 in the CS, in Section B.3 of the Response to CQs, and in response to Key Issue 5 in the TE response.

This method may in fact underestimate the true givinostat treatment effect at later clinical milestones (e.g., NIV or FVC decline) because it assumes a proportional delay based solely on the shift in LOA. However, in the clinical studies and in the CEM, patients continue treatment with givinostat beyond LOA, which may result in additional disease-modifying effects not captured by the AFs alone. As a result, the impact on later-stage outcomes could be greater than predicted, making this a conservative estimation approach.

Incorporating ITC results into the CEM via SOLVER

The outcomes of the ITCs for givinostat vs. ECM are available in Section B.2.8.5 in the CS, and in response to Key Issue 3 (sensitivity analyses) in the TE response.

The hazard ratios (HRs) derived for LOA, NIV, and FVC<1L from the ITCs reflect treatment effects on key clinical milestones, aligning with the UK real-world data available for ECM. However, the CEM is structured around multiple, granular transitions between functionally distinct health states. Applying the milestone-level HRs directly to these individual transitions would be inappropriate, as these clinical endpoints span several transitions in the CEM. For example, the transition to LOA involves progression through states 1 (early ambulatory), 2 (late ambulatory), 3 (transfer), and into state 4 (the first non-ambulatory health

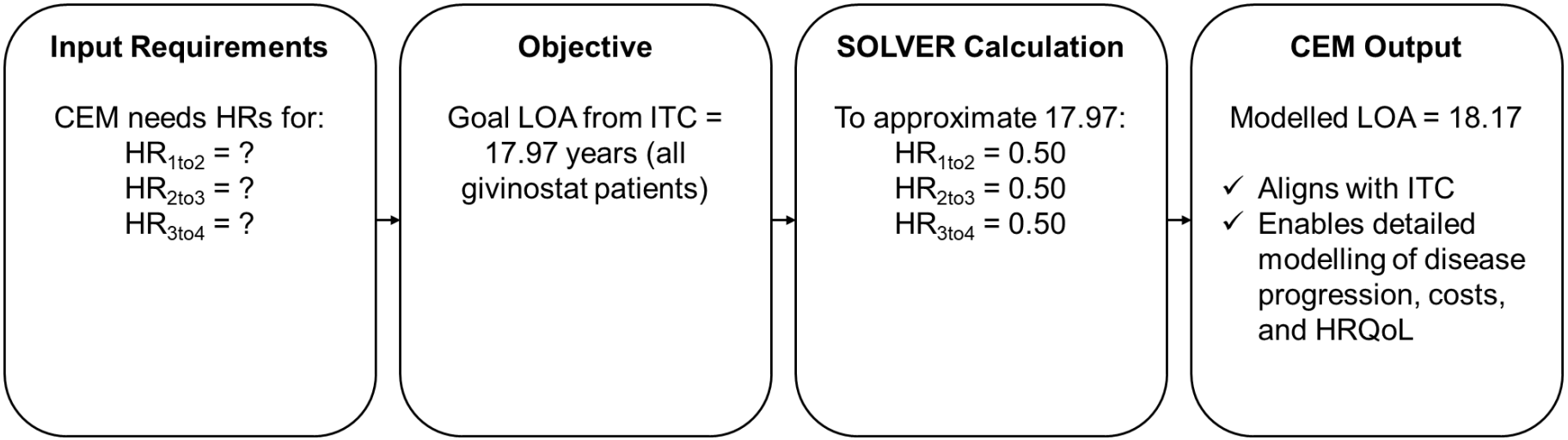
state). Applying a single HR to just one of these transitions would misrepresent both the timing and distribution of the treatment effect, and therefore the progressive stepwise trajectory of the disease. The CEM requires transition-specific HRs to accurately capture the dynamics of disease progression at a more detailed level. Applying a broad milestone HR to a single health state transition, such as from state 2 to state 3 as explored by the EAG (EAG report pages 24-25, Key Issue 11), inaccurately assumes the entire treatment effect occurs at that specific point, which does not reflect the clinical course of disease.

The CEM, developed by the Project HERCULES collaboration, was designed around health states that were extensively validated by clinicians and patient representatives. These states were identified as those most relevant to the treatment pathway and patient experience. Moreover, the health states align with further research conducted by Project HERCULES into healthcare costs, patient HRQoL, and carer HRQoL, with each area of research demonstrating clear and meaningful differences between health states. The CEM structure is also consistent with the one accepted by NICE in the appraisal of vamorolone for DMD (NICE TA1031).[18]

Although there is a structural difference between the milestone-based clinical endpoints used in the ITCs and the more granular health state transitions in the CEM, this does not limit the ability to incorporate ITC results into the CEM. The CEM uses Excel's SOLVER function to calibrate transition probabilities so that the timings of key clinical milestones (LOA, NIV, and FVC <1L) match the observed outcomes in the UK real-world data for ECM and the estimated outputs from the ITCs for givinostat. SOLVER estimates specific transition probabilities within the CEM to ensure that the modelled median times to each milestone align with the ITCs. Figure 2 provides an example of the inputs, the SOLVER requirements, and the CEM output for estimating the HRs predicting LOA for givinostat. This approach is followed for each of the endpoints and enables the CEM to accurately reflect disease progression for both treatment arms while maintaining consistency with the ITC results and the structure of the CEM. The

approach to applying the treatment effect within the CEM is described further in Section B.3.3.2 of the CS, Sections B.5 and B.20 in the CQ, and response to Key Issue 11 in the TE response.

Figure 2: Example of calibrating the CEM to estimate hazard ratios for givinostat | LOA endpoint



Notes: the givinostat goal LOA reflects the ITC using all patients i.e., the Company's updated base case, aligning with the Committee's preferences
Abbreviations: CEM, cost-effectiveness model; HR, hazard ratio; HRQoL, health-related quality of life; ITC, indirect treatment comparison; LOA, loss of ambulation.

In its call for additional evidence, NICE outlined the additional information and analyses required to support decision making on the estimation of givinostat's treatment effect and its application within the CEM:

1. Explore alternatives to the company's acceleration factor-based approach (for example, applying the HRs from the unanchored MAIC directly to the transitions); further justification that the relationship between outcomes would be the same between givinostat and ECM.

2. Clarify whether the company's current approach modelled a treatment effect beyond LOA; clear explanation distinguishing between direct effects of ongoing givinostat treatment in non-ambulant patients and indirect (or knock-on) effects resulting from delaying disease progression during the ambulatory phase.

3. If modelled, justify the magnitude of any post loss-of-ambulation treatment effect, and explore how uncertainty in longer-term treatment effects could otherwise be incorporated into decision making.

4. Present updated economic modelling based on plausible, evidence-based and fully justified approaches to modelling the givinostat treatment effect.

Each are addressed in turn below.

1a. Explore alternatives to the company's acceleration factor-based approach (for example, applying the hazard ratios from the unanchored matching-adjusted indirect comparisons directly to the transitions).

Before addressing this question, we would like to clarify the wording. The AFs are applied to the data prior to conducting the unanchored MAICs; they form part of the assumptions underpinning the ITCs and are not applied within the CEM itself. The Company's approach uses a SOLVER-based approach that relies on the medians derived from the unanchored MAICs. Even when the HRs from the MAICs are applied directly to the CEM transitions, the AFs are still involved, as they are an inherent component in

the MAIC analyses. The Company has addressed this question based on “Explore alternatives to the company’s *SOLVER-based approach* (for example, applying the HRs from the unanchored MAICs directly to the transitions)”.

As outlined above, the HRs derived from the ITCs for LOA, NIV, and FVC<1L represent treatment effects on key clinical milestones and align with the UK real-world data available for ECM. However, the CEM is structured around a series of granular, functionally distinct health state transitions. Applying milestone-level HRs directly to individual transitions is inappropriate, as each milestone spans multiple transitions. For instance, reaching LOA involves progressing through state 1 (early ambulatory), state 2 (late ambulatory), state 3 (transfer), and entering state 4 (first non-ambulatory state). Applying a single HR to just one transition (e.g., state 2 to 3) misrepresents both the timing and distribution of the treatment effect. The CEM requires HRs specific to each transition to accurately capture disease progression dynamics. Applying a broad HR to a single point, as done in the EAG analysis (EAG report pages 24-25, Key Issue 11), oversimplifies the modelling of treatment effect and does not reflect the clinical course.

Nevertheless, in response to the Committee’s concerns, we have extracted the per-cycle proportions of LOA, NIV, and FVC<1L from the CEM for both the ECM and givinostat arms. These are based on the Company’s base case, where SOLVER-calibrated HRs are used to align modelled outcomes with the UK real-world data (ECM) and ITC results (givinostat). We have then applied the HRs from the MAICs directly to the ECM values to assess the impact of an alternative approach, as suggested by the Committee:

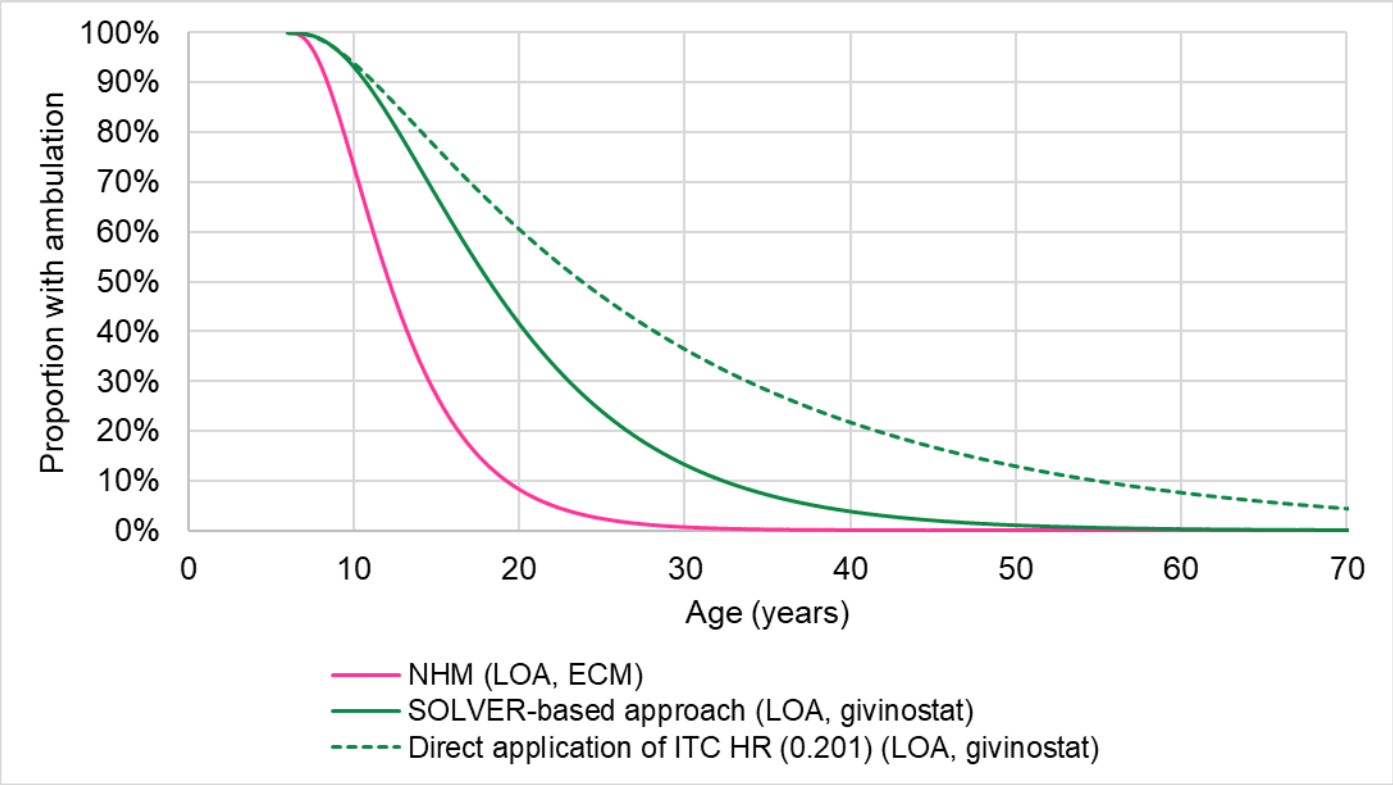
- Figure 3 compares the original SOLVER-based approach, which estimates granular health state HRs, with the ITC-based approach that applies HRs directly to the broader LOA milestones using the HR of 0.201 (updated Company base case, Committee’s preferred, including all givinostat patients).

- Figure 4 compares the original SOLVER-based approach, which estimates granular health state HRs, with the ITC-based approach that applies HRs directly to the broader NIV milestones using the HR of 0.206 (updated Company base case, Committee's preferred, including all givinostat patients).

- Figure 5 compares the original SOLVER-based approach, which estimates granular health state HRs, with the ITC-based approach that applies HRs directly to the broader FVC<1L milestones using the HR of 0.218 (updated Company base case, Committee's preferred, including all givinostat patients).

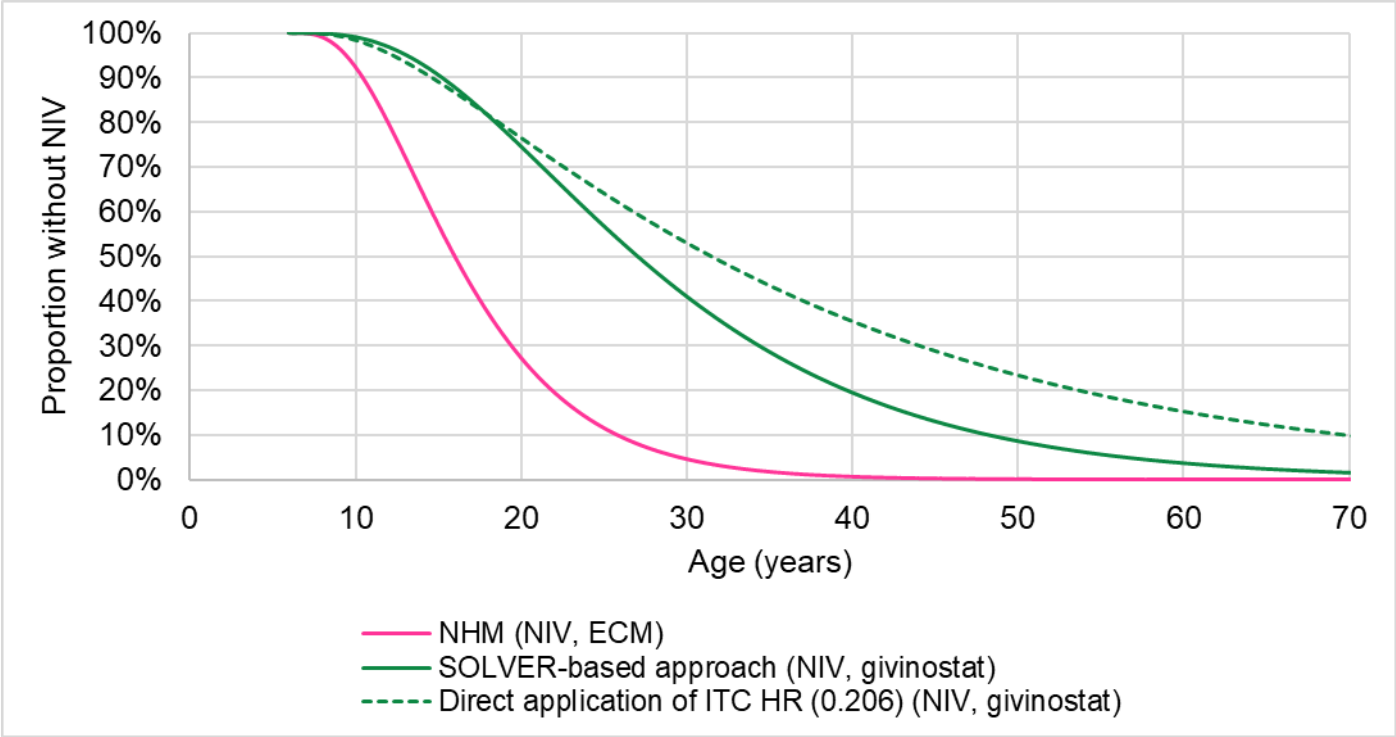
These data and figures are available in the "CforE" sheet in the CEM.

Figure 3: Comparison of LOA Outcomes: SOLVER-based approach HRs vs. Direct Application of ITC HRs



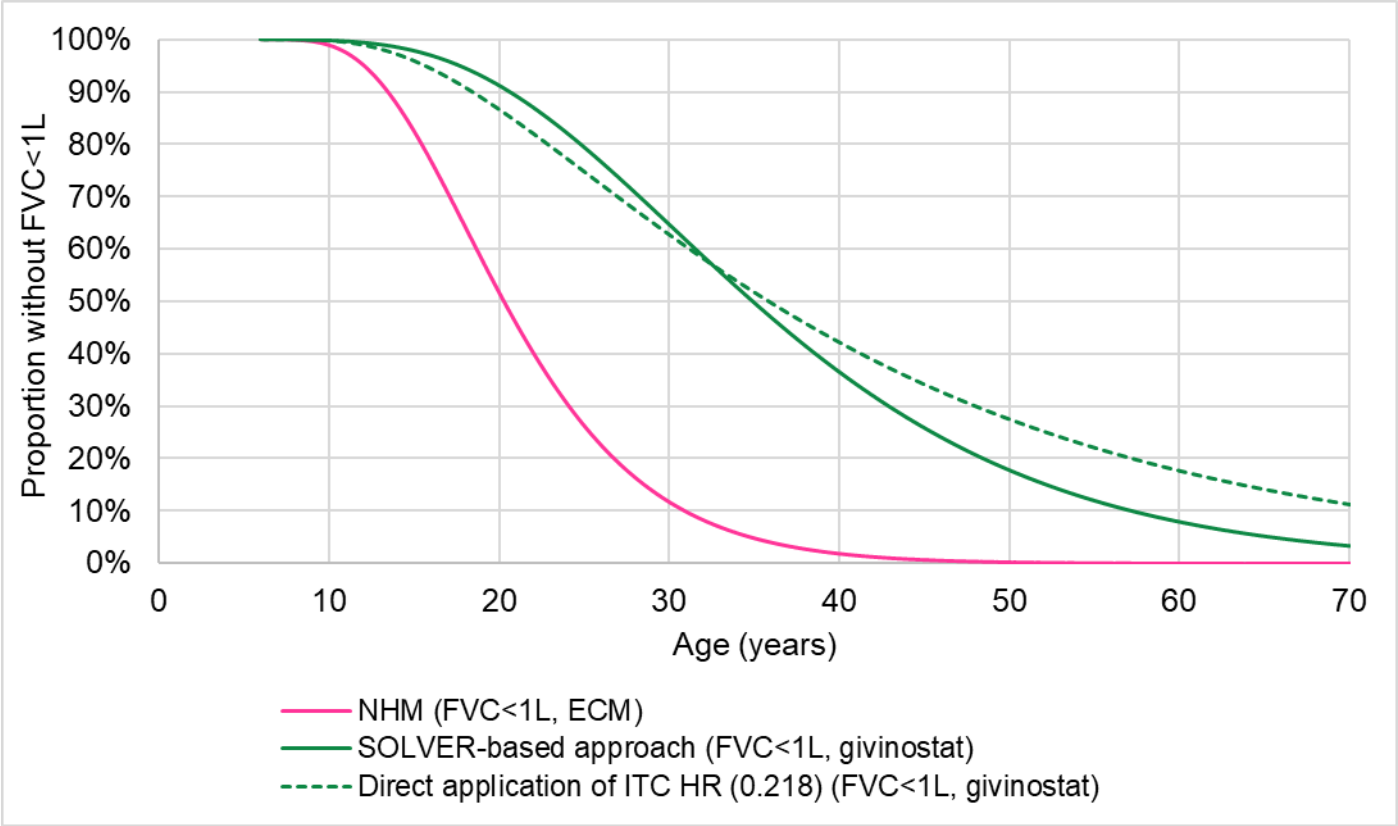
Notes: the ITC uses all patients i.e., the Company's updated base case, aligning with the Committee's preferences
Abbreviations: ECM, established clinical management; HR, hazard ratio; ITC, indirect treatment comparison; LOA, loss of ambulation; NHM, natural history model.

Figure 4: Comparison of NIV Outcomes: SOLVER-based approach HRs vs. Direct Application of ITC HRs



Notes: the ITC uses all patients i.e., the Company's updated base case, aligning with the Committee's preferences
Abbreviations: ECM, established clinical management; HR, hazard ratio; ITC, indirect treatment comparison; NHM, natural history model; NIV, non-invasive ventilation.

Figure 5: Comparison of FVC<1L Outcomes: SOLVER-based approach HRs vs. Direct Application of ITC HRs



Notes: the ITC uses all patients i.e., the Company's updated base case, aligning with the Committee's preferences
Abbreviations: ECM, established clinical management; FVC<1L, forced vital capacity <1 litre; HR, hazard ratio; ITC, indirect treatment comparison; NHM, natural history model.

The figures presented show that using SOLVER to calibrate the model so that it matches the median times from the ITCs consistently results in more conservative estimates of givinostat's impact compared to applying the HRs from the ITCs directly to

the relevant ECM curve. This difference likely arises from how medians and HRs represent treatment effects. The median time to an event (like LOA) is just one point on the curve - it tells us when half the patients have experienced the event, but it does not reflect what is happening before or after that point. In contrast, a HR considers the entire follow-up period and reflects differences at every time point between givinostat and ECM groups.

In the Company base case, we use the ITC median values to estimate the effects of treatment on each individual step in the disease progression. This allows us to preserve the detailed structure of the model, which has been extensively validated and aligns with meaningful differences in cost and HRQoL inputs. While medians are not always preferred over HRs, this method was chosen because it allows alignment between the data and the model structure. Based on the comparison shown in Figure 3 - Figure 5, this approach is likely conservative i.e., it may underestimate the full benefits of givinostat. Nevertheless, calibrating to the median ensures consistency with observed results.

While we have explored applying the HRs from the ITC directly in the model, as requested by the Committee, this approach produces outcomes that appear clinically implausible. Although early predictions align with observed data, the model predicts a median time to event that is much longer than what has been estimated to date. We believe our approach provides a more realistic reflection of the current evidence and avoids overstating the long-term benefits of givinostat. Note: This approach has not been implemented in the model, as the resulting outcomes are not considered clinically plausible. Additionally, it does not align with the cost and HRQoL evidence nor the clinician and patient insights that informed the Project HERCULES model structure.

1b. Further justification that the relationship between outcomes would be the same between givinostat and ECM.

Section B.3.12.2 of the CS and Committee papers pages 520, 547 and 550 present literature and clinician feedback supporting the long-term outcomes predicted for the ECM arm of the model. In addition, the response to Key Issue 5 in the TEs further summarises the evidence underpinning the extrapolation of outcomes from the EPIDYS trial to those used in the CEM. We believe the available evidence has been appropriately used to support both the ECM and givinostat modelled outcomes. However, we recognise ongoing uncertainty remains regarding the assumption underpinning the AFs used in the ITCs - specifically, whether the relationship between outcomes observed with ECM would be the same in the givinostat arm.

To explore this issue further, we have examined studies comparing outcomes before and after the introduction of steroids, to assess whether the relationship between outcomes achieved by steroid-naïve and steroid-treated patients supports the assumption underpinning the AFs. Although relatively few studies report median (or mean) values for both LOA and later relevant milestones (e.g., NIV, FVC < 1L), we identified two relevant studies.[19,20] Note: it is impossible to separate out the effect of delayed LOA on the later milestones vs. the treatment effect of ongoing steroids of the later milestones. This would require a study in which steroid treatment is discontinued after LOA, which would be unethical given the evidence of continued benefits from steroids beyond this point. Therefore, we must assume that the AFs from the two examples reflect both the effect of delayed LOA and the ongoing treatment effect of steroids.

For example, Bach and Martinez (2010) conducted a retrospective study comparing outcomes between steroid-treated and untreated patients.[19] In the untreated group, they reported mean ages of:

- 9.7 years for LOA

- 19.2 years for NIV
- 21.9 years for continuous ventilation (used here as a proxy for FVC < 1L).

In the steroid-treated group, these milestones occurred later:

- 10.8 years for LOA
- 22.9 years for NIV
- 28.9 years for continuous ventilation.

Table 2 presents the untreated means and uses our AF methodology (as applied in the CS) to estimate expected outcomes for the steroid-treated group. When applying the LOA-based AFs to the observed 10.8-year mean LOA in the treated group, the estimated mean ages for NIV and FVC < 1L are 21.4 years (vs. observed 22.9), and 24.4 years (vs. observed 28.9), respectively. While it is not possible to fully separate the impact of the delay in LOA from the ongoing effect of treatment with steroids beyond LOA, this analysis shows that the actual benefit on later milestones exceeds what is predicted using AFs. This reinforces our position that our ITC-based AF approach may underestimate the full treatment effect of givinostat.

Table 2: Validating the acceleration factors approach using data from Bach and Martinez (2010)[19]

	Untreated (mean)	AFs	Observed treated (mean)	Estimates of treated using AFs
LOA	9.7		10.8	

	Untreated (mean)	AFs	Observed treated (mean)	Estimates of treated using AFs
NIV	19.2	19.2/9.7 = 1.98	22.9	21.4
FVC<1L	21.9	21.9/9.7 = 2.26	28.9	24.4

Abbreviations: AF, acceleration factor; FVC<1L, forced vital capacity less than 1 litre; LOA, loss of ambulation; NIV, non-invasive ventilation.

Trucco et al. (2020) report on cardiorespiratory progression in patients with DMD treated with daily steroids, intermittent steroids, or no steroids, based on a single-centre retrospective study.[20] The authors present median ages for LOA and for FVC < 50% predicted, stratified by treatment group.

In the steroid-naïve group, the median age at:

- LOA was 10.5 years
- FVC < 50% was 13.2 years.

For the intermittent steroid group, these were:

- LOA was 12.0 years
- FVC<50% was 16.3 years.

In the daily steroid group:

- LOA was 12.5 years
- FVC < 50% was 16.1 years.

Table 3 presents the steroid-naïve group data, calculates the AFs using the method applied in our CS, and applies those AFs to the observed median LOA in the steroid-treated groups (12.0 and 12.5 years) to estimate the expected age at FVC < 50%. In both treatment groups, these AF-based estimates are lower than the actual observed values (i.e. the AF approach underpredicts the delay in respiratory decline). While the exact contributions of delayed LOA versus ongoing treatment benefit cannot be disentangled, this analysis supports the conclusion that steroids have a greater impact than is reflected by applying the AFs to LOA alone. As with the Bach and Martinez study, this highlights that the AF method may provide a conservative estimate of treatment benefit.

Table 3: Validating the acceleration factors approach using data from Trucco et al. (2020)[20]

	CS-naive (median)	AFs	Observed CS-daily (median)	Estimates of CS-daily using AFs	Observed CS-intermittent (median)	Estimates of CS-intermitted using AFs
LOA	10.5		12.5		12.0	
FVC<50%	13.2	13.2/10.5 = 1.26	16.1	15.7	16.3	15.1

Abbreviations: AF, acceleration factor; FVC<1L, forced vital capacity less than 1 litre; LOA, loss of ambulation; NIV, non-invasive ventilation.

In summary, using a historical control arm is a well-established approach in rare disease modelling where long-term comparative data are limited. While the use of AFs may be less common, the approach predicts outcomes which align with the observed data. The literature provides strong support for both the outcomes predicted in the ECM arm and the estimated outcomes for givinostat.

Studies comparing steroid-treated and untreated patients consistently show that the AF approach may be conservative following a step-change in LOA and ongoing treatment beyond LOA. Nevertheless, the AF approach produces results which are directionally consistent with the available literature. Additionally, alternative modelling using the HRs directly from the ITCs has produced results that are more optimistic for givinostat, further reinforcing that the Company's base case is conservative.

2. Clarify whether the company's current approach modelled a treatment effect beyond loss of ambulation; clear explanation distinguishing between direct effects of ongoing givinostat treatment in non-ambulant patients and indirect (or knock-on) effects resulting from delaying disease progression during the ambulatory phase.

As outlined above, outcomes beyond LOA (such as age at NIV or FVC<1L) are estimated by applying the AF observed between LOA and the subsequent milestones in the ECM arm. This approach uses the relationship between milestones seen in the ECM population, a group not exposed to givinostat, meaning the AF reflects only the natural history of disease progression and the effects of background treatments like steroids. As a result, the model does not apply any additional or specific givinostat treatment effect beyond LOA. The only effect of assumed givinostat is the delay in reaching LOA itself.

3. If modelled, justify the magnitude of any post loss-of-ambulation treatment effect, and explore how uncertainty in longer-term treatment effects could otherwise be incorporated into decision making.

As outlined above, the CEM does not apply any givinostat-specific treatment effect beyond the point of LOA. This is a conservative assumption, made due to the limited clinical data currently available for givinostat in the non-ambulatory health states. To date, the only information in non-ambulant patients comes from a small cohort of 36 young men who were ambulant at the initiation of givinostat and have become non-ambulant while participating in givinostat DMD clinical studies (34 patients as of the December

2021 data-cut). The ongoing ULYSSES (Study 50) in non-ambulant boys and male adolescents aged 9 to 17 years who have not previously received givinostat will provide additional information but is not anticipated to finish until mid-2028.[21]

We believe it is reasonable to expect that givinostat may continue to provide clinical benefit beyond LOA, given its mechanism of action and systemic activity. Dystrophin is an important cytoskeletal protein expressed at the plasma membrane of all muscles, including cardiac, smooth, and skeletal muscle, as well as some neurons, that supports the strength, stability, and functionality of muscle cells.[22,23] The dystrophin gene has a high mutation rate, with DMD mutations resulting in the absence of functional dystrophin proteins,[24–27] affecting all muscles in the body progressing from loss of lower limb function/walking muscle to loss of upper limb overhead reach and to advanced respiratory and cardiac complications leading to mortality.[28] Mutations in dystrophin and the consequent hyperactivation of histone deacetylase (HDAC) results in a sequence of pathological events comprising muscle fibre injury, the activation of chronic inflammatory pathways, the impairment of muscle regeneration mechanisms, and fibrogenesis and adipogenesis.[22,29–31] Givinostat is a class I and II HDAC inhibitor that modulates the uncontrolled HDAC activity in dystrophic muscles, which contributes to the pathology of DMD.[32] Givinostat HDAC inhibition has been shown to reduce muscle fibre damage, chronic muscular inflammation, fibrosis, fat deposition, and to promote mitochondrial biogenesis.[30,33–35] By acting on muscles across the body, the drug's functional and histologic benefits seen in muscle groups associated with walking[3,4] are expected to be replicated in muscle groups involved in transferring to a wheelchair, and in hand to mouth function, respiration and cardiac function.[36] As outlined above, the literature demonstrates that steroids provide benefits beyond LOA by acting on underlying disease processes that remain clinically relevant after LOA. Since givinostat also targets key disease mechanisms (e.g., inflammation and fibrosis) that persist beyond LOA, it is likely that treatment will continue to deliver meaningful benefits even after

ambulation is lost. While these longer-term effects have yet to be confirmed in clinical data beyond LOA, the biological rationale supports the likelihood of continued benefit.

Additionally, UK clinicians have expressed clear support for the view that delaying LOA with givinostat will represent a step-change in outcomes for patients with DMD, with meaningful long-term benefits for clinical progression, HRQoL, and survival. In their submission to NICE as part of the consultation for this technology appraisal, Consultant Paediatric Neurologist Dr Anne-Marie Childs emphasised the profound downstream benefits of delaying LOA in DMD. She noted that as recently as 2000, most boys with DMD lost ambulation during primary school, constituted 85% of children with neuromuscular disorders (NMD) requiring spinal surgery for neuromuscular scoliosis, and typically required overnight ventilatory support in their mid-teens. Since the introduction of corticosteroids, however, the clinical picture has changed dramatically: boys with DMD are now losing ambulation at a later stage, and as a result the need for scoliosis surgery has reduced substantially. This later LOA has also contributed to a delay in the need for ventilatory support.[37]

Clinicians anticipate that givinostat, which further extends both the early and late ambulatory phases, will represent a similar step-change in long-term outcomes. By delaying LOA beyond what is achieved with corticosteroids alone, givinostat is expected to translate into further gains in respiratory and cardiac health, improved HRQoL, and potentially prolonged survival.[37] Importantly, while these effects may not be directly observable in short-term trials, the natural history of DMD and the impact of corticosteroids already demonstrate that prolonging ambulation reshapes the entire disease trajectory.

Additionally, evidence from patients, carers, and patient advocacy groups included in the ACM1 Committee papers consistently illustrates the many long-term benefits of delaying LOA.[37] Even seemingly modest gains in ambulation time can have substantial

effects on the physical, emotional, and social wellbeing of individuals and families. Remaining mobile for longer mitigates corticosteroid-related complications such as weight gain and low bone density; allows young men to lose ambulation only after skeletal maturity, reducing scoliosis risk; and helps preserve lung and cardiac function. Note: the effects of delaying LOA on scoliosis and cardiomyopathy are also documented in the literature.[20,38–40] Families also highlight the considerable mental health benefits of preserving independence during the teenage years, arguably the most formative stage of life.[37]

One parent of a 19-year-old man with DMD treated with givinostat for six years explained:

"My son's cardiac and respiratory health is excellent, I strongly believe this is because he's been able to stay upright and mobile throughout his teenage years. Being able to stand, self-transfer and self-propel also helps keep him fit and healthy. He does not suffer with any spinal deformities, possibly because he continued to walk for so long. He was able to reach his full growth potential before he came off his feet at 18 years old, which has kept his bone density within normal range. This has given him time to build a great friendship group, which is so important for a teenager navigating this path into adulthood and is a good ground for his future years as an adult."

Another added:

"This drug has helped improve quality of life on a grand scale, because our son has enjoyed additional years being able to stay mobile and on his feet, walking up to the age of 18 years old. Being able to take part in daily activities without the use of a wheelchair kept him independent and allowed him to continue to access most activities during his school years."

Taken together, this evidence strongly supports the expectation of a post-LOA treatment effect with givinostat. While our modelling conservatively assumes no such benefit due to a lack of data in non-ambulatory patients, the mechanism of action of givinostat together with the lived experience of patients and families, provides compelling rationale that benefits will extend into non-ambulatory stages.

4. Present updated economic modelling based on plausible, evidence-based and fully justified approaches to modelling the givinostat treatment effect.

While we have intentionally taken a conservative approach by assuming no givinostat-specific treatment effect beyond LOA, it is important to note that we do expect givinostat to provide ongoing benefit in the non-ambulatory health states. Although current clinical data are not yet available to quantify this effect, the mechanism of action i.e., targeting all skeletal muscle through HDAC inhibition, supports a continued impact beyond LOA. To explore the potential implications of this, we have conducted scenario analyses that improve the HRs applied to the non-ambulatory health states (vs. ECM) by 20%, reflecting a modest treatment benefit beyond LOA. We have also explored a scenario analysis which use the AFs from Bach and Martinez (2010) (i.e., 1.98 and 2.26) to estimate the median outcomes for NIV and FVC<1L which are then used as the goal in the SOLVER calculation. Table 4 presents the HRs applied in the updated base case compared to these scenario analyses. Figure 6 shows the impact of these scenarios when assuming a 1.5% discount rate for outcomes; a 20% improvement in the historic HRs reduces the ICER from £[redacted] to £[redacted] and use of the AFs from Bach and Martinez (2010) reduces the ICER from £[redacted] to £[redacted]. Therefore, whilst we do not have the data to quantify the effect of givinostat post-LOA yet, we expect this to reduce the ICER compared to the base case.

Table 4: HRs for disease progression explored in post-LOA treatment benefit scenarios

Health state transitions	Hazard ratio		
	Updated base case (no givinostat treatment effect beyond progression)	20% improvement in NIV/FVC (some givinostat treatment effect beyond progression)	AFs from Bach and Martinez (2010; 1.98 and 2.26) (some givinostat treatment effect beyond progression)[19]
To state 2 - Late ambulatory	0.50	0.50	0.50
To state 3 - Transfer	0.50	0.50	0.50
To state 4 - HTMF, no ventilation	0.50	0.50	0.50
To state 5 - No HTMF, no ventilation	0.40	0.32	0.15
To state 7a - No HTMF, night-time ventilation	0.40	0.32	0.15
To state 8a - Full time ventilation	0.46	0.36	0.81
To state 6 - HTMF, night-time ventilation	0.40	0.32	0.15
To state 7b - No HTMF, night-time ventilation	0.46	0.36	0.81
To state 8b - Full time ventilation	0.46	0.36	0.81

Abbreviations: AF, acceleration factor; FVC, forced vital capacity; HR, hazard ratio; HTMF, hand-to-mouth function; LOA, loss of ambulation; NIV, non-invasive ventilation.

Table 5: Scenario analyses exploring the impact of post-LOA treatment benefit

	Base case 1: 1.5% discount rate (outcomes), 3.5% discount rate (costs)		Base case 2: 3.5% discount rate (outcomes), 3.5% discount rate (costs)	
	ICER step change	% change each step	ICER step change	% change each step
Updated Company base case (no direct post-LOA treatment benefit)	[redacted]	NA	[redacted]	NA
HR (20% improvement in NIV/FVC)	[redacted]	-8.4%	[redacted]	-6.3%

	Base case 1: 1.5% discount rate (outcomes), 3.5% discount rate (costs)		Base case 2: 3.5% discount rate (outcomes), 3.5% discount rate (costs)	
	ICER step change	**% change each step**	**ICER step change**	**% change each step**
HR (AFs 1.98 and 2.26)	[redacted]	-19.0%	[redacted]	-14.2%

Abbreviations: AF, acceleration factor; FVC, forced vital capacity; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LOA, loss of ambulation; NIV, non-invasive ventilation; QALY, quality-adjusted life year.

Figure 6: Scenario analyses exploring the impact of post-LOA treatment benefit and assuming 1.5% discount rate for health outcomes

Abbreviations: AF, acceleration factor; FVC, forced vital capacity; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LOA, loss of ambulation; NIV, non-invasive ventilation; QALY, quality-adjusted life year.

2 Carer health-related quality-of-life modelling and assumptions

Note: The application of carer HRQoL within the model has been detailed extensively in the CS, response to CQs, and in response to the TE. This response begins by summarising the previously submitted evidence, with references to where further detail can be found.

As stated in the Call for Evidence, the Committee recognised that it was important to ensure carer HRQoL was appropriately and robustly considered in decision making.[41] Evidence has been provided within the Committee papers and during the ACM emphasising the sensitivity and critical importance of the impact of DMD and its progression for patients and families. Its inclusion within the decision making and modelling also aligns with the approach taken in the vamorolone NICE submission for DMD (TA1031).[18]

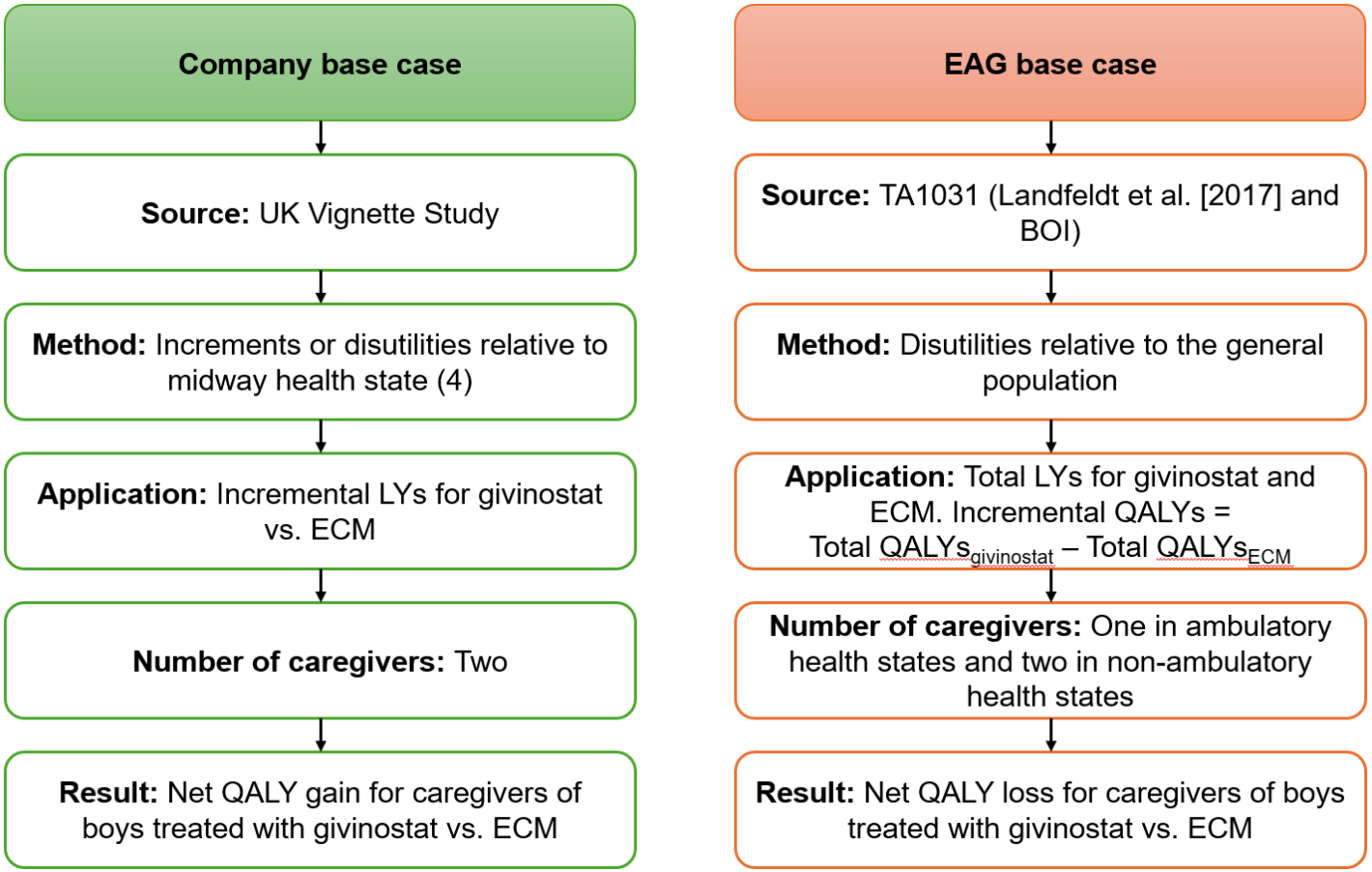
The Company base case presented in the TE response included caregiver HRQoL for two caregivers, utilities were sourced from a UK caregiver vignette study, and the methodological approach applied increments or disutilities relative to the midway health state (health state 4) to the incremental life years (LYs) accrued by givinostat relative to ECM.[42] This approach included a disutility applied within the death health state for a duration based on the incremental survival achieved by givinostat relative to ECM. Scenario analyses presented by the Company explored the impact of three caregivers, utilities sourced from Landfeldt et al. (2017), and alternative methodological approaches.[43] Further information can be found in Section B.3.4.6 of the CS, response to Questions B12 – B15 in the CQs, and in response to Key Issue 7 in the TE. The Company's approach resulted in an incremental quality-adjusted life year (QALY) gain for caregivers in the givinostat arm relative to ECM; extending time alive in the early health states i.e., (1) – (3) implied an improved HRQoL for caregivers, extending time alive in health state (4) had no impact, extending time alive

in health states (5) – (8) implied a worse HRQoL for caregivers, and extending overall time alive implied an improved HRQoL for caregivers.

The EAG preferred to model caregiver HRQoL for one caregiver in the ambulatory health states and two caregivers in the non-ambulatory health states, it preferred utilities sourced from the vamorolone NICE submission for DMD (TA1031), and the methodological approach which applied disutilities relative to the general population to the total LYs accrued by givinostat and ECM (Section 4.2.7 of the EAG report). The EAG's approach does not include any impact on caregivers after a patient's death. As outlined in response to Key Issue 7 in the TE, there was some confusion and misrepresentation regarding the utility values reported in TA1031 which inform the EAG's base case. Although these values were reported by caregivers, they reflect proxy assessments of patient HRQoL – not measures of caregiver HRQoL. The full burden of illness (BOI) report, which provides more detail on these data, has been shared with NICE and the EAG following the TE call to support clarification.[44] The EAG's approach results in an incremental QALY loss for caregivers in the givinostat arm relative to ECM; extending time spent alive in any of the patient health states implies a worse HRQoL for caregivers.

In response to Key Issue 7 in the TE response, Tables L, M, and N compared the inputs and approaches to modelling caregiver HRQoL used in the Company's base case and in the EAG's preferred approach. This information is summarised in Figure 7.

Figure 7: Comparison of the Company's approach to modelling caregiver HRQoL in the TE response with the EAG's preferred approach[18,43–45]



Abbreviations: BOI, burden of illness; EAG, External Assessment Group; ECM, established clinical management; HRQoL, health-related quality of life; LY, life year; QALY, quality-adjusted life year; TE, technical engagement; UK, United Kingdom.

In its call for additional evidence, the Committee concluded that carer HRQoL needed to be captured appropriately, but neither the Company's nor the EAG's approaches to quantify this had done so. The Committee concluded that further information and modelling was needed, specifically related to the:

1. Approach to modelling (increments from midway, disutilities):
    a. Comment on the rationale, implications and plausibility of each method, including the justification for using increments or disutilities compared to selected health states or general population values.
    b. Ensure that the approach captures the increasing impact on carers as the condition progresses.
    c. Explain why in the current model, the approaches produce different results if the numbers of carers are not equal in all health states (including in scenarios that do not model carers in state 9).
2. Utility source
    a. Clarify and justify how reported utility values were assigned to model health states. Justify the appropriateness of Landfeldt et al. (2017) versus Landfeldt et al. (2016a), and comment on the consistency in utility modelling between patient and carer utilities.
    b. Present analyses based on all sources of carer utilities.
    c. Explore different ways to differentiate between health states 7 and 8 for all possible sources.

