NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Givinostat can be used as an option to treat Duchenne muscular dystrophy in people 6 years and over who are ambulant (able to walk or stand, with or without support) at the start of treatment. Givinostat can only be used if the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with givinostat that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

What this means in practice

Givinostat must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Givinostat must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to suggest that givinostat provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Why the committee made these recommendations

Duchenne muscular dystrophy is a rare and fatal genetic condition that starts in childhood. It causes muscles throughout the body to gradually stop working, leading to increasing disability over time and early death.

There is currently no cure for Duchenne muscular dystrophy. The usual treatment is best supportive care focusing on preventing and managing complications.

For this evaluation, the company asked for givinostat to be considered only for people who are ambulant (able to walk or stand, with or without support) at the start of treatment, to reflect the populations in the clinical trials. This does not include everyone who givinostat is licensed for.

Clinical trial evidence shows that givinostat slows down the loss of ability to climb stairs compared with corticosteroids alone. But, there is no evidence yet on whether givinostat helps delay breathing problems because the trial is still ongoing.

When taking into account the condition's severity, and its effect on quality and length of life, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, givinostat can be used.

2 Information about givinostat

Marketing authorisation indication

2.1 Givinostat (Duvyzat, ITF Pharma UK) is indicated for 'the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for givinostat.

Price

2.3 The price of givinostat is £13,846 per 140 ml of 8.86 mg/ml oral suspension (excluding VAT, BNF online July 2025).

2.4 The company has a commercial arrangement. This makes givinostat available to the NHS for this indication with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 For information, ITF Pharma UK did not disclose its Carbon Reduction Plan for UK carbon emissions.

3 Committee discussion

The evaluation committee considered evidence submitted by ITF Pharma UK, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Duchenne muscular dystrophy is a fatal, rare genetic disorder that begins in childhood and causes systemic loss of muscle function and progressive disability. It is caused by mutations in the dystrophin gene, which is essential for maintaining the structural integrity of muscle fibres. Without dystrophin, muscles gradually weaken and deteriorate, which affects the entire body. Because the dystrophin gene is on the X chromosome, the condition primarily affects boys and young men, although in rare cases girls may also be affected. In the UK, it is estimated that around 100 people are born with Duchenne muscular dystrophy each year and around 1,183 people are currently living with the condition. Symptoms typically begin when a child is between 2 and 5 years old and include delayed walking, frequent falls, and difficulty rising from the floor.

Duchenne muscular dystrophy is a systemic condition, affecting multiple body systems. As it advances, people lose the ability to walk and use their arms. It can cause skin complications due to pressures applied by having limited mobility. Breathing muscles become progressively weaker, making it harder to breathe. The heart's ability to pump blood effectively is also reduced and cardiac problems can lead to unexpected death. Duchenne muscular dystrophy is also associated with neurobehavioural comorbidities, including intellectual disability, attention deficit disorders, and autism spectrum disorder. When walking is no longer possible, people with Duchenne muscular dystrophy must use mobility aids such as wheelchairs. They also need regular healthcare appointments to monitor their spine, heart, and breathing during sleep. The spine can develop scoliosis, which may need surgery. By their teens or early twenties, most people with Duchenne muscular dystrophy need night-time non-invasive ventilation

(NIV). This involves wearing a mask or mouthpiece connected to a machine that helps maintain oxygen levels and reduce the strain on their lungs while sleeping.

In the most advanced stages, people need continuous ventilatory support (full-time ventilation). Cough assistance is also often needed to help clear the airways. By adulthood, most people with Duchenne muscular dystrophy need help with all aspects of self-care, including eating, drinking, using the toilet, dressing, washing, and moving. People with Duchenne muscular dystrophy become increasingly dependent on others, including their families and carers, because they need continuous, day-and-night care to support them in their daily lives. Despite improvements in supportive care, Duchenne muscular dystrophy remains a fatal condition, with life expectancy typically under 30 years, most often due to respiratory or cardiac failure. The committee noted the considerable challenges in generating robust evidence for a rare, progressive childhood condition with a long-term disease course such as Duchenne muscular dystrophy. It concluded that it would take these challenges into account in its decision making (see section 3.39).

Disease progression and milestones

3.2 Some key milestones used to describe the progression of Duchenne muscular dystrophy are:

- loss of ambulation (LOA): no longer being able to walk with or without support or no longer being able to stand with support
- NIV: having to use a ventilator at night to aid breathing
- forced vital capacity (FVC) less than 1 litre: a proxy measure for when someone would need a ventilator all the time.

  The clinical experts highlighted that, while these milestones are useful, all aspects of disease progression are important. They explained that focusing on the 3 milestones can be too simplistic. For example, arm and hand function is important for independence. The patient experts agreed with this and highlighted that other outcomes are equally if not more important than the 3 key milestones. A patient expert explained that while LOA was

important, losing upper limb function was much more difficult for their son. This was because it meant there were many things he could no longer do, such as feed himself, adjust his glasses or scratch an itch. Another patient expert explained that delays in progression were invaluable to them all through the course of the disease. They explained that they still have some hand function and extending that would allow them to continue to do things they enjoy, such as playing chess, which was very important to their wellbeing. The patient experts also added that any delay from starting full-time ventilation would be incredible. The difference between night-time and full-time ventilation is very big and the impact of a full-time ventilator is enormous. The patient expert explained that the transition to full-time ventilation is extremely difficult, much harder than losing the ability to walk, and the value in delaying it is immeasurable.