3. Number of carers in ambulatory health states:

    a. Explore scenarios modelling between 1 and 2 carers in ambulatory states to better reflect the overall magnitude of effects on carer HRQoL (with 2 carers in the non-ambulatory health states).

4. Life-extension effect on carer HRQoL

    a. The committee was aware that modelling relating to the effects of life extension on carer HRQoL has a large impact on the ICER. The committee considered that it was unreasonable for the model to assume that there would be no negative effect of losing a child on HRQoL. But, it also considered that the company's approach and increment of -0.56 (implying a carer utility of 0) was not evidence based and may not be appropriate. It further acknowledged that extending time in health states with a negative effect on carers would extend that negative effect during that period.

    b. Therefore, explore and justify different approaches for modelling the effect of life extension on carers. This may include using different utilities for health state 9, and must consider strengths and limitations of different methodological approaches for modelling life-extension effect on carer HRQoL.

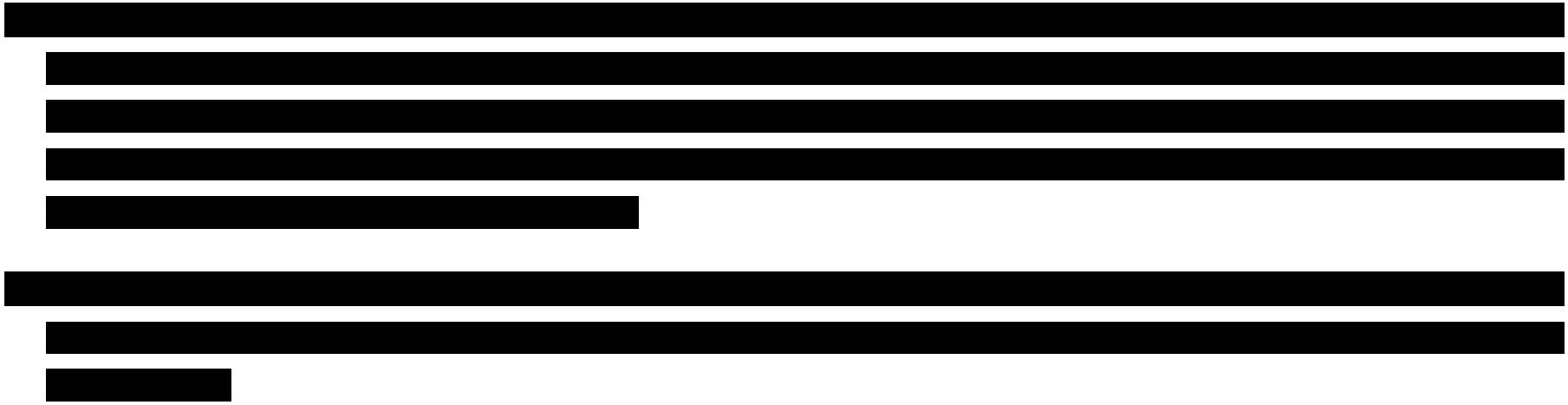
Each are addressed in turn below.

1. **Approach to modelling (increments from midway, disutilities):**
    a. Comment on the rationale, implications and plausibility of each method, including the justification for using increments or disutilities compared to selected health states or general population values.

b. Ensure that the approach captures the increasing impact on carers as the condition progresses.

c. Explain why in the current model, the approaches produce different results if the numbers of carers are not equal in all health states (including in scenarios that do not model carers in state 9).

As part of this Call for Evidence, new interim data have become available from an ongoing study led by the University of Sheffield for Duchenne UK: "*Health-related quality of life (HRQoL) impacts on Duchenne parent-carers: A qualitative survey*."[1] These interim findings provide further evidence on caregiver burden in DMD, EQ-5D values from UK caregivers mapped to health states consistent with the Project HERCULES CEM, and the number of caregivers involved. It should be noted that these results are provisional and confidential, as the quality assurance process and full analysis are ongoing. However, they have been provided at this stage to support the appraisal. The study consists of three parts:



[redacted]

Drawing on the newly available interim UK data, we have updated our base case to better capture the HRQoL of caregivers of individuals with DMD. This dataset, representing a relatively large caregiver sample, is currently the most comprehensive and robust source for this appraisal. In our updated base case, EQ-5D data are applied in alignment with the Project HERCULES CEM health states, assuming two caregivers in ambulatory states and three in non-ambulatory states.

Table 6 compares the rationale, implications, and plausibility of our updated base case with the EAG's approach to modelling caregiver HRQoL. Additionally, Figure 8 provides an updated visual representation based on our updated base case (update of Figure 7).

Table 6: A comparison of the rationale, implications and plausibility of the updated Company approach and EAG approach to modelling caregiver HRQoL

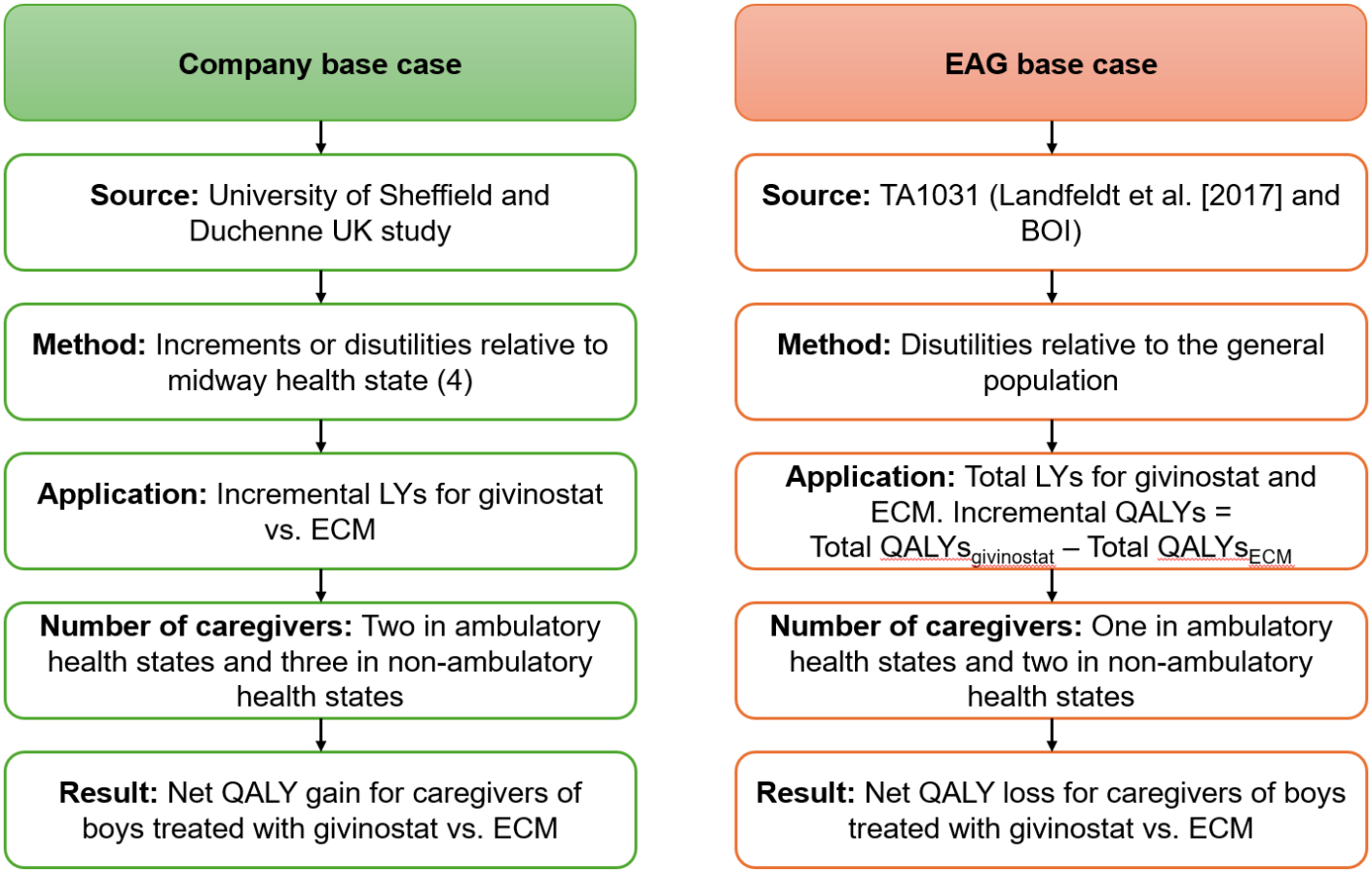
Approach	Updated Company Approach – Increments or disutilities relative to midway health state applied to incremental LYs	EAG Approach – Disutilities relative to general population applied to total LYs
Rationale	• **Source:** The University of Sheffield and Duchenne UK study.[1] This study reports EQ-5D-5L values for UK caregivers of DMD across the health states reflected by the Project HERCULES model structure, these data	• **Source:** NICE TA1031 which uses a blend of Landfeldt et al. (2017) and the BOI study.[18,43,44] The Landfeldt et al. (2017) study uses the EQ-5D and aligns with NICE precedent (e.g. TA1031). However, this study lacks

Approach	Updated Company Approach – Increments or disutilities relative to midway health state applied to incremental LYs	EAG Approach – Disutilities relative to general population applied to total LYs
	have been mapped to EQ-5D-3L values in line with NICE preferences.[2] *[new data]* • **Method:** Anchors caregiver utilities at *midway health state* (4). Realistic outcomes. Avoids "carer QALY trap" by assuming cure = best outcome, death = worst. • **Application:** By applying to incremental LYs only allows us to isolate the impact of givinostat relative to ECM. • **Number of caregivers:** Two caregivers in ambulatory health states and three caregivers in non-ambulatory health states. Aligning with data collected in the University of Sheffield and Duchenne UK study. As well as feedback from clinical experts and patient testimony in the ACM for this appraisal. *[new data]*	sufficient granularity for the health states in the CEM. Therefore, it was supplemented with the BOI. However, the BOI values reflected caregiver proxy values of patient HRQoL. • **Method:** Anchors caregiver utilities at *general population*. Aligns with NICE precedent (e.g. TA1031). Death state assumed = 0 carers. • **Application:** Applied to total LYs in both givinostat and ECM treatment arms. "Quality of life is accounted for on both ECM and givinostat arms, as otherwise an imbalance is created." • **Number of caregivers:** One caregiver in ambulatory health states increasing to two in non-ambulatory health states. Aligns with NICE precedent (e.g. TA1031).
Implications	• Allows for caregiver QALY gain/loss through extensions/reductions in time spent in the less severe health states i.e., the ambulatory health states and through extended/reduced patient survival. • Allows for caregiver QALY loss/gain through extensions/reductions in time spent in the more severe health states i.e., the non-ambulatory health states 5-7.	• Models a caregiver QALY loss/gain for extensions/reductions in any health state i.e., any gain in survival is shown to reduce caregiver QALYs.
Plausibility	• Intuitively appealing. Prevents perverse results. • Novel approach, not widely validated in NICE submissions. • Relies on the belief that a survival extension would improve caregiver HRQoL.	• Most common approach to modelling caregiver QALYs in NICE appraisals. • Risks the "carer QALY trap" and does not account for the treatment benefit impacting caregiver HRQoL i.e., only reflects the additional burden for caregiving for longer.
Justification of anchor	• Midway anchor allows the impact of treatment extending time in the earlier health states to have a positive impact on the caregivers.	• General population anchor means that the impact of treatment extending time in any of the health states will always have a negative impact on the caregivers.

Approach	Updated Company Approach – Increments or disutilities relative to midway health state applied to incremental LYs	EAG Approach – Disutilities relative to general population applied to total LYs
Overall assessment	• Stronger alignment with patient/caregiver lived experience, but methodologically novel and evidence-limited.	• Stronger alignment with methodological precedent, but risks underestimating caregiver value and producing counterintuitive results.

Abbreviations: ACM, Appraisal Committee Meeting; BOI, burden of illness; CEM, cost-effectiveness model; DMD, Duchenne muscular dystrophy; EAG, External Assessment Group; ECM, established clinical management; EQ-5D-3L, European quality of life 5 dimensions 3 level version; HRQoL, health-related quality of life; LY, life year; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; TA, technology assessment; UK, United Kingdom.

Figure 8: Comparison of the updated Company's approach to modelling caregiver HRQoL with the EAG's preferred approach[1,18,43–45]



Abbreviations: BOI, burden of illness; EAG, External Assessment Group; ECM, established clinical management; HRQoL, health-related quality of life; LY, life year; QALY, quality-adjusted life year; UK, United Kingdom.

In the Call for Evidence, NICE requested that the modelling approach should capture the increasing impact on carers as the condition progresses. Both the increments and disutilities relative to the midway health state and the disutilities approach reflect this impact. Under the increments and disutilities method, the potential for a positive caregiver impact is greatest in the least severe health state, then gradually reduces through health states 2 and 3, with no impact assumed in health state 4. Beyond health state 4, the method applies disutilities that increase in magnitude as disease severity worsens. In contrast, the disutilities approach begins with the smallest disutility in the least severe health state, with progressively larger disutilities applied in each subsequent, more severe state.

In response to the Committee's question on why the approaches produce different results when the number of carers is not equal across health states, this is driven by the differences in the anchor point across the two methods. To recap, the Company's approach anchors to the midway health state (health state 4) and the EAG's approach anchors to the general population utility value. Because the same underlying utilities are used in both approaches, if the number of caregivers is identical across all health states, then the relative differences between health states will cancel out when all health states are considered. In this situation, the choice of anchor has no impact, and both methods converge to the same overall caregiver QALY impact. This is illustrated in Table 7 and Table 8, which present an example using the Company's approach (increments and disutilities relative to the midway health state) and the EAG's approach (disutilities relative to the general population), both applied with two caregivers across all health states and the undiscounted patient LYs from the Company's updated base case. Both scenarios assume two caregivers in the death health state. While the incremental caregiver QALYs differ at the individual health state level, when all health states are included and the number of caregivers is held constant, the results converge to the same total incremental caregiver QALYs.

Table 7: Example of increment/disutility relative to midway approach (Company's preferred approach) based on constant (two) caregivers across all health states

Health states	Increment/disutility relative to midway	Number of caregivers	Incremental patient LYs (undiscounted)	Calculation	Incremental caregiver QALYs (undiscounted)
	A	B	C		
1 - Early ambulatory	0.16	2	3.90	=AxBxC	1.25
2 - Late ambulatory	0.11	2	2.19	=AxBxC	0.48
3 - Transfer	0.02	2	0.97	=AxBxC	0.04
4 - HTMF, no ventilation	0	2	2.52	=AxBxC	0.00
5 - No HTMF, no ventilation	-0.06	2	2.87	=AxBxC	-0.34
6 - HTMF, night-time ventilation	-0.02	2	1.87	=AxBxC	-0.07
7 - No HTMF, night-time ventilation	-0.05	2	1.33	=AxBxC	-0.13
8 - Full time ventilation	-0.08	2	-1.33	=AxBxC	0.21
9 - Death	-0.56	2	-14.31	=AxBxC	16.03
				Total	**17.46**

Abbreviations: HTMF, hand-to-mouth-function; LY, life year; QALY, quality-adjusted life year.

Table 8: Example of disutilities approach (EAG's preferred approach) based on constant (two) caregivers across all health states

Health states	Disutility relative to general population utility value	Number of caregivers	Total givinostat patient LYs (undiscounted)	Total ECM patient LYs (undiscounted)	Calculation	Incremental caregiver QALYs (undiscounted)
	A	B	C	D		
1 - Early ambulatory	-0.203	2	7.81	3.91	=(AxBxC)-(AxBxD)	-1.58

2 - Late ambulatory	-0.253	2	4.44	2.25	=(AxBxC)-(AxBxD)	-1.11
3 - Transfer	-0.343	2	1.99	1.02	=(AxBxC)-(AxBxD)	-0.67
4 - HTMF, no ventilation	-0.363	2	4.29	1.76	=(AxBxC)-(AxBxD)	-1.83
5 - No HTMF, no ventilation	-0.423	2	5.26	2.39	=(AxBxC)-(AxBxD)	-2.43
6 - HTMF, night-time ventilation	-0.383	2	4.15	2.29	=(AxBxC)-(AxBxD)	-1.43
7 - No HTMF, night-time ventilation	-0.413	2	3.22	1.89	=(AxBxC)-(AxBxD)	-1.10
8 - Full time ventilation	-0.443	2	4.24	5.57	=(AxBxC)-(AxBxD)	1.18
9 - Death	-0.923	2	34.60	48.92	=(AxBxC)-(AxBxD)	26.42
					Total	**17.46**

Abbreviations: EAG, External Assessment Group; ECM, established clinical management; HTMF, hand-to-mouth-function; LY, life year; QALY, quality-adjusted life year.

Whereas if the number of caregivers differs between health states, the methods will result in diverging incremental caregiver QALYs. This is because the approaches are anchored differently. With unequal caregiver numbers, the relative scaling of positive vs. negative caregiver effects diverges between methods. For example, adding extra carers in later non-ambulatory states increases the negative caregiver impact more in the disutility approach compared to the increment/disutility relative to midway health state approach. This is illustrated in Table 9 and Table 10, which present an example using the Company's approach (increments/disutilities relative to the midway health state) and the EAG's approach (disutilities relative to the general population), both applied with two caregivers in the ambulatory health states and three caregivers in the non-ambulatory health states and the undiscounted patient LYs from the Company's updated base case. Both scenarios assume two caregivers in the death health state.

The additional caregivers in the non-ambulatory health states is shown to have a greater impact in the disutility approach, resulting in fewer incremental caregiver QALYs in this approach compared to the increment/disutility relative to midway approach.

Table 9: Example of increment/disutility relative to midway approach (Company's preferred approach) based on two caregivers in ambulatory health states and three caregivers in non-ambulatory health states

Health states	Increment/disutility relative to midway	Number of caregivers	Incremental patient LYs (undiscounted)	Calculation	Incremental caregiver QALYs (undiscounted)
	A	B	C		
1 - Early ambulatory	0.16	2	3.90	=AxBxC	1.25
2 - Late ambulatory	0.11	2	2.19	=AxBxC	0.48
3 - Transfer	0.02	2	0.97	=AxBxC	0.04
4 - HTMF, no ventilation	0	3	2.52	=AxBxC	0.00
5 - No HTMF, no ventilation	-0.06	3	2.87	=AxBxC	-0.52
6 - HTMF, night-time ventilation	-0.02	3	1.87	=AxBxC	-0.11
7 - No HTMF, night-time ventilation	-0.05	3	1.33	=AxBxC	-0.20
8 - Full time ventilation	-0.08	3	-1.33	=AxBxC	0.32
9 - Death	-0.56	2	-14.31	=AxBxC	16.03
				Total	**17.29**

Abbreviations: HTMF, hand-to-mouth-function; LY, life year; QALY, quality-adjusted life year.

Table 10: Example of disutilities approach (EAG's preferred approach) based on two caregivers in ambulatory health states and three caregivers in non-ambulatory health states

Health states	Disutility relative to general population utility value	Number of caregivers	Total givinostat patient LYs (undiscounted)	Total ECM patient LYs (undiscounted)	Calculation	Incremental caregiver QALYs (undiscounted)
	A	B	C	D		
1 - Early ambulatory	-0.203	2	7.81	3.91	=(AxBxC)-(AxBxD)	-1.58
2 - Late ambulatory	-0.253	2	4.44	2.25	=(AxBxC)-(AxBxD)	-1.11
3 - Transfer	-0.343	2	1.99	1.02	=(AxBxC)-(AxBxD)	-0.67
4 - HTMF, no ventilation	-0.363	3	4.29	1.76	=(AxBxC)-(AxBxD)	-2.75
5 - No HTMF, no ventilation	-0.423	3	5.26	2.39	=(AxBxC)-(AxBxD)	-3.64
6 - HTMF, night-time ventilation	-0.383	3	4.15	2.29	=(AxBxC)-(AxBxD)	-2.14
7 - No HTMF, night-time ventilation	-0.413	3	3.22	1.89	=(AxBxC)-(AxBxD)	-1.64
8 - Full time ventilation	-0.443	3	4.24	5.57	=(AxBxC)-(AxBxD)	1.77
9 - Death	-0.923	2	34.60	48.92	=(AxBxC)-(AxBxD)	26.42
					Total	**14.66**

Abbreviations: EAG, External Assessment Group; ECM, established clinical management; HTMF, hand-to-mouth-function; LY, life year; QALY, quality-adjusted life year.

Similar to when the number of caregivers differs between health states, if one of the health states is excluded e.g., the death health state 9, the methods will result in diverging incremental caregiver QALYs. This scenario is the same as assuming zero caregivers for health state 9. Therefore, the logic as to why the incremental caregiver QALYs are different across the methods aligns with what is written above with regards to when the number of caregivers differs across health states. This is illustrated in Table 11 and Table 12, which present an example using the Company's approach (increments/disutilities relative to the midway health state) and the EAG's approach (disutilities relative to the general population), both applied with two caregivers in all health states but excluding the death health state 9. The exclusion of caregivers in the death health state is shown to have a greater impact in the disutility approach, resulting in negative incremental caregiver QALYs in this approach compared to the positive incremental caregiver QALYs in the increments/disutilities relative to midway approach.

Table 11: Example of increment/disutilities relative to midway approach (Company's preferred approach) based on two caregivers in all health states and excluding the death health state

Health states	Increment/disutility relative to midway	Number of caregivers	Incremental patient LYs (undiscounted)	Calculation	Incremental caregiver QALYs (undiscounted)
	A	B	C		
1 - Early ambulatory	0.16	2	3.90	=AxBxC	1.25
2 - Late ambulatory	0.11	2	2.19	=AxBxC	0.48
3 - Transfer	0.02	2	0.97	=AxBxC	0.04
4 - HTMF, no ventilation	0	2	2.52	=AxBxC	0.00
5 - No HTMF, no ventilation	-0.06	2	2.87	=AxBxC	-0.34
6 - HTMF, night-time ventilation	-0.02	2	1.87	=AxBxC	-0.07

7 - No HTMF, night-time ventilation	-0.05	2	1.33	=AxBxC	-0.13
8 - Full time ventilation	-0.08	2	-1.33	=AxBxC	0.21
9 - Death	-0.56	0	-14.31	=AxBxC	0.00
				Total	**1.43**

Abbreviations: HTMF, hand-to-mouth-function; LY, life year; QALY, quality-adjusted life year.

Table 12: Example of disutilities approach (EAG's preferred approach) based on two caregivers in all health states and excluding the death health state

Health states	Disutilities relative to general population value	Number of caregivers	Total givinostat patient LYs (undiscounted)	Total ECM patient LYs (undiscounted)	Calculation	Incremental caregiver QALYs (undiscounted)
	A	B	C	D		
1 - Early ambulatory	-0.203	2	7.81	3.91	=(AxBxC)-(AxBxD)	-1.58
2 - Late ambulatory	-0.253	2	4.44	2.25	=(AxBxC)-(AxBxD)	-1.11
3 - Transfer	-0.343	2	1.99	1.02	=(AxBxC)-(AxBxD)	-0.67
4 - HTMF, no ventilation	-0.363	2	4.29	1.76	=(AxBxC)-(AxBxD)	-1.83
5 - No HTMF, no ventilation	-0.423	2	5.26	2.39	=(AxBxC)-(AxBxD)	-2.43
6 - HTMF, night-time ventilation	-0.383	2	4.15	2.29	=(AxBxC)-(AxBxD)	-1.43
7 - No HTMF, night-time ventilation	-0.413	2	3.22	1.89	=(AxBxC)-(AxBxD)	-1.10
8 - Full time ventilation	-0.443	2	4.24	5.57	=(AxBxC)-(AxBxD)	1.18

9 - Death	-0.923	0	34.60	48.92	=(AxBxC)-(AxBxD)	0.00
					Total	**-8.96**

Abbreviations: EAG, External Assessment Group; ECM, established clinical management; HTMF, hand-to-mouth-function; LY, life year; QALY, quality-adjusted life year.

2. Utility source

a. Clarify and justify how reported utility values were assigned to model health states. Justify the appropriateness of Landfeldt et al. (2017) versus Landfeldt et al. (2016a), and comment on the consistency in utility modelling between patient and carer utilities.

b. Present analyses based on all sources of carer utilities.

c. Explore different ways to differentiate between health states 7 and 8 for all possible sources.

As described above, new interim data are now available from an ongoing study led by the University of Sheffield for Duchenne UK. Accordingly, the Company's preferred approach is to use the EQ-5D values from these interim results.

[redacted]

[redacted]

[redacted]

Table 13: Broad health state caregiver utilities measured using the EQ-5D-5L and mapped to the EQ-5D-3L using Hernandez et al. (2023)[2]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-3L, European quality of life 5 dimensions 3 level version; EQ-5D-5L, European quality of life 5 dimensions 5 level version.

[redacted]

Table 14: Non-ambulatory health state caregiver utilities measured using the EQ-5D-5L and mapped to EQ-5D-3L using Hernandez et al. (2023)[2]

Abbreviations: EQ-5D-3L, European quality of life 5 dimensions 3 level version; EQ-5D-5L, European quality of life 5 dimensions 5 level version.

In addition to these new data, caregiver utilities are also available from Landfeldt et al. (2016b), Landfeldt et al. (2017), and the UK vignette study.[42,43,46] To recap, the UK vignette study was applied within the original Company base case and the Landfeldt et al. (2017) values were explored in a scenario analysis. The differences between these two sources were discussed at length in response to Question B12 in the CQs.

The caregiver utility values reported in Landfeldt et al. (2016b) were not explored within the CEM as it appears they are derived from the same study as those reported in Landfeldt et al. (2017). However, there appears to be differences in the way health states were defined and analysed:

- Landfeldt et al. (2016b) classified patients into four groups based on a combination of ambulatory status and age: (1) early ambulatory (approx. 5–7 years), (2) late ambulatory (approx. 8–11 years), (3) early non-ambulatory (approx. 12–15 years), and (4) late non-ambulatory (≥16 years).

- Landfeldt et al. (2017) mapped utility data to disease-specific health states by fitting generalised linear regression models (GLMs) with a gamma distribution and log link. Health states were defined in terms of ambulatory status (GLM 1), total DMDSAT score (GLM 2), and ventilation status (GLM 3). Importantly, the models also adjusted for potential confounders including income class, mental and behavioural disorders, and presence of an additional household member with DMD.

Landfeldt et al. (2017) is considered more robust as it provides utility estimates directly mapped to disease-relevant health states aligned with modelling requirements, rather than age-based classifications. The regression-based approach accounts for confounding factors, reducing bias and improving generalisability of the results. Moreover, the exploration of ventilation status allows for distinguishing between night-time and full-time ventilation in the non-ambulatory health states in the CEM.

Nevertheless, in response to NICE's Call for Evidence, Table 15 compares caregiver utility values from multiple sources: the University of Sheffield interim data grouped into "ambulatory," "transfer," and "non-ambulatory" health states; the same interim dataset further disaggregated by specific non-ambulatory states; the UK vignette study; and published evidence from Landfeldt et al. (2017) and Landfeldt et al. (2016b).

Table 15: A comparison of sources of caregiver utility values[1,42,43,46]

Health states	University of Sheffield, Duchenne UK, interim results (Company preferred option)	University of Sheffield, Duchenne UK, interim results split by non-ambulatory status	UK vignette study (Company original base case)	Landfeldt et al. (2017)	Landfeldt et al. (2016b)
1 - Early ambulatory	[redacted]	[redacted]	0.72	0.86	0.76

2 - Late ambulatory	[redacted]	[redacted]	0.67	0.84	0.75
3 - Transfer	[redacted]	[redacted]	0.58	0.84	0.75
4 - HTMF, no ventilation	[redacted]	[redacted]	0.56	0.78	0.71
5 - No HTMF, no ventilation	[redacted]	[redacted]	0.50	0.78	0.71
6 - HTMF, night-time ventilation	[redacted]	[redacted]	0.54	0.78	0.74
7 - No HTMF, night-time ventilation	[redacted]	[redacted]	0.51	0.78	0.74
8 - Full time ventilation	[redacted]	[redacted]	0.48	0.77	0.74

Abbreviations: HTMF, hand-to-mouth-function; UK, United Kingdom.

With the availability of new data from the University of Sheffield and Duchenne UK study, the Company considers the caregiver utilities from this study to be the most appropriate source. This dataset represents a relatively large caregiver sample, collects EQ-5D-5L data from caregivers of individuals with DMD, maps these data to EQ-5D-3L which aligns with NICE's preferences, and reflects the most up to date reflection of HRQoL impact on caregivers in this setting. Table 16 and Figure 9 show the impact of alternative caregiver utility sources on the ICER.

Table 16: Scenario analyses exploring the impact of caregiver utility sources[1,42,43,46]

Source of caregiver utilities	Base case 1: 1.5% discount rate (outcomes), 3.5% discount rate (costs)		Base case 2: 3.5% discount rate (outcomes), 3.5% discount rate (costs)	
	ICER step change	% change each step	ICER step change	% change each step
Updated Company base case (University of Sheffield, Duchenne UK, interim results, broad health states)	[redacted]	NA	[redacted]	NA
University of Sheffield, Duchenne UK, interim results, split by non-ambulatory health state	[redacted]	2.2%	[redacted]	-2.3%
Vignette study	[redacted]	7.4%	[redacted]	4.1%
Landfeldt et al. (2017)	[redacted]	-11.5%	[redacted]	-10.8%

Source of caregiver utilities	Base case 1: 1.5% discount rate (outcomes), 3.5% discount rate (costs)		Base case 2: 3.5% discount rate (outcomes), 3.5% discount rate (costs)	
	ICER step change	% change each step	ICER step change	% change each step
Landfeldt et al. (2016)	[redacted]	-4.5%	[redacted]	-3.4%

Abbreviations: ICER, incremental cost-effectiveness ratio

Figure 9: Scenario analyses exploring the impact of caregiver utility sources and assuming 1.5% discount rate for health outcomes[1,42,43,46]

[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; UK, United Kingdom..

In Question B17 of the CQs, the Company was asked to provide a scenario differentiating between health states 7 and 8 in terms of costs and utilities. This request was not applicable to caregiver utilities, as both the UK vignette and Landfeldt et al. (2017) studies differentiated between health states 7 and 8 (see Table 15). The Company's preferred source (the University of Sheffield and Duchenne UK interim utilities for the broader health states) does not make this distinction. However, a scenario analysis presented in Figure 9 applies the Sheffield data split by non-ambulatory health states, which does differentiate between health states 7 and 8. On this basis, the Company considers that the caregiver utility analyses provided are responsive to the Committee's request.

3. **Number of carers in ambulatory health states:**
    a. Explore scenarios modelling between 1 and 2 carers in ambulatory states to better reflect the overall magnitude of effects on carer HRQoL (with 2 carers in the non-ambulatory health states).

The Company's original base case assumes two caregivers across all health states, whereas the EAG's approach assumes one caregiver in the ambulatory states, increasing to two in the non-ambulatory states. In the CS, the Company also presented an analysis with three caregivers across all health states, noting that based on patient testimony the assumption of two caregivers was conservative. The new interim data from the ongoing University of Sheffield study for Duchenne UK provide further support for this position, reinforcing that the assumption of two caregivers is conservative.

[redacted]

[redacted]

Table 17: Number of caregivers | Interim data from University of Sheffield and Duchenne UK study

[redacted]			

Abbreviations: SD, standard deviation

Although NICE have requested scenarios exploring modelling between one and two carers in ambulatory states and two carers in the non-ambulatory health states, these data suggest that assumptions of two caregivers across all health states is conservative. A more reflective approach would be to increase the number of caregivers: from two in the ambulatory states to three in the non-

ambulatory states. Drawing on the newly available interim UK data, we have updated our base case to reflect two in the ambulatory states to three in the non-ambulatory states and explore a scenario from three in the ambulatory states to four in the non-ambulatory states – see Table 18 and Figure 10.

Table 18: Scenario analyses exploring the number of caregivers

Source of caregiver utilities	Base case 1: 1.5% discount rate (outcomes), 3.5% discount rate (costs)		Base case 2: 3.5% discount rate (outcomes), 3.5% discount rate (costs)	
	ICER step change	% change each step	ICER step change	% change each step
Updated Company base case (two caregivers in ambulatory health states and three caregivers in non-ambulatory health states)	[redacted]	NA	[redacted]	NA
Three caregivers in ambulatory health states and four caregivers in non-ambulatory health states	[redacted]	2.2%	[redacted]	-2.3%

Abbreviations: ICER, incremental cost-effectiveness ratio

Figure 10: Scenario analyses exploring the number of caregivers and assuming 1.5% discount rate for health outcomes

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

4. **Life-extension effect on carer health-related quality of life**

    a. The committee was aware that modelling relating to the effects of life extension on carer HRQoL has a large impact on the ICER. The committee considered that it was unreasonable for the model to assume that there would be no negative effect of losing a child on HRQoL. But, it also considered that the company's approach and increment of -0.56 (implying a carer utility of 0) was not evidence based and may not be appropriate. It further acknowledged that extending time in health states with a negative effect on carers would extend that negative effect during that period.

    b. Therefore, explore and justify different approaches for modelling the effect of life extension on carers. This may include using different utilities for health state 9, and must consider strengths and limitations of different methodological approaches for modelling life-extension effect on carer HRQoL.

There is currently no evidence available to quantify the disutility associated with the death of a child from DMD, particularly over the period in which the child would have survived had they received treatment. This is an inherently challenging area in which to generate evidence, given the profound emotional burden and the ethical and methodological difficulties of collecting such data.

The limited data that do exist relating to the loss of child reflect contexts such as miscarriage or perinatal bereavement, which are not considered relevant to this disease setting for the loss of a child due to DMD.[47,48] In DMD, families endure a prolonged, progressive disease course, during which the child gradually loses abilities. The eventual death, though anticipated, comes after years of intensive caregiving, adjustment, and emotional strain, which shapes the bereavement experience very differently. Consequently, these sources cannot be applied in this appraisal.

It is important to highlight that part of the impact observed in our model arises from the incremental LYs gained with givinostat compared with ECM, with an anticipated survival benefit of 8.9 years (discounted patient incremental LYs in the Company's updated base case). When considering that this extended survival affects up to three caregivers, it is intuitive and expected that such an effect would exert a meaningful influence on the caregiver QALYs.

Our approach links caregiver HRQoL directly to the health states being experienced by the child: when the child is healthier and in earlier health states relative to the midway health state, the impact on caregiver HRQoL is positive; conversely, when the child's health worsens relative to the midway health state, the impact on caregiver HRQoL is negative. Within this framework, prolonged time in health state 1 i.e., early ambulatory represents the best possible outcome for caregivers, while death represents the worst. Although this assumption is not explicitly grounded in methodological recommendations, which are lacking in this area, it is an intuitive and transparent reflection of the relationship between child health and caregiver HRQoL.

The core challenge is that there are no established recommendations or empirical data to guide how such caregiver outcomes should be valued in health economic models. This methods and evidence gap reflects the inherent difficulty of conducting research in such a sensitive area. In this context, our approach provides a pragmatic solution that captures the directional extremes of caregiver experience in a way consistent with the lived reality of families affected by DMD.

3 Patient health-related quality-of-life modelling and assumptions

Note: The application of patient HRQoL within the model has been detailed extensively in the CS and response to CQs. This response begins by summarising the previously submitted evidence, with references to where further detail can be found.

Audhya et al. (2023) is the source of patient utility data for the base case – see Sections B.3.4.3 and B.3.4.6 of the original CS.[49] This study estimates utility values for clinical and functional health states in DMD, based on patient-reported health status. Study participants with DMD (aged 12-40) were recruited through Parent Project Muscular Dystrophy, an advocacy group in the US. A survey was developed using a web-based platform to capture self-reported data from study participants. The survey included a clinical questionnaire to document the extent and severity of DMD symptoms, a series of demographic questions to help characterise the study population, as well as a series of validated preference-based measures of HRQoL, including the health utilities index (HUI) and EQ-5D (5-level [5L] version). Utilities were derived using a US-specific value set. Table 19 presents the utilities from Audhya et al. (2023) applied in the CEM in the base case. While the utility measurements generally correspond with the CEM health states, some health state utilities were estimated as weighted averages due to slight differences in health state definitions (see footnotes in Table 19). Scenario analyses explored the use of the patient health state utilities reported in Landfeldt et al. (2017) and the BOI study.[43,44]

Table 19: Summary of patient utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in CS (section and page number)	Justification
Early ambulatory	0.79 (0.06)	0.66, 0.89	Section 3.4.3, page 175	Patient utilities are sourced from Audhya et al. 2023.[49] This study reports patient-reported EQ-5D values (aligning with the NICE preferred measurement), considers an extensive range of clinical and functional health states, and reflects recent data (published in 2023).
Late ambulatory	0.64 (0.11)	0.42, 0.83	Section 3.4.3, page 175	
Transfer	0.64 (0.11)	0.42, 0.83	Section 3.4.3, page 175	
HTMF, no ventilation	0.28 (0.02)a	0.24, 0.32	Section 3.4.3, page 175	
HTMF, night ventilation	0.25 (0.06)	0.14, 0.38	Section 3.4.3, page 175	
No HTMF, no ventilation	0.26 (0.03)	0.21, 0.31	Section 3.4.3, page 175	
No HTMF, night ventilation	0.14 (0.09)b	0.02, 0.36	Section 3.4.3, page 175	

Full ventilation	0.14 (0.09)b	0.02, 0.36	Section 3.4.3, page 175	

[a]Weighted across preserved upper limb, no daytime ventilation, without symptomatic cardiomyopathy; mildly impaired upper limb, no daytime ventilation, without symptomatic cardiomyopathy; mildly impaired upper limb, no daytime ventilation, with symptomatic cardiomyopathy; moderately impaired upper limb, no daytime ventilation, without symptomatic cardiomyopathy; and moderately impaired upper limb, no daytime ventilation, with symptomatic cardiomyopathy; [b]Weighted across loss of upper limb function, night-time, and daytime ventilation, without symptomatic cardiomyopathy and loss of upper limb function, night-time, and daytime ventilation, with symptomatic cardiomyopathy.

Abbreviations: EQ-5D, European quality of life 5 dimension; HTMF, hand-to-mouth-function.

In CQ Question B17, the use of identical patient utilities for health states 7 and 8 was questioned. This assumption was originally made due to limited data availability and a preference to source all utilities from a single dataset, thereby reducing uncertainty introduced by combining multiple sources. However, we acknowledged the EAG's concern that the transition from "no HTMF with night ventilation" to "no HTMF with full ventilation" would likely impose an additional burden on patient HRQoL. To address this, a scenario analysis was undertaken using multipliers derived from the literature to adjust the utility for health state 8 relative to health state 7. Specifically, based on Landfeldt et al. (2017), a multiplier of 0.6 (calculated as 0.051/0.129) was applied to the utility value for health state 7, generating an adjusted utility of 0.06 for health state 8. This adjustment reflects the expected reduction in HRQoL between these health states. The impact on cost-effectiveness results was minimal, with the ICER decreasing by only 0.9%.

1. **Clarify and justify how reported utility values were assigned to model health states. Justify the appropriateness of Landfeldt et al. (2017) versus Landfeldt et al. (2016b), and comment on the consistency in utility modelling between patient and carer utilities.**

In addition to Audhya et al. (2023), patient utility data are available from Landfeldt et al. (2017), the Project HERCULES BOI study, and Crossnohere et al. (2021), as described in Section 3.4.3 of the CS.[43,44,49,50] To recap, Audhya et al. (2023) informed the Company base case, while values from Landfeldt et al. (2017) and the BOI study were considered in scenario analyses.

Of these sources, only Audhya et al. (2023) and the BOI study report patient-reported HRQoL. In contrast, Landfeldt et al. (2017) and Crossnohere et al. (2021) are based on caregiver-proxy reports. Audhya et al. (2023) was preferred for the base case as it applied the EQ-5D-5L, a generic measure consistent with NICE preferences, whereas the BOI study used the disease-specific DMDQoL.

Utility values in Landfeldt et al. (2017) were measured using the HUI and proxy-reported by caregivers. These data were explored in scenario analyses to reflect NICE case precedence. However, with the availability of newer, more robust evidence aligned to NICE methodological preferences, Landfeldt et al. (2017) is considered outdated and insufficiently robust to inform the base case. Similar to the clarification provided regarding caregiver utilities reported across two Landfeldt publications, Landfeldt et al. (2016a) was not included in the CEM, as it appears to draw on the same study as Landfeldt et al. (2017), albeit with different methods of defining health states:

- Landfeldt et al. (2016a) classified patients into four groups based on a combination of ambulatory status and age: (1) early ambulatory (approx. 5–7 years), (2) late ambulatory (approx. 8–11 years), (3) early non-ambulatory (approx. 12–15 years), and (4) late non-ambulatory (≥16 years).[51]

- Landfeldt et al. (2017) mapped utility data to disease-specific health states by fitting GLMs with a gamma distribution and log link. Health states were defined in terms of ambulatory status (GLM 1), total DMDSAT score (GLM 2), and ventilation status (GLM 3). Importantly, the models also adjusted for potential confounders including income class, mental and behavioural disorders, and presence of an additional household member with DMD.[43]

Landfeldt et al. (2017) is considered more robust, as it provides utility estimates mapped directly to clinically relevant health states aligned with model requirements, adjusts for confounders, and allows differentiation between night-time and full-time ventilation in non-ambulatory health states. Additionally, Landfeldt et al. (2016a) did not report numeric utility values (only bar charts, requiring digitisation), introducing additional uncertainty.

Crossnohere et al. (2021) broadly supports the findings of Audhya et al. (2023), showing declining utilities across progressive health states and reporting values for non-ambulatory health states that are highly consistent. However, these were not applied within the CEM as HRQoL was proxy-reported for patients aged <18.

In response to NICE's Call for Evidence, Table 20 presents a comparison of patient utility values across sources: Audhya et al. (2023), the Project HERCULES BOI study, Landfeldt et al. (2017), and Crossnohere et al. (2021). Cells are merged across health states when utility values are only available for broader categories rather than for individual states (e.g., late ambulatory covering health states 2-3, early non-ambulatory covering states 4-6, and late non-ambulatory covering states 7-8).

Table 20: A comparison of sources of patient utility values[43,44,49–51]

Health states	Audhya et al. (2023)	BOI study	Landfeldt et al. (2017)	Landfeldt et al. (2016a)	Crossnohere et al. (2021)
Measure	EQ-5D-5L	DMD-QoL	HUI	HUI	EQ-5D-3L
Reported by	Patient reported	Patient reported	Caregiver proxy	Caregiver proxy	Caregiver proxy
1 - Early ambulatory	0.79	0.70	0.70	NR Fig2A	0.65
2 - Late ambulatory	0.64	0.49	0.61	NR Fig2A	0.49
3 - Transfer		0.38			
4 - HTMF, no ventilation	0.28	0.54	0.22	NR Fig2A	0.31
5 - No HTMF, no ventilation	0.25	0.51			

6 - HTMF, night-time ventilation	0.26	0.53			
7 - No HTMF, night-time ventilation	0.14	0.52	0.15	NR Fig2A	0.26
8 - Full time ventilation		0.33			

Abbreviations: BOI, burden of illness; DMD, Duchenne muscular dystrophy; EQ-5D-3L, European quality of life 5 dimension 3 level version; EQ-5D-3L.European quality of life 5 dimension 5 level version; HTMF, hand-to-mouth-function; HUI, health utility index; QoL, quality of life.

Table 18 and Figure 11 present the impact of alternative patient utility sources on the ICER. For studies that do not report utilities separately for late non-ambulatory stages, the approach outlined in response to CQ Question B17 was also explored, using multipliers from the literature to adjust health state 8 relative to health state 7. Specifically, a multiplier of 0.6 (0.051/0.129) from Landfeldt et al. (2017) was applied to the health state 7 utility. This adjustment, when combined with Audhya et al. (2023), had only a minimal effect on the ICER, consistent with the CQ response, while use of the Project HERCULES BOI values reduced the ICER. Notably, the BOI study is the only source providing patient-reported utilities for every health state in the CEM. In contrast, the caregiver-proxy sources marginally increased the ICER. Evidence in DMD indicates that caregiver-proxy and patient-reported HRQoL often diverge.[51,52] Given that validated patient-reported utilities are available, these are the preferred source for the base case.

Table 21: Scenario analyses exploring the impact of patient utilities source[43,44,49,50]

Source of caregiver utilities	**Base case 1: 1.5% discount rate (outcomes), 3.5% discount rate (costs)**		**Base case 2: 3.5% discount rate (outcomes), 3.5% discount rate (costs)**	
	ICER step change	**% change each step**	**ICER step change**	**% change each step**
Audhya et al. (2023) (base case)	[redacted]	NA	[redacted]	NA
Audhya et al. (2023) with adjustment for health states 7 and 8	[redacted]	-0.8%	[redacted]	-1.2%
Project HERCULES BOI	[redacted]	-1.8%	[redacted]	14.5%

Source of caregiver utilities	Base case 1: 1.5% discount rate (outcomes), 3.5% discount rate (costs)		Base case 2: 3.5% discount rate (outcomes), 3.5% discount rate (costs)	
	ICER step change	% change each step	ICER step change	% change each step
Landfeldt et al. (2017)	[redacted]	3.6%	[redacted]	4.3%
Landfeldt et al. (2017) with adjustment for health states 7 and 8	[redacted]	2.7%	[redacted]	2.9%
Crossnohere et al. (2021)	[redacted]	5.0%	[redacted]	7.8%
Crossnohere et al. (2021) with adjustment for health states 7 and 8	[redacted]	3.3%	[redacted]	5.2%

Abbreviations: BOI, burden of illness; ICER, incremental cost-effectiveness ratio

Figure 11: Scenario analyses exploring the impact of patient utilities source and assuming 1.5% discount rate for health outcomes[43,44,49,50]

Abbreviations: BOI, burden of illness; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

2. **Explore patient health-related quality of life informed by Crossnohere et al. (2021).**

As above.