Impact of the condition

3.3 Duchenne muscular dystrophy has a profound and far-reaching effect on the lives of people with the condition and their families and carers. Because it is a progressive disease, it leads to increasing physical disability and loss of independence. It also causes significant emotional and psychological strain for people with the condition and the people who care for them. Siblings may experience feelings of worry, guilt, or isolation, and their lives are often shaped by the needs and routines of the family member with Duchenne muscular dystrophy. As the condition advances, people need full-time support, day and night, for daily activities, personal hygiene, mobility, and medical care. This has a considerable and sustained impact on carers. Even in the earlier stages, support is needed to attend medical appointments or respond to emergencies. Patient and carer submissions described the diagnosis of Duchenne muscular dystrophy as devastating. One carer conveyed that witnessing their child progressively lose physical abilities and face a shortened life expectancy, while other children continue to develop normally, had been psychologically overwhelming. They reported severe and lasting emotional impacts, including a loss of identity, career, relationships, and personal wellbeing. They described living with constant grief, ongoing anticipatory loss, and a persistent need to remain vigilant, with no real moments of relief. Even positive experiences were overshadowed by the fear that each milestone could be the last.

Patient organisation submissions emphasised the importance of treatments that can slow the condition's progression and the positive psychological impact that slower progression can have on people with Duchenne muscular dystrophy and their families. Maintaining independent movement, use of their arms and hands, and delaying the need for full-time ventilation is seen as essential for preserving independence, mental wellbeing, and participation in everyday life. Delaying the loss of mobility and maintaining independence during the teenage years is particularly important. This is a time when most young people are becoming more independent, learning to drive, attending university, and spending more time with friends. By contrast, at the same point in life people with Duchenne muscular dystrophy are likely to be experiencing increasing dependence. This can be emotionally challenging and isolating. For some, the loss of mobility is also associated with experiences of bullying or social exclusion, further affecting mental health and self-esteem. Delaying this loss can help preserve a sense of autonomy and self-worth. It may also allow people to continue doing things that are important to them, such as attending university lectures, socialising, and pursuing their interests. These aspects of independence are not only practical but are also deeply connected to emotional wellbeing, identity, and inclusion. Clinical experts noted that people who lose ambulation later tend to manage better overall. They explained that delaying progression was valuable at any stage of Duchenne muscular dystrophy, not just in delaying LOA. The committee understood that Duchenne muscular dystrophy has a substantial and far-reaching impact on people with the condition, as well as on their families and carers. It concluded that there is a clear need for effective treatments for Duchenne muscular dystrophy and that any treatments that delayed progression would be valued by people with Duchenne muscular dystrophy and their families and carers.

Clinical management

Treatment options

3.4 There is currently no cure for Duchenne muscular dystrophy. Management focuses on slowing disease progression, preserving muscle function, and

improving quality of life through a combination of pharmacological treatments and multidisciplinary care. Established clinical management (ECM) includes using corticosteroids such as prednisolone and deflazacort. These are typically started in early childhood and have been shown to prolong the ability to walk independently and delay the onset of complications. The clinical experts explained that starting steroid treatment as early as possible not only delays LOA but also results in a more pronounced delay in other disease milestones. More recently, vamorolone has been recommended as an alternative corticosteroid (see NICE's technology appraisal guidance on vamorolone for treating Duchenne muscular dystrophy in people 4 years and over, from here TA1031). Supportive care is essential and includes physiotherapy, respiratory and cardiac monitoring, nutritional support, and orthopaedic interventions. As the condition progresses, people may need NIV for periods during the day, at night and then all the time. Other interventions may include spinal surgery for scoliosis and assistive technologies to support mobility and communication. Ataluren is available for people with Duchenne muscular dystrophy caused by a nonsense mutation in the dystrophin gene. Multidisciplinary care is delivered through specialist neuromuscular centres, known as NorthStar Centres. These provide coordinated access to physiotherapists, occupational therapists, respiratory and cardiac specialists, and neuromuscular clinicians.

Comparators

3.5 NICE's scope defined the comparators as ECM without givinostat, and ataluren for people 2 years and over who have a nonsense mutation in the dystrophin gene and are able to walk. In its submission, the company included only ECM without givinostat, consistent with the population and treatment regimens used in the EPIDYS trial (see section 3.9). The company did not include ataluren as a comparator, explaining that it is offered to only a small proportion of people with Duchenne muscular dystrophy (see section 3.4). The company also did not include vamorolone in ECM. It said that this was because the corticosteroid was only recently approved and its long-term efficacy is uncertain. The company said that it would also likely be used in both arms of the analysis, with minimal impact on the relative treatment effect. The EAG agreed that ECM is the most relevant comparator. It also agreed that including vamorolone would likely have little impact on the relative-effectiveness results. But the EAG noted that vamorolone

has a different adverse-event profile and cost compared with other steroids, which could affect resource use and health-state utility values. The clinical experts stated that vamorolone is currently prescribed to very few people; one centre reported that only 4 out of 100 people with Duchenne muscular dystrophy were having it. They explained that deflazacort was the most widely used steroid, followed by prednisolone, which aligns with the treatment patterns seen in EPIDYS. The committee concluded that ECM as defined by the company was an appropriate comparator for this evaluation.