3. **Capture the increasing impact on patients as the condition progresses; explore different ways to differentiate between health states 7 and 8 for all possible sources (for example, by combining models 2 and 3 from Landfeldt et al. 2017).**

As above.

4 Resource cost modelling and assumptions

1. Further explore tertiary care and medical aid costs.

In response to CQ Question B9, the Company explored inclusion of tertiary care and medical aids costs. To recap, Morgan et al. (2024) is used to inform health-state costs in the Company base case, as it is the most recent, UK-specific, and robust source aligned with the NICE reference case, showing expected cost increases across disease stages.[53] However, in the CQs, the EAG noted that it does not capture certain broader costs (e.g., community services, medical aids, devices, and home adaptations). These categories are included in Landfeldt et al. (2014), but this study is outdated, lacks health-state breakdowns, and may reflect out-of-pocket or non-NHS/PSS expenditures, limiting its suitability.[54]

To explore the potential impact of these broader costs, a +205.3% multiplier (derived from Landfeldt et al. (2014)) was applied to the Morgan et al. (2024) estimates. This percentage reflects the relative contribution of non-medical community services, medical aids, devices, and investments to the total costs. Table 22 and Figure 12 present a comparison of the base case ICER with the scenario including this multiplier for tertiary care and medical aid costs; the ICER is shown to increase by 5.4% relative to the base case. Nonetheless, given the limitations and uncertainties, and the fact that many of these costs fall outside the NHS/PSS perspective, Morgan et al. (2024) remains the most robust base-case source.

2. Ensure scenarios differentiate between health states 7 and 8.

In response to CQ Question B17, the Company was asked to provide a scenario differentiating between health states 7 and 8 in terms of costs and utilities. The assumption of equal health state costs across late non-ambulatory health states was originally made due to limited data availability and a preference to source all costs from a single dataset, thereby reducing uncertainty introduced by

combining multiple sources. However, we acknowledged the EAG's concern that the transition from "no HTMF with night ventilation" to "no HTMF with full ventilation", i.e., health state 7 to 8, would likely accrue additional costs. To address this, a scenario analysis was undertaken using multipliers derived from the literature to adjust the costs for health state 8 relative to health state 7. The Project HERCULES UK BOI study is the only source distinguishing costs between health states 7 and 8, this was not implemented in the base case due to low patient numbers and concerns about data validity.[44] Nevertheless, in response to the EAG's question, a multiplier was calculated from the UK BOI study reflecting the increase in costs from health state 7 to health state 8 (1.3 = £10,506/£7,978). This was then applied to the "non-ambulatory/with ventilation" i.e., health state 7 cost from the Clinical Practice Research Datalink (CPRD) study. This adjustment reflects the potential for increased costs associated with health state 8 relative to health state 7.

Table 22 and Figure 12 presents a comparison of the base case ICER with scenarios exploring the multiplier for tertiary care and medical aid costs and the multiplier for differentiating between health state 7 and 8; the impact of both adjustments is shown to increase the ICER by 3.2%. Nonetheless, given the limitations and uncertainties, and the fact that many of these costs fall outside the NHS/PSS perspective, and the additional uncertainties from combining multiple sources, Morgan et al. (2024) remains the most robust base-case source.

Table 22: Scenario analyses exploring the impact of tertiary care and medical aid costs[53,54]

Source of caregiver utilities	Base case 1: 1.5% discount rate (outcomes), 3.5% discount rate (costs)		Base case 2: 3.5% discount rate (outcomes), 3.5% discount rate (costs)	
	ICER step change	% change each step	ICER step change	% change each step
Costs as per Morgan et al. ((2024); base case)	[redacted]	NA	[redacted]	NA
Costs as per Morgan et al. (2024) and with adjustment for health states 7 and 8	[redacted]	-0.7%	[redacted]	-0.7%
Costs as per Morgan et al. ((2024) and multiplier from the BOI study	[redacted]	5.4%	[redacted]	5.4%
Costs as per Morgan et al. (2024) and multiplier from the BOI study with adjustment for health states 7 and 8	[redacted]	3.2%	[redacted]	3.2%

Abbreviations: ICER, incremental cost-effectiveness ratio

Figure 12: Scenario analyses exploring the impact of tertiary care and medical aid costs and assuming 1.5% discount rate for health outcomes [53,54]

Abbreviations: BOI, burden of illness; ICER, incremental cost-effectiveness ration; QALY, quality-adjusted life year.

Committee other considerations

5 Equality and discount rate

DMD is a rare, paediatric-onset, progressively disabling and life-limiting disease. The evidence base is limited by ethical constraints, the progressive nature of the disease, globally evolving diverging standards of care, and the small patient population. Moreover, there are substantial health technology assessment challenges that must be overcome before new therapies in DMD can be appropriately valued, due to the limitations of current health technology assessment processes and methodologies. The challenges with the evidence base, the rigidity of the NICE STA process, and the lack of tailored methodological guidance, all mean that the NICE STA process has limited suitability for chronic, paediatric, long-term progressive degenerative conditions. Importantly, although DMD is rare, it does not meet the criteria for the highly specialised technology appraisal route and therefore cannot benefit from the greater methodological flexibility and higher cost-effectiveness thresholds offered through that process. This inevitably leads to a lack of equality in provision of treatments for childhood, progressive diseases compared with other therapy areas.

In terms of the lack of tailored methodological guidance, there are significant gaps in how NICE methods apply to paediatric-onset, progressive degenerative conditions such as DMD. Unlike oncology, where NICE has developed sophisticated methods to evaluate complex disease trajectories, DMD has not benefited from similar methodological flexibility. HRQoL data in children and parent carers is not well collected, poorly understood, and often misinterpreted, and this, together with the lack of guidance on the application of HRQoL for caregivers and everyone who is impacted by these debilitating diseases leads to underestimation of disease burden and undervaluation of treatment benefits. The substantial caregiver impact is not adequately defined in standard

NICE assessment processes, and the Company has dedicated substantial effort to ensuring these impacts are appropriately reflected in its economic modelling.

A key methodological challenge for givinostat is valuing the health outcomes appropriately. Adlard et al. (2014) explored the influence of the UK NICE Reference Case on paediatric QALY measurement and found that there was significant variability in how QALYs are measured and valued in children.[55] In relation to the discount rate, four of the 43 studies used a 1.5% discount rate for health outcomes. While the 2014 study is somewhat dated, its findings indicate the challenges associated with applying standard economic methodologies to paediatric populations. More recent research has confirmed this, consistently highlighting the unique difficulties in measuring and valuing health outcomes in children.[56,57]

The NICE Methods Manual allows for a non-reference discount rate of 1.5% for technologies that provide sustained, long-term benefits in severe conditions.[58] However, a strict application of this guidance effectively excludes conditions like DMD, as they can never meet the third criterion: restoring a patient to full health.

As detailed in our response to CQ Question B23, givinostat meets two of the three criteria for non-reference discounting, as it is indicated for a severely impairing condition and is expected to provide sustained benefits. Given that givinostat meets all the criteria it feasibly could, the Company believes that using a 1.5% discount rate for health outcomes is both appropriate and fair. The standard 3.5% discount rate disproportionately penalises these long-term benefits, as they are accrued far into the future. Given these challenges, we have presented two base cases for consideration:

- **Company-preferred base case:** Applies a **1.5%** discount rate to health outcomes.

- **Reference base case:** Applies the standard **3.5%** discount rate to health outcomes.

The impact of these different discount rates on the updated Company base case can be seen above in Table 1.

In summary, none of the existing mechanisms designed to allow flexibility in decision making are applicable to this disease area. This creates an inequity, as children with progressive, life-limiting conditions are disadvantaged compared with patients in other therapy areas where such flexibilities do apply. In practice, this gap in process leads to unequal access to treatments for childhood progressive diseases.

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Single Technology Appraisal

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

EAG Clarification Questions Sent September 29th, 2025

1. Thanks for sending through the updated evidence on Carer HRQoL. We were able to trace the company's base case reported in table 13 [redacted] of *ID6323 Givinostat Stakeholder CfE_ITF Pharma_FINAL [CON]* to table 7 of *ID6323 givinostat Interim findings for Duchenne Duchenne UK 11.08.25 [CON]*. However, With regards to the smaller cohort of [redacted] respondents reported in table 1 of *ID6323 Givinostat EQ 5D_august request 2019.08.25 [CON]* there is unexplained discrepancy between the number of respondents [redacted] categorised ambulatory (stages 1-3) in comparison to number of respondents categorised ambulatory (stages1-2) [redacted] transfer (stage3) [redacted] reported in the company's base case .Table 14 of the company's response seems to suggests the breakdown of non-ambulatory patients belong to the larger cohort [redacted] . Can you please clarify if these are two different subsets of the respondents and provide sufficient description/data for us to compare the characteristics and results.

Response: There is a labelling error in Table 1 and Table 2 of *ID6323 Givinostat EQ 5D_August Request 2019.08.25 [CON]*. The first column should be titled "non-ambulatory" rather than "ambulatory." This first column represents the overall group of non-ambulatory participants, with the subsequent columns providing the breakdown by stage within this group. Once corrected, the patient numbers in Table 1 and Table 2 of *ID6323 Givinostat EQ 5D_August Request 2019.08.25 [CON]* are consistent with the non-ambulatory patient counts reported in Table 7 of *ID6323 Givinostat Interim Findings for Duchenne Duchenne UK 11.08.25 [CON]*.

2. We have received the number of caregivers reported in table 17 of *ID6323 Givinostat Stakeholder CfE_ITF Pharma_FINAL [CON]*, however it is unclear if these carers are involved full time or not, the *ID6323 givinostat Interim findings for Duchenne Duchenne UK 11.08.25 [CON]* does not seem to provide this information. The HRQoL survey relates to the parent carers, but the number of informal carers is more than that. Can the company comment on this discrepancy? Does the company consider that parent carer HRQoL apply to the informal cares?

Response: The survey was of parent-carers and the following definition was used: *"By 'parent-carer' we mean that you identify as having parental responsibility for and provide informal care for a child living with Duchenne. This may not necessarily be as a biological parent, but could also include as an adoptive parent, a new partner of a biological parent of a child with Duchenne with caring responsibility etc. While other relations to the child(ren) living with Duchenne may provide informal care, such as grandparents or siblings, we are interested in the perspectives of parent-carers in this survey."*

Utility data were collected from both mothers and fathers, and the results reported represent the average across all parent respondents. While a small amount of dyadic data were available, it remains challenging to generalise these findings to other groups of informal carers (e.g. grandparents, siblings, or others involved in providing care). Nevertheless, in the absence of data from these groups, the parent-carer utilities can be viewed as the best available proxy for the disutility experienced by informal carers more broadly.

Single Technology Appraisal

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

Call for additional evidence response form

Association of British Neurologists

1. Givinostat use in clinical practice requires intense monitoring which does not form part of current established clinical management of DMD. For example, monitoring requirements include fortnightly blood tests during drug initiation, a procedure which would ordinarily be done only once or twice a year. Furthermore, adverse effects are not uncommon in those receiving Givinostat (treatment-related adverse event rate in EPIDYS trial was 69% and treatment interruption rate was 14%). This adds up to a significant resource implication for clinical services which currently do not have capacity to support and absorb such demands. Thus, where decisions are made regarding access to this treatment, considerations should be given to the resource implications (i.e. costs to the healthcare system, not just of the drug itself) and how this will be delivered in practice.
2. Detailed efficacy assessments (e.g. NorthStar assessment) are not part of routine current established management, especially in adult centres. Even basic measures such as timed walking distance are difficult (and potentially dangerous) to carry out without appropriate support from physiotherapists. Again, NICE should integrate the full resource implications for use of this drug in practice, beyond simply the cost of the drug.
3. Those receiving Givinostat in EPIDYS continued to worsen, just at a decreased rate. Statistical models should clearly be able to capture this nuance, and in my experience (drawing from other disease areas primarily) patients find stabilisation and slowed rate of decline beneficial, even if they aren't "better". The NICE CfE letter mentions "…it also acknowledged that extending time in health states associated with a negative impact … would extend that negative impact" but without explaining what is meant by this and what states are being referred to. Clearly if a drug is not benefitting a patient it should be stopped. NICE should consider outlining clear stopping rules as well as eligibility criteria if the medication is approved.

Single Technology Appraisal

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

Call for additional evidence response

Clinical expert response

1. DMD and the Impact of the Condition

Patient experts and observers at the appraisal committee remain concerned that the committee have not appreciated the devastating and life changing impact of a diagnosis of DMD on affected individuals and their carers.

I have been supporting families living with DMD for almost 30 years now and I would reiterate the enormous challenge that children, young people and families face from the time of diagnosis. The resilience needed to deal with the many challenges to ensure an individual has the best possible care is significant. The logistics required to coordinate care and interaction between the multiple services involved are enormous, even before the 'battles' begin to fight for appropriate educational provision or suitable adaptations and wheelchairs. Sadly these battles are 'standard' and managing this whilst balancing the needs of work, other children and the other challenges that life brings takes a toll on even the most well resourced families.

Impacts are felt at home, school and the workplace and influence every decision a family makes - where they shop, what they do to celebrate a birthday, where to go - if anywhere - on holiday etc etc. All this whilst living with the certainty that the disease will inexorably progress and take away yet another function year on year.

I would also stress the fact that DMD is not simply a muscle disease. DMD is a multi-system condition with a high proportion of individuals also having primary neurobehavioral sequelae as a consequence of their dystrophin mutations affecting the Dp140 and Dp71 isoforms that are found in the brain. Cardiac, respiratory, bone, GI and renal impairments are also inevitable in time. Many of these are exacerbated by muscle weakness and thus are more commonly seen as the disease progresses. Slowing down the rate of decline in muscle strength therefore has significant impacts on physical well-being, as well as improving the psychological health of individuals which has such a key impact on an individual and their carer's quality of life.

Better physical health and upper limb function in adolescence has positive benefits on academic performance and peer relationships facilitating more opportunities for a

young adult, over and above the benefits to bone health, digestion and motor function. There are definite benefits for both patients and carers from remaining in each health state for longer as the disease progresses.

2. The estimation of givinostat treatment effect and its application in the model

The benefits of Givinostat have been proven in the Epidys study with further information on long term outcome now published from the OLE study (McDonald et al, Annals of Clinical and Translational Neurology, 2025; 0:1–14) The Ulysses study looking at the impact in a non ambulant population is ongoing.

There is literature defining minimal clinically significant change in particular motor milestones including timed 4 stair climb, which has already been referenced in my response to the technical engagement (attached again) confirming the importance of delaying loss of these motor skills.

The trial cohort is now old enough to calculate a median age for loss of ambulation including both the 'delayed' treatment group ie the cohort randomised to receive placebo in Epidys and the 'early' treatment groups. The median age of loss of ambulation at 17.2 years is significantly different to that seen in clinical practice or when comparing with natural history controls of 13-14 years. However, at this time point, the specific impacts on later disease milestones is unclear as no boys treated with Givinostat have reached an FVC threshold of < 50% predicted for height or of < 1 L, which have been correlated with the need for ventilatory support. This is of course a positive outcome in comparison to natural history data.

In the absence of specific data, it is reasonable to infer a similar impact from Givinostat on the disease course in DMD as has been seen with corticosteroid treatment. This is a good parallel to consider when modelling the treatment benefits of Givinostat, not only as the size of the effect appears similar but in that the treatment is targeted at all genetic subtypes of DMD, unlike so many other drugs currently in trial.

The impact of steroids on motor function was initially only evident in ambulant boys where the rate of functional decline was noted to be slower, resulting in delay in the age at loss of ambulation. However, in time the benefit of preserving skeletal muscle function was seen not just in the proximal muscles of the lower limbs, but in the upper limbs, trunk and respiratory muscles. Importantly, the delay in age at which other critical disease milestones occurred was more than expected from the age at loss of ambulation per se.

We now see more boys in the 'transition' state where despite using a wheelchair for mobility, boys can transfer and still use their arms and trunk to good effect, maintaining their independence and well being for longer. The delay in time to acquire later disease

milestones is greater than would be expected from simply shifting the curve to the right by the difference in age at loss of ambulation. This has been shown in the curves derived from the natural history datasets : CINRG, (McDonald et al) and Northstar: (Trucco et al) and in clinical practice with night time ventilation now typically being needed more than 4-5 yrs later than previously where the delay in loss of ambulation is around 3 yrs.

A disease profile that is shifted to the right with a more gradual, rather than parallel incline is seen with steroid use. This is the pattern that appears to be emerging with the addition of Givinostat in DMD. Although the full extent is not yet clear. This is a clinically plausible pattern and what would be anticipated as a result of treatment that provides some 'protection' for those muscles not yet irreversibly damaged ie in trunk and upper limbs.

3. **The carer health-related quality-of-life modelling and assumptions**

As noted in my response to the technical appraisal, carer HRQoL should not be limited to the degree of physical care required to support an individual living with DMD. The physical burden of care clearly increases as an individual with DMD becomes weaker and more dependent, moving across the health care states as outlined in Project Hercules.

However, the committee need to acknowledge the impacts on the emotional and psychological well being of carers which, in my experience, fluctuate considerably across various disease milestones. These are not necessarily related to specific motor milestones and often relate to life events for the affected individual. Clearly the time of diagnosis is hugely traumatic, but other life events for example starting high school, making choices about tertiary education, lack of peer groups and inability to engage in normal adolescent rites of passage all take their toll, over and above the knowledge that one's loved one faces major health challenges and early death.

I hope that the recent work from Project Hercules with SCHARR will provide more information to guide the committee re the calculation of the HU for carers.

I would however take issue with the committee's assumption *that "extending time in health states with a negative effect on carers would extend that negative effect during that period"* The patient and parent experts on the committee and indeed feedback from PAGs does not support this view. They are very clear that delaying progression across health care states is beneficial as it improves overall participation, independence and well -being of their loved ones, which in turn improves carers HRQoL

In my experience, the loss of a child with DMD often has devastating and life long impacts on carers. Sadly I have supported at least 1 family where a parent has taken

their own life after the death of their child and several others where the family unit has broken down with significant negative impact on carers and siblings.

4. **The patient health-related quality-of-life modelling and assumptions**

In my experience and that of others in the UK clinical network, the EQ-5D has not been a helpful tool in assessing QoL in DMD and thus is not used in clinical practice. The lack of an effective tool to capture QoL in DMD was the driver for Project Hercules to develop the DMD QoL

We have been piloting the use of the DMD QoL in clinical practice in Leeds, and although numbers are relatively small (56 responses from 42 patients) we can confirm that there is a stepwise decline in score as the condition progresses through early v late v transitional stage, with the lowest score overall being in the social domain across all 'groups'. (see attached document) and that it is a useful tool for capturing HRQoL.

There was a significant difference between carer (proxy) reported and patient scores in the early and late ambulatory cohort with the main difference in the physical domain, highlighting the greater concerns that carers have for their child's QoL at different stages

The range of scores varied more in the earlier disease states with more consistent responses in the non ambulant cohorts and less variability between patient and proxy reported scores

In my clinical experience, preserving certain motor skills has more impact on quality of life than others. Whilst providing a powered chair can improve independence in adapted environments - school and home, the capacity to independently stand and transfer is crucial for social activities, in particular travelling outside the home and using toileting facilities, reducing risks of isolation and exclusion in adolescence and in turn improving health and well being

Similarly, maintaining trunk and upper limb function is probably more critical for independence than maintaining lower limb function. Being able to operate controls, feed oneself, alter one's position enable a young person or adult to engage with education, social and work in an independent manner, which is of course critical to participation and overall well being.

Patient experts highlighted the importance of remaining in the transition and early non ambulatory states very eloquently at the committee meeting and I would concur with their testimony.

In addition to the benefits on social and psychological health, maintaining an upright, weightbearing posture through adolescence reduces the risk of contracture development, optimises bone health and reduces risk of spinal deformity, all of which can further compromise mobility and physical health.

There is evidence of benefits both to patients and health services of delaying motor decline with steroids. The risk of spinal deformity requiring operative spinal fixation has diminished as steroids have become a standard of care and boys have better preserved trunk power and posture as they go through puberty. Similarly preserving respiratory function has delayed the age at which significant respiratory complications occur, with very few patients with DMD requiring ventilatory support in childhood. Avoiding the need for early and significant interventions in childhood also has an impact on overall quality of life and well being.

I would concur with patient experts that there is a difference in QoL for health states 7 and 8, when permanent ventilatory support is required as the decline in respiratory muscle function is mirrored with decline in critical fine motor skills. This was outlined very clearly in testimony from Jon Hastie who highlighted the additional physical challenges and impacts for full time ventilatory support

The resource cost modelling and assumptions

I do not feel that I can comment specifically on this area

Summary of DMDQoL survey in clinical practice in Leeds

The DMD QoL has 14 questions exploring physical, social and psychological health related QoL. The maximum score is 42

Survey done over 8 months August 23- April 24. Offered to all DMD patients attending NM clinics in Leeds. 56 responses from 42 patients.

I do not have the ability to translate raw DMD QoL scores into health utility scores

[redacted] early ambulatory patients

Children and young people (CYP) [redacted]

Proxy reports from carers [redacted]

Note wide range in scores, though proxy reported scores, where matched, were on average [redacted] points lower than patient reported scores, largely in physical domain.

[redacted] late ambulatory patients

CYP: [redacted]

Proxy scores (carers): [redacted]

On average proxy reported scores were [redacted] points lower than those reported by CYP , again in physical domains

[redacted] transitional patients

CYP: [redacted]

Proxy scores [redacted]

Small numbers but better correlation between patient and proxy reported scores

[redacted] Non ambulatory patients

CYP [redacted]

Proxy ([redacted]

No difference in median scores for the [redacted] with matched scores. Median scores appear higher than transition but numbers in transition group small and more 'lower' scores in this cohort

[redacted] Non ambulatory patients +nocturnal NIV

CYP [redacted]

Proxy responses [redacted]

Numbers of CYP very small but reported QOL appears good.

Other points

In those with sequential scores ([redacted] boys in clinical trials in early ambulatory phase) their scores were consistent across 3 time points during the study.

Overall scores were lowest in the social domain

Where a difference existed between patient and proxy scores, this was on average in the physical domain. The difference in patient and proxy scores were only seen in the early and late ambulatory phases

BPNA
British Paediatric Neurology Association

12 September 2025

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]
Call for additional evidence - submission 12th September 2025.

BPNA comments:

DMD and the Impact of the Condition
DMD is a severe, progressive, and life-limiting condition that has a substantial impact on the physical health, psychological health and quality of life. This not only affects the child and young person (CYP) but also of their families and carers.

The estimation of givinostat treatment effect and its application in the model
It is difficult to be able to present new evidence from a clinical perspective as there is no further trial data or long term data to present, the OLE study is ongoing and there are two ongoing clinical trials with givinostat in DMD (in younger < 6 years old children as well as older, non ambulant patients). These studies will provide further evidence on givinostat across different populations.
The loss of ambulation in this cohort is significantly later compared to what is seen in clinical practice and this is evident in the trial data. It is well known and observed that these CYP who are ambulant for longer have a better outcome, start ventilation later and maintain arm function and hence independence for longer as well as often become independent and work/study compared to those who lose ambulation in their early teens around transition and struggle both physically and psychologically.
As with data that that we have seen from the impact of steroids and now accepted as standards of care . This has been shown in the curves derived from the natural history datasets (CINRG, McDonald et al and Northstar Trucco et al) this has resulted in a delayed requirement for commencement of night time ventilation by at least 5 years and hence 24 hour ventilation, this is a shift from 15 years ago when paediatric patients were ventilated, there has also been a delay in LOA on average by 3 years, and hence improvement in the need for scoliosis surgery and reduction from 90% to 10% (Cochrane review data). It can therefore be inferred that another medication which also delays these milestones will not only see a shift in these milestone but an exponential improvement and delay. Givinostat is already

starting to demonstrate this in the trials and therefore would be reasonable that clinically this would be an affect that would be seen.

The carer health-related quality-of-life modelling and assumptions

There is limited data on carers and the impact of DMD on parents and families, however the care and support that a person with DMD requires for physical care increases with the progression of the disease and moving across the health care states. The amount of carers that have anxiety, sleep deprivation, loss of work days, poor physical health and worry is evident in clinics and reports from families. All clinicians experience this and depending on the clinical MDT set up refer CYP and their families to the mental health teams, wellness team, neuromuscular care advisors or counsellors within the team.

As described above, a drug such as Givinostat that delays deterioration and shifts the timeline and enable longer time in better health states is likely to have a significant impact on carer health quality of life as well as the CYP quality of life.

The patient health-related quality-of-life modelling and assumptions

Again there is limited data on this area, as many teams do still not have psychology support in clinic and limited input from community services, however the lack of an effective tool to capture QoL in DMD was the driver for Project Hercules to develop the DMD QoL.

Psychological help and support is needed around the time of diagnosis, however for most of our CYP input was generally needed as the condition was deteriorating and they were reaching milestones, often around loss of ambulation/teenage years/transition to secondary school.

There are significant issues around adolescence and the transition to secondary school, a time when most of their peers are becoming independent and spending more time away from their parents. These YP are often losing their independence and are often subject to bullying, depression, low self esteem due to their body habitus as well as using a wheelchair, and this often marks a time period when they are requiring more hospital appointments and medications. The loss of ambulation is huge milestone for these YP and their families as this really does highlight the progressive nature of this condition and inevitable progression to early death.

The YP also start to recognise and realise the future of their condition, what their life is going to look like compared to their peers and the grief of what they will never have. They become withdrawn and lose motivation and often this causes further family stress and strain.

For patients who are in better health states for longer and lose ambulation around16-18 years, they appear to cope with this better, usually are confident in their self and have a good circle of friends who do not see the disability. This was also the view presented in the previous meeting by the patients and their carers. This seems to give them that psychological robustness that we do not see in the younger cohort that have to cope with school and bullying, a time of transition to secondary school, a time of hormonal change and wanting to be like everyone else. All this has an influence on family life, parental stress and

psychological well being as well as siblings and enables that YP to achieve and have self worth and a better quality of life.

The resource cost modelling and assumptions

Cannot comment specifically on this area

British Paediatric Neurology Association

Duchenne UK Response to NICE Call for Additional Evidence on Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

Submitted September 2025

Introduction

Duchenne UK welcomes the opportunity to contribute to the NICE evaluation of givinostat for the treatment of Duchenne muscular dystrophy (DMD) in individuals aged 6 years and over. As a patient-led organisation committed to improving the lives of those affected by DMD, we recognise the urgent need for effective treatments and the importance of robust, inclusive evidence to inform decision-making.
In this submission, we provide additional evidence that complements the company's modelling and addresses key areas of uncertainty identified by the appraisal committee, particularly around carer and patient quality of life, the lived experience of later-stage DMD, and issues of equality and inclusion. While we do not directly respond to the technical modelling requests outlined for the company, we highlight where further evidence is available and may support more accurate and representative modelling in future analyses.

Whilst we appreciate the opportunity to address some of the committee's concerns and to support them in making a fully informed decision, this additional call for evidence was initiated with a prohibitively short, four-week, turnaround time in which to provide the breadth and depth of evidence sought. We recognise that the timeframe reflects the need for swift decision making which we fully support as further delays are frustrating and detrimental, but it needs to be recognised that the timeframe causes limitations in data provision in a rare disease.

We are only able to provide the following additional quantitative and qualitative evidence within that timeframe because of the extensive work that had already been undertaken through the work of our unique initiative Project HERCULES - a ground breaking multinational collaboration set up by Duchenne UK to develop tools and evidence to support Health Technology Assessments.

It is vital that lessons are learnt from this experience and that in future appraisals the matters covered in this call for evidence, particularly in relation to quality of life and care giver health related quality of life are appropriately assessed and properly understood from the outset. In relation to the givinostat appraisal, these matters should have been addressed in full and evidence sought as required at the technical engagement stage.

Our submission includes:

- Interim findings from a subset of data from a collaborative study with Sheffield Centre for Health and Related Research (ScHARR) on parent-carer health-related quality of life (HRQoL) in DMD. *Please note – the timeframe of the call for evidence did not allow for full analysis and all data should be treated as academic in confidence.*
- A listening exercise involving patients, parents, and clinicians focused on the later stages of DMD.
- White paper addressing employment in caregivers
- White paper addressing inequality

We hope this evidence will support the committee's understanding of the real-world impact of DMD and the potential value of treatments like givinostat beyond clinical endpoints.

1. Carer Health-Related Quality of Life (HRQoL)

Response to NICE Call for Evidence: Carer Health-Related Quality of Life in Duchenne Muscular Dystrophy

1.1 Multiple carers

The Health-Related Quality of Life (HRQoL) impacts of Duchenne muscular dystrophy (DMD) are not confined to a single parent-carer. ScHARR's interim findings show that caregiving is a shared responsibility, often involving multiple informal and paid carers. Despite this, the emotional and psychological toll—particularly in the domains of anxiety and depression—is disproportionately borne by the parent-carer, who remains the central coordinator and emotional anchor.

Across all disease stages, families reported the following number of carers involved:

These figures confirm that multiple carers are involved at every disease stage, and that the intensity of coordination increases as the disease progresses. The parent-carer's HRQoL is impacted not only by their own responsibilities, but by the need to manage and support others in the caregiving network.

Even when paid carers are present, the parent-carer continues to:

- Coordinate rotas and training
- Manage medical appointments and equipment
- Provide emotional support and advocacy
- Step in when paid carers are unavailable or undertrained

Supporting quotes:

"It's a full-time job just managing the care team. I'm constantly checking stock, ordering supplies, coordinating shifts. Even with paid carers, I'm always

on call." — Parent, Listening Exercise

[redacted]

"I had to sleep on the floor next to my son in intensive care because they had no staff trained to care for him." — Parent Listening Exercise

Anxiety and depression affect multiple carers

ScHARR's qualitative data shows that anxiety and depression are prevalent across all disease stages—not just in the later stages—and affect more than one carer in the household:

- [redacted]

These figures reflect the emotional climate of the household, not just the experience of the primary carer. Siblings, partners, and extended family members are also affected, particularly as the condition progresses and the child's independence declines.

Supporting quotes:

[redacted]

"I cry at the drop of a hat. It's heartbreaking. I know what's coming." — Listening Exercise, transfer stage

[redacted]

[redacted]

These emotional states directly reduce HRQoL. They affect sleep, relationships, mental health, and the ability to participate in society. They are compounded by the knowledge that Duchenne is a progressive, fatal condition.

1.2: Emotional and psychological toll of caregiving

Caregiving for individuals with Duchenne muscular dystrophy (DMD) imposes a sustained emotional and psychological burden on families, particularly parent-carers. This burden evolves over time and varies by disease stage, but remains a consistent and measurable contributor to reduced health-related quality of life (HRQoL).

Quantitative evidence from ScHARR's interim findings from a UK-wide survey of 148 parent-carers provide robust data on the emotional impact of caregiving:

These figures reflect the cumulative emotional toll of caregiving, particularly in the transfer and non-ambulatory stages. Notably, anxiety appears to lessen slightly in later stages, which may reflect psychological adaptation or acceptance over time. However, this does not imply reduced emotional impact—rather, it suggests a shift in the nature of distress, from acute anxiety to chronic sadness, grief, and fatigue.

Thematic analysis of qualitative responses from ScHARR's work and the Listening Exercises across ambulatory, transfer, and non-ambulatory stages revealed consistent emotional challenges:

[redacted]

These findings are consistent with broader literature on rare disease caregiving, which highlights elevated psychological burden compared to carers of other conditions (e.g., Carlton et al., 2022).

The value of time and the emotional cost of progression

Carers consistently emphasised that their children—often young men in adolescence or early adulthood—continue to live meaningful lives, even in the later stages of Duchenne. They pursue education, maintain friendships, engage in hobbies, and express aspirations for the future. The emotional burden of caregiving is therefore not only about the tasks involved, but about the psychological weight of supporting a loved one through a progressive, life-limiting condition.

Supporting quotes:

"He's 19, non-ambulant, ventilated at night—but he's studying, gaming, laughing with friends. He's still living."
— Listening Exercise

"These boys don't want to die. And we don't want them to either. Every day we fight for more time, more independence, more dignity."
— Listening Exercise

[redacted]

This context is essential. Carers are not only managing the physical and emotional demands of care—they are fighting for time, for quality of life, and for the chance to delay the inevitable. The tension between hope and grief, between advocacy and helplessness, defines the emotional landscape of Duchenne caregiving.

While emotional distress may evolve over time, it remains a central and enduring feature of the caregiving experience. It must be recognised not only in clinical and support settings, but also in policy and reimbursement decisions that seek to understand the full impact of Duchenne on families HRQL.

Financial strain and HRQoL

The financial impact of caring for a child with Duchenne muscular dystrophy (DMD) is profound and sustained. It affects every dimension of Health-Related Quality of Life (HRQoL)emotional wellbeing, physical health, social participation, and long-term security. These pressures are not incidental; they are structural, predictable, and disproportionately borne by parent-carers.

National data reinforces this:
- 62% of parents of disabled children in the UK gave up work or worked reduced hours (Contact)
- 23% of families with disabled children have no one in paid employment
- 75% of parent-carers gave up their career due to lack of support (Disabled Children's Partnership, 2023)
- £751/month in additional costs for families with disabled children (Scope, 2025 inflation-adjusted)

Supporting quotes:

> "We literally hand over our life savings or increase our loans to pay a team of builders as a lift is installed, doors are widened, and disability wet rooms are built. This dual effect of risk of employment loss at a time of economic need makes Duchenne a bankruptcy diagnosis." — White Paper - Employment in Carers

> "I had to drop my hours to part-time because of the amount of stock checks, ordering, and coordination I do around Noah's care. It's a full-time job." — parent caregiver, Listening Exercise

These financial pressures are not just about income, they affect housing security, mental wellbeing, and the ability to plan for the future. They add another layer of stress to an already demanding role.

Giving up work: a psychological and identity shock

The decision to leave employment to become a full-time carer is often made out of necessity, not choice. Yet the psychological consequences are significant and enduring.

According to Carers UK's State of Caring report (2025):
- 43% of carers who had given up work reported bad or very bad mental health, compared to 35% of carers in paid employment
- 57% of carers feel overwhelmed often or always
- 65% say they feel overwhelmed because they cannot take a break from caring
- 56% of carers struggling financially report bad or very bad mental health, compared to 18% of those not struggling

These figures confirm that loss of income and career identity directly reduce HRQoL. The emotional toll includes:
- Loss of self-worth and professional identity
- Feelings of invisibility and being undervalued
- Guilt over not contributing financially
- Anxiety about future security and pension poverty

Supporting quotes:

> "The biggest regret of my life is not being able to work and use the qualifications I studied so hard for." — Carers UK Forum

> "My husband keeps our son's diagnosis separate at work. He's not suffering the same discrimination as me." — White Paper - Employment in Carers

These experiences reflect a widespread pattern of career disruption and identity loss, which compounds the emotional strain of caregiving and contributes to reduced HRQoL.

1.3: Physical and cognitive exhaustion

Caregiving in Duchenne muscular dystrophy (DMD) is physically demanding and cognitively relentless. As the condition progresses, the intensity and complexity of care increases, placing substantial strain on carers' bodies and minds. This burden is consistently reported across both quantitative and qualitative data.

Quantitative evidence from ScHARR's interim findings show that carers experience:

These figures reflect the sustained physical toll of caregiving, particularly in the later stages, when care is often required 24/7. The reduction in reported fatigue in non-ambulatory stages may reflect increased reliance on paid carers or assistive equipment, but does not imply reduced burden—rather, it may indicate a shift from physical to logistical and administrative strain.

Sleep disruption and musculoskeletal strain

Sleep disturbance is a well-documented issue among Duchenne carers. A study of caregiver-mothers found that over 60% had poor sleep quality, with longer sleep latency and reduced sleep efficiency compared to matched controls (Nozoe et al., 2016). As upper body function is lost, boys and young men need frequent repositioning at night to get comfortable and avoid pressure sores. .

"My sleep is light, any little noise will wake me up, he gives a little scream and I am awake, because I have to see what is happening to him."
— Caregiver-mother, Nozoe et al. (2016)

You have to start getting him up at 7:00 AM. So the carers' shifts have to change. They have to come earlier and by the time you get Noah up and ready to go out, he's fallen asleep before you get in the car because it's a hard job. Parent – Listening Exercise

Musculoskeletal strain is also common, particularly in transfer and non-ambulatory stages. Carers frequently report lifting, repositioning, and transferring their child multiple times per day and night, often without appropriate equipment or support. This contributes to chronic pain, fatigue, and increased risk of injury.

"Our child is now unable to walk so we have to carry him around the house most of the time or we hoist him… he's now too heavy to lift."
— Listening Exercise

Cognitive load and mental fatigue

Beyond physical strain, carers experience high levels of cognitive burden. This includes:
- Continuous planning and coordination of care
- Managing medications, appointments, and equipment
- Navigating fragmented services and funding systems
- Training and supervising paid carers

This cognitive load contributes to psychological exhaustion and burnout, particularly when combined with sleep disruption and emotional stress.

Progression-linked increase in complexity

As individuals with DMD transition from ambulatory to non-ambulatory stages, the nature of care shifts from mobility support to full physical dependency.

This increase in care complexity is accompanied by greater administrative burden, including managing rotas, training staff, coordinating across multiple services, and navigating funding and equipment provision.

"I had to drop my hours to part-time because of the amount of stock checks,

ordering, and coordination I do around Noah's care. It's a full-time job."
— Listening Exercise

Implications for carer wellbeing

The physical and cognitive exhaustion experienced by carers has direct consequences for their own health, employment, and family life. It contributes to:

- Increased risk of musculoskeletal injury
- Sleep deprivation and associated health risks
- Reduced capacity to maintain employment or social relationships
- Chronic stress and burnout

These impacts are not peripheral—they are central to the caregiving experience and must be recognised in service planning, support provision, and policy development.

1.4: Systemic impacts on carer HRQoL in later stages of DMD

As Duchenne muscular dystrophy progresses into later stages, the caregiving role becomes increasingly complex, intensive, and system dependent. Carers are not only responsible for direct disease-related tasks (e.g. ventilation, medication, transfers), but also for managing a wide range of indirect responsibilities — many of which stem from systemic gaps in care provision. These responsibilities significantly reduce carer health-related quality of life (HRQoL).

Care complexity in later stages

In non-ambulatory stages, individuals with DMD often require:

- 2:1 care at all times
- Tracheostomy management
- Ventilation and cough assist
- Hoisting and full physical transfers
- Medication administration and monitoring
- Coordination across multiple clinical specialties

These figures reflect the intensity of care required, even when professional support is present. Carers remain responsible for oversight, coordination, and often direct intervention when systems fail.
Supporting quote:

"Noah has 2:1 care at all times. Every carer must be tracheostomy-trained. We go through carers constantly because they're paid £14 an hour to keep someone alive. They leave to work in supermarkets."
— Listening Exercise

Multi-system progression

In later stages, Duchenne affects multiple organ systems beyond skeletal muscle. Carers must manage serious complications including:
- Gastrointestinal dysfunction, including impaired gut motility, constipation, and risk of pseudo-obstruction
- Cardiac complications requiring regular monitoring and medication
- Respiratory insufficiency requiring ventilation and airway clearance
- Endocrine and bone health issues due to long-term steroid use

These complications often require specialist input, but carers are frequently left to coordinate and deliver care across these domains.

Systemic failures and their impact

Carers frequently report that systemic barriers exacerbate their burden:
- Hospital exclusion policies prevent trained carers from accompanying patients, even when hospital staff lack relevant expertise.
- Fragmented services require carers to coordinate across multiple providers, often without support.
- Funding limitations delay or prevent access to essential equipment, adaptations, and therapies.
- The administrative load (e.g. payroll, rotas, training) falls on carers, even when care is externally funded.

Supporting quotes:

"If you have a healthcare budget, your carers can't come into hospital. But hospitals don't have staff trained to deal with Duchenne. It's ludicrous."
— Clinician

"He had a sore toe and needed antibiotics. But because he's ventilated, he had to go into intensive care. They're the only ones trained to look after him."

— Listening Exercise

Indirect care burden

In later stages, carers often take on responsibilities that are not strictly medical but are essential to maintaining quality of life. These include:

- Advocacy: fighting for access to treatments, trials, and services
- Education support: liaising with schools, colleges, and EHCP teams
- Social facilitation: enabling friendships, hobbies, and outings
- Mental health support: managing anxiety, depression, and grief in the individual with Duchenne

These roles are often invisible in formal assessments but are central to the lived experience of caregiving.

Supporting quotes:

"Advocating for him at every appointment, attending EHCP meetings, fighting every which way for proper treatment and care."
— Listening Exercise

In later stages of DMD, carer HRQoL is shaped not only by the direct demands of care, but by the systemic and indirect responsibilities that fall on families. These impacts are cumulative, sustained, and often under-recognised. Any assessment of HRQoL must account for the full scope of caregiving, including the failures of the system that carers are forced to compensate for.

1.5: Conflation of HRQoL and burden

Health-related quality of life (HRQoL) for carers of individuals with Duchenne muscular dystrophy (DMD) must be understood as a multidimensional construct—not simply as “burden.” While the term “carer burden” is often used in economic modelling, it risks oversimplifying the sustained and complex impacts of caregiving on emotional wellbeing, identity, autonomy, and social participation.

The NICE appraisal of givinostat has itself highlighted this conflation of burden

and HRQoL. The committee requested clarification on the number of carers affected in each health state and explored modelling approaches based on disutilities or incremental impacts. However, this framing risks reducing HRQoL to a numerical burden metric—focusing on how many carers are involved, rather than how deeply their lives are affected.

This approach overlooks the broader reality: HRQoL is not just about the effort of caregiving—it is about the total impact of the disease on the parent and family, including emotional, psychological, social, and financial dimensions. As Carlton et al. (2022) note, most instruments used to measure carer HRQoL lack sensitivity to these domains and often fail to capture the full scope of lived experience.

Supporting quote:

"It's not just the burden of care, it's the burden of watching your child lose function, of fighting for services, of losing your own life plans."
— Listening Exercise

Loss of autonomy and identity

These changes reflect sustained disruption to life plans, financial security, and personal development. Carers frequently report a loss of autonomy and identity, as their roles shift from parent to full-time coordinator, advocate, and care provider.

Supporting quote:

Emotional labour and psychological strain

Carers report chronic stress, anticipatory grief, and emotional trauma. The progressive nature of DMD means that carers live with the knowledge of inevitable decline, while managing intensive daily care. These emotional

impacts are not transient—they are sustained and cumulative.

Supporting quote:

"I'm not just tired. I'm grieving every day for what's coming. That's not burden. That's heartbreak."
— Listening Exercise

Carlton et al. highlight that most instruments used to measure carer HRQoL lack sensitivity to emotional domains such as grief, guilt, and psychological exhaustion.

Social isolation and systemic exclusion

Carers often experience social isolation, particularly in later stages of the condition. Their ability to participate in social, professional, or recreational activities is constrained by the demands of care and the lack of systemic support.

Supporting quote:

[redacted]

Systemic failures—such as exclusion from hospital care, lack of trained staff, and fragmented services—further isolate carers and reduce their trust in the system. These experiences contribute to a sense of invisibility and exclusion, which directly impacts HRQoL.

Resilience does not equal wellbeing

Many carers demonstrate extraordinary resilience, commitment, and love. However, resilience should not be conflated with wellbeing. Carers may continue to provide high-quality care and advocate for their child, while experiencing significant reductions in HRQoL.

Supporting quote:

"I love my son. I wouldn't change him. But I'm exhausted. I've had to fight for everything."
— Listening Exercise

HRQoL is not simply a measure of "burden." It encompasses emotional wellbeing, autonomy, identity, social inclusion, and long-term health. Carers of individuals with DMD experience profound and sustained reductions in HRQoL, even when they are resilient and committed. These impacts must be recognised in policy, modelling, and service design—not as secondary considerations, but as central to understanding the true cost of care.

2. Disease progression: Health states 7 and 8

In this section we set out lived experience evidence on stages 7 and 8 ventilation and upper body mobility in Duchenne muscular dystrophy.

Stages 7 and 8 represent the most advanced phases of disease progression, characterised by the loss of hand-to-mouth function (HTMF) and increasing reliance on ventilation support, either nocturnally or full-time.

These stages mark a profound shift in physical capability, independence, and care needs of individuals living with DMD. Individuals in these stages are no longer able to feed themselves, reposition their bodies, or perform basic personal care tasks without assistance. Many require non-invasive ventilation (NIV) at night, and later, full-time ventilation, often via tracheostomy. These transitions are associated with significant declines in health-related quality of life (HRQoL) for both individuals and carers, yet they are poorly represented in clinical trials and economic models.

We acknowledge that evidence in these stages is limited due to the rarity of the condition, but the qualitative data presented here offers valuable insights.

2.1: The impact of reliance on ventilation

Starting non-invasive ventilation (NIV): a critical and traumatic transition

While the progression to full-time ventilation is widely acknowledged as a major milestone in Duchenne muscular dystrophy, the initiation of night-time NIV is itself, a significant and often traumatic event. It marks a psychological and clinical turning point, often described as more distressing than the loss of ambulation.

Supporting quotes:

"Starting NIV is a massive deal. In my experience, it's more distressing than losing walking. That's what I see in the patients I deal with." — Clinician

"The first transition feels pretty awful. I remember being terrified… He put his full-face mask on me for the first time, and I just felt terrified. I was so anxious. It was claustrophobic. It covered my nose and mouth. It was just awful." — Person living with DMD

“I got pressure sores on my face. I was more tired because I wasn’t sleeping well, just because you’ve got this thing on your face.”

“I had panic attacks… I couldn’t sleep properly for years. It was really scary.”

The mask itself—often a full-face design—can trigger panic, claustrophobia, and anxiety. Clinicians report that many young men struggle to tolerate the mask due to psychological distress, and that significant effort is required to support them through this transition.

Supporting quotes:

"We have a significant number of young men who we feel should start NIV, but they find it so difficult to tolerate the mask because of anxiety. It's terrifying. We spend many hours chasing up people, trying different ways to encourage them to use it. We bring in our psychologist." — Clinician

This stage is often underestimated in clinical and economic models, yet it represents a turning point in disease trajectory, with significant implications for mental health, care needs, social life, and health system burden.

This stage is often underestimated in clinical and economic models, yet it represents a turning point in disease trajectory, with implications for:

- Mental health: panic attacks, sleep disruption, fear of dependence.
- Care needs: requirement for trained carers to manage equipment.
- Social life: reluctance to go out, fear of being seen with the mask.
- Health system burden: increased need for psychological support and respiratory monitoring.

Delaying the need for NIV—even by months—can preserve psychological stability, autonomy, and quality of life, and should be recognised as a meaningful outcome in health technology assessments.

Transitioning to full-time ventilation

Lived experience of people living with DMD who have made the transition to full-time ventilation demonstrates the significance of this transition and its profound impact on quality of life.

Supporting quotes:

“Initially you get a bit more energy back… but actually you know that your quality of life has deteriorated a lot. Suddenly you can’t breathe without a machine the whole time.”
— Person with DMD

“Suddenly you can’t breathe without a machine the whole time. So, you need carers with you at all times.”
— Person with DMD

Full-time ventilation marks a critical shift in dependency, requiring constant supervision and support. Individuals describe it as life-altering, with significant emotional and logistical consequences.

Panic and safety risks

The inability to speak during respiratory distress creates life-threatening situations, especially when alone or in public. Individuals describe constant fear and hypervigilance.

Supporting quotes:

"Every time it happens, it's instant panic. Oh my God, is someone going to realise I got disconnected? I can't talk when I can't breathe, so no one knows unless they're watching or there's an alarm."
— Person with DMD – Listening Exercise

"I smashed into a wall with my wheelchair just to make some noise so somebody would come in...I broke my ankle."
— Person with DMD – Listening Exercise

Barriers to routine medical care

Ventilation dependency limits access to diagnostics and routine care, leading to delayed or missed diagnoses, unmanaged symptoms, and increased health risks.

Supporting quotes:

"I can't have a colonoscopy because they didn't want to do it while I was on a ventilator. It was more complicated. So, I kind of got undiagnosed and unresolved bowel issues because they're too scared of the ventilator to do anything."
— Person with DMD- Listening Exercise

"It's very hard to get people into an MRI scanner if they're on NIV... People have scoliosis and contractures, and the BIPAP makes it even harder."
— Clinician - Listening Exercise

Transport and tracheostomy challenges

Even basic transport becomes risky and exhausting when managing a tracheostomy and full-time ventilation, contributing to social isolation and reduced participation.

"Every time you go over a stone on the floor in the car, his vent will pop off his trachy. So someone has to constantly put that back on. He doesn't like going out in the car."
— Parent

Public embarrassment and social stigma

The lived experience of those living with DMD using ventilators highlights the social stigma and exclusion they face. Being visibly dependent on a machine can make individuals feel like a spectacle, leading to withdrawal from public life.

Supporting quotes:

"When you're on full-time ventilation, everyone sees that you're suddenly very different. Everyone stares. Going out in public is really hard."
— Person with DMD

"There was a young man who went to the cinema in Epsom, and one of the other cinema-goers complained about the noise his ventilator made. They made the young man with the ventilator leave the cinema—not the person who complained."
— Parent

Systemic failures in hospital care

Hospital systems are often unprepared for ventilated patients, resulting in inappropriate ward placement, lack of trained staff, and exclusion of familiar carers—further compromising safety and wellbeing.

Supporting quotes:

"If you go to hospital, even with a swollen big toe, if you've got a tracheostomy, you're going to have to go to ITU... because there'll be no one else there to manage it."
— Clinician

"That carer is not allowed to be with them in hospital. And that's a huge problem because acute hospitals don't have the staff to deal with very disabled patients."
— Clinician

2.2: Upper body mobility and hand-to-mouth function

Independence and Dignity

Upper body mobility is essential for feeding, communication, hygiene, and autonomy. Its preservation is directly linked to mental wellbeing and social inclusion.

Supporting quotes:

“Everyone focuses on walking, but actually if you've got good upper limb function, you can be independent in a wheelchair. You can do the things other people do.”
— Clinician

“Once you lose your upper limb function… you really lose those independent skills, and you have to have someone with you all the time.”
— Clinician

Personal care, embarrassment, and health risks

Loss of hand-to-mouth function leads to complete dependence for intimate care, which is emotionally distressing and can result in neglected hygiene and preventable infections.

Supporting quotes:

“You need someone to help you with all of those things… suddenly you realise you have a preference for how you want to wash your face. It’s very easy to get frustrated… you lose all dignity.”
— Person with DMD

“I lost the ability to take myself to the toilet… I was too shy and anxious to ask people for help, especially female carers. I ended up getting infections because I was too embarrassed to ask.”
— Person with DMD

Clinical consequences

Upper body decline contributes to malnutrition, pressure sores, joint contractures, and fracture risk, increasing the complexity and cost of care.

Supporting quotes:

“You start to lose weight when you're not feeding yourself… that can lead to other problems, like feeling uncomfortable in your wheelchair and developing pressure areas.”
— Clinician

"When upper limb function is lost, we start to see contractures of the joints… discomfort, difficulty dressing, and increased risk of bone fractures."
—Listening Exercise

Technology and communication barriers

Loss of upper limb function means individuals cannot use phones or assistive tech, leading to social isolation, loss of independence, and barriers to accessing services (e.g. benefits portals, education platforms).

Supporting quote:

"He can't use his phone, and he can't communicate with people. That has a huge mental impact… not having friends, not being able to get a job."
— Parent Listening Exercise

Scoliosis and internal organ pressure

Scoliosis, often accelerated by upper body decline, leads to internal organ compression, worsening respiratory and gastrointestinal symptoms, and increases the need for complex interventions.

Supporting quote:

"When upper limb function is lost, scoliosis develops and puts pressure on internal organs. It affects breathing, digestion, and causes pain."
— Clinician - Listening Exercise

Conclusion

The qualitative evidence presented here for stages 7 and 8 demonstrates that ventilation dependency and loss of upper body mobility are pivotal moments in DMD progression, associated with dramatic declines in HRQoL for individuals and carers. These stages are underrepresented in clinical trials and economic models, yet they carry significant emotional, physical, and financial burdens.

Preserving hand-to-mouth function and delaying full-time ventilation—even for short periods—can yield meaningful improvements in independence, dignity, and wellbeing, and should be appropriately valued in health technology assessments.

3. Other Considerations: Death, bereavement, and life extension

3.1 Death is unpredictable and can occur at any stage of DMD

Duchenne muscular dystrophy is a progressive, life-limiting condition, but death does not always occur in the final stages. It can happen suddenly, and sometimes avoidably, at any point in the disease trajectory. This unpredictability is a critical consideration for NICE when evaluating the value of treatments that delay progression or extend life.

A consultant in neuromuscular diseases stated:

> "I don't think you can predict end of life in Duchenne at all. It's not like other conditions that are progressive. You cannot tell when somebody is going to die. I've been wrong. I've been doing this for a long time. And I've been caught out so many times in the past."

Real-world examples illustrate this unpredictability. One young man died during the first wave of COVID-19, not from the virus itself, but because his BiPAP machine was removed due to aerosol concerns. He was physically well, but the withdrawal of respiratory support proved fatal.

Another documented case involved a 15-year-old boy who died during induction of anaesthesia for a routine circumcision. The cardiac arrest occurred because the anaesthetic team was unaware of the impact of DMD on anesthetic agents. Despite the procedure being minor, the lack of specialist input led to a tragic and preventable death.

These examples highlight the physiological fragility of individuals with DMD, especially during surgery. Steroid use may mask their vulnerability, giving the appearance of robustness, but in reality, they are at high risk of respiratory and cardiac complications. Without specialist care, even routine procedures can become life-threatening.

This unpredictability and fragility must be considered in NICE's modelling and decision-making. The assumption that death is a distant endpoint fails to reflect the lived reality of families affected by Duchenne.

3.2 Bereavement and the misconception of 'burden relief'

When a child with DMD dies, the caregiving responsibilities may cease, but the impact on carer health-related quality of life (HRQoL) is profound and enduring. It is essential not to conflate the burden of care with carer HRQoL. The loss of a child is not a 'release' — it is a trauma.

Carers report long-term psychological distress, grief, and identity disruption following bereavement. The HRQoL decrement associated with losing a child is

not adequately captured in current models. NICE must consider that extending life — even in later stages — does not simply prolong burden, but preserves relationships, purpose, and emotional wellbeing.

In addition to the emotional devastation, the financial implications of bereavement are severe. Many DMD families have had to give up work or reduce hours to provide full-time care. As a result, they are often reliant on benefits such as Carer's Allowance or Personal Health Budgets. These are typically withdrawn immediately following the death of the child — at a time when the family is at its lowest point emotionally and psychologically.

Because DMD carers are of working age, the assumption that they can simply 'return to work' is flawed. The reality is that many have lost years of career progression, pension contributions, and professional networks. Even if they were emotionally and physically able to resume work, it is often impossible to re-enter the workforce or recover lost income. The financial shock compounds the grief and further reduces HRQoL.

This must be recognised in modelling and decision-making. The end of caregiving does not equate to the end of impact — it marks the beginning of a new and often more difficult chapter.

3.3 A small community living with loss

Duchenne is a rare condition, and the community of affected individuals is small and tightly connected. Boys and young men grow up alongside others with the same diagnosis — often attending the same clinics, schools, and support groups. They see their peers — and sometimes their brothers — die. This is not like losing older relatives to disease. It is part of everyday life.

Supporting quotes ScHARR"[redacted]

One parent described the impact of a friend's death on her son:
"It was the anniversary of a friend's passing and that's been really, really difficult time for Josh because the friend was younger than Josh and seemed so well compared to Josh. The anxiety that he's gone through since then has been really difficult."

Parent – Listening Exercise

This constant exposure to loss creates a unique psychological burden. Survivors' guilt, anxiety, and anticipatory grief are common. The community lives with the knowledge that any one of them could be next — and that

treatments, support, and decisions made by bodies like NICE may determine whether they live or die.

3.4 The value of life despite disability

Individuals living with DMD and their families consistently reject the notion that life with severe disability is not worth living.

As one adult with DMD stated: "Even at this stage, any bit of extra time would be amazing." Listening Exercise

Another said, "I'm still doing new things. I've got relationships, I work, I contribute. My life is worth living." Listening Exercise

A young man's words when faced with a life-or-death decision in response to a clinician presenting him with two options:

Stay on oxygen and be made comfortable to die or undergo a tracheostomy, with the warning that he might not survive and would lose the ability to eat or speak.

"He didn't scream or cry. He just said calmly: 'I'm 23 years old." I don't want to die. Do what you can to keep me alive.'" Listening exercise (reproduced with permission)

Dr. Quinlivan reinforced this point during the listening exercise undertaken by Duchenne UK stating:

"Every patient, I think bar one that I've spoken to in all my years as a consultant says, 'I want to live.' With Duchenne, you've grown with it. It's part of you. You're a young person and you want to live. If my patients want to live, I will do everything to help them."

These testimonies challenge assumptions embedded in some utility models that equate severe disability, which will have poor quality of life in some physical domains, with diminished value of wanting to live.

4. Equality and discrimination issues

4.1 Rare Disease Context and NICE's Systemic Omissions

Rare Diseases Disproportionately Affect Disabled and Paediatric Populations

According to the Rare Barometer survey (EURORDIS, 2025):

- 75% of rare diseases affect children.
- 87% of people with rare diseases live with disabilities, as measured by functional limitations.
- 88% self-identify as disabled, including those with invisible or progressive disabilities.
- 79% of pupils and students with rare diseases experience limited participation in school.
- 84% report limited participation in community life.

These figures confirm that age and disability are not incidental characteristics in rare disease appraisal—they are central. NICE's appraisal frameworks must reflect this reality to avoid systemic exclusion.

NICE's Methods Guide Fails to Operationalise Flexibility

The NICE Methods Guide:

- Acknowledges the need for flexibility in appraising paediatric conditions.
- Recognises challenges in rare disease but only refers to how these can be managed under HST.
- States that carer health-related quality of life (HRQoL) should be considered.
- Provides no structured guidance on how committees should interpret paediatric or carer data.

This lack of operational guidance results in inconsistent application of equity principles and may constitute discrimination by omission against protected characteristics such as age and disability.

HRQoL and Carer Impact Data: A Systemic Gap

The Givinostat appraisal presented data on paediatric HRQoL and proxy-reported outcomes, but these are inherently difficult to collect and interpret. NICE acknowledges that proxy measures—often completed by parents or clinicians—may not fully capture the lived experience of children, especially those with progressive or complex conditions. Despite this, NICE provides no structured guidance on how appraisal committees should interpret such data or apply flexibility in its use.

This lack of operational clarity is particularly problematic in rare paediatric conditions, where:

- Direct self-reporting is often not feasible, especially in younger children or those with cognitive impairments.
- Proxy responses may be influenced by caregiver distress, expectations, or adaptation.
- Longitudinal data is scarce, making it difficult to model disease progression and treatment impact accurately.

The ISPOR Task Force on Valuing HRQoL in Children and Adolescents has confirmed that no HTA body, including NICE, currently provides clear guidance on how to measure or value paediatric utilities. Key findings include:

- Most appraisals use adult-designed HRQoL instruments (e.g., EQ-5D), which are not validated for children.
- Only 10% of appraisals use child-specific HRQoL measures, and even fewer use child-specific tariffs.
- Committees frequently comment on the limitations of HRQoL data but lack a framework to address them.
- There is no consensus on whose preferences should be used (e.g., general public, parents, clinicians) or what perspective should be adopted in valuation exercises.

This methodological gap risks systematically undervaluing treatments for children, particularly in conditions like DMD where the burden is high but difficult to quantify using standard tools.

4.2 Inequality in the Givinostat Appraisal

Under the Equality Act 2010, disability and age are protected characteristics. NICE's appraisal of Givinostat for Duchenne Muscular Dystrophy (DMD) demonstrates systemic disadvantage through specific exclusions and omissions that disproportionately affect disabled children.

1. Discounting Rule (1.5%)

NICE applies a 1.5% discount rate only to treatments that restore patients to full health. This criterion is incompatible with progressive conditions like DMD. In the Givinostat appraisal, this rule structurally disadvantaged the treatment by undervaluing its benefits for disabled children, embedding an ableist assumption that only curative treatments are valuable. This approach risks breaching NICE's duty to consider equity and long-term societal impact.

2 Exclusion from Medicines for Children Policy

DMD was excluded from the Medicines for Children policy due to its paediatric-only onset. As a result, Givinostat was assessed under adult-centric models that fail to reflect paediatric realities. This exclusion may constitute direct discrimination by denying equitable policy coverage and access to treatment for disabled children.

3Paediatric HRQoL and Carer Impact Data

The Givinostat appraisal presented data on paediatric HRQoL and proxy-reported outcomes, but these are inherently difficult to collect and interpret. NICE acknowledges that proxy measures—often completed by parents or clinicians—may not fully capture the lived experience of children, especially those with progressive or complex conditions. Despite this, NICE provides no structured

guidance on how appraisal committees should interpret such data or apply flexibility in its use.

This lack of operational clarity is particularly problematic in rare paediatric conditions, where:

- Direct self-reporting is often not feasible.
- Proxy responses may be influenced by caregiver distress or adaptation.
- Longitudinal data is scarce.

The ISPOR Task Force confirms that no HTA body, including NICE, currently provides clear guidance on how to measure or value paediatric utilities. This gap risks systematically undervaluing treatments for children, particularly in conditions like DMD.

4 Exclusion of Non-Ambulant Children

Non-ambulant children were excluded from the appraisal due to the regulatory requirement for a measurable clinical endpoint (ambulation). While this reflects EMA trial design constraints, it does not align with the progressive nature of DMD or the ethical imperative to consider the most severely affected children.

Givinostat's mode of action is not limited to lower limb muscles—it targets inflammation and fibrosis across all skeletal muscle groups, including respiratory and upper body function. Although there is currently no trial evidence available for non-ambulant children, the European Medicines Agency (EMA) nonetheless granted a licence that includes this population, indicating that the mechanism of action was considered plausible and potentially beneficial.

This creates a dilemma for NICE: without evidence, the committee cannot formally consider this group within its cost-effectiveness framework. However, the exclusion of non-ambulant children risks perpetuating inequity, particularly when they are among the most clinically vulnerable and their families bear the highest care burden.

One potential solution would be to explore managed access arrangements for non-ambulant children. This would allow conditional inclusion of this group while evidence is generated. It is also notable that the company has offered a free-of-

charge Early Access Programme (EAP) for non-ambulant children, demonstrating a commitment to equitable access despite the current evidence gap.

5 Exclusion of Social Care Costs

Although NICE states that it considers both health and social care costs in its appraisals, the Givinostat evaluation excluded the substantial costs associated with late-stage care for children with DMD. This omission significantly underrepresents the true economic burden of the condition.

In advanced stages of DMD, the cost of paid care can exceed £200,000 per year, depending on the level of support required. These costs may be borne either by local authority social services or the NHS, depending on whether the child qualifies for Continuing Healthcare (CHC) funding. While the funding stream may vary, the societal cost remains the same—and critically, the need for care is not diminished by which budget it comes from.

This distinction, while relevant to commissioners, should not obscure the broader economic and ethical imperative: delaying progression to stages that require intensive care is clearly beneficial. Treatments that slow disease progression can reduce the need for high-cost interventions, alleviate pressure on families, and mitigate long-term public expenditure.

NICE's current framework struggles to account for these costs due to inconsistencies in how health and social care budgets are structured across the UK. However, this complexity should not justify their exclusion from appraisal models—particularly when the impact on families and public services is so substantial.

6 Lack of Trauma-Informed Practice

Families attending NICE meetings during the Givinostat appraisal reported emotional distress, including trauma and suicidal ideation. These testimonies were not acknowledged or supported, breaching NICE's duty to foster good relations under the Equality Act. A trauma-informed approach would have recognised the emotional toll of participation and ensured appropriate support mechanisms were in place.

7 Inappropriate Standards for Paediatric Disability

The STA process applies adult-centric standards to paediatric disability. In the Givinostat appraisal, the committee did not acknowledge developmental stages, long-term care needs, or societal impact. This resulted in systemic disadvantage and failed to reflect the lived experience of disabled children and their families.

4.3 Health Inequalities and Associative Discrimination in Employment of Duchenne Parent Carers

Legal Context and NICE's Health Inequalities Duty

Under Section 13(3) of the Equality Act 2010, discrimination by association is prohibited. This includes disadvantage experienced by individuals due to their relationship with someone who has a protected characteristic—such as disability.

NICE is also bound by the Public Sector Equality Duty (PSED) and its own health inequalities framework, which requires NICE to:

- Eliminate discrimination
- Advance equality of opportunity
- Reduce health inequalities across the population
- NICE's NG150 guideline on supporting adult carers explicitly states that unpaid care can have a significant impact on carers' health, wellbeing, and resilience, and that supporting carers is essential to preventing crisis situations and worsening health outcomes.

Impact of Disease Progression on Carer Health

As children with Duchenne Muscular Dystrophy (DMD) progress to later stages of the disease, the intensity and complexity of care increases. This includes:

- **Physical care**: lifting, feeding, toileting, managing respiratory equipment
- **Medical coordination**: navigating multiple appointments, therapies, and emergencies

- **Emotional strain**: coping with grief, uncertainty, and advocacy fatigue
- **Financial pressure**: funding equipment, therapies, and home adaptations

This progression directly impacts the health of parent carers. According to the ONS bulletin on unpaid care:

- 48.6% of unpaid carers report at least one adverse health effect from caring
- Female carers providing high hours of care are significantly more likely to attend A&E and report poor health
- Low mental wellbeing is more common among carers (19.5%) than non-carers (14.8%)
- Carers are 2.7 times more likely to be moderately or severely frail than non-carers
- Caring itself is now recognised as a social determinant of health by Public Health England

Systemic Oversight in NICE Appraisals

Despite this evidence, NICE's appraisal processes:

- Exclude unpaid care from cost-effectiveness models, even though it offsets NHS and social care costs
- Fail to quantify carer burden, despite acknowledging its impact in other guidelines (NG150, QS200)
- Do not stratify health outcomes by carer status, missing key inequality drivers
- Ignore the compounding effect of disease progression, which pushes carers into worse health over time

This omission is particularly stark in the Givinostat appraisal, with a lack of understanding of the care needs of boys in the later stages and also by not assessing non-ambulant children, despite their parents bearing the highest care burden. This exclusion not only denies treatment to the most vulnerable children, but also accelerates health decline in their carers, violating NICE's duty to reduce health inequalities.

Workplace Discrimination and Economic Impact

Parent carers of children with DMD report:

- **Career Limitation and Bias**: exclusion from promotions and leadership roles
- **Stigma Around Flexibility Requests**: penalisation for asking for part-time or remote work
- **Harassment and Hostile Work Environment**: being sidelined or "managed out"
- **Inadequate Implementation of Carer's Leave Act 2023**: poor awareness and uptake
- **Financial and Emotional Toll**: direct costs (equipment, therapies), indirect costs (lost earnings), and long-term insecurity (reduced pensions)

According to Carers UK's 2023 report:

- 47% of carers provide over 90 hours of care per week
- 74% report exhaustion, and 72% have had no breaks since the pandemic began
- Carers of children are most likely to cut back on essentials like food and utilities

Evidence from Duchenne UK's listening sessions and survey data further shows:

- Scope's 2025 Disability Price Tag estimates that families with disabled children face an average of £751/month in extra costs
- [redacted] and they are disproportionately affected by employment disruption, reduced pension contributions, and mental health strain

One parent shared:

"The economic consequences for job loss can be catastrophic for the Duchenne family... we literally hand over our life savings or increase our loans to pay a team of builders as a lift is installed, doors are widened, and disability wet rooms are

built. This dual effect of risk of employment loss at a time of economic need makes Duchenne a bankruptcy diagnosis."

Another stated:

"I regret even telling my employer about my son's diagnosis. Now I am treated completely differently, and it has taken all my job security away."

A Hidden Inequality Engine

The evidence presented demonstrates that Duchenne parent carers face systemic and compounding health inequalities driven by:

- Associative discrimination
- Gendered caregiving roles
- The escalating demands of disease progression

These inequalities manifest in:

- Reduced workforce participation
- Financial insecurity
- Deteriorating mental and physical health
- Social exclusion

—all of which are intensified in the later stages of DMD.

NICE has a statutory duty to prevent and reduce health inequalities under the Equality Act 2010 and its own guidance principles. This duty includes recognising the disproportionate burden on women, who are more likely to be primary carers and more vulnerable to long-term economic exclusion.

Failure to account for the real-world consequences of DMD progression—not only on patients but on their carers—risks perpetuating structural disadvantage and undermines the credibility and inclusivity of health technology assessments.

By failing to account for unpaid care, NICE's appraisal system:

- Exploits a hidden workforce
- Allows disease progression to drive carer health decline
- Violates its own health inequalities framework

- Undermines the Public Sector Equality Duty

This is not just a technical oversight — it is a systemic failure that perpetuates inequality and harms the very families NICE is meant to protect.

4.4 Intersectionality and Compounded Disadvantage

The Equality Act 2010 recognises a range of protected characteristics, including age, disability, sex, and pregnancy or maternity. In the context of rare paediatric diseases such as Duchenne Muscular Dystrophy (DMD), these characteristics often intersect in ways that compound disadvantage.

For example, disabled children with progressive conditions are often cared for by mothers, who may face gender-based barriers in the workplace. These carers are disproportionately affected by the emotional, physical, and financial toll of caregiving, and may also experience exclusion due to assumptions about reliability or availability.

In the Givinostat appraisal, non-ambulant children were excluded due to current lack of evidence—a common challenge in rare disease research. While this exclusion is not the fault of NICE, it nonetheless had significant consequences. The appraisal did not adequately reflect the progressive nature of disability in growing children, which is central to DMD. The focus on ambulant children fails to capture the broader lived experience of families navigating increasing levels of dependence and complexity.

Importantly, Givinostat is licensed for use beyond the ambulant stage, suggesting plausible therapeutic benefit post-ambulation. The absence of trial data in non-ambulant children should not be conflated with an absence of impact or value. NICE's own principles acknowledge that absence of evidence is not evidence of absence, particularly in the context of rare and progressive conditions.

Moreover, delays in issuing NICE guidance have had a direct impact on access to the Early Access Programme (EAP) for non-ambulant boys. This has created a circular problem: without timely guidance, fewer non-ambulant patients receive

the treatment, making it even harder to generate the real-world evidence needed to support future appraisals. These dynamic risks entrenching disadvantage and undermines the potential for inclusive, evidence-informed decision-making.

NICE's Public Sector Equality Duty (PSED) requires consideration of how different protected characteristics interact. A more intersectional approach to appraisal would help ensure that guidance does not inadvertently reinforce structural inequalities. Recognising and addressing compounded disadvantage is essential to delivering fair, inclusive, and legally compliant health technology evaluations.

5. Conclusion

Duchenne UK welcomes the committee's call for further evidence and the opportunity to clarify key aspects of disease progression, treatment impact, and lived experience. This submission is intended to support a more accurate and proportionate assessment of Givinostat, particularly in relation to children and young adults and their carers in all stages of Duchenne muscular dystrophy.

The initial committee meeting and EAG assessment did not sufficiently reflect the complexity of later stages, nor the cumulative burden on families and carers. Assumptions around quality of life, limited consideration of carer impact, bereavement and the absence of operational guidance on carer or paediatric HRQoL contributed to an incomplete picture of treatment value. These gaps risk reinforcing health inequalities and undervaluing interventions that address progressive, disabling conditions.

This submission provides targeted evidence to address those gaps. It highlights the relevance of unpaid care, carer burden, and associative impacts; clarifies the importance of early and sustained intervention across disease stages; and offers practical considerations for integrating paediatric and carer outcomes into future assessment. We hope this material supports a more informed and inclusive discussion at the next committee meeting.

Appendix: References and Supporting Sources

This response draws on a wide range of legal, methodological, economic, and experiential evidence to support its critique of the NICE appraisal process. The references below are grouped by theme and include both formal publications and internal documents.

- Equality Act 2010. UK Government. https://www.legislation.gov.uk/ukpga/2010/15/contents
- Public Sector Equality Duty (Section 149, Equality Act 2010)
- Carer's Leave Act 2023. UK Government. https://www.legislation.gov.uk/ukpga/2023/20/contents/enacted
- NICE Guideline NG150: Supporting Adult Carers (2021)
- NICE Quality Standard QS200: Supporting Carers (2021)
- NICE Equality Scheme (2021). https://www.nice.org.uk/about/who-we-are/equality-scheme
- NICE Methods and Processes for Health Technology Evaluation (PMG6, 2022)
- NICE Health Technology Evaluation Manual – Carer Quality of Life (2022)
- NICE Principles for the Development of Guidance (Principle 9, 2021)
- Givinostat Appraisal Documents. NICE. https://www.nice.org.uk
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- Office for National Statistics (ONS). Frailty and Carer Health Bulletin, 2023
- Public Health England. Caring as a Social Determinant of Health, 2022
- Disabled Children's Partnership. Left Behind Report, 2023. https://disabledchildrenspartnership.org.uk
- Contact. Employment and Disability Statistics, 2023. https://contact.org.uk
- Duchenne UK. White Paper Employment of Carers

- Duchenne UK. White Paper Inequality

- Duchenne UK. Interim Findings for Duchenne – 11.08.25, ScHARR Analysis
- Duchenne UK. Listening Exercise Transcripts, 2025
- Duchenne UK. Givinostat Response to NICE CFE, 2025

Transcript: Duchenne UK listening session on 3 September 2025

[redacted] 2:53
So hello everyone and thank you so much for being here today. And this listening session is being hosted by Duchenne UK as part of our response to the current NICE call for evidence on Givinostat potential treatment for Duchenne muscular dystrophy. What we're trying to do here is make sure that the voices of those most affected, the older individuals living with Duchenne and the families supporting them and the clinicians who work with them are heard, understood and reflected in the evidence that we submit. Our focus today is on the later stages of Duchenne. These are the realities that often go unspoken in clinical trials.
Or in policy discussions. So things like the impact on loss of upper body function, the impact on breathing and ventilation, cardiac and heart health, mental well-being and the wider ripple effects on family life, education, employment.
Care systems and the and clinical status.

I do want to gently let you know that this session will also include conversations about mortality and bereavement. These are difficult but very necessary parts of the story, and we will approach them with care and respect. If at any point you need to pause, step away or take a moment, please do, because this is a space where you.
Well-being does come first.
So what we're here to do is to understand what matters most to you, what's being missed and what needs to change. So not just in treatment, but how decisions are made. So this is about lived experience and making sure that NICE will see the full picture and not just not just numbers, but people.
So thank you again for being here and your time, your honesty, your courage are deeply appreciated and hopefully help shape a better future for people affected by Duchenne.
So for the for the record, I want to just take a moment to sort of set the scene around muscular dystrophy, so.
Duchenne muscular dystrophy is a severely disabling, life limiting condition. It begins in early childhood, but its progression is relentless. Over time, it leads to complete loss of mobility, including quadriplegia and the inability to carry out even the most basic physical tasks.
Breathing becomes dependent on ventilation. The heart weakens, communication, independence, dignity, all under threat. And for families, the emotional, physical and financial toll is profound. Givinostat is an investigational treatment that targets inflammation and muscle degeneration at a cellular level. It's not a cure. We know it's long-term effects are still uncertain, but what we do know.
And what we are certain of is what happens without it. We know the trajectory of Duchenne when left untreated. That's why this session matters. Your experiences, particularly later stages, are critical to shaping how NICE evaluates Givinostat. We need to make sure they see beyond the clinical trial endpoints and understand the real world impact, what it means to preserve our body function to delay.
Respiratory decline to hold on to independence a little bit longer.

So we will also be talking about bereavement and the fact that Duchenne is 100% fatal, but this is a space of respect, care and solidarity. We are here to support you.
So thank you for being here. Your voice is not just part of the evidence, but it's the the real true heart of it.
What I'd like to do is make sure that everybody can introduce themselves. So what we're going to do is bring in into every element that we discuss. We're going to talk to patients and people, people living with Duchenne. We're going to talk to parent carers.
Of of young men with in the later stages of Duchenne and we're going to talk to the clinicians as well about the impact that Duchenne has on those on those people. So please can I start by, well, I'll start by introducing myself. So I'm [redacted] I'm a health economist, but more importantly, I'm a mother to a young man with Duchenne, [redacted], who's now 19, has lost most of his upper body function, but is at university right now, which is.
Which is great for him, but I'm here to like, tell my story as much as anything else, but from a position of understanding. So, [redacted], could you introduce yourself, please?

[redacted] 7:38
Yeah, I'm [redacted] I am mum to five children all together with a stepson there. My youngest [redacted] has Duchenne. He is 26. We live in Herefordshire and but we have our care. Uh, in London at Queen's Square with [redacted]

[redacted] 8:00
Thanks, [redacted]

[redacted] 8:03
Hi, I'm [redacted] I'm a 44 year old man living with Duchenne and I'm completely dependent on a ventilator and apart from a few tiny movements of.
I think it's a toast guy pretty much effectively paralyzed the labor.

[redacted]
Thank you, [redacted]

[redacted] 8:30
Hi, I'm [redacted] I'm a 50 year old male living with Duchenne. I'm dependent on ventilation 24/7 and have 24/7 care from PAs.

[redacted] 8:55
Thank you

[redacted] 9:00
I'm mum to four boys. My third son, [redacted] has got Duchenne. He's 21. He is tracky and vented and he's peg fed.

[redacted] 9:23.
I think what we explained at the beginning was what we're trying to do is get the lived experience of older boys and young men who are older and living in the later stages of Duchenne and then the impact on them, the impact on their caregiver and the impact on the clinicians as well.
So we'll go through each element of the of the disease and ask for your experiences and your how you would rate your quality of life, if that's OK.

[redacted] 9:54
Thank you.

[redacted] 9:55
Thank you.

[redacted] 9:58
My name is [redacted] I've been a consultant in neuromuscular diseases since 1995. I lead the service, for adults with Duchenne at the National Hospital for Neurology and Neurosurgery, Queen Square.
And we have a cohort of 270 adult men with Duchenne attending our service.

[redacted] 10:28
Thank you, [redacted]

[redacted] 10:48
Thank you.
OK, right. What we're going to do now is move into the the listening session. Does anyone have any questions?
No. Well, if you have any questions you want to stop, you want to step out, please just let us know. The priority today is for us to cover the key aspects of duchenne in in older boys and and.
I'll explain why this is important. So this is important because in the previous committee meeting for Givinostat, it was clear that NICE and the EAG had.
Fundamentally misunderstood the severity of Duchenne muscular dystrophy and what benefit there might be in delaying its progression or or moving some of these later stages to to later in life. So we're going to talk about.
The the disease, but using the stages of the economic model that that that Duchenne UK provided. So this is the Hercules model and within the Hercules model I'm just going to share what that looks like.

[redacted] 12:32
Yeah. So when when NICE review a disease, what they tend, what they look at is costs and effects of what would happen without a medicine intervention and what would happen with it.
So to do that you need to look at what stages there are in the in the disease and then apply costs and effects in terms of quality of life and clinical effectiveness to each of those stages.
So the way that we look at duchenne or the way that NICE are now looking at duchenne.
Is in is in this in this state. So we have a number of health states and what we're really interested in today are these health states which go beyond stage 4. So obviously as the as the patients are diagnosed they tend to be.
Around between 3:00 and 5:00 and that's the ambulatory stage when they can still walk.
The early ambulatory stage they can rise from supine and walk 1010 metres. The late ambulatory stage they would struggle to rise from supine but be able to still be able to walk 10 metres.
A state sort of in the middle between being able to walk and not being able to walk is something that is now termed the transfer state where patients can still wait there. So while you can still wait there, then that makes things an awful lot easier in terms of whether you need to transfer to.
Transport, whether you need transferring in the bathroom, when transferring to bed to different bits of furniture that while you can still, while a young man can still wait there, then that's an awful lot easier than than becoming non ambulatory and has.
Once you become non-ambulatory, then that has significant impacts on your health, well-being and your quality of life, plus financial impacts on the family and society. So the non-ambulatory states we've divided into.
Several states HTMF is hand to mouth function, so that's whether you can still lift your hand to your mouth and also whether you are ventilated at night or full time so.
And what we do know is that these things aren't necessarily progressive like you may be, you may still have hand to mouth function but be ventilated or you might not have hand to

mouth function and be ventilated or the other way around. So sometimes we just need to. So that's why we've got so many states in that.
Non ambulatory area, but it's really important to try to understand what the impact of those states are on people.
Sure.
Is that clear? So what I will be doing is talking about the the the states as we move into the sort of non ambulatory sort of later stages of the disease and asking for your experiences within those.
OK, I shall stop sharing because otherwise you'll just all look at the screen. So starting with. Starting with the sort of the later stages of of of Duchenne, I'd like to sort of focus on maybe upper body mobility first of all and I think maybe [redacted] and and.
[redacted] to start with.
When you realised that you'd lost your upper body mobility, what impact that had on you? So maybe [redacted], if you could start that, if you can remember that.

[redacted] 16:27
Absolutely. It was quite a while ago, but yeah, it's it's hard to put an exact time on it because the progression is is gradual and it's, you know, multifaceted. So kick it to bed like sometimes when you're tired you can.

[redacted] 16:31
Yes.

[redacted] 16:46
You could do less than you could otherwise, so it's kind of a gratile thing. But yeah, but I think it's it. It was probably when I came back from university and it didn't make a massive difference to me.
Just in terms of what I could do for myself, I mean out of get the medicines and control I had so I can never get like, can I touch my face or wash my face or clean my teeth and give me something you need something to help you with.
With all of those things, I think it's a mental impact because well, of not being able to do things for yourself is it takes a lot of adapting to. It's quite hard. It's very difficult at the beginning to.
To do that, something you need a lot more help and you can't. You often can't be left alone by that point because you can't do things like have a drink or have something to eat by yourself, so you need something with you.
All the time, and that's a massive shift for you. It's very difficult mentally to to manage that. I think kind of health wise along with not being able to move your limbs.
Get like you can't really shift position when you've lost that cover body strength, so you get more pain, come more discomfort. Certainly that's really the the main things I'd say.

[redacted] 18:21
And then did you find that you had to start learning how to direct carers?

[redacted] 18:28
Yes, yes. So I think I I did have carers by that point, but they waited. They just weren't so intrusive in my life because I could purchase needed them to help me with transfers and stuff like that. But when you need them to help you with everything that it does.
It changes a lot and then suddenly you like you know you've got to direct somebody on how to wash your face. You don't realise that you actually have a preference for how you want to wash your face because you've always done it yourself. Suddenly you do have a preference, so you need to be able to communicate this.
It's very easy to get frustrated, can't find that depressed with that. But yeah, you can get frustrated with carers because you can't tell them how to do things properly. You just you'd lose all dignity at that point as well.

[redacted] 19:23
[redacted], that's really, really sobering and something I've witnessed with my own, my own son as well in terms of having to scratch his nose or put his air pods in those types of things. And he does like it done in a certain way.
[redacted], can you give us some, give us some some thoughts about this and maybe if you agree with what [redacted] said, say that's was your experience too, but also notice that you are.
Very reliant on technology. So as your as your disease progresses and you lose more function, so not just hand to mouth, but the ability to move your arms and fingers, how much you rely on technology.

[redacted] 20:15
Yep, I pretty much echo what [redacted] says.
I love upper body strength in my early twenties, about the same time at Jon.
It's hard to explain how much that does change your whole life. You can't hold your drinks and you can't feed yourself.
You rely on other people to wash your private parts and things like that. So you lose dignity. For me, it's also other little things, like I couldn't fix my own computer at this point, because before I could sort of fix things myself. Now I have to try to direct people on how to do that. And other things like shaking somebody's hand or hugging a baby, stuff like that. You just can't do those normal things.

[redacted] 21:40
And what impact do you think that had on your mental state, your and your health related quality of life?

[redacted] 21:49
Quite a bit. I mean, not long after I got anxiety and panic attacks and I've been, have developed agoraphobia for about ten years. I couldn't leave the house for about 10 years, so it's a pretty huge impact.

[redacted] 22:19
That that's that's really distressing to hear. What what what support did you get when you were agoraphobic?

[redacted] 22:25
Not much. I got the psychiatrist who came down a couple of times and basically told me that all my reasons were valid for being afraid because I'd also started ventilation. So yeah, he just said it was down to me to get over it myself, and then signed me off.

[redacted] 22:57
And how how did you, how did you get past that?

[redacted] 23:02
I started making friends online and people who had also gone through anxiety and panic attacks and then slowly they encouraged me to try and yeah, it took a while, but eventually bit by bit I started going around just down the road and yeah, it's a long process, but it was friends and people helping.

[redacted] 23:34
I'm very glad that you came out the other side of that.
[redacted] what's what's been your experiences with [redacted] with upper body mobility?

[redacted] 23:48
Yeah, [redacted] lost his upper body mobility when he was probably around 1415. It was in his last year of school and it was COVID. He was the the GCSE year during COVID, so it it was hard to.
We weren't really being normal, so to speak. You know, he wasn't in school, he wasn't doing all them things like art or things that he was supposed to do. We were trying to do them at home. So we noticed a lot more because we were around him doing everyday things a lot more. And he, yeah, so he's not been able to.
Feed himself since he was probably around 14.
Actually, before that he had his, he had his rods done and obviously he couldn't bend to put the fork to his mouth, so that was a struggle for him to lift it up. But it was when he was around 1415 when he completely lost his upper body strength.
But he's always been really positive. He's accepted everything really, really well, things like that. So physically he accepted it quite well. It was as he got older and all the other health. Deteriorations kicked in, like his breathing, his gut. They've all been the things that he struggled with the most. But physically, the walking and the moving, he seemed to accept it quite well, I think.
And he would, he would say the same. He always loved his food, so be not being able to eat was a bigger thing to him than not being able to walk because he had his wheelchair so we could still get around. He has his carers or or us to do, you know, move and do things for him.
It was it's it's the things like eating and things like that that affected him the most.

[redacted] 25:49
And in terms of like the the the loss of hand to mouth, not so not just hand to mouth function, but being able to pick things up off the desk or or scratch himself or any of those things, how, how, what sort of impact did that have on him?
Him and also on you, as I assume you were his primary carer at that point.

[redacted] 26:16
Yeah, it's just time consuming and he he doesn't want to be a burden. Obviously we keep telling him he's not a burden. So that's probably the biggest thing and once we over overcome that.
We just have to be around him 24/7 to do all them things for him and he's he's quite a good teacher. So when he has new carers like I can look at him and like you guys, I'll look at him and I'll know exactly that his head's not in the right comfy position that he likes it in or his arm's not in the right place he likes it.
But every time you get a new carer or you meet somebody new, you obviously have to go through this again and again and again. And [redacted] quite vocal, so he's he's quite good at teaching. He's the best teacher for new carers.
Because he just obviously likes things done in a certain way. It just takes a long time to, you know, process all this.

[redacted] 27:17
Thanks, [redacted] I'm going to move to to [redacted] now. You can tell us about [redacted] experiences and I'm particularly sort of interested in this like that any preservation of upper body is going to be helpful.

[redacted] 27:32
Yeah [redacted] always was aware that he would need a wheelchair and lose the ability to walk. And he actually, like like [redacted] is son, he actually managed with that transition so well.

That we weren't quite prepared for the impact of losing upper body and I think so much from when he was first diagnosed, there was so much emphasis on this ability to walk, being the be all and end all of everything that actually that becomes a bigger monster than it But so once we got past that, we thought, oh, wow, you know, this isn't as bad as we thought it was going to be. But then as it progressed, [redacted] was probably a little bit older when he started to use lose sort of upper body function, but he's very good at.
Making adaptations to his movement and his environment to ensure that he can still do things. So he's 26 now, but his table is quite high, so when he's eating, if we prop his arm up, he can still feed himself.
It was one of the reasons that he didn't want the spinal surgery was knowing that he wouldn't be able to dip his head and lean forwards and that that would mean that loss. You know, he knew that that that he wouldn't be able to feed himself. He coped.
Fairly well with the transition, but I've noticed more and more like if we go out, he's avoiding going out now because he knows that that the table isn't set up to the right height for him, that if he wants to eat a burger, somebody else is going to have to feed that thing because there's no way that he could actually.
Raise that to his mouth. So I've noticed more and more that he's become much more of a home bird. He doesn't go out. He's lost stomach independence in his confidence of going out. He doesn't like people staring. He's he's very aware. You can tell that he's on edge when he's.
You can see he's looking around, who's watching him. So it's the the mental impact of that and other people's opinions of him and other people's perceptions of his disability that that affect him most. I think when he'd still got upper body strength that he could do. Everything that anybody else could do when they were sitting down, he could visibly demonstrate that he was a functioning adult, whereas now I feel like he's very much he's seen as the disabled person and he's never seen himself as a disabled person until this point.
So I think upper body is far more of an impact on [redacted] it has been, you know, with the ability to walk things like being able to move himself, reposition himself, that's been lost now for for a couple of years.
We're very lucky. We've got a team now of of 12 carers that work with [redacted] 24/7 and it's taken him a long time to not to realise he doesn't have to say please every time.
Please could you scratch my nose? Please could you push my glasses up my nose? And after every time anybody did anything for him, he apologised. And that that's quite hard.

[redacted] 31:07
[redacted] I'm so sorry. I I was going to ask how it made you feel. But there is no need. There's no need to ask, literally. And if and I'm sorry, this is so hard and I send you all of my sympathy because I'm exactly the same.

[redacted] 31:07
We.
It's it's that it's not the physical stuff is is heartbreaking but the mental stuff is just it's it's it kills you to watch somebody you love going through this this loss and I think the older these boys get and the more friends they've had.

College or, you know, through local connections, elder young men with Duchenne.
They see more and more what's coming. The impact of that on them is just horrific.

[redacted] 32:02
I know, [redacted] No, don't. Don't you apologise. Please don't. This is so important and I'm so and honestly, should we take a, should we take a little 2 minute break?

[redacted] 32:03
Sorry.
I'm I'm OK, I'm OK. I think it's because it's been the anniversary of a friend's passing and that's been really, really difficult time for [redacted] because the friend was younger than X[redacted] and seemed so well compared to X[redacted]

[redacted] 18
And.

[redacted] 32:34
And the anxiety that he's gone through since then has been has been really difficult. I mean, physically, he's doing so well for a 26 year old with Duchenne. He's not ventilated. His cardiac issues aren't too severe.
So he knows that that actually he's in far better shape than the many, many of the young men that he he knows and has known. But I think he feels guilt as well that that he's OK, you know, he's comparatively well.
Compared to so many others. So yeah, it's it's tough. It's really tough.

[redacted] 33:13
It's it is really, really tough and thank you for sharing.
Maybe if we sort of pull this this, this element of upper body function together with with Roz, like what's your experience as you as you watch the as you're seeing your your patient that must be so difficult for you as a clinician to see patients just get worse and worse.

[redacted] 33:39
Absolutely. Notice it's very, very difficult and we don't have any effective treatment to slow this down other than steroid treatment, but it still progresses and I can relate to everything that.
Has been said so far, actually. Um.
I once referred a patient to Moorfields Hospital because I felt so sorry for him because his glasses kept slipping down his nose, which, you know, somebody who wears glasses and contact lenses. I know exactly how awful that is. It's so frustrating. So I refer.
Him to Moorfields and they actually did laser surgery on him so that he didn't have to wear glasses anymore. And that was life changing for him. Just won't have one thing less to worry about. And I had another patient recently with exactly the same problem and now.
I referred him to Moorfields and they've come back with, well, I'm sorry, but we can't do this on the NHS anymore. So we had one thing to offer somebody in the past that we can't offer anymore. I I think also what I would add to what I've heard already is that.
What I see is when people are no longer able to feed themselves that and somebody else is feeding them, it takes longer to eat a meal. And because it takes longer to eat a meal, there are two things that happen. One is the food goes cold quickly.
So it's not so appetizing.
But also you fill up, you feel full before you finish that meal. And what happens with the consequence of that is weight loss. And so actually we see people start to lose weight when they're not feeding themselves.
And that can lead to other problems, so feeling uncomfortable sitting in your wheelchair and developing pressure areas.
I I think upper limb function is much more important, as we've heard, for maintaining independence. Everyone focuses on walking, but actually you can be if you've got good upper limb function, you can be independent in a wheelchair.
You can do the things other people do, but once you lose your upper limb function, as we've heard, you really lose those independent skills and you have to have someone with you all the time. And I think that must be really frustrating, not being able to.
You know, be on your own without a person there to help you all the time. It must be just very frustrating. And I think the only other thing I would add as well is that when upper limb function is lost, we start to see contractures of the joints occurring and that can result. In discomfort can make it harder to put for people to dress and undress and can increase the risk of bone fractures as well because everything's so stiff and the bones are weaker.
So I think losing upper limb function has a very major impact on general health, well-being and also emotional, psychosocial well-being.