Positioning of givinostat

Company's positioning

3.6 The company restricted the population in its submission to people 6 years and over who are ambulant at the start of treatment (although there was no restriction in its submission on people continuing givinostat after LOA). This is consistent with the population in the EPIDYS trial and the EPIDYS open-label extension (OLE) study (see section 3.9 and section 3.10). 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.

Defining ambulant

3.7 The definition of ambulant used in Study 43, EPIDYS and the OLE study was the ability to walk independently. This was assessed by tests such as 4-stair climb test, the time to rise from the floor test or 6-minute walk test (see section 3.9 and section 3.10). In the UK real-world study, LOA was assessed using the 10-metre walk test (see section 3.12). The Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS) used full-time wheelchair use to define loss of ambulation (see section 3.13). The EAG expressed concern about differences between how ambulation is defined in clinical trials and clinical practice, and the challenges of applying a consistent definition across the NHS. Some of the assessments used in the trials, such as the 4-stair climb test, may not always be practical or routinely used in clinical

settings. Clinical experts felt that the definitions used in trials and in practice were broadly similar. They noted that some measures, for example the 10-metre walk test, might not give the same results in a clinical trial setting and clinical practice. Both the clinical and patient experts emphasised that the real-world understanding of ambulation is broader and more closely aligned with what is known as the transfer stage. In this stage, people are no longer able to walk or rise from the floor unaided but can still stand with support. This transfer stage is considered an ambulatory state in the economic model (see section 3.19). The clinical and patient experts agreed that the definition of ambulant should include the transfer stage. Clinical experts considered this definition of ambulant to be clinically meaningful and practical to apply consistently in routine care. The committee thought that the definition of ambulant was relevant because of the company's restriction to the ambulant starting population and because it reflected how people transitioned through the economic model, and it could affect how the clinical trial evidence was interpreted. The committee agreed that defining ambulant as being able to walk or stand, with or without support, was appropriate for this evaluation.

Non-ambulant starting population

3.8 The company restricted the population to people who are ambulant at the start of treatment (see section 3.6). This restriction only applied to the starting population, so people who started givinostat when ambulant and later lost ambulation could continue treatment. The clinical experts noted however that people who are non-ambulant at the start of the treatment may still benefit from treatment. So, restricting treatment start based on ambulation status could exclude people who might otherwise experience important benefit from treatment. The patient experts thought that givinostat should be available to all people with Duchenne muscular dystrophy and that it would be unfair to deny it to people who had already lost ambulation. A patient expert explained that using LOA as a cut-off is an arbitrary choice and that they felt it did not make sense to base access on this endpoint. A patient expert organisation submission stated that not extending any recommendation to a non-ambulant starting population would constitute discrimination (see section 3.40). The company explained that at the time of submission, it only had evidence for the ambulant starting population. So, it could only model the cost effectiveness of givinostat in this

population. It noted there is a trial in progress called ULYSSES, which is assessing givinostat in a non-ambulant starting population. The committee acknowledged the broader licensed population and the views of clinical and patient experts. It discussed whether excluding the non-ambulant starting population from any recommendation could be considered discrimination, and considered NICE's commitment to eliminating discrimination, advancing equality, and fulfilling its legal and wider equality obligations. The committee felt that excluding a non-ambulant starting population because of a lack of evidence would be a proportionate means of making evidence-based recommendations and ensuring a cost-effective use of NHS resources. It stated that, while it prefers to consider the full population in the marketing authorisation, it could only do so where there is sufficient evidence. It acknowledged the potential benefits in the non-ambulant starting population, but it explained that no evidence in this population was presented. It also explained that it would expect the nature and scale of clinical benefits and the cost effectiveness to be meaningfully different in this group, given the possibility that the ambulant starting population might get a carryover effect from delaying LOA but the non-ambulant starting population would not (see section 3.25). The committee concluded that it was only able to make recommendations for people who start givinostat while ambulant, in line with the evidence that was presented by the company.

Clinical effectiveness

EPIDYS trial

3.9 EPIDYS was a multicentre, randomised, double-blind, placebo-controlled phase 3 trial that enrolled 179 people aged 6 years and over with genetically confirmed Duchenne muscular dystrophy. All participants were having stable corticosteroid treatment at the start of the trial. The inclusion criteria specified that people had to still be able to walk without help at the time of enrolment. This meant that all recruited people were ambulant at the start of treatment, according to the trial definition of ambulant. Specifically, people had to complete the 4-stair climb test twice, each in 8 seconds or less and within 1 second of variance. They also had to do the time to rise from the floor test in 3 seconds or more but less than 10 seconds. People were stratified into 2 groups based on vastus lateralis fat

fraction (VLFF) at baseline:

- group A (n=120), with VLFF over 5% and less than or equal to 30%
- group B (n=59), with VLFF less than or equal to 5% or over 30%.