[redacted] 37:20
Thank you, [redacted] Anyone have I think, [redacted] have you put a comment in? Is there something that you wanted to add? Should we, should we go, should we like circle round again around upper body?

[redacted] 37:31
Yes.

[redacted] 7:37
Function. So obviously we're going to spark off each other with things unless you're going to ask for eye surgery.

[redacted] 37:44
No, that's fine. So would you like me to just say what I've said in the chat?

[redacted] 50
Yes, please.

[redacted] 37:50
Yes, OK. So I just said that I wanted to clarify because I said something about losing dignity earlier, but I don't think I was specific enough to clarify what I meant. So I just meant the I lost the ability to take myself to the toilet.
I lost couple in function, got lost the ability to wash my private baths as well as well. And you know, I was in my early 20s. I was kind of too shy and anxious to ask people for help, particularly if like.
Can I work where I am in front of like female carer, like ask them to help me with that. I was way too embarrassed because I ended up getting some infections because I was too embarrassed to ask for help when I was just trying to.
And they tried to manage with without it and I just really couldn't. So yeah, it was actually really bad for my toy Health and like it took me a while to learn, like to be OK with that and to accept that.
I also kind of felt like I lost something when I when I adapted to that I lost, I stopped caring about my my dignity and my and that was quite that's quite hard really to to deal with it to realize.
Like how different you are.

[redacted] 39:18
Especially as a as a young adolescent male.

[redacted] 39:22
Yeah, it's much worse when when you're younger. I've got the maturity these days today. It's just kind of natural because I need help. I should, I should ask for it, but I didn't have that maturity when I was younger.

[redacted]
No, no. Thank you for thank you for sharing that.

[redacted] 39:46,
I had many mental health and anxiety issues. It meant that all my hospital visits had to be via an ambulance on a stretcher with paramedics and attendants, so that was a huge cost to the NHS as well because all my outpatient appointments were in London and I live in Gloucestershire.

[redacted] 40:34
Oh my goodness. And I'm sure. And how how did you feel from a your quality of life point of view about having to be on a stretcher taken to London?

[redacted] 40:47
Well, I was still having this sort of panic attack all the way there, so mentally I was still suffering and physically stretchers aren't that comfortable, especially if you're on them for six hours. Yes, it wasn't a good experience. A couple of times they had to put the blue lights on because they were so worried about how much I was panicking.

[redacted] 41:17
Well, completely understandable to panic when you've got no control. I can, I can understand that. Well, thank you for sharing, sharing that. [redacted] , do you have anything else to add on upper body?

[redacted] 41:33
Function before we move into respiratory.

[redacted] 41:39
I think, I think it's for me at the moment where we are, it's not just obviously it's it's all about doing your own thing, being independent, you know, scratching your your nose or whatever. But it's it's such.
It's such a wide thing because [redacted] can't use his phone and he can't communicate with people. So that has the the mental impact, you know, not having friends because I think he just feels like he's so different and he can't make friends with.
Can't get a job. He's just had his Universal Credit taken off him because he wasn't checking his portal on his phone that he can't pick up. So we're having to go through the whole process of Universal Credit again, having meeting after meeting after meeting, face to face meetings where these people can see that he can't move any part of his body.
But then we're still having to justify, justify it all. And so it's it's just so vast. It's, you know, it's huge. It affects every single part of your life. It's not just the little things, you know, it's just so vast.
And and yeah, and and upsetting because you just want to be, you know, like everyone else, I suppose. And and then you try your best to be like everybody else. But then there's just so many barriers people don't understand, people don't get it, people don't try and get it.
So it just there's so many battles and barriers just because you can't move and it's no fault of your own, you know? So that's what what upsets me. I think the fact that there's just so many barriers that shouldn't be there.

[redacted] 43:32
Yeah, no, I and I I completely understand like watching my own son at the same at the same stage, being unable to do things that 19 year old boys should be doing and having all that control taken away from from him.
[redacted] anything else to add on upper body before we move on to respiratory?

[redacted] 43:56
Yeah, we've had a lot more skin issues. I know [redacted] was saying about contractures and I've noticed that under [redacted] arms in the crux of his elbows, we're getting constant.
Source. It's it's every day. There's handover notes between the carers and and us that we have to keep on WhatsApp so that we can share photos of of how his skin is. So suddenly there's so many issues that we didn't have before for things like skin issues.
And also as [redacted] was saying about being able to wash yourself, I know [redacted] is still trying, but I don't think he's doing it effectively. So we're getting a lot more sort of issues of the skin around the groin area and these have an impact on you know the the care staff having to.

Do that additional check to make sure that they're handling him and drying him in a in a way that that is going to cause these damage, but also then we've got more input from GP services and.
The community nurse has to come in quite often to to sort of advise on on on, you know, how these things are going. So again, you know, you do get sort of more of an impact. It's not just the physical abilities, it's the other knock on effects of that.
And what you're saying about the pushing the glasses up the nose, that's that's all we do is basically [redacted] has got somebody stood by him most of the day to scratch his head, scratch his beard or push his glasses up his nose, put his headphones on. They're not quite comfortable or they've slipped, you know, I mean, we're very lucky in this day and age.
To have the the tech that we've got. But I know that once [redacted] can't use his keyboard, we're going to have more major issues. So it's it's, you know, coping with what you've got at the moment, but knowing what's coming.
And it's all those little things that you didn't think of like the skin issues that that we've not even contemplated that we know there's going to be more ahead than we can even see and and that we're unaware of, but there are going to be more issues, so.
Yeah.

[redacted] 46:16
Thank you, **X**[redacted], is there anything else that you'd add for the clinical complications piece?

[redacted] 46:22
Yeah, the only other thing I'd add actually is when you lose hand function, you, as we've heard, you can't use your phone, you can't use your, you can't use a keyboard. But you can't. Also, it's very difficult. You can't drive your wheelchair.
And that's a problem because electric wheelchairs are very heavy. They can't be pushed. It needs someone else to then drive it. And so actually, you know, it leads back to.
Social isolation and not going out anymore, which has a profound psychosocial impact on mental health, actually, I think.

[redacted] 47:12
Yeah. Thank you, **X**[redacted]. And I suppose this the upper body function sort of links into the next two areas we're going to discuss, which are around maybe we do cardiology 1st and the impact on the heart.
So maybe start with with [redacted] I mean you are, I'm just in awe. I've known you for a long time. I'm still in in awe of your strength, resilience.
How's your How's your heart holding up?

[redacted] 47:47
Up till the last year, great, but it's just started to show some slight decline over the last good year and a half. So I guess it's quite scary because it's always been, always been good, but it's a decline.

[redacted] 48:07
I'm really, really sorry to to hear that. Are you being, uh, constantly measured? Have they changed your medication? What's the?

[redacted] 48:15
Good. So there was a good change made to the medication that increase with something I was taking and introducing a new a new medication, but unfortunately I had some side effects from that so I had to discontinue. I'm waiting to to see a specialist again.
Come to to get a test, see if there's anything else I can take. It's actually really difficult to get a call to my cardiologist. He's wasted to to get some advice on this and the GP is just.
Not equipped to manage with to share that they don't, they don't have a clue come out what to suggest. So yeah, we're kind of waiting on that, but yeah, good plan now down for like 6 monthly.
Check-ups, but again, I think that we got the appointment for that matter is going to be next month, so I think [redacted] will have to be chasing them off to get the proper care already.

[redacted] 49:17
Yeah, absolutely. It's a it's a constant struggle. [redacted], how, how are you doing in the cardiac department?

[redacted] 49:30
Technically not great. My results are pretty, pretty bad, but I haven't noticed any symptoms personally from it yet, which is surprising.
Like [redacted] was prescribed some different heart medication when it did start to decline. But after I've been on it about 10 years, [inaudible] So, I was rushed into hospital and eventually they realised it was my heart medication that was causing it.
I was there for a week this just in case I needed surgery as they weren't sure what was wrong. [inaudible] but crash car in the room just in case.
And once I came off the meditation, that sort of eased off parts.
They haven't actually replaced that medication so now I'm on less heart medication, so my heart will get worse, but it doesn't seem to be. [inaudible] It's difficult.

[redacted] 51:21
For anyone living with a progressive heart condition, it's it's it's really challenging to know what to do.

X[redacted] 51:30
Yeah.

[redacted] 51:32
How's [redacted] X holding up?

X[redacted] 51:39
XX [redacted] got slight cardiomyopathy. He's very always been really proud of his heart and I know it's a it's not a good subject and he's lost a lot of a lot of his friends.
Due to heart problems who were all younger than him. So that's all that's been really difficult. But then he's always been proud that his heart is is always been good. He was on a a heart drug trial years ago so we don't we we still don't know if he was on.
The drug or the placebo, but I'd like to think that he was on the drug and it's kept his heart healthy. He has had over the last couple of years, he has had some slight deteriorations, but they're only slight. So it's not, it's not something that we talk about a lot because it's.
We say it's the least of his problems, which is a crazy thing to say, but but that's how it feels to us. The only the only thing that I would like to bring up to to do with his heart is we've moved recently over to adult services.
And it's been just drastic, the change. So in in Alder Hey, we would go and see [redacted] neurologist and he would pull everybody together. So we would go and we would have his heart appointment, respiratory, we'd try and do everything.
Since going over to adults, it's not like that at all. Everything's in one hospital except his neuro, so his neuro consultant is in a different trust, so she doesn't get to see any of [redacted] notes for anything else and vice versa.
X[redacted] went in because he's tracking and vented. He has to go to the ventilation ward. So we went to the ventilation ward with gut issues and we'll be looked after by the respiratory Dr. His neuro doctor didn't even know he was in. I had to coordinate and let them know that he was in.
And we didn't see anybody from cardiology had high blood pressure and we we've we've not been able, we've seen somebody once and we went to the appointment and they didn't even do an ECG. I've had to request them because they're talking about him going on TPM. So for us to make a decision, we need to know where his heart's up to, but nobody seems to add that into the mix. So it's all been down to me to coordinate everything and and try and tell other people. But what about this? And this is important. Nobody seems.
To leave their field to know about when it's duchenne, it's a muscle wasting condition and your whole body is a muscle. We all need to pull together. Nobody seems to pull together and talk to the next person. That's been the most frustrating thing to me because I know we will come to.

To a point where [redacted] heart will be declining and I will need them people. So trying. I'm trying to get them on board now so that we can try and keep [redacted] heart healthy, but it just seems sometimes like you're hitting a brick wall all the time.
With with every, every department, I suppose.

[redacted] 55:03
Yeah, I hear you,X[redacted]. And yes, it's the, you know that you need to protect their heart and that it's really important, but then trying to get that energy from your positions.
Present company excluded was is it can be really difficult.
And the impact on you as a carer is around your concern and worry and the time and organization it takes just to manage one of the specialities that we need to to see.

[redacted] 55:40
Yeah, but the for example, the last appointment we went to was the only one we've ever been to in adult services and there was 21. And he said, Oh yeah, your heart's doing OK, that's it. End of, end of appointment, end of.
You know, are we going to come again? Are we going to keep checking it? Because in three months time it could be completely different story. We need to keep monitoring it and making sure that it's staying healthy. But you just don't seem to be able to. They don't understand the Duchenne that I feel like the specialists.
Doctor is there for that specific thing, but they don't pull in the duchenne side of it as well.
So they don't coordinate with like neuro, you know? Yeah, it's frustrating. It's a full-time job.

[redacted] 56:30
Yeah, I know, absolutely. [redacted] how about [redacted] and the cardiac?

[redacted] 56:39
We had similar problems when we moved into adult services which is which was one that was more local to us and so we switched to to go to the neuromuscular complex care centre so that we had.
The input of everybody while we visit and there's a coordination. So if there's a problem we can phone up and you know, I know that when **X**[redacted] got COVID, I phoned up and straight away then [redacted] phoned me within an hour and.
The nursing staff phone me and you know a plan of action was put in place and you feel like the support is there, but it does worry me about the local issues. So obviously if **X**[redacted] goes into our local hospital that any issues whatsoever.
I don't trust them to to actually contact the people that they need to speak to and we have had one occasion where [redacted] was rushed into A&E because he got some chest pain.
And they kept trying to give him medication and said I don't want you to give him anything until you've spoken to his cardiologist in London and they were convinced he was having a

heart attack from his blood test results and it took them about four hours to actually. Speak to the people I I'd advise they speak to. And then I was told, oh, actually he can go home. He's not having a heart attack. This is normal blood readings for [redacted]. They've compared them to his latest blood tests in in London.
And it's just some indigestion.
I'd hate to think what would have happened if it was a different situation and they hadn't spoken to his cardiologist. There isn't any joined up care when it's local and it's it's an emergency, so that is worrying.
As far as [redacted] heart is concerned, his ejection fraction was in the normal, low normal range. He wasn't in heart failure and it had stayed that way. The progression had been very, very gradual up until he had COVID.
And then the following echo that was done found his injection fraction had actually dropped quite quite a bit to just just below the 40%. So you know that that was that was really concerning for me and that was quite a blow for me emotionally.
And trying not to make [redacted] panic about it when he could see that I was obviously quite shocked about the changes. You know, it was was anxiety provoking for me, but also for for [redacted] himself.
And I do think it's the one. It's the one appointment that I dread the most because I know it's got the biggest impact to find that there's been there's a sudden issue with the heart is it's going to be huge. [redacted] is on different medication now since the decline.
They immediately acted and put him on a couple of different medications and then it did improve. So we've actually gone back up slightly.
But it is. It is a major anxiety for me personally. I don't think [redacted] tends to think about it unless he gets breathless or he gets any sort of indigestion, chest pains or anything. Then he goes into a panic.
Um.
So it's one of those that it's it's a massive cloud and it does cause us a lot of anxiety, but at the moment he's doing OK. But again, I do worry about the local care if there's an emergency.

X[redacted] 1:00:26
Thank you, [redacted] XXXput something in the in the comments. I'm not going to read all of your results out there, but this your point is so I'm just going to read this for [redacted]
I'm also always worried if I have a palpitation. I've been told by my palliative consultant I cannot have CPR as my heart has moved behind my ribs, so there is no access. So I that must be terrifying to think that any palpitation might be something that could lead to.
To to more from from my perspective, [redacted] heart's read to be healthy. He's on a whole cocktail of of medicines, but what I see are his friends and contemporaries.
Suddenly dying because of heart, heart failure. So, [redacted] would you sort of give us the clinician's sort of view of cardiac and the complications in later stages of Duchenne, please?

[redacted] 1:01:33
Sure. Yeah. And and I can really relate to everything I've heard so far. Absolutely. I I can certainly relate to the lack of experience clinicians in local district general hospitals, which

is a.
Massive problem for patients and also the lack of facilities in hospitals as well, lack of hoists, lack of accessible toilets and so on. When it comes to the heart, I mean we.
I find it, you know, we have within our cohort of patients, people have normal heart function and people have very, very poor heart function and there's we see the whole range and it doesn't really correlate with the severity of the muscular dystrophy. So it's it seems to progress at a.
Different rate in some people. Um.
That it causes a lot of anxiety for for us and also for people, as you've heard, you know, it's it's a worrying aspect of the condition because it leads to sudden death and that's very distressing. It's, you know, for everybody concerned.
But we do scale up medications to try and protect the heart and keep the heart functioning as well as we can for a long as long as we can. But those medications lead to side effects.
And we've heard about allergic side effects, which we've had some patients who can't tolerate certain drugs because they get a rash or they get, you know, angioedema or they get a cough. So we have to change those medications.
But also we have known side effects of those drugs and that includes side effects on the kidney function. So as the heart function declines and the medication doses increase, the risk for acute kidney injury becomes very high, so.
I think I I last checked our result. I think we've had about 11 patients now have had acute kidney injury as a consequence of cardiac drugs. So what happens is you get a a minor infection and you don't drink as much and then.
You've got the drugs on top and then you get acute kidney injury. Some of those have been severe, but they we've managed to get everybody to recover with putting up being very aggressive with fluid treatment.
We had one patient where it was really touch and go, whether he was going to need dialysis. We have a super kidney specialist that we liaise with. That patient actually had to have erythropoietin injections.
For six months to keep his haemoglobin up because anemia is one of the consequences of acute kidney injury.
Other side effects of the drugs that we've seen are gout. So from the diuretics is a patients who in have very poor heart function who are on furosemide as well as.
Epiranone. So we've had one patient who's had quite two very severe episodes of gout and we've had to treat that with steroids and get our rheumatologist involved and obviously at the late stages of of.
Cardiomyopathy. We see a lot of very frequent hospital admissions due to an increased. So if you like an increase in symptoms associated with even minor infections, you get an infection, then you get more symptoms.
Sometimes you have to go to hospital and they go to the local hospital and they local and it becomes very difficult. So lots of frequent admissions and and then also it gets to the point in a very few small number of people where.
The symptoms, they develop heart failure and it can be very distressing because they're on maximum treatment and yet we can't improve on the treatment anymore because of the balance with kidney function.
And you know, that can really have an adverse effect on quality of life because the symptoms are really severe. So it can be abdominal pain, loss of appetite, fatigue, breathlessness.
And they can be really unpleasant symptoms.
So I think you know managing the heart from our perspective is is it's a big part of Duchenne and it's it isn't a huge burden for patients and families.

[redacted] 1:06:57
Thank you, [redacted] I think it's it's it's a bit too easy to sort of just compartmentalise it into cardiac problems. But then when you talk about all the sequelae of treatment and the and the conditions themselves, it's obviously a lot. There's a lot more to it.
Before we sort of wrap up on the cardiology piece, is there anything that anyone else wants to that's that sprung to mind for anybody else?

[redacted] 1:07:29
Conditions at local hospitals are dire. They haven't got a clue how to deal with Duchenne and they don't have the specialists.

[redacted] 1:07:54
Yeah.

[redacted] 1:07:56
But I thought of something else, which is just how difficult when you're in the later stages, it is to have an accurate heart scan, say like a cardiogram, just the difficulty of getting a good image.
Like I've got a cardiologist who's seen a lot of patients with Duchenne that is for like one of the only ones who's been able to actually kill a catacid criteria for how my heart is. And so it's kind of it feels like sometimes it's a bit of gas work, which isn't very.
It's very reassuring, really. I think kind of, uh, it does make treatment much more difficult.

[redacted] 1:08:38
I think that's a really good point, [redacted] , as well. And it's not just for the echo, is it? It's, you know, it's very hard to get people into an MRI scanner if they're on NIV as well. And also, you know, just literally, you know, people have scoliosis and contractures getting them into a.

[redacted] 1:08:46
Yeah, with a ventilator, yeah.

[redacted] 1:08:58
MRI scanner is difficult, but the BIPAP makes it even harder. Absolutely. It's a really good point. I forgot to also add one of the other complications that we see as well is is when people have to go on anticoagulants if they've got.
Cardiomyopathy as well. And then we get problems with bleeding as well. So we've had people who've had, you know, had to have ENT treatment for nosebleeds, we've had rectal bleeding. So you know, there's a lot of complications related to to the medication.

[redacted] 1:09:33
Yeah, they are on a huge cocktail of of of medicines and there's there's going to be interactions and contraindications and all sorts of things going on.

[redacted] 1:09:41
So then that's.

[redacted] 1:09:45
OK, I would suggest that we have a a 5 minute break. I certainly go. I need a cup of tea, something like that. So should we sort of regroup at 25 past?
And then we'll then we've then we'll have about an hour still to go if that's OK. And are are you all OK with doing this because I know that it's it's it's really difficult and I I know that I'm just checking that you're all OK with with doing this because we'll be moving on to some other challenges in our next hour.

[redacted] 1:10:02
Yeah.

[redacted] 1:10:21
Is there anything that you'd like to change or suggest?

[redacted] 1:10:26
I was going to say, is everyone OK? Because I am giving you information that maybe some of

you might not have been aware of before because it's about we're talking about rare situations. So I hope everyone's OK with some of the detail I'm giving.

[redacted] 1:10:42
Yeah, it's actually really helpful was like things I hadn't thought of. So should we have a 5 minute break and then then regroup? Thank you everyone.

[redacted] 1:10:43
Yeah.

[redacted] 1:16:51
Good. I think this was something else I was talking to someone about. It's like it's it's not just the impact of because when you when you say that you're caring and you're doing these things like, Oh yes, well that's I'm doing that for my for my mother and it's like, yeah, I'm doing it for my mother as well.

[redacted] 1:17:08
Yes. Yeah, that's right.

[redacted] 1:17:09
Like, not mutually exclusive. So it's just have been another dawning realisation over the last last year or two.

[redacted] 1:17:10
Yeah.

[redacted] 1:17:20
Yeah. Wow. It's tough. Yeah. Yeah.

[redacted] 1:17:25
Yeah, I think there's a couple of things which I hadn't didn't have on our list, but we may need to talk about our gut, which I haven't spoken about.

[redacted] 1:17:38
Yeah.

[redacted] 1:17:39
Much and metabolic impact as well and puberty and all the all those things that go with it. I don't know if we want to, I think maybe we move on to respiratory.

[redacted] 1:17:42
Yes.

[redacted] 1:17:56
Challenges and then then spend a bit of time talking about gut and metabolic issues before we go on to disability in general, if that's OK with everyone.

[redacted] 1:18:13
Yep.

[redacted] 1:18:14
And I I just want to reiterate, I know this is really difficult and I am so appreciative of you sharing your stories, but it's it's so important for people like NICE and NHS England to understand.
What the reality really is.

[redacted] 1:18:47
Well, thanks everyone. So we've had a quick break and now we're going to move on to respiratory challenges and particularly around the impact of.
Ventilation both both night time and and full ventilation and the how that has impacted you

and how it makes you feel. So in our in our usual order I'm going to start with start with [redacted] if that's OK.

[redacted] 1:19:22
Yeah, absolutely. So there's a a first thing to say, massive difference between starting ventilation overnight and current to use it full time during the day and that's how I got it. Can talk about those two transitions. Obviously you don't know that it can get worse when you're when you start the first transition. So the first transition feels pretty awful. I remember being terrified.
The clinician, I think he was a technician, actually. He was setting me up with a ventilator mask just there. He was heating his cache while watching the cricket and doing my mask at the same time and he put his full face mask on me.
For the first time, and I just felt terrified. I was so anxious. So it was like claustrophobic. It covered my nose and mouth. It was just awful. Yeah, you've got this big breathing kind you and you.
You've got to relax, breathing. I do like it. How am I going to sleep with this thing on? Like, I think that was the hardest transition I've ever had with with Duchenne. Much harder than, like, get it going into a wheelchair. Just having to have it to adapt to something breathing for you.
Yeah, kind of just like mentally. It took a real total of me and I was just so anxious, you know, suddenly I can't manage without the machine. You know, you need to have electricity wherever, wherever you're going. I remember one time my dad.
I was only given one ventilator and it broke and I'd probably been for a couple of years, leaving it overnight. I had to stay awake all night because I was so worried about what would happen if I went to sleep until we could get the new machine.
Machine like get the machine replaced. I will say once I'd started ventilation, things like coughs and colds became much more much more of a problem going out because especially. Until I could get a cough assist machine, which kind of helped a bit. But even then, suddenly, like, if I'd got a cold before I was on ventilation, it wasn't a big deal. I knew I'd recover from it, but 'cause it's something you had for new people who were on ventilation.
They got just a simple cold and then they died a few days later because it's terrifying really. I just knowing that you know your ventilator might disconnect overnight. I don't you don't know if you could.
They shout loud. I'll have to get help to that back when I could still maybe make myself louder. I think just, you know, the coach to adapt to a mask. I got pressure sores on my face. Got me done being more tired because I wasn't sleeping well, just because you've got this thing on your face. Yeah, I suddenly had to change my whole way of life to be a bit more sensible. I was at university and I was.
To the quite a wild student, but I had to stop. I had to be like very, very conscious of my breathing and being able to instruct the BA how to use, like how to put the mask on. But yeah, I was terrified then by actually looking back at it.
If I could go back to that stage of my life, Oh my God, that would be amazing. But going on to the full time ventilation because initially you, you know, you get a bit more energy back. Get your talking improves just because you were struggling before.
All that, but actually you know that your quality of life has deteriorated a lot. Like that's that's even more scary because suddenly like you can't breathe without a machine the whole time. So you need carers with you at all times.

God, you can never switch off and you can never relax properly because, you know, at any point by two of my ventilator could disconnect. It happened when I was out and about, but I've always had somewhere there. But like every time it happens, it's instant panic. Oh my God, is someone going to realise?
I got disconnected. I can't talk when I can't breathe, so no one knows because they're watching or there's an alarm. So it's it's absolutely terrifying really because it's completely changed my care that I need the cost of that. So now that I'm.
I can only breathe like 30 seconds without a ventilator before I start to, you know, struggle to suffocate. It wouldn't take much longer. So yeah, you got to think about that.
You're using a ventilator while you're doing all the other things, so like being hoisted, doing transfers and going in the shower, you still need your ventilator, so it means that my my care needs have increased that I need.
2 to one care at all times. It's also affected my ability to access other care. So we did talk about MRI machines, for example, can be a more difficult to grab, but things like can I can have a Texas scan because they weren't equipped for me.
Can also it's not always that you can't do it, but you need an expert team to do things and it's going to be more complicated. So for example, I've had bowel issues over the last like few years.
I had investigations, but then they got to a point where usually they do a colonoscopy, but they didn't want to do it because I was on a ventilator and it was more complicated. So I kind of got undiagnosed and resolved like.
Now issues because they're too scared of the the ventilator to do actually anything. I'm sorry, I'll call out a bit, but the last thing I wanted to say was go around like mental health. Go and say when you're on the ventilator in just at night.
They're already nose. You can pretend that you're not really a ventilator user, apart from the big sore that most people have on their nose. But you know, suddenly when you're on full-time ventilation, everyone sees that you're suddenly very different. Everyone stares. Can you?
When you go out of the mail, you're probably interested. It's just like completely unpacks it. That's really bad. Like mentally, it took me quite a while to get used to that, to be able to get out of the mask and I definitely did have a.
Period of depression to begin with.

[redacted] 1:26:30
Yeah, and I remember there was a young man near us went to this, went to the cinema in Epsom, I think it was, and one of the other cinema goers complained about the noise his ventilator.
Made and he and they made the young man with the ventilator leave the cinema, not the person who complained and.

[redacted] 1:26:56
I think I remember that.

[redacted] 1:26:59
That's just heartbreaking because it's, yeah, honestly, thank you. Thank you, [redacted] And you know, I don't think I haven't certainly realised all of the extra challenges that go with it.

[redacted] 1:27:02
OK.

[redacted] 1:27:14
Can I ask a bit about getting your masks and things? Did it take a long time to get the right the right ones?

[redacted] 1:27:24
Yes, yeah, absolutely. So I I went through a period of having pressure sores all over my face until I could find the right mask and then like I managed to find one that fits me. But then then they all seem to get discontinued when the manufacturers.
Decide they want to release a new, you know, a new version. So I'm actually using discontinued masks that I've still got the spares for, but yeah, at some point I'm going to start that process kind of like.
Searching for a mask. I've also paid a lot out of my own pockets to get the mask that actually works for me without causing me issues. But I could rather avoid a tracheostomy if I can. If I need it, I need it. But yeah, one I can too.
Not invasive. It does give you the option to like I could use a mouthpiece to get it off my face for example, but still it's problematic. It causes a problem for intimacy as well.

[redacted] 1:28:31
Yeah, well, clearly. Thank. Thank you, [redacted] [redacted] does that all resonate with you?

[redacted] 1:28:40
Similar. I was in university when I started with the local team.
The local team did all sort of do all sorts of tests, including gastro tests, stuff like that, local sleep studies, but they don't look for carbon dioxide levels. They looked at the oxygen levels. So for about a year or two, I was going through tests and they couldn't find anything wrong. I was getting worse and worse. I knew what it was, my mum knew what it was. But you are just arguing, arguing.
Eventually my mum broke down and cried on the phone to a GP who's got a referral to the Royal Brompton. I went down there for a week or two. They took a blood test. [redacted]
They put me straight of ventiliation.My first experience was similar to Jon. I sort of had a

panic attack, blacked out. I couldn't see anything. I could just hear people in the room.
It was really scary, but it wasn't so much the actual mask. I just didn't mind that part. I think it was just because I had the full oxygen intake for such a long time.
My body just sort of went, well, what's this? I just freaked out.
But yeah, I got used to the mask and time goes on very quickly, but like [redacted] lots of open sores. But I tried different ones. You find after a while that it's discontinued, there's all sorts of trouble around it and again, the same as Jon going out when it's become 24/7.
Ventilation going out is scary. Every time you go out, you're in constant, constant fear mode. I think my hose has come out and I panic or that my mask has slipped off, but one time it's slipped off. Well, my aunt was there, but she didn't notice, and I was out for a walk, so I sort of rushed home and they couldn't hear me. So I smashed into the furniture to make some noise so somebody would come in and I broke my ankle.
It was a really scary thing.
Another time, I think it just stopped working. I was out for about 5 minutes. Luckily I had a good carer with me. He turned it off, turned it back on and it suddenly started working.
I was seriously considering driving myself into [inaudible] But yeah, it's tough.

[redacted] 1:33:14
So.
And you know that and I'm guessing like travelling far is really out of the question.

[redacted] 1:33:25
Oh, I still do it. I mean, I won't let it stop me. It's scary. It's scary.

[redacted] 1:33:26
Yes.

[redacted] 1:33:34
I've got a second machine now, so yeah, I'll still do it. I'll push myself. Otherwise I'll just really go back to moving inside, so I don't want to go back to that to that.

[redacted] 1:33:52
No, of course you don't. And why would you?
Thank you, [redacted] That was really tough to hear. Thank you for sharing.

[redacted] 1:34:03
I'll move to [redacted] I'm just going to remind everyone that if you if you're finding this too hard, you can step away if you need to. We it's it is. I know this is really difficult, but you know, please let me know if you if you are finding it too tough to to keep talking.
[redacted] you look like you're poised. I know that [redacted] had lots of infections and struggled. Tell us about [redacted]

[redacted] 1:34:32
[redacted] started on NIV overnight when he was quite young, so he was about 8:00 or 9:00. So the same goes for trying different masks and getting the right one and then him getting used to it and him growing and having to change the mask.
But it was only when he was about, he was about 17 when he was having to use it during the day at different times and then when he was 18 he became reliant on it during the day. But it just wasn't giving him the support that he needed. So he was admitted.
Into hospital and and he was told that if he didn't have full-time ventilation then he wouldn't leave the hospital. So it was they they they asked would he have a tracheostomy because it meant that they could give it to him more.
His his settings wouldn't go any higher and it was explained to him that he needed more ventilation than what they were able to give him. So at first he refused it because he they said he would probably lose his voice. And he said, Mum, who am I without my voice? I can't move. I need my voice to give.
Instructions for everything. I need my voice. It's the only independence I have. So he refused the tracheostomy, which was very hard for for me because you know, I from what I was hearing was I was going to lose my son if he didn't.
We had to have some very, very horrible conversations at that point and he was quite grown up about it and he listened to what everybody had to say. We had hours and hours and hours of just chatting to consultants and doctors and palliative care.
And trying to work out the best things. Obviously my first thing was I ran out and got every communication aid that I possibly could. I had an eye gaze within two days. You know, I had I made boards, communication boards, everything to try and persuade him without persuading him because it was 100% his decision.
Decision. So we had to respect his decision. But then he came to the decision where his his life was good. He was happy. You know, he loved going to college and he loved learning. He loved his his family and his friends and he he.
He weighed it all up and decided that he would go to have the surgery. So he had the tracheostomy done and he woke up in intensive care and asked for a mirror to see himself, which surprised everybody. But obviously everybody cried happy tears because he was able to speak.
So he's now he's ventilated 24/7. He can't, he's not, he cannot come off the vent at all. We've tried and he can't come off the vent at all. But it's given him a new life. It's come, he's got no mask on his face anymore and because he can now breathe better, he can speak better.
So he can have telephone conversations with people and it's just it's given him that new life that we all thought he was going to lose. So to us it's been a massive positive experience. Although it was not something that you want to go through, having the tracky and the vents has given [redacted] a new life. But obviously from a mum and a carer point of view, there's so

much more into it. Training every single person that looks after [redacted]
Has to be tracky trained, which takes time. He's he's 2 to one because he's tracky vented. So I always have two carers in my house all the time with him in consumables and equipment. We've just got a house full of boxes of equipment and.
Consumables and they all come from different people. So I I also work full time. I've had to drop down my hours, so I'm now only part time, but that's only because of the amount of stuff I have to do around [redacted] So it's checking, doing stock checks, ordering, then keeping all the.
[redacted] has a personal health budget. The personal health budget is not what it says on the tin. So I can't keep carers. We go through carers like nobody's business because they won't do the job for the little amount of wages to get paid because they're basically keeping him alive and you know they get.
I pay 14 lbs an hour and I've had people leave us to go and work in a supermarket because you can get paid more and you're not taking the job emotionally home with you. And I, you know, I would go and work at a supermarket. I'm not putting that down, but it's it's such a demanding.
Important thing, you're keeping someone alive, but we just can't keep them because we can't pay them enough. So we've got positives and negatives because obviously the the biggest positive is it's given [redacted] this new lease of life and you know we're so thankful that it's.
Happened in a positive way for us because I know it doesn't always, it's not always positive for some families. But then you know going to college, he has to have his carers with him. He can't just go to college and sit in class with with any class friends because he's always got to have a tracky trained person with him, even when we go to our local Hospice when he goes. They have their groups together. They're not. There's not enough staff that are tracking training, so [redacted] can't be left to just, you know, be there with his mates. He always has to have someone with him, whether that's a carer or or me. Yeah, it.
I've got a list. I've been writing a list as we've been going along and I'm trying to get through it. But yeah, it's it's not, it's not been easy, but it it was probably one of the best decisions that he made because it's it's kept him alive, but.
There's it's just so much more, so much more forever.

[redacted] 1:40:48
Thank you, [redacted] And I think when when we're talking about sort of bodies like NICE, what they will look at is tick boxes, somebody ventilated and assign a cost to that which is probably around the cost of the machine and the cost of the some consumables.
They won't be looking at the personal costs and the and the challenges with quality of life that that brings, whether it's improved in [redacted] case, it's probably.
Not so, not so good in yours.

[redacted] 1:41:22
No, I mean, even in the car, obviously you have to have a van. The van's got no suspension. Every time you go over a stone on on the floor in the car is is vent will pop off his tracky. So someone has to constantly put that back on. He doesn't like going out in the car. There's certain places he won't go.

[redacted] 1:41:26
Yes.

[redacted] 1:41:41
He goes to because he knows them roads are too too bumpy. So it you know it's it's it's it just it just has a massive impact on the whole on your whole life from you know everything takes so much longer. It takes about two hours to get him up in the morning and get him into the point where he's in.
In his wheelchair and he's ready for the day. It's about two hours because that's doing all the tracky tapes and everything. We're used to it now. It's just way of life to us, but obviously it has an impact on. So he's he's he's still in college, he loves learning, he's still in college, but if it's a 9:00 start.
You have to start getting him up at you know 7:00 AM. So the carers shifts have to change. They have to come earlier and and by the time you get no we're up and you get him ready to go out. He's fallen asleep before before you get in the car because it's it's it's a hard job but.

[redacted] 1:42:35
Yes.

[redacted] 1:42:37
And like I say, we try and put a positive on it because if it wasn't for them things, he wouldn't be here. So we're grateful that we've got the tracky, we're grateful we've got the the vent.
But it's not an easy. It's not an easy job.

[redacted] 1:42:58
Well, thank you. Thank you, [redacted] [redacted] how's how's [redacted] s respiratory?

[redacted] 1:43:06
Right now, [redacted] doesn't ventilated, so he has his overnight sleep studies still once a year. He he's aware that he will need a ventilator and he's been aware of that since he was about 8 or 9 because we knew other boys.

Starting on ventilators that young. So it's been something that he's been aware of all that time and we've been expecting it all that time. I'm kind of dreading it. I do feel like, as [redacted] said, we will lose carers because right now.
Our care staff, they already feel that huge responsibility of the steroid medications and the other medications that he's on and looking at the side effects and you know, is it going into adrenal crisis is one of the major sort of conversations that we have and.
Emergency steps to take if if these things happen and I think adding a ventilator on top of that might tip the balance for some of the carers that we've got.
It's it's not something I'm looking forward to. Let's let's put it that way. We have talked about tracheostomies and initially [redacted] said I don't want to be dependent on on a machine to keep me alive and then he had to base the fact that even if you.
Your non-invasive ventilator, you're still reliant on that machine to do your breathing for you. So there's been a lot of conversations about what what do I do? What do I say when he's an adult?
If he's in that position where he can't speak for himself and we're with a medical team in an emergency situation, am I saying you ought to do everything you can or am I saying this is the line? And when he doesn't know, that's a really difficult call to make.
So even if that only happens once in our lifetime, that worries me every single week. You know that these, these, these once in a lifetime emergencies, you know, are a very hard, you know, you're probable to actually be facing that at some point.
But as you know, as things stand right now, while we have anxiety and concerns about him going on to ventilation, that's not something that we're living with just yet. And you know, I don't want to worry him with all these other.
These other issues about it's going to take a while to to find a mask that fits and all the other concerns that go along with ventilation. I don't want to worry him about those just yet because we'll cross those when we come to it. But I take on that worry for him and I think a lot of family members do that they would.
Take on those concerns so that their adult child isn't worrying about it.

[redacted] 1:46:04
Yes.
Thank you. Yes, I my son's not ventilated yet either, but I know that it's it's coming. I was. I'm just going to read a a sort of a blog from.
A duchenne parent, something which has happened quite recently and then maybe get your reactions to it and then [redacted] as well. So this is.
We are going through absolute hell at the moment. What started off as a chest infection last Saturday has ended up in intensive care. If it wasn't for my son's muscle team, I'm convinced he would not be here today. Was brought in by ambulance on Saturday, kept in A&E until Monday, then moved to a respiratory ward.
Straight away, he contacted his muscle team via the WhatsApp number. One of the nurses said she'd pop in and see him the next day. In the meantime, we've been called into a side room and told our son's left lung is full of an infection. Antibiotics aren't doing much and to prepare for the worst because they've rung intensive care and they won't take him because of his condition.
And he won't survive any treatment they could give.
Fast forward 24 hours, the nurse from his muscle team turns up and is horrified at the state of him. She took over the desk on the ward, made some phone calls and within an hour he

was in intensive care, all due to his consultant demanding they take him and treat him under her guidance. This morning we had a doctor come in and tell a 23 year old boy he has to make a decision on the worst case scenario.
One, would he like to stay in the oxygen machine and be made comfortable to die? Or would he agree to be intubated? But bear in mind you may not even survive that. Number two, worst case scenario, would you like us to let you die or put in a trackie, although you wouldn't be able to eat or talk and you'd have no quality of life.
Let's be honest, young man, your quality of life won't be the same when you came in anyway.
My heart absolutely broke for him. He didn't scream or cry. He just said calmly. I'm 23 years old. I don't want to die. Do what you can to keep me alive. I'm an absolute mess and he's taking it all on the chin. He's the bravest boy I know, and I'm praying he pulls through because no one deserves it more than him.
They've had a teams meeting this afternoon as Heart Respiratory Duchene consultants and consultants from intensive care who are now treating them under the guidance from three other hospitals. I'm forever grateful to his team.
Um.
So that was that happened and then.
I can't find the one after that, but um.
He pulled through with the antibiotics and the treatment and the respiratory. He pulled through and was discharged 5 days later.
Although the next piece, you couldn't make this up only out of hospital 5 days and we're back in A and EA nurse dropped dropped our son's leg when he was in intensive care, causing it to fall off the bed. A doctor said there was nothing wrong with it. Two weeks later it's still hurting, so we bring him in for an X-ray only to be told that they.
Fractured dysfemur.
So he's back in hospital again, which, but I think what I was just reading that out and I'll ask her permission to to to share it, but it was just the the conversation that they had to have with a 23 year old boy that I found incredible.
So [redacted] like over to you in terms of the impact of infections and ventilation and tracheotomies and all of those things.

[redacted] 1:49:44
Well, sadly, the blog that you've just read out is a very familiar story. You know, we come across this time and time again and it's it's due to ignorance local.
Acute hospitals have no knowledge of how to manage duchenne. They don't understand the condition. They they don't understand that it's it's a treatable condition.
And that the Natural History is not what it used to be.
I think starting NIV is a massive deal. It's in my experience, it's more distressing than losing walking.
That's what I see in the patients, you know, that I deal with. Um.
We have.
A significant number of young men who.
In whom we feel they should start an IV, but as [redacted] mentioned, they find it so difficult to tolerate this mask. They because of anxiety and.
It's it that it's terrifying. Um.
And it's, it's, it's really hard for us as clinicians. We have, you know, spend, I spend many

hours, you know, chasing up people. Have you tried it yet? We try different ways to encourage them to use it.
We bring in our psychologist. Um.
To try and help to reduce anxiety. We're so fortunate at the moment that we had a grant from Duchenne UK to provide some psychiatry time.
And and this is a limited period of time, but that psychiatrist has even been trying medication to reduce anxiety, to help some of these men tolerate their NIV because these are young men, you know, they're in their late teens, early 20s.
And it's really, really distressing if a patient of ours dies because they can't use NIV that I find that one of the most upsetting, you know, scenarios that we have because we know how effective it is as a treatment.
So you can't underestimate the mental health impact on NIV and unfortunately the psychiatrist, that grant is going to come to an end, so we won't have access to that psychiatric time in the future.
As [redacted] says, you know we do see pressure areas and and another complication of NIV is is tummy bloating that can be really troublesome for some people.
Also, why do people get chest infections? Well, because they can't clear their chest so well because their cough is weaker. So we then provide people. If it's not too bad, we use something called an LVR bag to assist with the coughing.
But then that progresses to cough assist machines. So people need a cough assist machine at home to help clear the chest, otherwise they're at risk of choking. And the cough assist can help to prevent infections, as can the NIV.
Um.
People who do tolerate nighttime NIV, which is the majority, feel much better once they're established on it. As [redacted] said, you suddenly you suddenly feel better. You're not groggy anymore. You you have got more energy, you've got more appetite.
You can speak better, you can swallow better. So those sort of things improve. But of course you need a carer or somebody to put the NIV on and to take it off in the morning.
And of course, as our patients are getting older, so are their parents. Some of the parents we look, you know, are getting on a bit actually for some of our patients.
Another point to make is about being admitted to hospital if you're on NIV.
Um.
Some hospitals, they will not take you into a general ward. You have to be admitted to an HDU because the nursing staff aren't trained in looking after NIV.
And of course, if you have a tracheostomy, usually you have to be admitted to ITU. Even if you've got a swollen big toe, you have to go to ITU because you need tracky chain trained staff. And at home you might have two carers 24/7 funded on a healthcare.
Budget.
But that health care budget will not allow those carers to support people when they're admitted to hospital.
And I think that's a real problem for many, many of our patients because they're used to their carer doing their - Personal needs, but that carer is not allowed to be with them in hospital. And that's a huge problem because acute hospitals don't have the staff to deal with.
Very disabled patients moving to full time ventilation as [redacted] said is also very distressing and and you know it causes a lot of anxiety and distress for.
People, it also in we have to make sure people have two ventilators. You know, we can't just have one set of equipment because as [redacted] said and as [redacted] said, if it breaks down, you're in trouble. So we have to make sure everybody's got.
Two of everything. So we do that if they have over 16 hours a day of use.
Um.

Trachy and and tracheostomy is, as you've heard is has some advantages, but there's also some disadvantages and that is that just the amount of care is so much more. You then need a suction machine as well.
And you have to train everybody and to to know how to change that Trachy tube if it comes out. And as I said, if you go to hospital, even with a swollen big toe, if you've got a Trachy, you're going to have to go to ITU probably if it's a General Hospital because there'll be no one there to to manage it.
So I think those are the the main points I want to make and I I think also that stepping down from when people are acutely unwell that the DGH is just having no idea what to do and.
We had one terrible scenario during COVID, actually at the right at the start of the pandemic. At the start of the pandemic, the first wave of COVID actually didn't really affect Duchenne patients badly at all. They got because they were young people, they got.
Fairly minor symptoms, usually just loss of smell. We had one patient who.
Whose parents both got COVID and was seriously ill and he was perfectly well. He just lost his smell, but all three of them had to be admitted to hospital because there was nobody to look after him and because of the COVID policy of a GP, which is.
The aerosol effect from Bipap. They said he couldn't use his Bipap machine. They took it off him.
And he passed away.
So he actually died because the hospital took his his machine off him.
I've had another patient who died because he was admitted to hospital and he didn't want to use a a bedpan because he had some autistic feet autism.
And because of that, he went to hospital with something minor that was that was treatable. But because he didn't want to use a bedpan, he stopped eating and drinking. So I think we can't underestimate.
The impact of.
Losing these skills and the impact of going into the the NHS, not being able to cope with people with Duchenne and and the problems that they have. And I'm sorry, this is very distressing for people.
But you know, it's something that we feel very upset about at times and I just feel the NHS can do better for people with Duchenne.