Participants were randomised in a 2:1 ratio to have either givinostat (n=118) or placebo (n=61) for 18 months. The primary objective was to assess the effect of givinostat on disease progression. Disease progression was measured by the change in the results of the 4-stair climb test between baseline and 18 months. In the full EPIDYS population (groups A and B; n=179), the log-transformed geometric least-squares mean ratio in change from baseline was 0.84 (95% confidence interval [CI]: 0.73 to 0.96; p=0.012). This indicated that givinostat significantly slowed decline in stair-climbing performance compared with placebo. Following completion of EPIDYS, people in the study were eligible to enter the OLE study.

EPIDYS OLE study

3.10 The OLE study (n=207) evaluated the long-term safety, tolerability and efficacy of givinostat. It included people from EPIDYS and Study 43. Study 43 (n=20) is a phase 2 and 3, open-label clinical trial designed to evaluate the safety, tolerability, pharmacokinetics, and early efficacy of givinostat in people with Duchenne muscular dystrophy. As with EPIDYS, people in the study were also having stable corticosteroid treatment at study start. The inclusion criteria specified that people had to be able to walk independently at the time of enrolment. Specifically, people had to complete the 6-minute walk test twice, achieving at least 250 metres and within 30 metres of variance. People who completed EPIDYS and Study 43 or who were eligible for EPIDYS but were not enrolled could enter the OLE study for continued monitoring of long-term safety and efficacy. In the OLE study, everyone had oral givinostat twice daily, with dosing adjusted based on body weight and blood parameters. Monitoring included regular assessment of platelet counts and other safety markers, with predefined criteria for dose adjustment or treatment discontinuation. Key clinical outcomes included time to LOA (defined as inability to walk 10 metres in 30 seconds or less), changes in motor function (such as stair-climbing ability and NorthStar Ambulatory Assessment scores), and respiratory function (including

the need for NIV, or FVC less than 1 litre). At the start of the OLE study, 12 people (6%) were non-ambulant (having lost ambulation during EPIDYS or Study 43). The reported key results from the OLE study for median age at LOA were:

- 16.7 years in people who had givinostat in EPIDYS and Study 43 (the givinostat group; n=119)
- 17.3 years in people who had placebo in EPIDYS (the delayed givinostat group; n=58)
- not calculable in people who were recruited to EPIDYS (all group B) but because of timing were not randomised and were instead entered directly into the OLE study (the givinostat-naive group; n=30).

  No results are available for non-ambulatory outcomes such as NIV or FVC less than 1 litre because the data is immature (not enough events occurred). The OLE study is ongoing and is expected to provide further insight into the long-term impact of givinostat on disease progression and safety.

Indirect comparisons

The available data

3.11 The company did not use relative-effectiveness data from EPIDYS in the economic model because of its short follow up (18 months). Instead, it did unanchored matching-adjusted indirect comparisons (MAICs). The company reweighted givinostat individual patient data from EPIDYS and the OLE study (see section 3.10) to better match the ECM data from both the UK real-word dataset (see section 3.12) and the CINRG DNHS (see section 3.13). The committee acknowledged that the clinical evidence is immature.

ECM data

UK real-world dataset

3.12 The company used a multicentre, retrospective case-note review study in the relative-effectiveness analyses. The study included 209 people who had treatment at some of the specialist NorthStar Centres at University College London, Newcastle upon Tyne or Oxford University Hospitals NHS Foundation Trusts (from now, the UK real-world dataset). People were stratified into 3 groups:

- corticosteroid-naive (used corticosteroids for 12 months or less; n=53)
- corticosteroid stopped (used corticosteroids for at least 12 months but stopped before moving to adult services; n=43)
- corticosteroids continued (continued corticosteroids into adulthood; n=113).

Of these, 156 people were included in the unanchored MAIC. People who had corticosteroids for less than 12 months were not included in the analysis because this group is not reflective of UK clinical practice. Age at initiation of corticosteroid treatment was the only prognostic factor available in the UK real-world dataset. This was used as a matching variable in the company's preferred unanchored MAIC. In addition, Kaplan–Meier curves are available only for age at NIV and FVC less than 1 litre in the UK real-world dataset, while data for age at LOA is limited to median only. Therefore, the company approximated a Kaplan–Meier curve for age at LOA by applying an acceleration factor (the median age at LOA divided by median age at NIV) to the Kaplan–Meier curve for age at NIV. The EAG accepted that the UK real-world dataset was an appropriate source for the natural history model (see section 3.19), but considered a different dataset to be more appropriate for the MAIC.

CINRG DNHS

3.13 The EAG preferred to use the CINRG dataset to estimate relative effectiveness in the MAIC because it was a better match with the EPIDYS and the OLE study data.

The company did a sensitivity analysis using international data from the CINRG DNHS. In this dataset, 3 prognostic factors are available and were used as matching variables:

- age at corticosteroid initiation
- age at diagnosis, and
- deflazacort use.