[redacted] 1:59:37
Thank you, [redacted] I'll I'll share one of the experiences that that [redacted] and I had which sort of links links to this was he got cholecystitis and needed to have his gallbladder out.
And it started with us going to the local hospital where because he was 17, he went to the paediatrics ward and they had no idea how to cope with someone in a wheelchair who needed care. So it was me and my one of his one of we had bond carer at the time of taking it in turns to sleep next to him.
We had to move his bed into the middle of the hospital, middle of the ward to be able to hoist him out, couldn't use the toilet and they just and even trying to do the scan for the gallstones was like really, really difficult. But so there was a week at the our local hospital and then they said, well, he needs to have his gallbladder.
But we're not going to do it because we just we don't know how. So then we had to go back to Great Ormond St. where he was just transitioning out. Great Ormond St. Great Ormond St. said well they we we can't do it because it's not a it's not a pediatric operation needs to be done by.

A specialist team. So then we had to go to the Royal Free, who also had no idea how to handle someone with with muscular dystrophy. I had to have a stand up argument with the anaesthetist about what they should and shouldn't use.
And put a complaint in to be able to get the right care for him. So and then we had to have two sleep studies. So before we even got to the Royal Free, it was took about 6 to 8 months when he was in constant pain because of the cholecystitis.
Um.
Eventually we got into the hospital. We had to have a night before in a respiratory ward to make sure that his respiratory function was OK that had no disabled access. He couldn't use the toilet. The hoists were all wrong and they had no idea. I had to sleep in the room next to him, which was.
Like they didn't really like that because that's not what you do. And then he had the operation the day after and had to go into intensive care for two days afterwards. After they'd scrubbed it, they had to scrub out the theatre and all the anaesthetic machines.
Do the surgery. Surgery was actually quite quick, but then he was in ITU for for two days afterwards and I was sleeping on the floor next to him because they had to have someone to care for him, which was me. So then the point of this is that actually.
Well, if you looked at, if you looked at that on his medical records, it would be cholecystectomy which would be charged out at, I don't know, 500 lbs or something.
Actually in reality that whole process would have cost 10s of thousands.
Not to mention all of the impact that it had on us, but it was all around the fact that hospitals cannot cope with people with a condition like Duchenne when it's even when they're looking for something else.

[redacted] 2:02:45
Absolutely. No, it's terrible. And as I said, they, you know, most hospitals can't cope and if you have a healthcare budget, they won't allow the carers to come into hospital. We had a very.
Um.
Complex patient admitted to our ward and he again had autism and wanted he wanted his own carers and we allowed that. That's what you know, we would do whatever would support the patient, but then we had the.
The local authority demanding that we pay them back all the money for the carers during that time because they're not allowed to do it, apparently. And this is a really significant problem as well because you know the if you've got a healthcare budget.
If those carers can't come into hospital, those hospital wards have got to employ extra staff to deal with the patient. So it seems absolutely ludicrous. But you know, so just thinking about the the cost of admissions will go up massively.

[redacted] 2:04:00
And that's probably largely about them being disabled rather than the rather than the the fact they've got duchenne. It's the disability that's the problem.

[redacted] 2:04:03
Yeah.
It's the disability. That's right. That's right.

[redacted] 2:04:10
[redacted] welcome back. Put your hand up.

[redacted] 2:04:15
Yeah, it was just on that point. I think, I think that might be one of them postcode things again because [redacted] has a personal health budget and the both children's and adult hospital where he goes, they've always welcomed his staff in because they haven't got enough staff. So and we've had it cleared with the authorities and and we've always had his own staff come in. So and I know lots of people who who in other hospitals they don't allow it. So I don't know whether we've just been lucky.
But there's not enough staff, so we have to do it. So they don't have a choice. So yeah, so we've always been quite lucky with with [redacted] having day and night carers continually in with him because that's his biggest fear, not not having someone who knows him.

[redacted] 2:04:57
Yeah.
Yeah, it's very good.
Exactly. That's right. You're right. It probably is related to different IR BS now or they were CCGS. It depends on that each one probably, but that's great that you do.
Yes.

[redacted] 2:05:18
Yeah, that's really.
Well, thank you all for sharing your stories and then we've we've been galloping through our our time we've got here. So and I don't want to close this session before we start talking about.
I'm not even going to call it the elephant in the room, but I'm just going to say, you know, talking about death because that's something which is, you know, it comes, it's going to come to us all. But in the in Duchenne, it comes a lot faster than you would like and it's it happens.
And as well as you've described so eloquently, like in very strange, sometimes in unusual ways, sometimes predictable ways. [redacted] you got your hand up.

[redacted] 2:06:08
I'm sorry, it's me again. I had to leave because the carer was leaving and the night carer hadn't showed up, so I had to go and get my son. So I think I missed a little bit. And was it? Were you talking about gut? Did you move on to gut?

[redacted] 2:06:23
Uh.
We were going to talk about gut, but I don't know if we've got enough, I don't know if we've got enough time.

[redacted] 2:06:28
No, that's OK. I just didn't think. I thought maybe I'd missed. I I'd missed that little bit.

[redacted] 2:06:32
No. Was that was there something in particular that's that's caused you problems gut wise?

[redacted] 2:06:37
That's that's our biggest thing at the moment. That's all. There's not enough. There's there's nobody. No, I've not met one gastro team that understands Duchenne at all. Not not one.
[redacted] is now on palliative care because he's got dysfertility. He's got his bowel.
And his bladder are all failing and he was in. He was admitted into hospital onto the ventilation ward because that's the only one he can go on to with his gut problems.
And we didn't see a single person from the gastro team. He was in the end. He discharged himself after three weeks because not one single person came to visit him on the ward in the whole 3 weeks. And we've since seen two more gastro teams and we've seen some really honest doctors who.
You know, they're honest and tell us we don't know anything and and we'd rather have that than no one turn up. But it just seems to be a reoccurring thing that everything is a muscle. We can't see the muscles on the inside, but your whole system works with muscles. It's not rocking.
Science that we need to be putting more, more into. Like if it was me and I had my gastro problems and I went, they'd be able to sit down with me and they would help me and they would do surgery or they would do something to fix it. We we're not stupid. We know we cannot fix this.
But nobody seems to want to touch him because he's got duchenne. That's his main condition. So even his neuro consultant, she talks to us about his gut and she'll say, I don't know anything about gut. It's not my field. I don't know about it. Well, that's not very helpful when my son can't. He's in agate.
And he's got, it looks like he's nine months pregnant every day and he's in absolute agony when I'd all I want to do is is help him to, you know, we've we've been given this new life

with his trackie and his vent and then we've taken it off him in the other hand by not giving him a quality of life because nobody knows anything about gut problems.
So at the moment that's our biggest, the hospice of being our our biggest support at the moment because there isn't anybody who knows anything about Duchenne and Gut.
Put them together and just help us with anything at all. We're we're literally, we're literally just winging it ourselves. My niece is is also disabled. She's got a lot of the same problems.
No, but their conditions are not related at all and she's a lot further on.
With the gut problems than what [redacted] is. So I go to my sister for advice and you know, if something was to go wrong, it's on her head. But I don't have anybody else to who we can go to because everyone keeps telling me they haven't got a clue. That is literally the last person we saw.
Said to me, Oh well, we're just a small hospital. We don't know anything about the gut. So thanks for coming today. And that was it. We were literally there 10 minutes and it's just, it's heartbreaking because you just want to do more, you just want to do something and the people who.
Who are in the field and you just feel like you're just talking to a brick wall all the time. So yeah, that is my that's our biggest thing at the moment because this is, this is where we are with [redacted] It's our biggest thing, so.
Yeah.

[redacted]:10:18
So sorry to hear that, [redacted] I yeah, I mean, I don't. Yeah, you hear it all the time, like with them boys spending like 5 hours on the on the Louvre and just, yeah, I don't know. [redacted] do you have anything to?

[redacted] 2:10:31
Yeah.

[redacted] 2:10:37
Yeah, no, it's. I mean, the gut is a big issue that we see in patients. We're fortunate. I'm sorry to hear [redacted] about about your son, about [redacted] we.
We we have a gastroenterologist who tends to organise imaging, so we do CT scan, see what's going on and there are there are different problems that can occur in the gut, so they need to be.
Properly diagnosed. So we've seen more gallstones actually in Duchenne than in other conditions. It seems to be related. So we've had a number of patients who've had to have cholecystectomy, which we do at UCH.
We've seen a number of people who've had something called Volvulus where the gut gets really distended and the treatment for that is to decompress it. So with a sigmoidoscopy or to deflate from a PEG tube if you've got one.
But sometimes you can get bacterial overgrowth and that's so that we do a breath test for that and also our gastroenterologist use he uses various drugs for motility.

So I think it, you know, we have. I think this is something where we need to develop more guidelines nationally so people can access the right advice.
And I think also we've had a few patients who've needed TPN at home as well because of the gut issues. So I think this is a really tricky problem.
Uh, but uh uh, yeah.
I think our gastroenterologist was trying to set up some guidelines.

[redacted] 2:13:01
Hopefully that's that's at least something that's that's come out of our our session. Gosh, I'm, I'm, I'm sorry, I'm really I am really struggling with with this. It's I'm so grateful to you all for sharing your stories because.

[redacted] 2:13:03
Yes.

[redacted] 2:13:20
Yeah, people like nice need to hear it and I'm I'm sorry that I'm that I've put you through it and I'm sorry that it's it's it's people who would just want to put a number.
On it, but it's that's what that's what needs to happen.
We've got a little bit of time left and I'd really like to like talk to talk about mortality and end of life, but also about.
How life is still worth living. [redacted] and [redacted] and [redacted] I'm not going to use the word inspiration because you're you've stayed alive. That's that's fantastic. I don't like the word inspiration. I find it.
Patronising. Maybe you don't. I don't know. Anyway, I think what would be it would be really useful to hear your your thoughts on on mortality, the life you live now and.
How How you feel?

[redacted] 2:14:36
Yes.

[redacted] 2:14:37
Yeah, absolutely. So first thing I'll tell you is I've over 44 years I've learned how to compartmentalize. So I can talk about this without thinking about it too much, but it's taken a long time to learn that. But.
I am. I'd always have been very scared of dying because it's something I've lived with ever since I've really been aware of Duchenne. Really, I think my thinking back, I could even

think like when I was 11.
I was aware that my life expectancy was shorter. I think by my goal when I was 11 was that I would live to 21, to go to, yeah, now I'm 44 because I because I feel like I've achieved a lot and I've got a lot of stuff.
Because I'm really, really happy to appeal them out for when because a lot of friends have not had the same chance because they've died from from Douchette. But you have like even right now even in the.
Dates and stages when I've started to struggle with a lot more things. I've still, you know, I'm still working for a charity that supports other people with muscle conditions connected part time. I work around where I can.
Can manage, but it's really important and it does like make a big difference to the lives, not just to me, but to everybody that that we support as a charity. I said that charity up to other people with Douchette who are no longer with us certainly, but.
As well as my work, you know, I'm also it speaks person for disability enthusiast work as a like play expert. I don't know what is my word, but call it NIHR committee representing.
Patience. I hope for a continue of 12 BA's who will either have high. If I died, they'd be all out of the job. Get through my work. I'm coming forward to research, complaining to try to improve social care for the support group for people.
People who employ BA's like all of these things give my life value. I may be, you know, when you look at a piece of paper, my health quality of life is quite poor, but actually I've got so many things going on that like he would.
Through my free time, I got relationships. You know, I was. I was previously married. I have just got friendships. I love gaming. I can still game with the right technology. I love going out for walks. Good nature. I'm still doing two things.
But this year was the first time I managed to go swimming in an outdoor pool. It gosh, it took five people to let me do that. But I'm still doing new things, so.
But my life is is great, I would say, because I want to have as much of it as I can. I'm a humanist, so I believe we've only got one life and that we we get value by, you know, contributing to.
To society and helping people. Yeah, I'd be really, really anxious recently because of my my cardiac deterioration. But I'm wondering, you know, how many years have I got left? What can I squeeze in to the to the time I've got left? I still want to.
Write a book. I want to do a sequel to the documentary film. I want to see our campaigning efforts through. So, you know, I hope I've got as much time as I can and honestly, it's not, you know, any any bit of extra time, even at this stage.
Would be amazing, but if I'd have had the extra time when I still had had to malfunction and didn't need a ventilator while I would have really made waste of that.

[redacted] 2:18:56
You [redacted] and the the world is a better place for you in it and your contributions and you know as a friend and also it's just everything you do your your your life is worth living, which I know was the title of your.
Documentary that you made. So thank you for being so, so honest about it and very moving.

[redacted] 2:19:19
Thank you.

[redacted] 2:19:23
And.
[redacted] do you feel able to say anything?

[redacted] 2:19:27
Yeah, like [redacted] I really do have a fear of dying. Uh, I was younger. I used to go to sleep at night, just wondering if I'm wake up the next day. It was a constant sort of fear, but again, I sort of push it back in my head now and just get on with life and do.
You as much as I can to be nice to make sure I know to be charities and a trustee of a charity.
There's a lot I can still do and enjoy, and there's a lot I can do to make a difference for other people.

[redacted] 2:20:56
Yeah, it's a horrible subject, isn't it? [redacted] doesn't open up to me about how he feels about dying. I think he's just trying to protect me as his mum. So he'll talk to, he's got one carer who he'll talk to or he talks to his support worker.
At the Hospice he will he does say when his when his guts been really bad recently he will say to me I'm I'm I'm going to die of this aren't I mum I'm going to die. No one's helping me. I'm going to die and we just have to have a conversation with him where we try and get through that conversation and.
Without getting upset and and negative because I mean how how on earth do you have have them conversations with your 21 year old son. But also from my perspective it's it's so hard because we we obviously are our circle of friends is.
Families, duchenne families and we see we're losing young boys and and and boys and girls constantly and your heart absolutely goes out to them. But then you can't help but having a selfish feeling because.
I feel like every time we lose someone, we're moving up that ladder and then you feel guilty for for putting it about you because it's not at all about me, it's about that other person. So it's just this mixed mix of emotions, which is.
You just don't want to be in, obviously, and it just it you find you're constantly talking about it like [redacted] been in the middle of writing his advanced care plan.
With with his Hospice. So that's been incredibly difficult. Although we, you know, we've had fun while we've been writing it, we're trying to make it a positive thing, but you have to make some really difficult decisions with with your son, you know it.
It's not the conversations you don't want to have, you want to be having with him. But then you also start to think about, for example, like I go to work because [redacted] wanted care and says I could be his mum again, he said. I want you to just be my mum again. I want you to go back to work and I'll have.

I have carers, so I do that, but then we lose carers. So I really need to be at home physically looking after him. But then you start thinking, well, if I keep my job up and I haven't got [redacted] anymore, I haven't got an income because because I get paid from [redacted] Personal health budget.
But if I haven't got him and that incumbent, so you've got it's there's so many practical things to think about as well that people are people are talking to me about practical things and keeping the house and paying the bills and and it's not something that you want to be thinking about when you just want your son to live forever.
You know, you don't want to be thinking about the emotional side of it when people are throwing practical things in, but they all need to be thought about. Everything needs to be thought about. And you know, he's, he's now on palliative care. We thought he wouldn't live to see the end of this year, but we're already in September, so we're doing.
Doing well, all he wanted to do was go to university. It's all he wanted to do. So he started a college course and then the university told him that he wouldn't get in on one a level. So we started another college course taking him four years to get to this point of doing just.
Two little A levels. He's still got a year left because he kept getting ill. And then we found out that universities might take on exceptional circumstances. So every single professional that is involved with [redacted] has sent a letter to the university saying, you know, he just wants to go to university like his peers. You know, he's probably not going to last.
You know, the first year, can we let him come and live out his dream because it's on his bucket list and he was turned away. They said no, you can't get in on 2A levels, you need all the qualification. So it's things like that. That's just heartbreaking. You know, we're ticking things off his bucket list and he just wants to live normal.
Like everybody else. So yeah, if there's lots of emotions that come into it, practical and my emotions is brother's emotions, you know, as well as trying to keep [redacted] on the steady path that he wants to be on. So yeah, it's not an easy and easy.
Right. Unfortunately, it's not one that we can just get off.

[redacted] 2:25:39
Thank you. I'm so sorry to hear about the university. That just seems utterly ridiculous. [redacted] got in. He did. He didn't do a levels. He did a.

[redacted] 2:25:48
I know.

[redacted] 2:25:55
Something Level 3 or something which was the equivalent of a levels and that was enough. And and and I, yeah, totally everything you're saying. I I hear when I a friend of mine who had stopped working to look after her son, he died and then all of her benefits disappeared the day after.
So you you can't. Not only can you not, you can't. You've got no time to grieve, nothing. And if you have given up work, then you're off the pension and you're not contributing to a

pension. It's not like you're going to snap back into it at the point of bereavement, and it's ridiculous to assume.

[redacted] 2:26:20
Yeah.

[redacted] 2:26:39
He would.
[redacted] have you got anything to add?

[redacted] 2:26:45
Yeah, no, no, I'm OK. The thing about your income and and your job as a parent with a child with Duchenne, most parents know that one of them is probably going to have to either revert to part-time work or.

[redacted] 2:26:46
You don't have to if you don't want to.

[redacted] 2:27:03
Stop work for some time until their child goes to school at the age of five. Obviously when you're a Duchenne parent, that doesn't change at five. That goes on and on and and never ends. I.
I have to give up full time work and I work part time. I have to work a flexible job so that I can drop everything should a carer not turn up for XXXX. [redacted] lives independently. He's been away from.
Day one that that Duchenne would affect his life, life expectancy. He's quite um.
He's quite determined to outlive the odds, and he doesn't like to focus on it too much.
But As for sort of quality of life, as I said, he's he's one of five siblings. He's the happiest out of all of them. And I can say that hand on heart. And I will ask him if you could be anybody else in this world.
Who would you be? And he's like me. But yeah, I'm living. I'm living my best life. I'm doing exactly what I want. I've got a great team of carers. I can go out when I want. If I really want to do something, we will find a way of me being able to do it. Even if it's a different way, we will do it.
Your priorities change, so you don't put off the things that are we'll save up for that cruise or we'll save up for these things that we want to do. You do them now because you know I might not have next year, I might not have next week, you know, so his quality of life is so.

I can't even compare it to his siblings and I know that my daughters went through quite serious sort of problems when when they went through periods and endometriosis, childbirth and when my one daughter was suffering.
With endometriosis severe periods.
[redacted] said. I'm so glad I'm not a girl. He was about 15 at the time. He was off his feet. He wasn't able to keep up with his peers. He was having to make difficult decisions about college because his local college couldn't take him.
So he was having to move away from home, you know, and having to to go through all those different choices and and concerns. And and yet he said, I'm so glad I'm not a girl, I said. But the reality **is** [redacted]
If you've been a girl, you probably wouldn't have to share.
And he sat and thought about it. And then he said, no, I'd still rather be me than be a girl.
And he's turned what everybody thought about how terrible this condition is and how what an awful.
Limitations on his life. He doesn't see it that way. He sees that he's living his best life. He's living independently. He runs his own home. He runs his own budget. He he employs who he wants. He interviews them. He spends time with who he wants.
He's got a volunteer job that he does two days a week, but if he doesn't feel well enough, doesn't have to go. He's got a girlfriend. She comes over and stays when he wants her to. He goes over to see her when he wants her to.
He's living without all these constraints that that so many of us live with, worrying about upsetting other people. He's got none of that. He'd do exactly what he wants, when he wants. And he's the happiest person. He's an uncle, he's a brother. He, you know, there's so much to him and he wouldn't be.
Wouldn't choose to be anybody else, despite everything that Duchenne has bought. So this this concept that somebody with Duchenne who's got no use of their arms, who is facing this?
Devastating prognosis this this idea that that somehow that is is a poor quality of life. Mentally for him it isn't and actually out of my five kids.
He's probably the one that I'm normally worried least about because he's happy and he's content and he's doing what he wants and if he needs help, he asks for it. The others I worry far more about and actually I'd say mentally and emotionally the Duchenne seem to affect his.
Siblings far more than him and obviously his parents. So this quality of life as far as [redacted] is concerned, 9 out of 10 most of the time.

[redacted] 2:31:54
That is so thank you [redacted] because that's that's what I see with my son as well. It's we don't think about things like that. It's just that I want to do something and we're going to damn well find a way to do it, but it's.

[redacted] 2:31:56
So.
Mhm.

[redacted] 2:32:10
It's always, it's always a challenge. But thank you all because that's a very tricky subject and I know it's, you know, comes comes to all of us. But as you say, [redacted] I mean, I personally I compartmentalise it. I don't, I don't think about it because if you did you that way, madness lies.

[redacted] 2:32:13
Mhm.

[redacted] 2:32:29
[redacted] do you have anything to to add on on this?

[redacted] 2:32:35
I do, yes. I I don't think you can predict end of life in Duchenne at all. It's not like other conditions that are progressive. You cannot tell when somebody is going to die. I've been wrong. I've been doing this for a long time.
And uh, I've been caught out so many times in the past.
So that's the first thing to say. So the idea that you could say to someone, well, this is the end, I think actually it's very hard to do that because, you know, I'm sure a lot of you have been in this situation where people have had these conversations. Oh, hey, you got better, you know?
And and you know our patient, every patient I think bar one that I've ever spoken to in all my years as a consultant says I want to live. So the Duchenne men are not like.
People with ALS or motor neuron disease, and I think many clinicians make that mistake because somebody who's got motor neuron disease is in their 50s and 60s, they've lived their life and they can. They make those choices. But with Duchenne, you've grown with it. It's it's been it is you, it's part of you.
And you're a young person and you want to live. And I have, you know, I I would do everything if my my patients want to live. I do everything to help them to live and.
You know, we have, we're honorary aunties. We've got, you know, our patients who've had children who attend our clinic. I love looking at their photos. They show us every, you know, this says it's grown up.
People, you know, who've got PhDs, go to, done degrees, PhDs, run their own businesses, live their own lives and you know it.
And we should give them every chance we can. That's how I feel about it.

[redacted] 2:34:47
Well, thank you everyone. I know we've gone over a bit, but that was really, really powerful.

Meeting ends

[redacted]
I just said about "losing dignity" earlier, I meant losing the ability to take myself to the toilet and to wash my private parts and having to ask someone else to do that for you, which I lost when I lost hand function. I had some genital infections when I first lost function because I was too shy to ask people to do it properly

[redacted]
Just for reference as it's too complicated to read out - Cardiac function in 2023
Summary-
• Procedure Details: Limited visualisation and assessment. No apical windows. Occasional ectopic beats noted during
the scan.
• Left Ventricle: Severely dilated. Severely reduced systolic function. The estimated ejection fraction is <20%.
• Left Atrium: Not well visualised.
• Right Atrium: Visually appears normal size.
• Right Ventricle: Appears normal size with preserved systolic function.
• Tricuspid Valve: Trivial TR. Unable to estimate PASP.
• Pericardium: There is a trivial pericardial effusion. The location is anterior to the right ventricle and adjacent to the
diaphragmatic surface of the right ventricle (0.4-0.5cm). There is no haemodynamic compromise.

and I'm happy to share that information with anyone

[redacted]
my EF was 50-55% up until 2 years ago, has now declined to 45%. Not awful yet but the decline has started

[redacted]
I am also always worried if I have a palpitation and have been told by my palliative consultant I cannot have CPR etc. as my heart has moved behind my ribs so there is no access

Can I also mention that doctors have been pushing me to have a trachy since my 20's and are still pushing for it even though I don't need it. I see some benefits but I'm too scared of surgery and also infection etc. and don't want extra care

[redacted]
It makes me so angry how clinicians don't understand how good quality of life on a trachy can be

[redacted]
I have luckily never needed a full face mask, I am sure I would panic too

[redacted]
I have had to learn how to manage bowel and bladder problems myself. I struggled a lot as a young adult before I figured it out

[redacted]
I have had no gut support really either

[redacted]
I just want to say I am friends with 3 people with DMD with children and I knew someone in the US with DMD who lived to be a grandparent. Their children definitely think their lives are worth living

[redacted]
I also have many doctors and consultants who are negative and say I won't live for another year, that's been going on for many years. I am now 50 and know most doctors have no idea

[redacted]
Also an adult with DMD in the NL is 60 (oldest I know) and just got back from a holiday that looked great!

Single Technology Appraisal

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

Call for additional evidence response

Muscular Dystrophy UK and Action Duchenne

This is a joint response by Muscular Dystrophy UK and Action Duchenne to the call for additional evidence for the NICE technology of givinostat for treating Duchenne muscular dystrophy (DMD) in people 6 years and over.

As patient organisations advocating for people with DMD, we welcome the opportunity to respond to NICE's targeted call for additional evidence for givinostat (TA11373). While we are not submitting new economic modelling, we wish to support the committee in its decision-making by highlighting key considerations around assumptions and methods used in the health technology evaluation.

Our role is not to build models, but to help inform them. By sharing lived experience, structured insight, and condition-specific expertise, we can help guide which assumptions are most appropriate and meaningful. This is critical because assumptions are not neutral – they shape the results of the evaluation. When they fail to capture the real-world impact of slowing disease progression, models underestimate both the true impact of DMD and the value of treatments. This can lead to decisions that do not reflect clinical reality and create barriers to access for therapies that deliver meaningful benefits to patients and families.

Before responding to the specific points raised in the "call for evidence" document, we want to address a broader and critical issue: how NICE approaches evidence and uncertainty in the context of rare diseases like DMD.

Evidence limitations in rare diseases like DMD

The committee recognises the importance of slowing disease progression in DMD and its impact on independence, wellbeing, and inclusion. Yet it continues to seek more quantitative evidence for health-related quality of life (HRQoL), exposing a deeper issue: a gap between what patients report and what models can show.

In rare diseases, this gap is unavoidable. Small patient populations, ethical constraints, and limited funding make perfect data impossible. Most studies have design or scope limitations, so uncertainty is inevitable. The focus should not be on eliminating uncertainty, but on managing it transparently, using clinical expertise and lived experience to guide assumptions.

Assumptions matter. If they fail to reflect real-world impact, models undervalue treatments and risk denying access to therapies that deliver meaningful benefits. Where direct evidence is lacking, qualitative data and expert opinion should play a central role. Yet these insights are often excluded from economic models and have little impact on the incremental cost-effectiveness ratio (ICER). This means assumptions default to narrow interpretations of limited data, producing models that ignore the emotional, social, and practical realities of living with a rare disease such as DMD. The result is a systematic undervaluation of treatments that slow progression.

Qualitative evidence is not anecdotal – it is essential. It should inform assumptions, shape utility values, and guide interpretation of outcomes. How NICE handles uncertainty and assumptions has direct implications for the specific modelling issues raised in the call for evidence. Below, we outline how these challenges affect assumptions around treatment effect, carer quality of life, and patient utilities for givinostat.

1.0. Treatment effect beyond loss of ambulation

1.1. Delaying LOA is likely to delay other health states

In the current economic modelling, no treatment effect is applied after loss of ambulation (LOA), as there is no direct evidence to support this yet. While this is a cautious and reasonable approach, it is equally reasonable and clinically supported to expect that delaying LOA would alter the overall disease trajectory.

Natural history data and clinical expert opinion consistently identify LOA as a key predictor of subsequent milestones. Earlier LOA is associated with faster decline in pulmonary and upper limb function, earlier onset of ventilation, and increased risk of complications[1]. There is also evidence that improved standards of care, including corticosteroid treatment, are associated with delayed LOA and mortality[2-4].

Importantly, clinical experts in the first committee meeting stated that it is implausible to assume that the treatment only has an impact whilst ambulant and additional data currently being collected should clarify this. They also mentioned that treatment would likely not just shift all milestones to the right, i.e. to a later timepoint, but potentially have an exponential effect. Their insights reflect the real-world experience of managing DMD, where slowing progression in one domain often delays deterioration in others. This reflects the lasting impact of earlier intervention, rather than ongoing pharmacological action.

We therefore welcome further modelling to explore how best to incorporate the potential impact of givinostat in a way that is both clinically and methodologically robust. To do this effectively, it is essential that the committee fully considers the views

of clinical experts – not only as commentary, but as a key source of evidence to guide assumptions where direct data is lacking.

We suggest the committee allows the indirect impact of delaying LOA to be reflected in later health states within their preferred assumptions. We hope the additional scenario and modelling approaches asked for through this "call for evidence" will help support the committee to include this, so that the model captures the full value of slowing disease progression, reflecting clinical reality and the lived experience of people with DMD.

We recommend that NICE:

- Recognise that delaying LOA is likely to delay other health states and reflect this in the model structure and assumptions.

1.2. There may be ongoing benefits after LOA

While there is no direct clinical evidence at present to suggest that givinostat will provide a treatment effect after LOA, it is biologically plausible that earlier treatment may have residual effects on muscle pathology beyond this point. Givinostat's mechanism of action is systemic and not limited to muscles used for walking.

This was raised several times in the committee meeting by clinical experts, and we believe this expert opinion should be taken seriously. We appreciate that this is an assumption, and that uncertainty remains. However, DMD is a rare, life-limiting and progressive condition. While cost-effectiveness decisions should be evidence-based, there must also be a degree of pragmatism while data continues to emerge.

We recommend that NICE:

- Consider the biological plausibility of residual effects beyond LOA, even if not directly modelled as a treatment effect.
- Use expert opinion/elicitation to inform these assumptions where direct evidence is limited, ensuring the model reflects real-world experience.

2.0. Carer health-related quality of life modelling and assumptions

2.1. The Impact of Slower Progression and Life Extension

Current modelling approaches assume that extending time in a health state associated with high carer burden simply prolongs that burden. While models account for the duration spent in each health state, they often assume that the burden within that state remains constant. This binary view fails to reflect the lived experience of progressive conditions like DMD.

Treatments such as givinostat do not stop the disease, but they do slow its progression – and that matters. Slower progression can meaningfully alter the experience within a health state, even if the classification of that state remains unchanged. For carers, this can mean:

- A less intense or physically demanding caregiving role for longer
- More time to emotionally adjust to changes
- A greater sense of stability and predictability in daily life

One parent shared: *"Givinostat has given us hope for the future, allowing us to spend more time and feel a bit more confident when planning our future."*

These are not marginal gains. They represent a real difference in lived experience, yet they are not captured when models rely on static utility values.

This issue is described as the "caregiver QALY trap" (Landfeldt & Sandhu, 2024), where models that include caregiver burden may inadvertently penalise treatments that extend life in high-burden states. The committee acknowledged this nuance in discussion, but the call for evidence document still states:

"Extending time in health states associated with a negative impact on carers would extend that negative impact."

This framing overlooks the reality that the *rate* of decline affects the *quality* of time spent in each health state. A carer supporting a child whose condition is deteriorating slowly will have a very different experience – emotionally, practically, and psychologically – from one facing rapid decline.

In rare, life-limiting conditions like DMD, where cures still remain out of reach, slowing progression is one of the most meaningful outcomes we can achieve. The unmet need is not only clinical, but emotional and social. A slower decline can delay the need for intensive care, reduce psychological distress, and give families more time together – with greater control and dignity. Ignoring that slowing disease progression fundamentally changes the caregiving experience undervalues the treatment and the impact for the family.

When asked about what slowing progression would mean to them, a parent shared: *"It would mean everything to us. For my son to be able to continue to walk and not need to be hoisted just to move about. To try and live as independently as possible for as long as he can, would make everyone very happy."*

We recommend that NICE:

- Recognise that static carer utility values underestimate the impact of slower progression and incorporate the variation in health states in the model structure and assumptions.
- Use expert clinical and carer insight to capture this variation in health states and provide a more realistic basis for modelling.

2.2. Utility Sources

We recognise that the committee is seeking clarity on the utility values used in the model – including the choice between Landfeldt et al. (2016a) and Landfeldt et al. (2017), and how carer utilities are applied across health states. However, there are very few published sources of carer utility data in DMD, and those that exist are limited in scope, consistency, and granularity.

This is especially true for later health states, such as health state 7 and 8. This transition – from night-time ventilation to full-time ventilation – marks a significant escalation in carer burden and impact on their quality of life.

In health state 7, individuals typically require ventilation support during sleep but may retain some independence during the day. They can often be left alone for short periods, allowing carers time to rest, work, or manage other responsibilities. In contrast, health state 8 involves full-time ventilation and the need for constant supervision. The person cannot be left alone, not even briefly, due to the risk of equipment failure, respiratory distress, or medical emergencies.

For carers, this shift means:

- No time alone, as leaving the person unattended is unsafe.
- No flexibility, as every outing, appointment, or moment of rest must be planned around intensive care needs.
- No margin for error, as the consequences of being absent could be catastrophic.

This level of responsibility is emotionally and physically exhausting. It can lead to isolation, burnout, and a loss of identity outside the caregiving role. Yet these realities are not reflected in utility values, which often fail to account for supervision needs, psychological strain, and the intensity of care required. This gap in sensitivity is particularly problematic when assessing treatments that slow progression, as the lived experience within a health state can vary dramatically over time.

We recommend that NICE:

- Ensure meaningful differentiation between health states 7 and 8.

- Use caregiver testimony, and clinical expertise, as essential evidence to inform utility estimates, particularly where traditional data is lacking.
- Triangulate qualitative insights with expert opinion and available data to reflect the real-world impact of disease progression.

2.3. The Impact of Bereavement (State 9)

We welcome the committee's consideration that "it was unreasonable for the model to assume there would be no negative effect of losing a child on HRQoL". However, it also noted that the company's proposed decrement was "not evidence-based and may not be appropriate". This highlights a key challenge: there is very little published evidence quantifying the utility impact of bereavement, particularly in the context of rare paediatric conditions.

This lack of evidence makes it difficult to assign precise values, but it does not diminish the importance of recognising this stage in the model. In fact, the absence of data reinforces the need to draw on expert clinical and carer insight, especially from those with lived experience.

If bereavement is excluded from the model, the analysis fails to capture one of the most profound impacts of DMD – the lifelong emotional and psychological consequences for carers. This omission systematically underestimates the true impact of disease and the value of interventions that delay progression. In most cases, carers are not professional or paid caregivers – they are parents. The death of a child is not simply the end of a care episode; it is a life-altering event with enduring effects on mental health, relationships, employment, and overall wellbeing. Ignoring this stage in modelling risks producing decisions that do not reflect the real-world impact of DMD on families.

This incomprehensible impact was, bravely, highlighted by a patient expert during the committee meeting. This testimony was deeply moving and should be taken seriously. It must also be recognised that speaking about bereavement – particularly the potential loss of a child – is incredibly difficult. Many carers understandably find it too painful to articulate. When they do feel able to share, their lived experience offers vital insight that cannot be captured through numbers alone.

In the absence of robust data, these personal accounts must guide the way we model and understand this stage of the carer journey.

We recommend that NICE:

- Ensure bereavement is explicitly modelled as a distinct health state with an appropriate disutility.

- Use expert elicitation to support this, given the lack of published data and the committee's concerns about the appropriateness of the company's proposed value.

This would help ensure that the model reflects the full trajectory of the carer experience – including the profound impact of loss.

2.4. Number of Carers Across Health States

We understand the committee has asked for clarification on modelling approaches and scenarios for number of carers across health states.

We believe the model should assume two carers are affected throughout the disease course, across all health states. This reflects the reality for most families, where typically both parents act as caregivers from the earliest stages – emotionally, practically, and often financially. From the moment of diagnosis, families begin navigating complex care needs, medical appointments, emotional strain, and future uncertainty together. The impact is rarely borne by one person alone.

We believe a key issue here may be a conflation between carer burden and carer health-related quality of life (HRQoL). According to the NICE reference case (NICE manual, section 4.2), carer HRQoL – not burden – is the relevant outcome. Carer burden refers to the time, effort, and practical responsibilities of caregiving, and is only included in the model if it directly affects health outcomes. HRQoL, on the other hand, encompasses emotional wellbeing, mental health, relationships, and social functioning, and is impacted from the outset, not just when caregiving intensifies. These impacts can manifest as, but are not limited to, anxiety, depression, sleep disturbance, chronic stress, and social isolation.

The suggestion that two caregivers are only affected in the non-ambulant stages appears to reflect an assumption that carer impact is driven solely by increasing care demands. While it's true that time demands and physical strain may grow as the condition progresses – affecting things like sleep, pain, and fatigue – this overlooks the significant emotional and psychological toll that begins at diagnosis and continues throughout the disease course.

Both parents are typically affected from the earliest stages. They face uncertainty, grief, and anxiety about the future, alongside the practical demands of care. These HRQoL impacts are not limited to high-burden stages and should not be modelled as such. Reducing the number of carers in earlier health states risks underestimating the true emotional and psychological impact on families.

In progressive, life-limiting conditions like DMD, the caregiving journey is shared. To reflect this reality, the model must consistently account for the presence and impact of both carers, from diagnosis through to bereavement.

We recommend that NICE:

- Assume two carers are affected across all health states to reflect the shared nature of caregiving and bereavement in most families.
- Ensure consistency in how carer numbers are applied, to avoid underestimating impact in later stages of disease.
- Ensure modelling decisions align with the NICE reference case focus on carer HRQoL, not caregiving effort.

3.0. Patient health-related quality-of-life modelling and assumptions

We welcome the committee's request to better capture the increasing impact on patients as the condition progresses, particularly between health states 7 (night-time ventilation) and 8 (full-time ventilation). We also want to reiterate the lack of data in this area and draw attention to the patient testimony submitted during Technical Engagement, and the committee meeting, which clearly highlighted meaningful differences between these two health states.

This testimony, reproduced below, provides essential insight into the lived experience of progressing from night-time to full-time ventilation. It describes profound changes in independence, privacy, anxiety, care needs, and cost – none of which are adequately captured if these health states are treated as equivalent in utility terms.

"I have experienced both the full ventilation state and night ventilation state, as an individual living with Duchenne muscular dystrophy and having progressed through the stages. In the night ventilation stage, no one apart from my family and carers knew that I used ventilation. Now in the full ventilation stage, I have a mask over my face at all times. I simply cannot overstate how inaccurate the claim is that these two states are the same.

There are significant differences in both cost and quality of life between these two states. Quite simply for cost, eligibility criteria for NHS continuing healthcare is to score severely in two domains. People with DMD at this stage will usually score severely in the mobility domain by default. On the breathing domain the score is more variable, and it is only in the full ventilation state that eligibility is guaranteed. This makes the cost of providing care a cost to the NHS, significantly greater than social care.

In the full ventilation state, any time off the ventilator endangers life. On night ventilation, during the day I didn't require round-the-clock care, and could be left on my own for several hours during the day. Overnight, I didn't require waking night care, and a carer sleeping nearby was sufficient in the event of any difficulties. This meant

significantly lower costs for care staff and varied as my condition progressed - from approximately £40k-£100k per year.

Currently I am in the full ventilation state and require round-the-clock care from two personal assistants. This includes waking nights. It is critical that there is always a carer with me as a ventilator malfunction or disconnection could otherwise mean death. The overall cost of my care package is around £250-300k per year.

In terms of quality-of-life, my anxiety has increased dramatically moving in to the full ventilation state. I live with the constant fear that if the ventilator malfunctions my carer cannot fix the issue or does not realise. I know that people with my condition have died where this has happened and they have not had adequate support. I am no longer able to enjoy any privacy as any time alone is life-threatening. As I manage my own social care support and don't have family nearby, I have to spend hours every day managing my care package to ensure there is cover in emergencies. This interrupts every enjoyable part of my life - for example at a family birthday recently I had to step away from the celebrations in order to fix my care package so that I wouldn't be on my own within the next few hours. The ability to have intimacy is significantly impaired as the ventilator gets in the way of intimate activities as the mask is a permanent feature on my face. Every time I leave the house I am stared at by passers-by, who think I am either infectious or belong in a hospital ward. With a mask on my face at all times it is difficult to shower, get a haircut, clean my teeth, eat, be dressed and undressed or use a hydrotherapy pool. It has significantly impacted on my speech and ability to swallow while eating with a ventilator.

I would give absolutely anything to move back to the night ventilation state or have preserved it for a little longer."

This account demonstrates that the transition to full-time ventilation is not a marginal change, it is a significant shift in quality of life and care burden. If utility values do not reflect this, the model risks underestimating the true burden of disease and the value of delaying progression.

We urge the committee to ensure that distinct utility values are applied to health states 7 and 8. These values should be informed not only by available data, but by patient and caregiver testimony, expert elicitation, and clinical insight.

We recommend that NICE:

- Ensure meaningful differentiation between health states 7 and 8.
- Use patient and caregiver testimony as essential evidence to inform utility estimates, particularly where traditional data is lacking.
- Triangulate qualitative insights with expert opinion and available data to reflect the real-world impact of disease progression.

Conclusion

Throughout this response, we have highlighted the limitations of evidence in DMD and the need for NICE to take a more pragmatic and inclusive approach to uncertainty. In rare diseases, perfect data is rarely achievable. This is not a failure of research, but a reflection of the inherent challenges in studying small, diverse populations with complex needs.

In this context, assumptions are unavoidable. The challenge is not to eliminate uncertainty, but to manage it responsibly, guided by clinical expertise, biological plausibility, and the lived experience of patients and families. These forms of evidence are not supplementary; they are essential. They should not only inform discussions but actively shape the model – driving assumptions, influencing utility values, and guiding scenario analyses so that the ICER reflects real-world impact. When these insights are sidelined, the model risks undervaluing treatments and producing decisions that do not align with patient priorities.

For givinostat, this is critical. The assumptions adopted in the updated modelling will determine whether the evaluation reflects the true benefits of slowing disease progression or risks creating inconsistencies in how therapies for rare diseases, like DMD, are assessed. We urge NICE to adopt the following preferred assumptions when interpreting the updated modelling from the company and EAG:

- Delaying LOA is likely to delay subsequent milestones such as respiratory decline and loss of upper limb function. The model should reflect indirect effects beyond LOA.
- The biological mechanism of givinostat supports residual effects beyond LOA, even if direct evidence is limited.
- Two carers are impacted across all health states, reflecting the shared nature of caregiving in most families.
- Carer HRQoL should be modelled as dynamic within health states, recognising that slower progression reduces emotional distress and improves stability.
- A bereavement disutility should be included for health state 9, informed by expert and carer insight.
- Health states 7 and 8 should be differentiated in terms of carer impact, with full-time ventilation requiring constant supervision and significantly greater emotional and physical burden.
- Health states 7 and 8 should also be modelled with distinct utility values for patient HRQoL, reflecting the profound differences in independence, anxiety, and care needs.

Without these assumptions, the model is unlikely to capture the full impact of givinostat and DMD, which could affect access for families who stand to benefit most. While our response focuses on givinostat, it highlights a broader need for NICE to strengthen how it handles uncertainty across all rare disease evaluations. Doing so will help ensure that decisions consistently reflect what matters most to patients and that treatments are not undervalued.

References

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Single Technology Appraisal

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

Call for additional evidence response

British Paediatric Neurology Association (Muscle Interest Group)

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323] Call for additional evidence - submission 12th September 2025.

Following the appraisal meeting on Thursday 10th July 2025, the committee explored the nature of the condition and the evidence for givinostat, but was unable to reach a full conclusion because more information is needed; more specifically;

1. the estimation of givinostat treatment effect and its application in the model

2. the carer health-related quality-of-life modelling and assumptions

3. the patient health-related quality-of-life modelling and assumptions

4. the resource cost modelling and assumptions.

DMD and the Impact of the Condition

As a clinician treating DMD and looking after the children and young people from the time of diagnosis to when they die, I have had over 20 years experience of these CYP and their families. DMD is a severe, progressive, and life-limiting condition that has a substantial impact on the physical health, emotional wellbeing and quality of life not only of the affected person but also of their families and carers is well received.

The estimation of givinostat treatment effect and its application in the model

Whilst it is difficult to be able to present new evidence from a clinical perspective as there is no further trial data or long term data to present, data from my clinical cohort (n=59) of children and young people (CYP) with DMD has been reviewed and presented.

The OLE study is ongoing and there are two ongoing clinical trials with givinostat in DMD (in younger < 6 years old children as well as older, non ambulant patients). These studies will provide further evidences on givinostat across different populations.

The loss of ambulation in this cohort is significantly later compared to what is seen in clinical practice and this is evident in the trial data. It is well known and observed that these CYP who are ambulant for longer have a better outcome, start ventilation later and maintain arm function and hence independence for longer as well as often become

independent and work/study compared to those who lose ambulation in their early teens around transition and struggle both physically and psychologically.

As with data that that we have seen from the impact of steroids and now accepted as standards of care . This has been shown in the curves derived from the natural history datasets (CINRG, McDonald et al and Northstar Trucco et al) this has resulted in a delayed requirement for commencement of night time ventilation by at least 5 years and hence 24 hour ventilation, this is a shift from 15 years ago when paediatric patients were ventilated, there has also been a delay in LOA on average by 3 years, and hence improvement in the need for scoliosis surgery and reduction from 90% to 10% (Cochrane review data). It can therefore be inferred that another medication which also delays these milestones will not only see a shift in these milestone but an exponential improvement and delay. Givinostat is already starting to demonstrate this in the trials and therefore would be reasonable that clinically this would be an effect that would be seen.

The carer health-related quality-of-life modelling and assumptions

There is limited data on carers and the impact of DMD on parents and families, however the care and support that a person with DMD requires for physical care increases with the progression of the disease and moving across the health care states, carer health related quality of life is affected by much more than the physical burden of care.

There have been studies that have shown a high incidence of psychological problems, such as anxiety and low mood, poor sleep and stress in the cares in over 50%, and many of our parents have experienced this.

In our cohort of CYP 44% of consultations were for families and parents/siblings requiring input. 54% of families that accessed psychological input were for CYP (<18 years) with DMD. Most of these were around the time of transition and loss of ambulation and how to support their CYP around this time as well as for themselves as they experienced anxiety and stress, worry, fatigue and unable to cope.

The patient health-related quality-of-life modelling and assumptions

Again there is limited data on this area, as many teams do still not have psychology support in clinic and limited input from community services, however the lack of an effective tool to capture QoL in DMD was the driver for Project Hercules to develop the DMD QoL.