The EAG highlighted that CINRG has more prognostic factors available for matching than the UK real-world dataset. They also noted that Kaplan–Meier curves are available for all 3 milestones (age at LOA, NIV, and FVC less than 1 litre). The clinical experts explained that CINRG data had an unexpectedly low age of diagnosis of 2.7 years, which did not reflect their experience in the UK. They also believed that CINRG may have included people with other neuromuscular conditions, such as Becker muscular dystrophy, which is less severe than Duchenne muscular dystrophy. They did not believe that this historical dataset aligned with clinical practice.

Choice of data source for ECM

3.14 The clinical experts explained that the NorthStar Registry collects data on age at LOA, NIV, and FVC less than 1 litre. They considered the UK real-world dataset used by the company to be representative of UK clinical practice. The clinical experts explained that it is difficult to predict the prognosis in Duchenne muscular dystrophy. So, they said that it is hard to identify all the prognostic factors and there may be some that are unidentified. Although, they did say that age of starting corticosteroids is likely the most important prognostic factor available. They explained that age at diagnosis could also have prognostic value but that much of this might be linked to age at starting steroids. For example, someone diagnosed later can only start steroids later. The EAG pointed out that when trying to inform relative effectiveness in a MAIC, it was more important for the 2 datasets to match each other than to match UK clinical practice. This was noted by the committee, but it thought that the possible misclassification bias in the CINRG database was a substantial limitation. It also felt that, ideally, the whole NorthStar Registry would have been used to inform the ECM arm of the

MAIC, but it noted that this was not available. It was reassured that the UK real-world dataset provided a reasonable proxy for the whole NorthStar Registry. The committee acknowledged the uncertainty linked to the lack of potential prognostic variables and the need to approximate LOA Kaplan–Meier data using an acceleration factor. But despite this, it concluded that the UK real-world dataset should be used to inform the unanchored MAIC.

Givinostat data

EPIDYS and the OLE study

3.15 At the first meeting, the company included a post-hoc group from EPIDYS and the OLE study (n=148) in the relative-effectiveness analyses. The group excluded 58 people who had placebo in EPIDYS but who went on to have givinostat in the OLE study (the delayed givinostat group). This was because the company considered that an 18-month period of disease progression without givinostat could be a confounder. The company also excluded people in Study 43 (n=18) because of different inclusion and exclusion criteria and givinostat exposure. But it included 17 people from EPIDYS who did not enter the OLE study. During technical engagement the company also provided a MAIC scenario using the full population from EPIDYS and the OLE study (n=224). The EAG noted that the naive givinostat group (n=30) that was included in the post-hoc group appeared to perform better than the other subgroups. But it also noted that the company's excluded delayed givinostat group (n=58) results appeared in line with the rest of the subgroup. So, it preferred to include analyses with the full population from EPIDYS and the OLE study (n=224) in its base case. The committee did not think that having 18 months of disease progression without givinostat was likely to be a confounder. This was because EPIDYS included people aged 6 years and over. So, the age when they started givinostat would differ across the EPIDYS and the OLE studies anyway. It also noted that the results for the delayed givinostat group were similar to the group that had givinostat in EPIDYS. The committee concluded that the full givinostat population from EPIDYS and the OLE study (n=224) should be used for decision making.

Approximated givinostat data

3.16 The EPIDYS and OLE study data is immature and has very few recorded NIV events and no recorded FVC less than 1 litre events in the givinostat population (see section 3.10). So, the company approximated givinostat median values for age at NIV and FVC less than 1 litre using acceleration factors calculated from the UK real-world dataset. It said that this approach did not model a treatment effect beyond LOA. The company approach was to calculate acceleration factors by dividing the median age at NIV or FVC less than 1 litre by the median age at LOA (see table 1). This gave acceleration factors of 1.50 for age at NIV, and 1.94 for age at FVC less than 1 litre, implying that these endpoints happened 1.50- and 1.94-times later than LOA. The acceleration factors were then applied to the observed givinostat Kaplan–Meier curve for LOA to approximate Kaplan–Meier curves and medians for givinostat NIV and FVC less than 1 litre.

The EAG explained that the use of acceleration factors assumes that the relationship between outcomes for givinostat is the same as for ECM. It also assumes that the givinostat treatment effect is constant across all 3 milestones. The EAG considered both assumptions to be highly uncertain. The committee recognised that the need to approximate givinostat age at NIV and FVC less than 1 litre presents additional uncertainties when modelling givinostat's cost effectiveness.

Unanchored MAIC results

3.17 In response to the call for additional evidence, the company updated the MAICs using the committee-preferred datasets, the UK real-world dataset (see section 3.12) and the full givinostat population from EPIDYS and the OLE study (see section 3.10). But it still used acceleration factors to estimate age at NIV and FVC less than 1 litre. The unanchored MAIC results suggest that givinostat increases observed age at LOA, estimated age at NIV, and estimated age at FVC less than 1 litre compared with ECM. The results showed:

- for age at LOA:
  - hazard ratio: 0.201 (robust standard error 0.142 to 0.285)

  - givinostat observed median: 17.97 years
  - ECM median: 12.28 years
- for age at NIV:
  - hazard ratio: 0.206 (robust standard error 0.145 to 0.293)
  - givinostat estimated median: 27.00 years
  - ECM median: 18.46 years
- for age at FVC less than 1 litre:
  - hazard ratio: 0.218 (robust standard error 0.149 to 0.321)
  - givinostat estimated median: 34.90 years
  - ECM median: 23.86 years.