As a paediatric neurologist with a specialist interest in neuromuscular disorders, I have children who are both trial participants as well as EAP patients receiving Givinostat and those that are not yet accessing this. I also have the advantage of looking after both paediatric and adult patients. As part of our MDT we have a clinical psychologist who is integral to the team and part of the MDT and in clinic wen these boys/young men and

families attend. This gives us data on how the patients and families access this service and the needs of these young people and their families.

We have therefore reviewed our data with regards to access to our psychologist and the input required as an example as to how Duchenne muscular dystrophy impacts on families as well as children and young people;

This was taken from a cohort of 59 CYP with DMD. In general 46% of the DMD population accessed specific sessions with our Psychologist (entailed up to 6 weeks of sessions, more or less depending on need, at home, school or clinic, wherever the young person preferred). The psychologist was also involved in schools and input regarding the CYP with DMD in 32% of the cases and 44% of consultations were for families and parents/siblings requiring input.

For those that were seen; 52% were >18 years old; 47% were >10yrs and <18 years old, and only 1% were under 10 years.

54% of families that accessed psychological input were for children and YP (<18 years) with DMD.

37% were not seen specifically for additional sessions but were seen by the psychologist whilst they were in clinic.

8% have been offered sessions and not yet seen; 80% (n=4) of these cases were aged between 5-8 years and 2 of these are on new drug treatments and 1 in a clinical trial. The other has significant learning difficulties.

The other case is an adult aged 33 years and has significant input via the team and the joint palliative care team addressing his main issue, pain and managing his pain control, so that he can continue to live his life as well as he can. This has been particularly challenging as has had cardiovascular consequences due to severe cardiac function impairment.

For some of these families psychological help and more support is needed around the time of diagnosis, however for most of our young people input was generally needed as the condition was deteriorating and they were reaching milestones, often around loss of ambulation/teenage years/transition to secondary school.

These young people have significant issues around adolescence and the transition to secondary school, a time when most of their peers are becoming independent and spending more time away from their parents. These YP find that their world rather than opening up starts to become smaller and they are subject to bullying, have low self esteem due to their body habitus as well as using a wheelchair, and start to need further medication and hospital visits to address pubertal delay, bone health, cardiac medications starting and pain. The loss of ambulation is huge milestone for these YP and their families as this really does mark a tangible deterioration and realisation of this horrendous disease and it's inevitable progression to early death.

The young people also start to recognise and realise the future of their condition, what their life is going to look like compared to their peers and the grief of what they will never have.

For patients that are later in losing ambulation 16-18 years, they are usually able to cope with this transition, they have their circle of friends already, have mostly finished high school and often have learnt to drive. Two of my patients who have been fortunate to reach this milestone are both independent, working in paid employment, can drive and have a good social life. Whilst they have deteriorated subsequently, psychologically they are more mature and feel more able to cope with this loss of function.

Unfortunately, this is not the usual case, as most will lose ambulation during early teens and therefore their trajectory is not as good. As put by one of my patients; he grieves for the love he will never feel, the relationships he will never have, the father he will never become. He describes that the only touch he has is from carers, who mean well but they are doing a job and will go home at the end of the day. And this is a reality for these YP, but also for their families, who every milestone that is not met or is lost, is yet another reminder of what is to come in this inevitable disease.

We also have had 4 recent deaths in the last 3 years; (ages 22-39)

3 out of the 4 were seen by the psychologist in clinic and requested input and sessions with the psychologist; In 2 of the 3 cases; the psychologist did work with the parents and family separately.

The one patient that did not have psychology input had numerous offers to be seen by psychology but refused although had a lot of input from the team and one of our male specialist nurses who he had known from a young child at the children's hospice. He struggled always accepting his condition and whilst he attended clinic, he did not want to see other YP with DMD, he distanced himself from others and refused interventions that were visible, such as ventilation. Unfortunately he deteriorated to the point where he needed ventilation, but at that time of crisis could not tolerate it and realised that this would be *'the end'* for him. He had been involved with the adult palliative care team, as part of our service, which is a joint clinic, and therefore he had palliative care input and anticipatory medication around the time of death.

I think these figures indicate the implications and psychological stress that these families and CYP face with this relentless disease. Shifting the timelines of these milestones and enabling more time in the better health states improves not only their physical outcomes but their psychological health, as they are often more mature and able to cope with the transition to non-ambulant after high school and puberty and hence this is less stressful for families as they can also see their CYP is less impacted psychologically. Whilst we cannot yet cure this disease at least we can delay these milestones to enable these CYP to achieve goals and dreams and potentially have a better quality of life with purpose and meaning.

The resource cost modelling and assumptions

I cannot comment specifically on this area

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with Duchenne muscular dystrophy or caring for a patient with the condition. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with Duchenne muscular dystrophy

Table 1 About you, Duchenne muscular dystrophy, current treatments and equality

1. Your name	Dr Jon Hastie
2. Are you (please tick all that apply)	☒ A patient with Duchenne muscular dystrophy? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Duchenne muscular dystrophy ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Duchenne UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Duchenne muscular dystrophy? **If you are a carer (for someone with Duchenne muscular dystrophy) please share your experience of caring for them**	I was diagnosed with Duchenne muscular dystrophy when I was three years old, so living with this condition is all I have ever known. So it is quite difficult to have an objective view. I am aware that everyone, members of the public but especially medical professionals, look at me and consider I have a very poor quality-of-life. I've heard "I don't know how you do it, if I were you, I'd rather be dead", or similar such sentiments from random strangers on a regular basis. I'm a very positive, optimistic and driven person so I tend to focus on what I can do and living the best life I possibly can. So maybe I underestimate how bad things are. Throughout my life I have been excluded from the activities and opportunities of my peers. At primary school I was the boy who needed extra help. Classes had to be moved and I could only go on school trips if one of my parents came with me. I had a hideous tricycle for getting around that I was embarrassed to be seen on. At age 10 I fractured my femur in a bad fall. I was rushed into hospital and had to be transferred to a London specialist clinic for surgery. It was plated and I was back on my feet within 3 days, the most painful experience of my life. I had to leave all of my friends at age 11 to move to a school that was more accessible for me, and it's the first time I really struggled mentally – I was sad for months. At the same time, I had to start using a powered wheelchair for getting around a big school. I enjoyed school and studying but I couldn't go round friends' houses or anywhere that had stairs. I missed out on many events because I couldn't climb stairs. I was required to take fewer GCSEs because I couldn't do PE. I required regular physiotherapy and hydrotherapy to keep me ambulant, which took up much of my time. I was in an early steroid trial between the ages of 11-16. I lost ambulation at 16. It was a relief not to have the constant worry of falls and the physical strain of

	walking. Throughout my childhood years my Mum was my primary carer, involved in all of my personal care. My dad developed back problems from lifting me. At 18 I went to university. During term time, I was reliant on two carers funded by the local authority, which was a fight to get. I required help with transfers throughout the day, help with toileting, washing, dressing, making food, getting around and turning during the night. It was embarrassing and awkward to need help. During the holidays I still relied on my parents for care. I had been required to choose a university which was accessible and could support me, which ruled out some of the best institutions despite being a straight-A student. I stayed at the same university to do a Masters and PhD - because it was accessible. At 22 I started using a ventilator to breathe overnight and cardiac medication after struggling with low energy and very broken sleep. I struggled with the transition to this and what it meant for my overall health and future life expectancy, and was diagnosed with anxiety and depression. On leaving university I had very little work experience. Most casual jobs require physical work or were located in inaccessible office spaces. I struggled to find work and I started volunteering. Eventually I moved into a role in the charitable sector, which did not reflect my academic experience. I required more care by this point, requiring support with absolutely everything that involved personal care or movement, and my care package increased. I was able to move out and live independently, which is not the norm for somebody with my condition, because my family had money and could buy a flat for me which we could make it accessible. At this point I needed 24/7 care from personal assistants who are employed by me. Employing carers gives you choice and control, but comes with a lot of work and emotional baggage, constantly worrying whether you will find somebody willing to look after you or whether you will be

	abandoned. I moved location in 2018 which took a year to plan, and required careful coordination between NHS continuing healthcare teams. In 2024 my care needs increased to such an extent that I now require 2-to-1, 24 seven care at a cost of £380,000 per year to the NHS. This is actually cheaper than it could be because I take of the management and employment of my own care team. My experience of DMD has been fighting for every scrap of support, being excluded from venues, events and activities that other people take for granted, constantly worrying about whether I will have carers, feeling guilty about needing your family to help and never getting a break. And that is just dealing with society. I have also lived with the shadow of death over me, have lost countless friends with DMD, and have lost ability after ability until I can do nothing for myself. I have been one of the very few people with DMD to be able to find employment, make a documentary, set up a charity and travel. I have done this through sheer force of will because I didn't want ongoing decline, weakness, dependence and loss to be my only story. I have made my life good despite DMD and I want as much of it as I can get.
7a. What do you think of the current treatments and care available for Duchenne muscular dystrophy on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**It's focused on children, so as an adult you feel completely abandoned by the health system in regards to new treatments.** **Steroids have evidently improved outcomes but many people seem to die of somewhat related conditions e.g. adrenal shock. They often stunt growth and delay puberty, leaving patients looking infantile for the rest of their lives.** **New treatments are promising but the huge delays in bringing them to patients are extremely disheartening.**
8. If there are disadvantages for patients of current NHS treatments for Duchenne muscular dystrophy (for example, how they are given or taken, side effects of treatment, and any others) please describe these	**I took steroids only for a few years below the currently used dose, and I still experienced delayed puberty, bone density decline, cushingoid features and a huge appetite. I wouldn't take them again because the side-effects were not worth it.** **Non-invasive ventilation is horrible, delivered via masks that scar your face with pressure sores, make it harder to eat and talk, cause painful stomach**

	bloating and the worst part is, in the later stages you are completely dependent on it. **Cardiac treatments are generally fairly easy to tolerate, although as cardiac function declines, the more intensive medications are harder to tolerate, e.g. causing excessive urination and rashes.**
9a. If there are advantages of Duchenne muscular dystrophy over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Duchenne muscular dystrophy help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I have no experience of the specific treatment
10. If there are disadvantages of Duchenne muscular dystrophy over current treatments on the NHS please describe these. For example, are there any risks with givinostat? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have no experience of the specific treatment
11. Are there any groups of patients who might benefit more from givinostat or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I don't know enough about the specific treatment, but I can say that throughout the life-cycle of Duchenne, there is always a need for treatments that can slow progression. Even now, at 44 I would love to receive a treatment that could maintain the tiny but vital amount of hand function I currently have

12. Are there any potential equality issues that should be taken into account when considering Duchenne muscular dystrophy and givinostat? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Not that I can think of
13. Are there any other issues that you would like the committee to consider?	Simply that adults of all ages have something to gain from treatments which slow progression

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- DMD shapes your personality and experiences throughout your life
- You lose ability after ability every year, it is depressing, constant and relentless
- Providing support is so expensive, especially in later years
- When DMD is all you know, you try to live the best life you can, which makes life worth living
- Everyone with DMD would tangibly benefit from delayed progression

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]

Patient expert statement

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To help you give your views, please use this questionnaire with our guide for patient submissions.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Fleur Chandler**
2. Are you (please tick all that apply):	☐ **X**☐ a carer of a patient with the condition?

	X☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Duchenne UK
4. Did your nominating organisation submit a submission?	**X**☐ yes, they did – for first appraisal ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X**☐ yes, I agree with it - YES ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	**X**☐ I have personal experience of the condition X ☐ I have personal experience of the technology being appraised **X**☐ I have other relevant personal experience. Please specify what other experience: X I am a parent of a young man who has DMD ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Duchenne muscular dystrophy is devastating, depressing, and exhausting. It is relentless in its progression. I have supported my son Dom through every stage of his life as he has lost physical capability, while managing the psychological damage this has caused to him, to me, and to our family. Dom was diagnosed with DMD at age 3 in 2009. We were told our healthy-looking child would lose the ability to walk and die in his teens. There was no treatment beyond steroids, and no emotional or practical support offered. The diagnosis shattered our world. I was thrust into a role I never asked for—carer, advocate, medical coordinator, and emotional anchor.

	In his early years, I managed hospital appointments, fought for educational support, made complex medication decisions, and tried to avoid snake oil promises of miracle cures. By age 6, Dom needed a wheelchair. Watching his peers grow and thrive while he declined was psychologically brutal—for him and for me. School inclusion was minimal. He was confined to a small area of the classroom, excluded from activities, and we were told to be on call from home to assist with toileting. Coordinating his care across education, social services, GPs, and specialist centres was a full-time job. I had to become an expert in navigating fragmented systems that were never designed for children like Dom. Our family was deeply affected. My husband had a mental breakdown and lost his job. I became the sole financial and emotional provider. Holidays and socialising were vital but inaccessible and prohibitively expensive. Dom faced daily discrimination and isolation. Steroid-related weight gain and delayed puberty required testosterone therapy. We moved to a bungalow area dominated by pensioners, and spent six years fighting for adaptations—costing over £100,000, with only £30,000 covered by the Disabled Facilities Grant. As Dom entered adolescence, the psychological toll intensified. He became anxious and depressed, aware of how different he was from his peers. He couldn't go out, play sport, ride bikes, or form relationships like other teenagers. I had to fight for mental health intervention—pushing through waiting lists, under-resourced services, and professionals unfamiliar with the emotional impact of progressive disability. Watching him grieve the life he couldn't have was unbearable. Meanwhile, his care needs escalated. I dressed, showered, fed, and hoisted him. He needed repositioning 7–8 times a night. He joined a clinical trial in Newcastle, requiring flights for a two day assessment and infusion every four weeks. The trial failed. I had to take Surrey Council to tribunal to secure specialist secondary education—costing me £30,000. Secured a specialist school in which Dom thrived and took his GCSEs early and supported him through A levels at a mainstream 6th form.

	As he lost upper body function, I did everything for him: brushing his hair, brushing his teeth, dressing, washing, facilitating, adjusting his glasses, scratching his nose, putting his headpohoes on, passing him whatever he needed. Feeding him when his arms were too difficult to move. Moving his body became like lifting a futon—heavy, awkward, no resistance. He developed cholecystitis, likely due to steroids. What should have been a routine procedure became a six-month ordeal across three hospitals, with ICU stays and sleep studies. I slept on hospital floors. The surgery cost over £20,000—ten times the standard. The stress was compounded by the death of a friend's son under anaesthetic. My daughter discovered Duchenne was fatal via a school science poster. She developed anxiety, depression, and a severe eating disorder that lasted three years. I became clinically depressed, prescribed antidepressants, and received EMDR therapy from the children's hosp. The psychological damage this disease has caused me is profound. I have lost my sense of self, my career, my relationships, and my health. I have lived in a state of chronic grief, anticipatory loss, and relentless vigilance. There is no respite. Even joy is tinged with fear—knowing that every milestone might be his last. When Dom turned 18 the transition to adult services was challenging. He wanted to attend university. I had to say to social services I could no longer care for him. This painful statement was the only way to unlock adult support. He completed his first year with a team of carers. I am finally able to be his mum again—not just his carer.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Care is fragmented and treatment includes high dose steroids. He has been on steroids for 15 years, and the side effects have been awful, but he is at least still with us. Transition to adult services has been a challenge.
10. Is there an unmet need for patients with this condition?	Yes. Anything that delays or slows progression would be needed, and impact on cardiac or respiratory systems.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	That it slows progression and keeps muscle in a useful state. Every stage we go through I wish he was in the one before as it gets harder and harder.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	That it isn't prescribed for older non ambulant boys. It works systemically across all muscle groups, not just lower limbs, so loss of ambulation should not be an endpoint. Platelets need to be carefully monitored.
Patient population	
13. Are there any groups of patients who might benefit	I think useful for all, and certainly as early as possible to prevent muscle damage. WOuld be very useful in non ambulant boys – preserving upper body function which has more impact on living than loss of walking. .

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Age** – this is for children – and NICEs processes do not allow for fair assessment of paediatric evidence – particularly in progressive paediatric diseases. **Disability** – NICE processes do not account for living with a severe disability or for those who will become wheelchair users. **Disability by association** – impact of caring for a person with a disability. Health inequalities – Disabled people suffer worse health state and have worse health outcomes. Parent carers also suffer poor health and health outcomes and these are female in the majority – so **gender** also affected.
Other issues	
15. Are there any other issues that you would like the committee to consider?	Understanding the impact of a paediatric, progressively disabling and fatal disease on the health and care system.
Key messages	
17. In up to 5 bullet points, please summarise the key messages of your statement:	

- Watching your child lose physical function and face early death while peers thrive is psychologically shattering.
- Progressive disability in DMD leads to total dependence, complex care needs, and irreversible decline.
- The mental health impact on both child and carer includes anxiety, depression, trauma, and chronic grief.
- Medical care for severely disabled children is riskier, more complex, and significantly more expensive.
- Families face extreme financial and emotional burdens due to systemic gaps in health and social care.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

EAG response to ID6323 Call for Additional Evidence

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over [ID6323]: A Single Technology Appraisal

Produced by: Bristol Technology Assessment Group, University of Bristol

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors to addendum
CLM, ET, DC, and HP summarised and critiqued the clinical effectiveness data submitted by the company as part of the Technical Engagement process. CC critiqued the literature searches and systematic literature reviews submitted in the company submission. HP and HT critiqued the statistical aspects of the submission. AS and HT critiqued the health economic analysis submitted by the company. AS, HP and HT critiqued the evidence

submitted by the company following the committee's call for additional evidence. All authors were involved in drafting and commenting on the EAG's response and addendum to the main EAG report.

[redacted]

[redacted]

Abbreviations

Abbreviation	Definition
1L	One litre
4SC	Four Stair Climb
6MWT	Six-Minute Walking Test
ACM	Appraisal Committee meeting
AE	Adverse Event
AFT	Acceleration Factor
AIC	Akaike Information Criterion
BMI	Body Mass Index
BNF	British National Formulary
BSA	Body Surface Area
BOI	Burden of Illness
CfE	Call for Evidence
CI	Confidence Interval
CINRG	Cooperative International Neuromuscular Research Group
CRD	Centre for Reviews and Dissemination
CRO	Contract Research Organisation
CS	Company Submission
DCO	Data Cut-Off
DMD	Duchenne Muscular Dystrophy
DMDSAT	DMD Functional Ability Self-Assessment Tool
DNHS	Duchenne Natural History Study (DNHS)
EAG	Evidence Assessment Group
ECG	Electrocardiogram
ECM	Established Clinical Management
ECRF	Electronic Case Report Form
EK	Egen Klassifikation
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5 dimensions (standardised instrument for use as a measure of health outcome
ESS	Effective Sample Size
FIM	Family Impact module
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HHM	Hand Held Myometry
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HST	Highly Specialised Technology
HTMF	Hand-to-mouth Function
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICER	Incremental Cost Effectiveness Ratio
ICMJE	International Committee of Medical Journal Editors

IPD	Individual Participant Data
IQR	Inter Quartile Range
ITC	Indirect Treatment Comparison
ITT	Intention To Treat
KM	Kaplan-Meier
LOA	Loss of Ambulation
LYG	Life Year Gained
MAIC	Matched-Adjusted Indirect Comparison
MFMS	Motor Function Measure Scale
MHRA	Medicines and Healthcare products Regulatory Agency
MMF	Mycophenolate Mofetil
MRS	Magnetic resonance spectroscopy
NE	Not evaluable
NHM	Natural History Model
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NI	No Information
NIV	Non-invasive Ventilation
NR	Not Reported
NSAA	North Star Ambulatory Assessment
OLE	Open-Label Extension
PedsQL	Pediatric Quality of Life Inventory
PEF	Peak Expiratory Flow
PODCI	Paediatric Outcomes Data Collection Instrument
PRO	Patient Reported Outcomes
PSM	Propensity Score Matching
PUL	Performance of Upper Limb
PSS	Personal Social Services
PY	Probably Yes
PN	Probably No
QA	Quality Assurance
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
REF	Research Excellence Framework
RoB2	Risk of Bias 2 tool
ROBINS-I	Risk of bias in non-randomized studies of interventions
ROBIS	Risk Of Bias In Systematic reviews
RWE	Real-World Evidence
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SCHARR	Sheffield Centre for Health and Related Research
SD	Standard Deviation
SE	Standard Error
SF	Short Form Health Survey
SLR	Systematic Literature Review
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TAG	Technology Assessment Group
TEAE	Treatment Emergent Adverse Event
TSD	Technical Support Document

TTO	Time Trade-Off
UITC	Unanchored Indirect Treatment Comparison
UK	United Kingdom
US	United States
VLFF	Vastus Lateralis Fat Fraction

TABLE OF CONTENTS

LIST OF ADDENDUM TABLES

1. Overview of EAG report addendum

This addendum to the Evidence Assessment Group (EAG) report presents the EAG's critique of the additional evidence provided by the company in their response to the call for

evidence (CfE), post-Appraisal Committee Meeting (ACM) 1. The EAG do not provide a direct critique to other evidence submitted to the CfE.

2. Description and critique of additional evidence

Key issue 6: Use of 1.5% discounting

In Section 5 of their submission the manufacturer give an argument on whether the criteria for applying 1.5% are equitable for equitable for chronic, paediatric, long-term progressive degenerative conditions such as DMD. The company make the valid point that DMD is rare but does not meet the criteria for highly specialized technology appraisal, so greater methodological flexibility of such appraisals do not apply. The NICE Methods Manual that therefore applies specifies that non-reference-case discounting can be applied only if the following three conditions are met:

1. The technology is for people who would otherwise die or have a very severely impaired life.
2. It is likely to restore them to full or near-full health.
3. The benefits are likely to be sustained over a very long period.

The company agree with the EAG position that givinostat does not meet these current NICE criteria for applying a 1.5% discount rate. They argue that givinostat meets condition 1 and condition 3 but that no treatment in DMD could meet criterion 2.

The EAG position is that the long-term effect of givinostat is uncertain and it thus does not meet criteria 3. The company's claim for long-term benefit is the randomised period of EPIDYS which was only 18 months and the OLE which was only 1204.2 days (i.e., about 3.3 years) while the model time horizon is lifetime for patients initially aged 6 years old.

The EAG also agree that givinostat in DMD is unlikely to retore a patient to full health (criteria 2). On whether a treatment in DMD could restore a patient to full-health, the EAG have sought input from an independent clinical advisor.

They advised that DMD leads to muscle degeneration so the muscle that is lost can't be restored by means that have been yet available. The dystrophin gene is the largest of our genome, posing difficulties to the development of gene therapy. In 2023, micro-dystrophin gene therapy was approved in the USA with better but not striking results in the younger and ambulant patients. The older age groups had more serious side-effects with some associated deaths. Further on, gene therapy is not suitable for all gene variants and there were risks for patients with deletions involving exons 8 or 9. In the UK, micro-dystrophin trials exclude patients with deletions between exons 1 to 17. The clinical concluded that we are still a long way from an efficacious gene therapy, but did not rule out development of

such a therapy in the future. They noted that there are pre-clinical studies involving induced pluripotent stem cells which will probably be the answer in the future.[1-3]

The EAG therefore do not agree with the company's position that no treatment could restore a patient to full-health in the future. Despite this, to assist the committee in decision making, the EAG have conducted a scenario analysis on the base case applying a 1.5% discount rate for health outcomes (i.e., QALYs and not costs).

Key issue 7: Over estimation of caregiver utility impact

The committee identified the carer health related quality of life, modelling and assumptions as one of the areas with the most uncertainty, requesting further information and modelling to address:

i. The sources of utility values.

ii. Approaches to calculating the utility increments / decrements to carers' quality of life and the number of caregivers.

iii. Application of the utility values in the death state.

We take these points in turn and consider the relevant submission by the company.

i. The sources of caregiver utility values used

The committee did not support the company's modelling of carer quality of life using values from the vignette study. It requested a comparison of the alternative studies, Landfeldt et al (2017) into Landfeldt et al (2016a), and justification as to their appropriateness for modelling. Furthermore, it requested the company to explore different ways of differentiating utilities between health states 7 and 8.

The company has revised their base case using interim data on caregivers' utility values from an ongoing study by the Sheffield Centre for Health and Related Research (SCHARR): "Health-related quality of life (HRQoL) impacts on Duchenne parent-carers: A qualitative survey".[4] The study is welcome as is the change in the company's base case because there is insufficient evidence to support the use of the vignette study for decision making (key issue 7 discussed in section 2.5 of the addendum to our report at technical engagement).

In this new data [redacted] parents of patients with DMD residing in the UK responded to questions from the PedsQL Family Impact module (FIM) survey. Of these respondents [redacted] completed the EQ-5D-5L questionnaire out of which [redacted] provided sufficient data to enable the mapping of responses to EQ-5D-3L resulting in a mean (SD) utility of [redacted]. The company's base case is formed of a breakdown of the utility values into ambulatory [redacted], transfer [redacted] and non-ambulatory [redacted] health states, as reported in the company's submission matching table 7 in the SCHARR interim report.

A sub-sample of [redacted] respondents was used to estimate carers of non-ambulatory patients' utility scores by health state with more granularity, giving utilities for HTMF, no ventilation (state 4, [redacted]; No HTMF, no ventilation (state 5, [redacted]; HTMF night-time ventilation (state 6, [redacted]; No HTMF night-time ventilation (state 7, [redacted]; and Full-time ventilation (state 8, [redacted]. [redacted] Noteworthy is that health states 5-8 are estimated using a very small sample and we undertake further analysis with this data by taking the weighted average of the carer utility values for health states 5-8 for [redacted] respondents. The carer utility values for the company's base case and EAG base case are reproduced in Table 1.

The EAG prefers to model the caregiver utility values on the EQ-5D-3L scale as per the NICE methods guide. At the previous stage of this appraisal, two publications by Landfeldt et al. using the UK value set were considered relevant for decision making.[5] Data for these publications pertain to caregivers to patients with DMD recruited as part of a multinational cross-sectional observational study. In both publications the caregiver HRQoL was categorised according to progression of DMD, but do not include the transfer health state as it is a unique feature of the HERCULES model.

Landfeldt et al. 2017[6] classified patients to the DMD Functional Ability Self-Assessment Tool (DMDSAT), a patient-reported outcome (PRO) scale designed to measure and categorize functional ability across the entire lifetime of disease progression in patients with DMD.[7] The DMDSAT was developed to address limitations with the North Star Ambulatory Assessment (NSAA) scale, the Vignos scale and the Brooks scale all of which are used in the HERCULES model. The utilities are categorised by ambulatory status in model 2 and by ventilatory status in model 3. The EAG undertook a scenario combining model 2 for ambulatory status & model 3 to distinguish between night-time and full-time ventilation.

Landfeldt et al. 2016[8] classified patients into four groups defined first in terms of current ambulatory status and second in terms of age: (1) early ambulatory (approx. age 5–7 years), (2) late ambulatory (approx. age 8–11 years), (3) early non-ambulatory (approx. age 12–15 years), and (4) late non-ambulatory (approx. 16 years of age, or older). The EAG observed that these analyses aligned with the average ages in the HERCULES data set and were preferred at technical engagement prior to the availability of the interim results of the SCHARR study. The EAG notes that patient testimony at the committee meeting determined that the transfer health state is within the ambulatory phase of the disease. Patients in this state retain upper limb function and retain the ability to be independent.

Table 1 Carer health related quality of life

Health states	University of Sheffield, Duchenne UK, interim results	Landfeldt et al.

	Updated Company base case	Split by non-ambulatory status (5-7)	Updated EAG base case, health states 5-8 combined	**(2016)[8]** Previous EAG base case	**(2017)[6]** DMD-SAT[7] Model 2* & 3**
1 - Early ambulatory	[redacted]	[redacted]	[redacted]	0.85 (0.17)	0.858 (0.017)*
2 - Late ambulatory	[redacted]	[redacted]	[redacted]	0.83 (0.19)	0.839 (0.017)*
3 - Transfer	[redacted]	[redacted]	[redacted]	0.83 (0.19)	0.839 (0.017)*
4 - HTMF, no ventilation	[redacted]	[redacted]	[redacted]	0.77 (0.20)	0.784 (0.021)*
5 - No HTMF, no ventilation	[redacted]	[redacted]	[redacted]	0.79 (0.20)	0.784 (0.021)*
6 - HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]	0.79 (0.20)	0.775 (?)**
7 - No HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]	0.79 (0.20)	0.775 (?)**
8 - Full time ventilation	[redacted]	[redacted]	[redacted]	0.79 (0.20)	0.774 (?)**

ii. Approaches to calculating the utility increments / decrements to carers' quality of life

The committee requested commentary on the rationale and plausibility of calculating increments or disutilities relative to health states or general population values. This is to ensure that the selected approach would capture the progressive condition's impact on carers.

The EAG previously used a disutility approach which applied a reduction in utility to carers based on the health state of their patients. This introduces a "QALY trap" as the disutility goes to zero after patient death, so that earlier death increases total carer QALYs. The EAG have now switched to a utility approach, where the absolute QALYs of a carer are calculated. These are positive during a patient's lifetime and go to zero after a patient dies, meaning earlier death reduces total carer QALYs.

The relative to midway approach was discussed in section 4.2.7 of the EAG's report and criticisms include that it is poorly documented, and that it could not be reliably assumed equivalent to either the disutility and utility approaches.[9] The relative to midway approach suffers from the carer QALY trap because anchoring at midway creates negative disutilities at the most severe heath states, leading to a benefit from earlier patient death.

The company has incorrectly stated that the EAG's approach includes anchoring caregiver quality of life to the general population's. The EAG assumes that health-related quality of life in the model is reflective of the DMD-specific condition of patients and carers, not the quality of life of healthy individuals from the general population. The EAG model the impact of disease progression on the quality of life of carers, and maintains the anchoring of carer quality of life to those caring for patients at the least severe health state, and this progresses to the most severe states.

In the company's base case, using the approach relative to midway health state, or using the disutility approach, the anchoring is used to calculate the utility values or disutilities for the

health states and death (the bereavement disutility). The anchoring does not impact the utility approach used in the EAG's base case. The effect of changing the anchoring is explored in standalone scenarios. The utility values by increments / decrements approach for anchoring at general population are in Table 2Table 2 Carer utilities, decrements for the disutility approach, and increments / decrements for the relative to midway health state approaches. Follows company's preferred utility data from the SCHARR and anchoring at the General population. and anchoring at least severe health state in Table 3.

Table 2 Carer utilities, decrements for the disutility approach, and increments / decrements for the relative to midway health state approaches. Follows company's preferred utility data from the SCHARR and anchoring at the General population.

Health states	Utilities	Disutilities*	Increments: relative to midway*
Anchoring at General population (age 30-50)	0.923	0.000	[redacted]
1 - Early ambulatory	[redacted]	[redacted]	[redacted]
2 - Late ambulatory	[redacted]	[redacted]	[redacted]
3 - Transfer	[redacted]	[redacted]	[redacted]
4 - HTMF, no ventilation	[redacted]	[redacted]	[redacted]
5 - No HTMF, no ventilation	[redacted]	[redacted]	[redacted]
6 - HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]
7 - No HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]
8 - Full time ventilation	[redacted]	[redacted]	[redacted]
9 - Death (bereavement - all deaths)	0.000	-0.923	[redacted]

*Approach reliant on anchoring at the general population.

Table 3 Carer utilities, decrements for the disutility approach, and increments increments / decrements for the relative to midway health state approaches. Follows EAG preferred utility data from the SCHARR study merging health states 5-8 and anchoring at the least severe health state.

Health states	Utilities	Disutilities*	Increments: relative to midway*
Anchoring at least severe health state, not General population (age 30-50)**	NA	0.000	[redacted]
1 - Early ambulatory	[redacted]	[redacted]	[redacted]
2 - Late ambulatory	[redacted]	[redacted]	[redacted]
3 - Transfer	[redacted]	[redacted]	[redacted]
4 - HTMF, no ventilation	[redacted]	[redacted]	[redacted]
5 - No HTMF, no ventilation	[redacted]	[redacted]	[redacted]
6 - HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]
7 - No HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]
8 - Full time ventilation	[redacted]	[redacted]	[redacted]

9 - Death (bereavement - all deaths)	NA	[redacted]	[redacted]

*Approach reliant on anchoring at the least severe health state.

** The Utility displayed anchors at the least severe health state [redacted] rather than the general population 0.923.

iii. The number of care givers

The committee requested scenarios exploring modelling between 1 and 2 carers in the ambulatory health states along with 2 carers in non-ambulatory health states.

The company has provided updated data from the SCHARR interim survey on the number of informal carers and has followed this to increase the number of carers in the non-ambulatory states from 2 to 3. However, the SCHARR survey does not specify if the reported number of informal caregivers relates to full-time or part-time carers; the EAG believe it is more likely to relate to part-time with, for example, caregivers caring on certain days of the week or times of day. The model accounts for the average full time informal care patients receive over the time horizon so using the number of caregivers from the SCHARR survey would be an overestimate.

The EAG assumes the maximum number of fulltime informal carers is on average not expected to exceed the number of carers in the SCHARR survey. The EAG agrees with the committee and company that the increasing severity of the condition has an impact on carers and assumes this in their base case as detailed in Table 4.

Table 4 number of caregivers

Health states	EAG base case	Updated Company base case	SCHARR interim results (no.) Informal carers***
1 - Early ambulatory	1	2	[redacted]
2 - Late ambulatory	1	2	[redacted]
3 - Transfer	1	2	[redacted]
4 - HTMF, no ventilation	2	3	[redacted]
5 - No HTMF, no ventilation	2	3	[redacted]
6 - HTMF, night-time ventilation	2	3	[redacted]
7 - No HTMF, night-time ventilation	2	3	[redacted]
8 - Full time ventilation	2	3	[redacted]
9 - Death (bereavement - all deaths)	NA*	3	NA**

* The utilities approach avoids the carer QALY trap.

**The SCHARR survey did not investigate the impact of bereavement on carers.

***SCHARR survey does not specify if this is for full-time carers, rather than contribution of several part-time carers. The model (EAG and company base case) assumes that each informal caregiver is full-time.

iv. Application of the utility values in the death state

The committee requested to explore and justify different approaches for modelling the effect of patient life extension on carers. This is because it was unreasonable for the model to assume that there would be no negative effect of losing a patient on carer's HRQoL.

The company's approach to modelling the effects of life extension on care quality of life was not evidence based and may not be appropriate. As previously described, the EAG has changed its base case to the utility approach which to avoid the carer QALY trap. This approach is not affected by the inclusion of a bereavement utility. For the benefit of the committee, the EAG explored a standalone scenario modelling the survival benefit of the treatment, the bereavement utility.

A survey of mothers and fathers who experienced a perinatal death in England was identified as possible source for estimating the effect of bereavement on the carers of DMD patients. Respondents (n=256) experienced an EQ-5D-5L utility value of 0.774 (95% CI 0.752–0.796), 13% lower than the general population.[10] The EAG estimated an average carer QALY loss of -0.224 relative to general population for a period of 3 years.[11] The average QALY loss is applied in the model to the per cycle proportion of carers experiencing death, it was not extended over the time horizon. This scenario affects the results for the approaches to modelling the carer quality of life; relative to midway health state and disutilities.

Table 5 EAG's scenario, QALY loss due to bereavement applied to carer utility increments / decrements. Follows company's preferred utility data from the SCHARR study and anchoring at the general population.

Health states	Utilities	Disutilities	Increments: relative to midway
Anchoring at General population (age 30-50)	0.923	0.000	[redacted]
1 - Early ambulatory	[redacted]	[redacted]	[redacted]
2 - Late ambulatory	[redacted]	[redacted]	[redacted]
3 - Transfer	[redacted]	[redacted]	[redacted]
4 - HTMF, no ventilation	[redacted]	[redacted]	[redacted]
5 - No HTMF, no ventilation	[redacted]	[redacted]	[redacted]
6 - HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]
7 - No HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]
8 - Full time ventilation	[redacted]	[redacted]	[redacted]
9 - Death (bereavement - all deaths)	0.000	-0.224	-0.224

Key issue 8: Costs and quality of life assumed the same in full ventilation states and night ventilation states

The committee requested arguments to justify the patient utility values assigned to health states. A specific request was to explore different ways to differentiate between health states 7 and 8 for all sources of utility values, and to explore tertiary-care and medical-aid costs ensuring differentiation between health states 7 and 8.

Patient's HRQoL and utility values were previously discussed at length in section 4.2.7 of the EAG report. The EAG requested mapping of trial-based utilities to EQ-5D for use in the economic modelling which the company declined by deeming it infeasible.

Alternative sources of utility values from observational studies were made available by the company for the purposes of modelling. Two studies capture patient health related quality of life reported by patients; Audhya et al.[12] and the BOI study.[13] Three studies capture patient quality of life by reported in proxy by caregivers: Landfeldt et al. (2017),[6] Landfeldt et al. (2016)[8] and Crossnohere et al.(2021).[14]

Two studies which capture utility values on the EQ-5D scale were not preferred by the EAG. The study by Audhya et al.[12] used in the company's base case, has patient reported EQ-5D-5L values specific to US patients, and valued with a US-tariff value set. The alternative study by Crossnohere et al.[14] is a multinational study, respondents are a mix of adult patients with DMD (23%) and caregivers by proxy (77%), and the EQ-5D-3L responses were valued with a US-tariff value set.

The BOI study (Evans,2020[13]) was found by the EAG to be the only UK study with patient reported utility values and aligns with the HERCULES model especially differentiating between health states 7 and 8, but was not on the EQ-5D scale. The company did explore a scenario where a multiplier was applied to the Landfeldt utility values, but this was not found to be robust because it inadvertently included costs not appropriate decision making and the Landfeldt study was not a preferred source for data in patient HRQoL.

The EAG has previously reviewed and discussed the evidence on resource use and cost in section 4.2.8 of its report. The EAG was keen to account for costs differentiating health states 7 and 8 by relying on the BOI study which aligns with the HERCULES model. In addition, the EAG corrected the company's model to account for treatment and monitoring costs with Givinostat. However, the EAG criticized the model for not considering the additional requirement for tertiary care. This was especially pertinent considering clinical experts outlining the role of specialty NM centers in supporting patients treated with Givinostat.

At technical engagement the company argued the BOI study was unreliable due to the small numbers of respondents on some of the health states. They preferred the analysis of CPRD data by Morgan et al. and estimated a multiplier of 1.3x to distinguish between the health states 7 & 8. Furthermore, they estimated a multiplier 2.05x to account for additional costs not captured by the model. However, this multiplier was not preferred by the company for its base case.

The EAG notes the committee's request for costs that differentiate between health states 7 and 8. In response the EAG revert to using the BOI study and specifically to values that were accepted for decision making in TA1031. The company's base case did not differentiate between health states 7 and 8 as presented in Table 6. The EAG explores modeling

additional costs in standalone scenarios but notes the high degree of uncertainty. A first scenario uses a previously estimated multiplier of 0.57x discussed in the same section of the EAG's report and applied to all health states. A second scenario uses a 30x multiplier applied to non-ambulatory health states estimated from a patient's testimony that around the clock care is required due to the severity of their disease. The EAG notes the company has not taken steps to reliably quantify costs in tertiary care and refers to ABN's response to the Call for Evidence stating that the treatment with Givinostat "adds up to a significant resource implication for clinical services which currently do not have capacity to support and absorb such demands".

Table 6 Direct medical costs

Health states	**Morgan et al Direct medical costs**	**BOI Direct medical costs**	**Scenarios exploring additional care costs added to BOI direct medical care costs**		
	Company base case	Company scenario	EAG base case (TA 1031 values)	EAG multiplier (0.57x) applied to all health states	Patient expert multiplier (30x) applied to non-ambulatory health states 4-8
1 Early ambulatory	£3,298	£5,592	£7,680	£12,058	£7,680
2 Late ambulatory		£3,097	£3,391	£5,324	£3,391
3 Transfer		£3,592	£3,625	£5,691	£3,625
4 HTMF, no ventilation	£6,681	£2,370	£2,472	£3,881	£74,677
5 HTMF, night ventilation		£3,349	£3,507	£5,506	£105,943
6 No HTMF, no ventilation	£9,843	£8,430	£7,837	£12,304	£236,749
7a No HTMF, 7b night ventilation		£7,978	£7,771	£12,200	£234,7559
8a, 8b Full ventilation		£10,506	£12,579	£19,749	£380,000

Key issue 11: Implementation of treatment effect within the economic model

The committee requested additional evidence that could help reduce uncertainty around the estimation of the givinostat treatment effect and its application in the model. In their response, the company start by summarising the previously submitted evidence and reiterating their justification for the treatment effect approach used within their model. The EAG have critiqued this extensively already in Section 3.4.3.1 of the EAG report and Section 2.7 of the post-TE addendum to the EAG report.

The EAG would like to highlight an inaccuracy in the company's CfE response. The company state "*Applying a broad milestone HR to a single health state transition, such as from state 2 to state 3 as explored by the EAG (EAG report pages 24-25, Key Issue 11), inaccurately assumes the entire treatment effect occurs at that specific point*". Post-TE, the EAG's preferred model does not just apply the treatment effect to a single health state transition, but it is instead applied to all health state transitions from ambulatory states to progressed disease states (1 -> 2, 2-> 3, 3-> 4). Using a discrete-time Markov model the treatment effect cannot be applied in a more continuous way, without extending the number of health states further.

The challenge is that, as highlighted by the company, the milestones within the UK registry do not directly align with states in the HERCULES model. To resolve this, the company use SOLVER to calibrate the HERCULES transition probabilities so that the median ages at each milestone align between the NHM and the UK registry data. Similarly to the EAG, the company do this by applying a single HR to transitions for multiple states (though theirs is calibrated using a SOLVER-based approach). However, this results in various biases that are explained in more detail below.

The company have responded to each of the committee's requests for further evidence in relation to this key issue.

1a Explore alternatives to the company's acceleration factor-based approach (for example, applying the hazard ratios from the unanchored matching-adjusted indirect comparisons directly to the transitions)

The company compare the per-cycle proportions for each milestone using their preferred approach and applying the ITC-based HRs directly to the natural history model (UK registry ECM data). The company highlight in Figures 3-5 of their CfE response that their SOLVER-based approach is likely conservative compared to applying the ITC-based HR to LOA milestones. As explained above, the company's approach is not conservative but is still likely to be an overestimate of the age at each of the milestones. However, it does provide less biased estimates than applying the ITC-based HR directly.

Figure 3 of the company's CfE response highlights the issue of using the SOLVER-based approach for age at LOA, since this is the milestone for which data is available on both ECM and givinostat. If the NHM proportions of patients with ambulation were well fitted to the UK registry ECM data, then applying the ITC-based HR directly to this should produce a curve that aligns with the MAIC-weighted givinostat data, given that proportional hazards appear to hold in the MAIC. However, since the SOLVER-based approach does not preserve the underlying survival distribution, this results in survival quantiles that only align at the median and are overestimated towards the tail in the company's NHM (Figure 1).

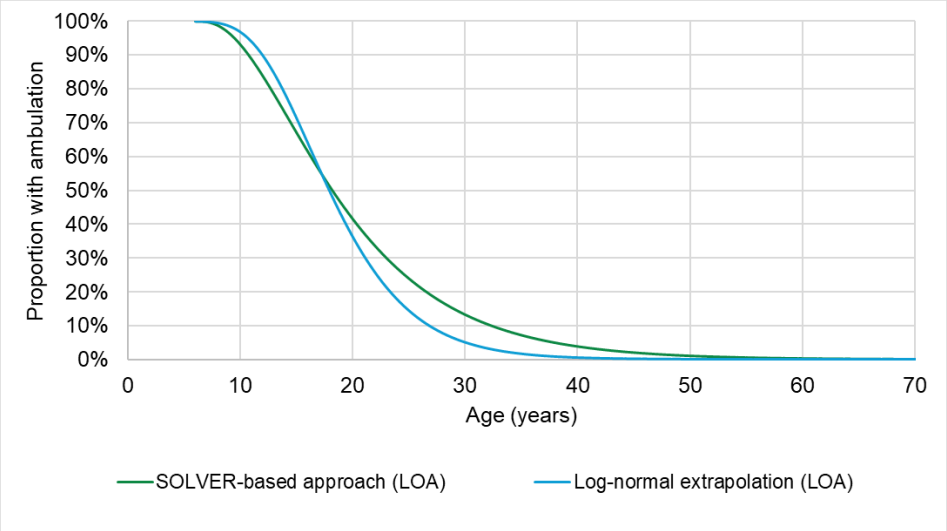
Table 7: Comparison of the proportion of patients with ambulation for ECM (company's Natural History Model versus ECM data from UK registry) and for givinostat (company's model versus Log-normal distribution fitted to MAIC-weighted givinostat data from EPIDYS/OLE) at different ages

% patients with ambulation	ECM		Givinostat	
	Company base-case (using SOLVER-based adjustment)	ECM data (UK registry study)	Company base-case (using SOLVER-based adjustment)	Company extrapolation (log-normal) fitted to MAIC-weighted givinostat data
75%	9.8	10.2	13.6	14.5
50%	12.1	12.2	18.2	17.9
25%	15.3	13.7	24.6	22.1

For the HERCULES NHM distribution it is therefore inappropriate to assume a proportional hazards treatment effect, and this therefore leads to per-cycle ambulatory proportions that are clinically implausible for givinostat when the ITC-based HR for age at LOA is applied to the NHM (as seen in Figure 3 of the company's CfE response) and also when applying the HR directly to ambulatory state transitions (as in the post-TE EAG base-case).

Using the SOLVER-based approach for treatment effects to align the company's model age at LOA to the EPIDYS/OLE givinostat data only at the median also suffers from failing to preserve the survival distribution. As with the NHM, this approach overestimates the tail, leading to a higher proportion of ambulatory patients on givinostat than would be expected in the MAIC-weighted population (Figure 1).

Figure 1: Comparison of age at LOA in the company's base-case between the SOLVER-based approach and the selected extrapolation (Log-normal) fitted to the MAIC-weighted givinostat data



Given the structural issue in aligning state transition probabilities in the HERCULES model with the milestones in the UK registry study the EAG acknowledge that the company's SOLVER-based approach may provide a less biased estimate of the treatment effect than applying the ITC-based HR, and this is the approach that we are therefore forced to adopt. As a result we have changed our base-case to use the same SOLVER-based approach that the company has used to model a treatment effect, whilst acknowledging that this is likely to produce biased results. Disagreement between the company and the EAG remain regarding extrapolation of the treatment effect (see further details below).