The committee noted that the company had updated the MAIC in line with its preferences (see section 3.14 and section 3.15). It thought that the MAIC results were still associated with some uncertainty because of the uncertainties in the approximated givinostat data (see section 3.16) and the ECM data (see section 3.14).

Economic model

Non-reference discounting

3.18 The company base case applied a non-reference 1.5% discount rate to health outcomes only for the full time horizon of the analysis. The committee may consider a discount rate of 1.5% per year to cost and health outcomes for the full time horizon of the analysis if specific criteria are met. The criteria are that the technology:

- is indicated for people who would otherwise die or have very severely impaired life

- is likely to restore people to full or near-full health
- has benefits that are likely to be sustained over a very long period.

The company acknowledged that givinostat does not meet all 3 criteria, but it suggested that the criteria for non-reference discounting excludes Duchenne muscular dystrophy. This is because people with the condition cannot, by definition, be restored to full or near-full health, despite benefits accruing over a long time. The patient experts agreed with the company. They also suggested that this may be a discrimination issue because it implies that curing disability is the ultimate goal and that disabled people do not lead fulfilled lives. They also stated that this criterion may breach NICE's duty to consider equity and long-term societal impact (see section 3.40). The EAG's clinical expert thought that it was possible that in the future, treatments may cure or at least stop the progression of Duchenne muscular dystrophy. Previous evaluations in Duchenne muscular dystrophy have consistently applied the reference-case discount rate of 3.5% across the full time horizon.

The committee recognised that there is no provision in NICE's methods for only applying the 1.5% discounting rate to health outcomes, as the company had done in its base case. It stated that, if it were applied, the reduced rate should also apply to costs. The committee understood the role of the NICE methods and that changing those methods is beyond its remit, but it acknowledged the concerns around the 'restoring to full or near-full health' criterion. It considered how it should interpret and apply this criterion, including in the context of the equality issues raised. The committee noted that 'restoring to full or near-full health' could be interpreted in different ways and did not think that it would necessarily exclude progressive conditions. It recalled NICE's highly specialised technologies guidance on onasemnogene abeparvovec for treating spinal muscular atrophy, which looked at another progressive condition affecting children. In that evaluation, the committee applied the 1.5% discounting rate to the treatment even though many of the children who had it would never be able to walk independently. So, the committee did not think that progressive conditions were excluded from using non-reference-case discounting under the existing criteria. It also thought that in the context of a severe progressive condition such as Duchenne muscular dystrophy, it might reasonably interpret 'restoring to full or near-full health' to mean stopping progression. It noted that while

givinostat delays disease progression, it does not stop it. In addition, the committee recalled that longer-term clinical effectiveness of givinostat is uncertain (see section 3.17), so it was unclear if the benefits would be maintained over a very long period. It concluded that givinostat does not meet the second criteria for applying a lower discount rate and might not meet the third criteria, and that a 3.5% discount rate should be applied to both costs and health outcomes.

Natural history model

3.19 The company's model structure is based on the HERCULES natural history model. It was developed through Project HERCULES, a collaborative initiative led by Duchenne UK. It is a Markov model that captures the progression of Duchenne muscular dystrophy though 8 clinically defined health states before death (state 9) and was previously used in TA1031. But the clinical experts in TA1031 found that the original natural history model overestimated survival compared with clinical expert opinion. So, the company updated the model. It used the SOLVER function to calibrate transition rates for the first 3 transitions in the model and for mortality transitions from health state 8. It did this to better reflect the UK real-world dataset on 50-year survival and key clinical milestones, such as LOA and initiation of ventilation. The EAG agreed that the UK real-world dataset is an appropriate source to inform the natural history model (see section 3.12). The clinical experts considered the median milestone values in the updated natural history model to be broadly consistent with what is seen in clinical practice. The EAG noted that the natural history model matched the median values from the UK real-world dataset but overestimated the tail of the curve. For example, the median (50th percentile) LOA was 12.2 years in the UK real-world dataset and 12.1 years in the natural history model. But, at the 75th percentile the UK real-world dataset was 13.7 years and the natural history model 15.3 years. The EAG thought that this showed the updated natural history model does not reflect the underlying survival distribution from the UK real-world dataset, and was a source of residual uncertainty. It noted that this may explain why applying the MAIC hazard ratios directly in the model led to implausible results (see section 3.22). The committee noted these residual uncertainties but concluded that the updated natural history model was suitable for decision making.

Model transitions

3.20 The HERCULES natural history model was used to estimate health-state occupancy for the ECM arm. There are 8 overall health states. These are implemented as 10 health states in the model, depending on the order in which hand-to-mouth function is lost and night-time ventilation is started (differentiating health states 7a and 7b, and 8a and 8b). In the model there are 9 transitions covering the various living health states. There are 3 ambulatory health states (1 to 3) and 5 non-ambulatory health states (4 to 8):

- health state 1: early ambulatory
- health state 2: late ambulatory
- health state 3: transfer
- health state 4: hand-to-mouth function and no ventilation
- health state 5: no hand-to-mouth function and no ventilation
- health state 6: hand-to-mouth function and night-time ventilation
- health states 7a and 7b: no hand-to-mouth function and night-time ventilation
- health states 8a and 8b: full-time ventilation.

Modelling approaches from the first meeting

3.21 At the first meeting, the company used the unanchored MAIC results with the UK real-world dataset and the post-hoc group from EPIDYS and the OLE study to inform the clinical effectiveness of givinostat. But the company did not use the MAIC hazard ratios directly in the model. It thought that this would triple count the treatment effects on the outcomes. Instead, it used the givinostat MAIC-adjusted medians to estimate model transitions using the SOLVER function (see section 3.23). Each givinostat median was used to estimate hazard ratios for 3 transitions, as follows:

- LOA for informing ambulatory transitions (transitions to health states 2, 3 and

4)

- NIV for informing transitions to health states 5, 6, and 7a (non-ambulatory transitions), and
- FVC less than 1 litre for informing transitions to health states 7b, 8a and 8b (non-ambulatory transitions).

The company said its base case did not model any treatment effect beyond LOA because its SOLVER approach preserved the proportional relationship between the 3 milestones from the ECM in the givinostat arm. The EAG used the unanchored MAIC results with the CINRG DNHS dataset and the post-hoc group from EPIDYS and the OLE study to inform the clinical effectiveness of givinostat. Unlike the company, it applied the MAIC hazard ratio for age at LOA directly to the model. The EAG:

- used the LOA hazard ratio for informing ambulatory transitions (transitions to health states 2, 3 and 4) and
- assumed no difference between givinostat and ECM for all other transitions (hazard ratio of 1 for non-ambulatory transitions).

The EAG explained that their approach relies only on the observed data. It thought that the company's approach did model a treatment effect after LOA. It also thought that if the aim was to not model any treatment effect beyond LOA, the SOLVER approach was needlessly complicated, unlike the EAG's approach. The committee was concerned about the estimates and application of the givinostat treatment effect using the 2 different approaches. It wanted to ensure that the givinostat treatment effect was correctly reflected in the model. So, in its call for additional evidence, it asked for further exploration of modelling the givinostat treatment effect and its application in the model.

Additional evidence: modelling approaches

Direct application of MAIC hazard ratios

3.22 The company explored using the MAIC hazard ratios directly in the model using the committee-preferred datasets (see section 3.17). It found that this produced clinically implausible results such as a median age at LOA of over 30 years. The EAG thought that applying hazard ratios from the MAIC directly to the transitions is technically the most appropriate approach. It thought that proportional hazards appeared to hold in the MAIC and so applying the MAIC hazard ratios directly to the natural history model transitions should model plausible outcomes for givinostat. It also thought that using the SOLVER function to adjust the natural history model (see section 3.19) might have contributed to the implausible predictions under this approach. Alternatively, the lack of adjustment for possible prognostic factors in the MAIC (see section 3.14) might mean that the MAIC hazard ratios overestimate the effectiveness of givinostat, resulting in implausible estimates. The committee acknowledged that the predictions made by applying the MAIC hazard ratios directly to the model were clinically implausible and that other approaches would have to be considered. It concluded that this was associated with uncertainty.

The SOLVER approach

3.23 The company retained using the SOLVER function used at the first meeting (see section 3.21). Given the limitations of applying the MAIC hazard ratios directly (see section 3.22), the EAG switched to using the SOLVER function. The SOLVER function simultaneously modifies all 9 transition probabilities in the model to match the modelled medians with the clinical medians. The company used medians from the unanchored MAIC based on the committee-preferred datasets (see section 3.17). The EAG noted there were several uncertainties with the SOLVER approach. Specifically:

- it does not have any estimates of uncertainty and so treatment effect is excluded from the probabilistic sensitivity analyses
- it is focussed solely on the medians and, given that when the SOLVER approach was used in a similar way to calibrate the natural history model

(see section 3.19) it overestimated the tail of the distribution, the same could be true for givinostat, and

- the company's use of SOLVER relies on the MAIC medians for age at NIV and FVC less than 1 litre, which are based on acceleration factors and are therefore uncertain (see section 3.16).

Because of this last point, the EAG used the SOLVER function but estimated the missing givinostat milestones for median age at NIV and FVC less than 1 litre in a different way (see section 3.24). The committee acknowledged the uncertainties associated with using the SOLVER function and the lack of other approaches available. On balance, it concluded that using the SOLVER function to estimate hazard ratios for model transitions is appropriate for decision making and it would decide on which givinostat medians to use for the SOLVER inputs for age at NIV and FVC less than 1 litre.