1b Further justification that the relationship between outcomes would be the same between givinostat and ECM.

The company have provided additional evidence to support the AF relationship between outcomes from studies investigating the use of steroids. The two studies presented, Bach and Martinez (2010)[15] and Trucco et al. (2020),[16] are retrospective observational studies, and a more detailed critique of each is given below.

No attempt is made within these studies to balance prognostic factors between untreated and steroid-treated patients, meaning that other patient characteristics that differ between these groups may be the cause of the observed results (e.g. patients who accept the adverse effects of steroid-treatment may also better tolerate other interventions that might delay LOA and ventilator use).

Furthermore, as the company acknowledges, the steroid-treated patients within these studies continue to receive treatment beyond LOA, so it is not possible to fully separate the

delay in endpoints from the ongoing effect of treatment. If patients are continuing to receive steroids then it is reasonable that the treatment effect (i.e. the AFs between outcomes) for steroids remains constant. However, this is not representative of what would happen to patients receiving givinostat, where the majority do not remain on treatment indefinitely within the model.

Bach and Martinez (2010)[15]

Bach and Martinez (2010)[15] compared 117 untreated patients with 17 steroid-treated patients for age of wheelchair dependence (used as a proxy for LOA), age of part-time NIV (used as a proxy for NIV) and age of full-time NIV (used as a proxy for FVC <1L).

The company assumes constant AFs and estimates these by dividing the median ages at each of the endpoints, using age of wheelchair dependence as the reference. The high uncertainty in the AFs is not reflected in the evidence presented by the company, and this should be clearly stated given that the sample size in the steroid-treated group is very small (N=17). No attempt was made to balance prognostic factors between untreated and steroid-treated patients.

The AFs calculated in both the untreated group and steroid-treated groups are substantially higher than those observed in the UK registry study (Table 8), suggesting that patients spend considerably more time in later disease states, and that this population is not representative of the ECM source used to inform the model.

The steroid-treated patients within this study continue to receive treatment well beyond LOA (though the duration of treatment is not specified), so it is not possible to fully separate the delay in endpoints from the ongoing effect of treatment.

Table 8: AFs for each endpoint versus LOA calculated within different treatment groups from Bach and Martinez (2010) and the UK registry study

AFs for endpoint versus age at LOA	Untreated - Bach and Martinez (2010)	Steroid-treated - Bach and Martinez (2010)	ECM - UK Registry Study
Age at LOA	Reference	Reference	Reference
Age at NIV	1.98	2.12	1.50
Age at FVC <1L	2.26	2.68	1.94

Trucco et al. (2020)[16]

Trucco et al. (2020) compared 22 naïve (untreated) patients, 182 intermittent steroid-treated patients, and 66 daily steroid-treated patients. No attempt was made to balance prognostic factors between untreated and steroid-treated patients. Only 14% of the steroid-treated patients discontinued steroids during the follow-up, indicating that the majority of treated patients remained on treatment. As with Bach and Martinez (2010), this therefore makes it impossible to fully separate the delay in endpoints from the ongoing effect of treatment.

2. Clarify whether the company's current approach modelled a treatment effect beyond loss of ambulation; clear explanation distinguishing between direct effects of ongoing givinostat treatment in non-ambulant patients and indirect (or knock-on) effects resulting from delaying disease progression during the ambulatory phase.

In the company's model the same benefit of givinostat (in terms of accelerated survival) that is estimated for age at LOA is also applied to age at NIV and age at FVC <1L, despite the fact that the modelled median age at discontinuation of givinostat is 22.58 years, which is substantially earlier than the median age at NIV (27.0 years, company base-case).

The company continue to argue that they are not modelling a givinostat-specific treatment effect at later health states but are only maintaining the relationship between outcomes observed on ECM. However, their argument is simply over semantics as their model mathematically implies an identical AF treatment effect for givinostat versus ECM for LOA and for later health states.

In Figure 1 of the company's CfE response, they illustrate applying AFs between health states to maintain the same AF relationship in both givinostat and ECM. The AF that this then implies between ECM and givinostat for each health state is mathematically equivalent (Table 9, AF = 1.46), highlighting that the company's model does in fact assume a treatment effect for givinostat that is constant over time and extends throughout the time horizon of the model (i.e. beyond LOA). This constant treatment effect is applied to all givinostat patients, regardless of whether they have discontinued treatment or not.

Table 9: Median age from company base-case (calculated by applying AFs calculated between endpoints in ECM to age at LOA in givinostat) and the corresponding AF treatment effect for givinostat versus ECM, for each endpoint

Endpoint	Median age at each endpoint		Treatment effect (AF) between ECM and givinostat
	ECM	Givinostat	
Age at LOA	12.28	17.97	17.97/12.28 = 1.46

Age at NIV	18.46	17.97 x (18.46/12.28) = 27.01	27.01/18.46 = 1.46
Age at FVC <1L	23.86	17.97 x (23.86/12.28) = 34.92	34.92/23.86 = 1.46

3. If modelled, justify the magnitude of any post loss-of-ambulation treatment effect, and explore how uncertainty in longer-term treatment effects could otherwise be incorporated into decision making.

The company argues that treatment may continue to provide clinical benefit beyond LOA, though no further data is provided to support this for givinostat. This is largely supported by patient group and clinical expert submissions, though many responses do not clearly differentiate between delaying later milestones (e.g. age at NIV, age at FVC <1L) and *extending the time* between these milestones.

The company further highlights that givinostat is likely to have a systemic effect, and to provide benefit to all muscle groups, including those that relate to respiration and cardiac function. The EAG's clinical advisors agree with this assessment and believe that it is therefore likely that patients continuing to receive givinostat may have benefits to subsequent milestones (NIV, FVC <1L), though whether this benefit is the same as the treatment effect during ambulation is very uncertain. As muscle fibrosis accumulates, givinostat may become less effective, and so the treatment effect may be attenuated for later milestones. However, there is an additional uncertainty regarding the treatment effect in patients who have discontinued givinostat, which is not specifically explored by the company CfE response or in patient/expert submissions.

Finally, the company recommends that NICE recognise that delaying LOA is likely to delay other milestones and that they reflect this in the model structure and assumptions. This is exactly what the EAG have modelled in their original and updated base-case. This is shown in Table 11, where the EAG's base-case clearly extends the average age in all states, indicating that delaying LOA does delay other health states in the model.

The EAG acknowledge that there may be some continued treatment effect beyond LOA, and even beyond discontinuing treatment, but that assuming a constant treatment effect indefinitely for a patients' lifetime that is independent of whether patients are receiving treatment or not is clinically implausible. This remains a significant uncertainty that the additional evidence provided by the company does not address.

A more useful model structure would allow detailed exploration around the treatment effect by applying a HR for givinostat selectively when patients are on treatment (potentially with an extended treatment effect if the committee believes there is sufficient clinical rationale for this), in order to ensure that costs and utility gains are aligned. However, that would require a different model structure, and it was not possible for the EAG to implement

such a model within the timelines of the appraisal. However, this model structure would also not be easily compatible with the SOLVER-based approach, due to the limitations described above.

To explore uncertainty in the longer-term treatment effect of givinostat, the EAG have performed additional scenario analyses that apply the AF treatment effect for age at LOA to additional health states beyond ambulation (see section below).

4. Present updated economic modelling based on plausible, evidence-based and fully justified approaches to modelling the givinostat treatment effect.

The company has run two scenarios that explore the impact of post-LOA treatment benefit. The first improves the SOLVER-based HRs applied to non-ambulatory state transition probabilities by 20% for givinostat vs ECM, which leads to a reduction in the ICER.

The company states that this "reflects a modest treatment benefit beyond LOA" yet, as stated in part 2 of our critique of the company's CfE response for this issue, the company already have been modelling a constant AF treatment effect of givinostat beyond LOA (and throughout the lifetime horizon of the model). Therefore, any further improvement to the SOLVER-based HR is in fact modelling a treatment effect for givinostat *that increases over time, even when patients have discontinued givinostat*. This lacks any clinical plausibility, and as such this scenario analysis is not meaningful.

The second scenario explored by the company is using AFs for age at NIV vs age at LOA and for age at FVC <1L vs age at LOA estimated from the untreated group of Bach and Martinez (2010), instead of AFs estimated from the UK registry study. These AFs are slightly higher than those estimated from the UK registry study, and so when applied to givinostat patients this leads to later age at NIV and age at FVC <1L, and subsequently to a reduction in the ICER.

The specific critique of this source of evidence is given in the report section on Bach and Martinez (2010). Due to the way in which the company has extrapolated outcomes using AFs, applying a set of AFs to the givinostat patients that are greater than the UK registry study AFs again implies that the treatment effect for givinostat *increases over time, even when patients have discontinued givinostat*. As stated above, this lacks clinical plausibility.

To highlight this, we have calculated the givinostat-specific treatment effect using the Bach and Martinez (2010) data, for givinostat versus ECM for age at LOA (Table 10).

Table 10: Median age from company base-case (calculated by applying AFs calculated between endpoints from Bach and Martinez (2010) to age at LOA in givinostat) and the corresponding treatment effect between givinostat and ECM, for each endpoint

Endpoint	Median age at each endpoint		Treatment effect (AF) between ECM and givinostat
	ECM	Givinostat (age at LOA x Bach and Martinez AF)	
Age at LOA	12.28	17.97	17.97/12.28 = 1.46
Age at NIV	18.46	17.97 x 1.98 = 35.58	35.58/18.46 = 1.93
Age at FVC <1L	23.86	17.97 x 2.26 = 40.61	40.61/23.86 = 1.70

In the absence of a model structure that selectively applies a treatment effect whilst patients are on treatment, the EAG base-case attempts to align the treatment effect in the model with the expected health state the average patient would be in when they discontinue treatment. This is estimated using median age at givinostat discontinuation (21.92 years), aligned with the health state whose mean age in the state is most closely aligned (HTMF no vent, Table 11). Given the variability in the age at which patients discontinue treatment, there is likely to be significant uncertainty around this.

Table 11: Mean age and mean time spent in health states within the company and EAG's base-case models on both givinostat and ECM. Mean health state occupancy that is closest to median discontinuation of givinostat is highlighted in bold for the company and the EAG's base case.

	Mean age in state (years; undiscounted)			Mean time in state (years; undiscounted)		
	Givinostat		ECM	Givinostat		ECM
	Company	EAG		Company	EAG	
Early Amb	13.74	13.66	9.86	7.81	7.73	3.91
Late Amb	18.13	18.00	12.07	4.44	4.39	2.25
Transfer	20.13	19.98	13.10	1.99	1.97	1.02
HTMF no vent	**24.44**	**22.76**	14.87	4.29	2.76	1.76
No HTMF No vent	34.49	29.91	19.63	5.26	3.61	2.39

HTMF night vent	32.91	28.61	19.62	4.15	2.82	2.29
No HTMF night vent	37.81	32.05	21.78	3.22	2.27	1.89
Full vent	43.33	38.24	28.48	4.24	5.11	5.57

The EAG has also provided a range of scenarios that explore extrapolation of the treatment effect beyond ambulation in the clinical data. These are implemented by applying a AF treatment effect for givinostat relative to ECM to the difference in the median ages at later milestones for ECM in order to calculate the difference in median ages at later milestones for givinostat (Table 12). The difference in median ages represents the respective time intervals for LOA → NIV and for NIV → FVC <1L. These time intervals are then cumulatively added to the median age at LOA on givinostat to estimate the median age at NIV and median age at FVC <1L for givinostat.

As an example, for the EAG base-case, to calculate the median age at NIV for givinostat, we take the LOA -> NIV for ECM (6.18), multiply it by the AF treatment effect for LOA -> NIV (AF=1), and then add this to median age at LOA (17.97 + (6.18 x 1) = 24.15).

For EAG Scenario 3, in which the treatment effect is extended to NIV, to calculate the median age at NIV for givinostat, we take the LOA -> NIV for ECM (6.18), multiply it by the AF treatment effect for LOA -> NIV (AF=1.463), and then add this to median age at LOA (17.97 + (6.18 x 1.463) = 27.01).

The company base-case assumes the same treatment effect applied to median age at LOA, LOA → NIV and NIV → FVC <1L. The EAG base (Scenario 1) applies the AF treatment effect only to age at LOA. EAG Scenario 2 applies half of the AF treatment effect estimated for age at LOA to the LOA → NIV time interval. EAG Scenario 3 applies the same AF treatment effect estimated for age at LOA to LOA → NIV.

Note that any scenario that does not model a constant treatment effect over the time horizon of the model for the time intervals (LOA → NIV and NIV → FVC <1L) implies a reduction in AF for later milestones (age at NIV and age at FVC <1L).

Table 12: Median age/time to different milestones estimated from the clinical data for ECM (UK registry) and givinostat (EPIDYS/OLE) with different assumptions regarding the Acceleration Factor treatment effect. Median age at NIV and age at

FVC <1L are calculated by adding the respective time interval onto the relevant milestone.

Milestones / time intervals	ECM	Company base-case		EAG base-case (Scenario 1)		EAG Scenario 2		EAG Scenario 3	
		Givinostat	AF*	Givinostat	AF*	Givinostat	AF*	Givinostat	AF*
Median age at LOA	12.28	17.97	1.46	17.97	1.46	17.97	1.46	17.97	1.46
Median LOA → NIV	6.18	9.04	1.46	6.18	1.00	7.48	1.21	9.04	1.46
Median NIV → FVC<1L	5.40	7.90	1.46	5.40	1.00	5.40	1.00	5.40	1.00
Median age at NIV	18.46	27.01	1.46	24.15	1.31	25.45	1.38	27.01	1.46
Median age at FVC <1L	23.86	34.92	1.46	29.55	1.24	30.85	1.29	32.41	1.36

* Acceleration Factor represents the treatment effect for givinostat versus ECM

Note that median ages/times to event are from the clinical data (i.e. before applying SOLVER). Therefore medians reported here may not align perfectly with those that calibrate state transition probabilities from the HERCULES model

The per cycle transition probabilities from models exploring the scenarios above are shown for the proportion of ambulatory patients (Figure 2), patients without NIV (Figure 3) and patients without FVC <1L (Figure 4). All models use the SOLVER-based approach to align the medians ages in the model with the median ages at each milestone. For the proportion of ambulatory patients EAG and company model results are identical as they all make the same assumption for the age at LOA treatment effect. However, for the proportion of patients without NIV and without FVC <1L, the EAG base-case shows a more rapid progression to each of the milestones, with each of the scenario analyses shifting the curve closer towards the company's base-case, depending on the degree of extrapolation of the treatment effect.

Figure 2: Per-cycle proportions for patients with ambulation from the company base-case and each of the EAG's scenario analyses. EAG base-case and scenario curves are all overlapping

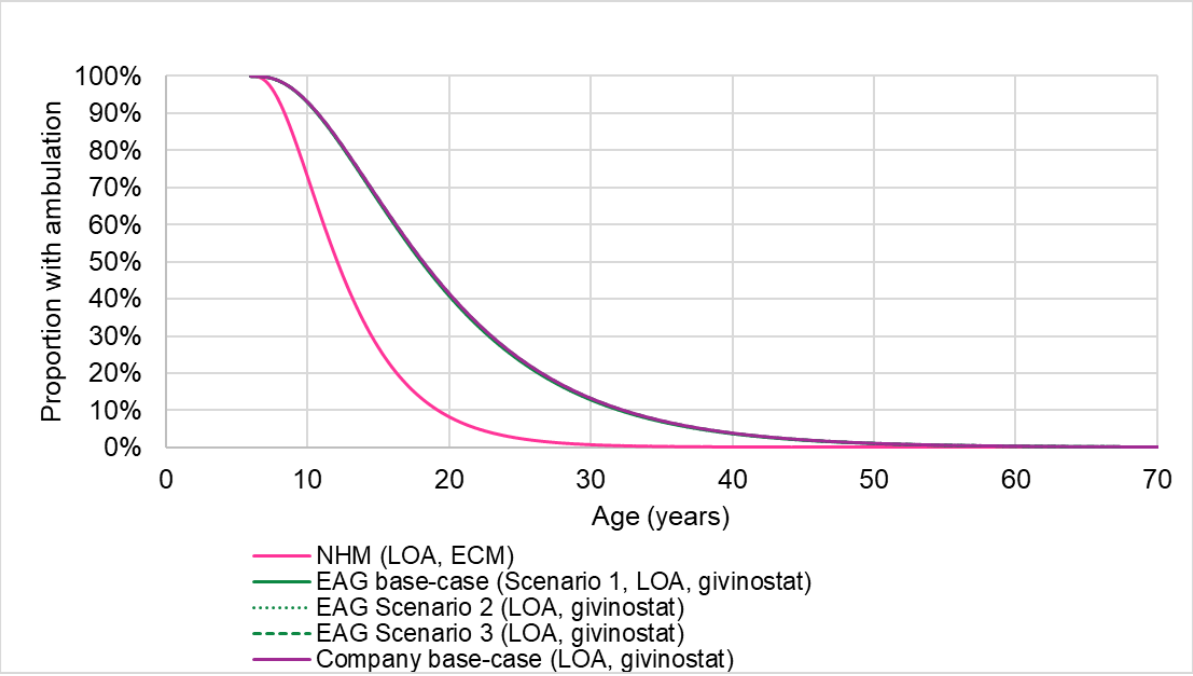


Figure 3: Per-cycle proportions for patients without NIV from the company base-case and each of the EAG's scenario analyses.

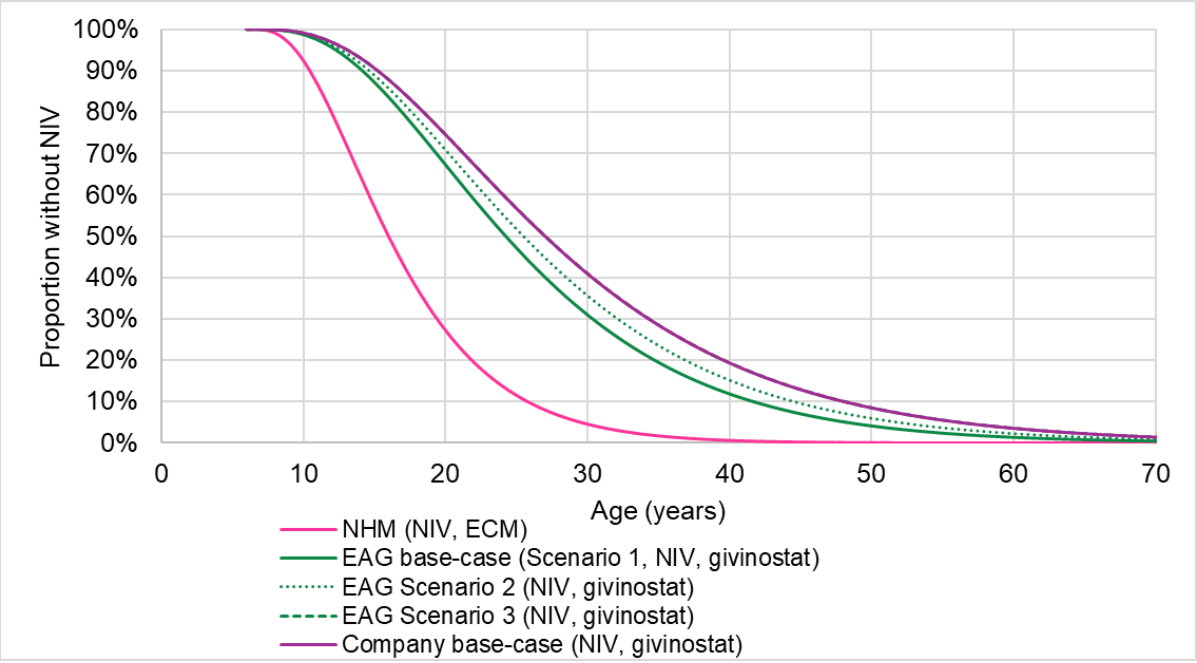
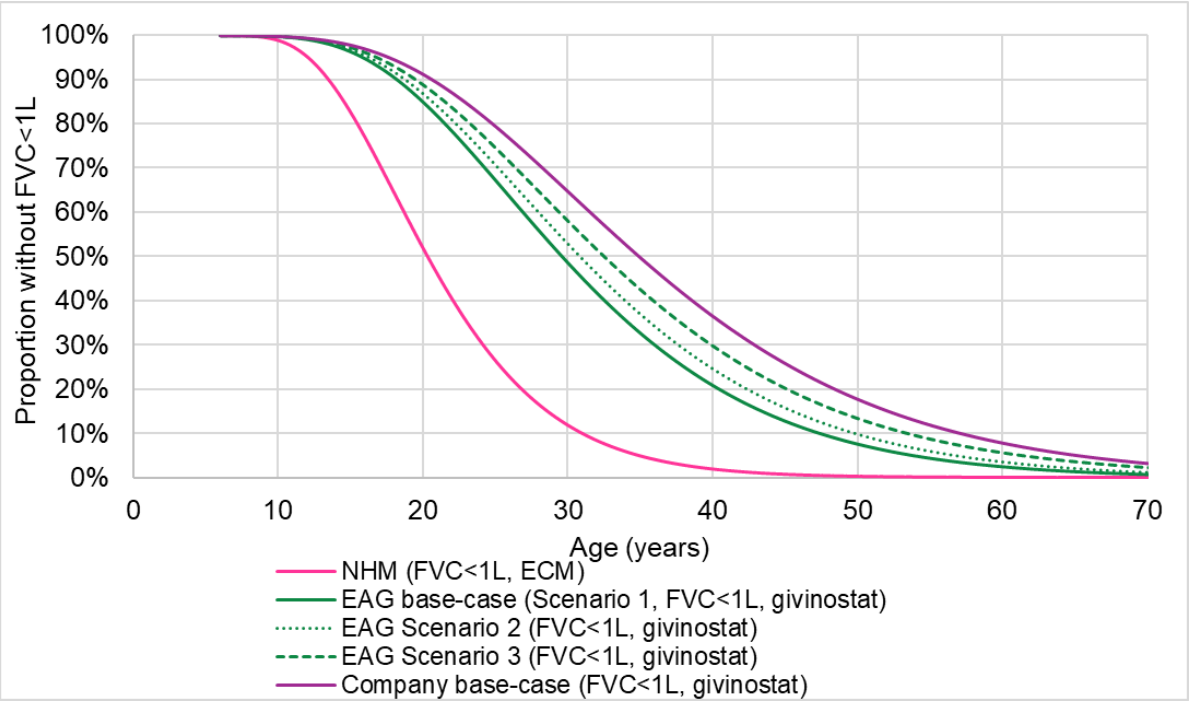


Figure 4: Per-cycle proportions for patients without FVC <1L from the company base-case and each of the EAG's scenario analyses.



3. Additional analyses in response to additional issues raised in Call for Evidence

In response to the call for evidence the EAG undertook scenario analyses as described in Table 13. These were conducted deterministically on the company's base case 2 which applies a 3.5% discount factor to costs and effects. Results presented by approach to modelling carer utility decrements / increments; the relative to midway approach (Scenarios A) in Table 14, the disutilities approach (Scenarios B) in Table 15, and the utility approach (Scenarios C) in Table 16.

Table 13 Description of scenario analyses undertaken by EAG

Analysis	Section(s) of report	Details
Scenario 1: EAG base-case	Key issue 11 Section 4	The EAG base-case aligns the treatment effect with the median state that patients are in when they discontinue treatment, by applying an AF for givinostat versus ECM only to median age at LOA. The time spent in later health states is assumes to be the same for givinostat and ECM, though the age at which patients transition from these health states will be later due to delay in LOA. The model

		uses SOLVER to calibrate state transition probabilities so that they match the milestones in the clinical data.
Scenario 2: - Extend half AF treatment effect to NIV (Scenario 1)	Key issue 11 Section 4	The company has argued that givinostat may delay the progression of the disease such that the time spent in later health states is also extended. EAG Scenario 2 explores this by extending the treatment effect to non-ambulatory states, for which there is no clinical data at present. This is achieved by applying half the AF treatment effect estimated for age at LOA to the time between LOA and NIV. This time interval is then added on to median age at LOA to obtain the median age at NIV. For many patients this will mean that the treatment effect continues after they have discontinued givinostat.
Scenario 3: - Extend AF treatment effect to NIV (Scenario 2)	Key issue 11 Section 4	EAG Scenario 3 further explores the extrapolation of the treatment effect in EAG Scenario 3 by applying the full AF treatment effect estimated for age at LOA to the time between LOA and NIV. This time interval is then added on to median age at LOA to obtain the median age at NIV. For most patients, this will mean that the treatment effect continues after they have discontinued givinostat.
Scenario 4: SCHARR carer utilities split by non-ambulatory	Key issue 7.i	The company's base case adopts the SCHARR carer utilities classified into 3 health states: ambulatory, transfer and non-ambulatory. The EAG explore a scenario where non-ambulatory health states (5-8) are differentiated.
Scenario 5: SCHARR carer utilities health states 5-8 combined	Key issue 7.i	The SCHARR carer utilities for the non-ambulatory health states are based on a small sample, the EAG explore a scenario taking a weighted average of the scores in health states (5-8).
Scenario 5a: SCHARR carer utilities health states 5-8 combined and anchoring at the least severe health state	Key issue 7.i	The economic model is specific to the health-related quality of life patients with DMD and their carers. The EAG explores a scenario where and utility values are reflective of the condition by anchoring of carer quality of life at the least severe health state. This combined with scenario 5.

Scenario 5b: modelling carer quality of life using the utility approach	Key issue 7.ii	Exploring a scenario to avoid the carer QALY trap. The utility approach, where the absolute QALYs of a carer are positive during a patient's lifetime and go to zero after a patient dies.
Scenario 6: Landfeldt a2017 carer utilities models 2 & 3	Key issue 7.i	Modelling carer HRQoL using the Landfelt 2017 values with models 2 and 3 combined.
Scenario 7: anchoring carer utlities at the least severe health state	Key issue 7.ii	Modelling utility values are reflective of the condition by anchoring of carer quality of life at the least severe health state.
Scenario 8: 1 carer in ambulatory health states, 2 carers in non-ambulatory health states	Key issue 7.iii	Changing the caregiver impact by varying the number of caregivers: 1 at ambulatory states and 2 at non-ambulatory states
Scenario 9: 2 carers in all health states.	Key issue 7.iii	Changing the caregiver impact by varying the number of caregivers: 2 at ambulatory and non-ambulatory states
Scenario 10: utilities that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation")	Key issue 8	Utilising BOI study patient utilities to account impacts of moving from only nighttime ventilation to needing full ventilation.
Scenario 11 : costs that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation")	Key issue 8	Utilising BOI health state direct medical costs (TA 1031 values) to account impacts of moving from only nighttime ventilation.
Scenario 12: including costs due to tertiary care and medical aids	Key issue 8	Utilising a multiplier of 0.57x previously estimated in the EAG's report and applied to BOI health state direct medical costs (TA 1031 values) to estimate the health state costs inclusive of non-medical community services, aids, devices, and investments increases.
Scenaro 13: Burden of care in the most severe health state	Key issue 8	Utilising patient testimony on the cost of care package to the NHS to estimate a multiplier of 30x applied to non-ambulatory health states (5-8) of the BOI study direct medical costs (TA 1031 values).

Scenario 14: 1.5% discounting	Key issue 6	A scenario modelling the company's position: no future treatment could restore a patient to full-health applying a 1.5% discount rate for health outcomes only (i.e., QALYs and not costs).
Scenario 15: Life-extension effect on carer health-related quality of life / bereavment utility decrement	Key issue 7.iv	A scenario exploring the effect of bereavement using the EAG's estimated average carer QALY loss of -0.224 relative to general population for a period of 3 years.

Table 14 Results (deterministic) of the EAG's scenario analyses under modelling approach. Scenarios A: relative to midway approach

Scenario	ECM			Givinostat			Incremental costs (£)	Incremental Patient QALYs	Incremental QALYs (w/ severity Modifier)	ICER (£/QALY)	Change from base-case ICER (%)
	Total costs (£)	Total QALYs		Total costs (£)	Total QALYs						
		patient	carer		patient	carer					
Company base-case2	£99,448	6.08	0	[redacted]	9.65	10.51	[redacted]	3.57	16.57	[redacted]	-
Scenario 1	£99,448	6.08	0	[redacted]	9.20	7.80	[redacted]	3.12	13.10	[redacted]	19%
Scenario 2	£99,448	6.08	0	[redacted]	9.33	8.56	[redacted]	3.25	14.08	[redacted]	12%
Scenario 3	£99,448	6.08	0	[redacted]	9.52	9.52	[redacted]	3.43	15.36	[redacted]	5%
Scenario 4	£99,448	6.08	0	[redacted]	9.65	10.90	[redacted]	3.57	16.96	[redacted]	-2%
Scenario 5	£99,448	6.08	0	[redacted]	9.65	10.84	[redacted]	3.57	16.90	[redacted]	-2%
Scenario 5a	£99,448	6.08	0	[redacted]	9.65	10.84	[redacted]	3.57	16.90	[redacted]	-2%
Scenario 5b*	£99,448	6.08	24.78	[redacted]	9.65	32.42	[redacted]	3.57	13.70	[redacted]	21%
Scenario 6	£99,448	6.08	0	[redacted]	9.65	12.52	[redacted]	3.57	18.58	[redacted]	-11%
Scenario 7	£99,448	6.08	0	[redacted]	9.65	10.51	[redacted]	3.57	16.57	[redacted]	0%
Scenario 8	£99,448	6.08	0	[redacted]	9.65	6.91	[redacted]	3.57	12.97	[redacted]	28%
Scenario 9	£99,448	6.08	0	[redacted]	9.65	7.20	[redacted]	3.57	13.26	[redacted]	25%
Scenario 10	£99,448	6.08	0	[redacted]	10.66	10.51	[redacted]	3.30	14.47	[redacted]	15%
Scenario 11	£106,699	6.08	0	[redacted]	9.65	10.51	[redacted]	3.57	16.57	[redacted]	0.2%
Scenario 12	£162,904	6.08	0	[redacted]	9.65	10.51	[redacted]	3.57	16.57	[redacted]	1.8%
Scenario 13	£1,944,358	6.08	0	[redacted]	9.65	10.51	[redacted]	3.57	16.57	[redacted]	-48.4%
Scenario 14	£99,448	7.00	0	[redacted]	12.11	18.25	[redacted]	5.12	24.38	[redacted]	-32%
Scenario 15	£99,448	6.08	0	[redacted]	9.65	0.59	[redacted]	3.57	6.65	[redacted]	149%

*Scenario switching the relative to midway approach in modelling carer utility decrements / increments to the utility approach

Table 15 Results (deterministic) of the EAG's scenario analyses under modelling approach. Scenarios B: disutilities approach.

Scenario	ECM			Givinostat			Incremental costs (£)	Incremental Patient QALYs	Incremental QALYs (w/ severity Modifier)	ICER (£/QALY)	Change from base-case ICER (%)
	Total costs (£)	Total QALYs		Total costs (£)	Total QALYs						
		patient	carer		patient	carer					
Company base-case2 (disutilities approach)	£99,448	6.08	-42.94	[redacted]	9.65	-31.25	[redacted]	3.57	17.75	[redacted]	-
Scenario 1	£99,448	6.08	-42.94	[redacted]	9.20	-33.98	[redacted]	3.12	14.26	[redacted]	17%
Scenario 2	£99,448	6.08	-42.94	[redacted]	9.33	-33.22	[redacted]	3.25	15.24	[redacted]	11%
Scenario 3	£99,448	6.08	-42.94	[redacted]	9.52	-32.24	[redacted]	3.43	16.53	[redacted]	5%
Scenario 4	£99,448	6.08	-42.94	[redacted]	9.65	-34.09	[redacted]	3.57	18.00	[redacted]	-1%
Scenario 5	£99,448	6.08	-42.94	[redacted]	9.65	-32.45	[redacted]	3.57	17.94	[redacted]	-1%
Scenario 5a	£99,448	6.08	-42.94	[redacted]	9.65	-18.72	[redacted]	3.57	17.07	[redacted]	4%
Scenario 5b*	£99,448	6.08	24.78	[redacted]	9.65	32.42	[redacted]	3.57	13.70	[redacted]	30%
Scenario 6	£99,448	6.08	-42.94	[redacted]	9.65	-25.19	[redacted]	3.57	19.19	[redacted]	-8%
Scenario 7	£99,448	6.08	-42.94	[redacted]	9.65	-17.52	[redacted]	3.57	16.88	[redacted]	5%
Scenario 8	£99,448	6.08	-42.94	[redacted]	9.65	-20.12	[redacted]	3.57	14.15	[redacted]	25%
Scenario 9	£99,448	6.08	-42.94	[redacted]	9.65	-22.25	[redacted]	3.57	13.26	[redacted]	34%
Scenario 10	£99,448	6.08	-42.94	[redacted]	10.66	-31.25	[redacted]	3.30	15.65	[redacted]	13%
Scenario 11	£106,699	6.08	-42.94	[redacted]	9.65	-31.25	[redacted]	3.57	17.75	[redacted]	0.2%
Scenario 12	£162,904	6.08	-42.94	[redacted]	9.65	-31.25	[redacted]	3.57	17.75	[redacted]	1.8%
Scenario 13	£1,944,358	6.08	-42.94	[redacted]	9.65	-31.25	[redacted]	3.57	17.75	[redacted]	-48.4%
Scenario 14	£99,448	7.00	-83.28	[redacted]	12.11	-63.50	[redacted]	5.12	25.92	[redacted]	-32%
Scenario 15	£99,448	6.08	-9.09	[redacted]	9.65	-11.41	[redacted]	3.57	3.75	[redacted]	373%

*Scenario switching the disutilities approach to modelling carer utility decrements / increments to the utility approach

Table 16 Results (deterministic) of the EAG's scenario analyses under modelling approach. Scenarios C: utilities approach

Scenario	ECM			Givinostat			Incremental costs (£)	Incremental Patient QALYs	Incremental QALYs (w/ severity Modifier)	ICER (£/QALY)	Change from base-case ICER (%)
	Total costs (£)	Total QALYs		Total costs (£)	Total QALYs						
		patient	carer		patient	carer					
Company base-case2 (utilities approach)	£99,448	6.08	24.78	[redacted]	9.65	32.42	[redacted]	3.57	13.70	[redacted]	-
Scenario 1	£99,448	6.08	24.78	[redacted]	9.20	29.76	[redacted]	3.12	10.28	[redacted]	25%
Scenario 2	£99,448	6.08	24.78	[redacted]	9.33	30.52	[redacted]	3.25	11.26	[redacted]	16%
Scenario 3	£99,448	6.08	24.78	[redacted]	9.52	31.43	[redacted]	3.43	12.49	[redacted]	7%
Scenario 4	£99,448	6.08	24.78	[redacted]	9.65	29.57	[redacted]	3.57	13.95	[redacted]	-2%
Scenario 5	£99,448	6.08	24.78	[redacted]	9.65	31.22	[redacted]	3.57	13.89	[redacted]	-1%
Scenario 5a	£99,448	6.08	24.78	[redacted]	9.65	31.22	[redacted]	3.57	13.89	[redacted]	-1%
Scenario 6	£99,448	6.08	24.78	[redacted]	9.65	38.48	[redacted]	3.57	15.14	[redacted]	-10%
Scenario 7	£99,448	6.08	24.78	[redacted]	9.65	32.42	[redacted]	3.57	13.70	[redacted]	0%
Scenario 8	£99,448	6.08	24.78	[redacted]	9.65	19.09	[redacted]	3.57	10.10	[redacted]	36%
Scenario 9	£99,448	6.08	24.78	[redacted]	9.65	26.65	[redacted]	3.57	13.26	[redacted]	3%
Scenario 10	£99,448	6.08	24.78	[redacted]	10.66	32.42	[redacted]	3.30	11.60	[redacted]	18%
Scenario 11	£106,699	6.08	24.78	[redacted]	9.65	32.42	[redacted]	3.57	13.70	[redacted]	0.2%
Scenario 12	£162,904	6.08	24.78	[redacted]	9.65	32.42	[redacted]	3.57	13.70	[redacted]	1.8%
Scenario 13	£1,944,358	6.08	24.78	[redacted]	9.65	32.42	[redacted]	3.57	13.70	[redacted]	-48.4%
Scenario 14	£99,448	7.00	31.02	[redacted]	12.11	45.54	[redacted]	5.12	20.66	[redacted]	-34%
Scenario 15	£99,448	6.08	24.78	[redacted]	9.65	32.42	[redacted]	3.57	13.70	[redacted]	0%

4. EAG updated base case results & scenario

In table1 of the response to call for evidence document, the company outline changes made to their revised base case and presented two versions. Base case 1 with 1.5% discount rate applied to the outcomes, but the company's application of this discount rate to the QALY shortfall calculation is incorrect. Base case 2 uses the 3.5% discount rate in line with the NICE methods guide, both the committee's and EAG's preferred assumptions and is outlined below as follows:

- Use the full givinostat population from EPIDYS and the OLE study (n=224) as a source of givinostat data for the unanchored MAIC
- Source of caregiver utilities (University of Sheffield and Project HERCULES new interim data)
- Source of caregiver utilities (University of Sheffield and Project HERCULES new interim data)

The company's base case 2 probabilistic ICER is [redacted], and the deterministic ICER is [redacted], whereas the base case at technical engagement probabilistic ICERs was [redacted] and the deterministic ICER was [redacted]. These have been reproduced by the EAG for the incremental analysis in Table 18 and Table 19. Note the probabilistic results will not match, highlighting the uncertainty in the results.
Following the call for evidence, the EAG incorporates the additional evidence provided by the company. The EAG further modifies the company's base case 2 by adding the assumptions presented in Table 17. This summarises the scenarios and outlines the changes made to the EAG base case.

The EAG models the effect of bereavement as discussed in key issue 7.iv by applying scenario 15 to the EAG's updated bases case, results are presented in Table 20. The bereavement issue was explored in conjunction with the approaches to modelling carer HRQoL as scenarios to the EAG's updated base case; the relative to mid-way health state approach in
Table 21, and the disutilities approach in Table 22.

Table 17 EAG Preferred assumptions following the call for evidence

Scenario	Changed from previous base case? (Relevant Key Issue)
Scenario 1. Treatment effect.	Yes, Due to the company's use of SOLVER applied to the HERCULES model state transitions for NHM, the survival distribution no longer matches that of the UK registry data for ECM. This means that applying the ITC-based HR produces clinically implausible results. Due to the use of HERCULES and the SOLVER-based approach, the per-cycle proportions will be biased. However, the EAG accepts that the bias is likely to be less than directly applying the ITC-based HR and has now updated their base-case to use this approach. The EAG continues to apply a treatment effect only to age at LOA in their base-case. (Key Issue 11)
Scenario 5& 5a: **Change caregiver utility impact calculation (the source of the utility values used)**	Yes, SCHARR Care giver utilities, taking the weighted average of utilities in non-ambulatory health states (5-8), and anchoring at least severe health state. (key issue 7)
Scenario 5b. Change caregiver utility impact calculation (the approach for calculating the utility increments / decrements)	Yes, The EAG are using the utility approach to model carer health related quality of life, this avoids the carer QALY trap. (key issue 7)
Scenario 8: Changing the number of caregivers	No brief description (key issue 7)
Scenario 10. Utilities that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation")	No, The EAG have kept the prior source for utilities, the BOI study. (Key Issue 8)
Scenario 11. costs that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation")	Yes The EAG have reverted to the direct medical costs from the BOI study, without the use of the multiplier to estimate costs associated with tertiary health care. (Key Issue 8)

Table 18 EAG preferred assumptions added incrementally to EAG base-case (deterministic results)

Interventions	Total Costs	Total Patient QALYs	Total Carer QALYs	Incremental Costs	Incremental Patient QALYs	Incremental QALYs (w/ severity Modifier)	ICER
Company's base-case 2							
ECM	£99,448	6.08	0.00				
Givinostat	[redacted]	9.65	10.51	[redacted]	3.57	16.57	[redacted]
Company's base-case 2 + EAG's preferred assumption S1: treatment effect							
ECM	£99,448	6.08	0.00				
Givinostat	[redacted]	9.20	7.80	[redacted]	3.12	13.10	[redacted]
Company's base-case + S1 + EAG's preferred assumption S5 (5 & 5a): Change caregiver utility impact calculation (the source of the utility values used)							
ECM	£99,448	6.08	0.00				
Givinostat	[redacted]	9.20	8.17	[redacted]	3.12	13.47	[redacted]
Company's base-case + S1 + S5 + EAG's preferred assumption S5b: Change caregiver utility impact calculation (the approach for calculating the utility increments / decrements)							
ECM	£99,448	6.08	23.39				
Givinostat	[redacted]	9.20	28.61	[redacted]	3.12	10.52	[redacted]
Company's base-case + S1 + S5 + S8 +EAG's preferred assumption S8: Changing the number of caregivers							
ECM	£99,448	6.08	14.13				

Givinostat	[redacted]	9.20	16.57	[redacted]	3.12	7.75	[redacted]
Company's base-case + S1 + S5 + S8 +EAG's preferred assumption S10: Utilities that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation")							
ECM	£99,448	7.36	14.13				
Givinostat	[redacted]	9.82	16.57	[redacted]	2.46	5.40	[redacted]
Company's base-case + S1 + S5 + S8 + S10 +EAG's preferred assumption S11: costs that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation")							
ECM	£106,699	7.36	14.13				
Givinostat	[redacted]	9.82	16.57	[redacted]	2.46	5.40	[redacted]

Table 19 : EAG preferred assumptions added incrementally to EAG base-case probabilistic results after 1000 iterations run

Interventions	Total Costs	Total Patient QALYs	Total Carer QALYs	Incremental Costs	Incremental Patient QALYs	Incremental QALYs (w/ severity Modifier)	ICER
Company's base-case 2							
ECM	£98,966	6.08	0.00				
Givinostat	[redacted]	9.64	10.56	[redacted]	3.56	16.61	[redacted]
Company's base-case 2 + EAG's preferred assumption S1: treatment effect							
ECM	£99,060	6.09	0.00				
Givinostat	[redacted]	9.20	7.80	[redacted]	3.11	13.09	[redacted]
Company's base-case + S1 + EAG's preferred assumption S5 (5 & 5a): Change caregiver utility impact calculation (the source of the utility values used)							
ECM	£99,332	6.08	0.00				
Givinostat	[redacted]	9.20	8.17	[redacted]	3.12	13.47	[redacted]
Company's base-case + S1 + S5 + EAG's preferred assumption S5b: Change caregiver utility impact calculation (the approach for calculating the utility increments / decrements)							
ECM	£99,127	6.10	23.39				
Givinostat	[redacted]	9.20	28.61	[redacted]	3.10	10.49	[redacted]
Company's base-case + S1 + S5 + S8 +EAG's preferred assumption S8: Changing the number of caregivers							
ECM	£99,180	6.10	14.13				

Givinostat	[redacted]	9.20	16.57	[redacted]	3.11	7.73	[redacted]
Company's base-case + S1 + S5 + S8 +EAG's preferred assumption S10: Utilities that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation")							
ECM	£98,862	7.35	14.13				
Givinostat	[redacted]	9.82	16.57	[redacted]	2.48	5.42	[redacted]
Company's base-case + S1 + S5 + S8 + S10 +EAG's preferred assumption S11: costs that distinguish between states 8 ("no HTMF with full ventilation") and 7 ("no HTMF with night ventilation")							
ECM	£106,226	7.37	14.13				
Givinostat	[redacted]	9.82	16.57	[redacted]	2.45	5.39	[redacted]

Table 20 Scenario 15, the effect of bereavement applied to EAG's updated base case (deterministic results)

Scenario	ECM			Givinostat			Incremental costs (£)	Incremental Patient QALYs	Incremental QALYs (w/ severity Modifier)	ICER (£/QALY)	Change from base-case ICER (%)
	Total costs (£)	Total QALYs		Total costs (£)	Total QALYs						
		patient	carer		patient	carer					
EAG's updated base-case	£106,699	7.36	14.13	[redacted]	9.82	16.57	[redacted]	2.46	5.40	[redacted]	-
Scenario 15	£106,699	7.36	14.13	[redacted]	9.82	16.57	[redacted]	2.46	5.40	[redacted]	0%

Table 21 Scenario 15, the effect of bereavement applied to EAG's updated base case using the relative to midway heath state approach to modelling carer HRQoL (deterministic results)

Scenario	ECM			Givinostat			Incremental costs (£)	Incremental Patient QALYs	Incremental QALYs (w/ severity Modifier)	ICER (£/QALY)	Change from base-case ICER (%)
	Total costs (£)	Total QALYs		Total costs (£)	Total QALYs						
		patient	carer		patient	carer					
EAG's updated base-case (relative to mid way approach)	£106,699	7.36	0.00	[redacted]	9.82	5.40	[redacted]	2.46	8.35	[redacted]	-
Scenario 15	£106,699	7.36	0.00	[redacted]	9.82	0.35	[redacted]	2.46	3.30	[redacted]	153%

Table 22 Scenario 15, the effect of bereavement applied to EAG's updated base case using the carer disutility approach to modelling carer HRQoL (deterministic results)

Scenario	ECM			Givinostat			Incremental costs (£)	Incremental Patient QALYs	Incremental QALYs (w/ severity Modifier)	ICER (£/QALY)	Change from base-case ICER (%)
	Total costs (£)	Total QALYs		Total costs (£)	Total QALYs						
		patient	carer		patient	carer					
EAG's updated base-case (disutilities approach)	£106,699	7.36	-19.81	[redacted]	9.82	-14.25	[redacted]	2.46	8.52	[redacted]	-
Scenario 15	£106,699	7.36	0.00	[redacted]	9.82	-1.88	[redacted]	2.46	3.18	[redacted]	167%

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