Estimates of relative effectiveness

3.24 The company retained its original base case using acceleration factors to generate MAIC-adjusted medians for the SOLVER (see section 3.17). The company still thought this approach was conservative because it said it did not model a treatment effect beyond LOA even though such a treatment effect was likely in reality. The EAG acknowledged the testimony from the clinical expert at the first meeting, who said that givinostat would not be expected to only affect ambulation and could plausibly affect all outcomes. But, the EAG noted there was no evidence for this. So, it preferred to model its base case with no treatment effect beyond LOA and then explore additional treatment effects in scenarios (see section 3.26). The EAG applied the treatment effect to the time between milestones, rather than the milestones themselves. It used the same ECM data, but instead used the delays in the ECM data milestones (that is, absolute time between the milestones rather than proportional relationship between them) to estimate givinostat median age at NIV and FVC less than 1 litre. The company's and EAG's base-case estimates are summarised in table 1. The EAG thought that the company base case actually models a constant treatment effect across the lifetime of the model. This is shown by:

- a 46% improvement (compared with ECM) in medians for all 3 milestones,

and

- the same acceleration factors being applied to the givinostat arm as the ECM arm (1.50 for NIV and 1.94 for FVC less than 1 litre).

The EAG further explained that if, as the company stated, no treatment effect beyond LOA is assumed, the ratio of givinostat median to ECM median should decline for each subsequent milestone. This is shown in the EAG base case by:

- a smaller improvement in givinostat medians versus ECM medians for later milestones (46% for LOA, 31% for NIV and 24% for FVC less than 1 litre), and
- smaller acceleration factors for givinostat than for ECM (1.34 for NIV and 1.64 for FVC less than 1 litre).

The company's and EAG's approaches result in different medians for the 3 milestones and so the SOLVER-estimated model transition rates are also different. The committee examined the 2 methods and concluded that:

- the EAG base-case approach did not model a treatment effect beyond LOA
- the company base-case approach did model a treatment effect beyond LOA, although it was unclear whether this was direct treatment effect, carryover effect or a combination of both (see section 3.25).

The committee noted that it would explore the direct and indirect carryover components of treatment effects in the different modelling approaches.

Table 1 Company's, EAG's and committee's preferred medians for key milestones

Milestone	ECM (company, EAG and committee preferred)	Givinostat (company preferred)	Givinostat (EAG preferred)	Givinostat (committee preferred; EAG scenario 2)
Age at LOA (years)	12.28	17.97	17.97	17.97
Age at NIV (years)	18.46	26.96 (approximated)	24.15 (approximated)	26.99 (approximated)

Milestone	ECM (company, EAG and committee preferred)	Givinostat (company preferred)	Givinostat (EAG preferred)	Givinostat (committee preferred; EAG scenario 2)
Age at FVC less than 1 litre (years)	23.86	34.86 (approximated)	29.55 (approximated)	32.39 (approximated)

Abbreviations: EAG, external assessment group; ECM, established clinical management; FVC, forced vital capacity; LOA, loss of ambulation; NIV, non-invasive ventilation.

Plausibility of ongoing treatment effect

3.25 Both the company and EAG agreed that treatment effect beyond LOA is clinically plausible but uncertain. The patient experts agreed and noted that as people lose the ability to walk and stand with support this does not mean that they will stop benefitting from givinostat. The clinical experts explained that, based on experience with steroids and on the mechanism of action of givinostat, any treatment effect could be made up of a direct effect on muscles and an indirect cumulative or carryover effect of delaying earlier disease milestones. For example, being immobile and sitting in a wheelchair for long stretches of time puts more pressure on the lungs, heart and other bodily systems. So, delaying LOA could reduce damage to the muscles in the respiratory and cardiac systems too. This would be in addition to the direct effects of givinostat on those systems. But, the clinical experts also noted that, given givinostat's mechanism of action, it was plausible that there might be a greater direct treatment effect when there is more muscle available to preserve. And, in contrast, there might be a smaller direct effect at the later stages. Overall, taking into account the direct effect and the carryover effect, the clinical experts thought it was plausible that givinostat could delay later milestones by a greater absolute amount than it delayed LOA. The clinical experts also noted that people losing ambulation earlier have a very different trajectory than those who lose it later, with much worse outcomes. A patient expert said that having steroids early meant they did not lose ambulation until they were 16 years old, which they feel has put them on a better trajectory. The patient expert added that benefits are not restricted to ambulation and that being able to use upper limbs is important for self-care and mental wellbeing.

The committee recalled how important delaying disease progression is for people with Duchenne muscular dystrophy and their carers (see section 3.3). It noted

that there was no evidence beyond LOA and considered the testimony from the clinical and patient experts. The committee concluded:

- a treatment effect beyond LOA should be included in the model
- this treatment effect would comprise a direct effect of givinostat on muscle tissue and an indirect or carryover effect of delaying a previous milestone
- it is plausible that the direct treatment effect of givinostat would decrease as the disease progresses and there is less functional muscle tissue remaining
- there is no evidence on treatment effect beyond LOA, and the magnitude of any treatment effect and the contributions of direct and carryover effects are highly uncertain.

  The committee acknowledge that the lack of evidence on treatment effects beyond LOA means the modelling will rely on assumptions and predictions and will therefore carry additional uncertainty.

Scenarios for treatment effect beyond LOA

3.26 The company included scenarios conditional upon its base case exploring treatment effect beyond LOA. They were:

- scenario 1: additional 20% reduction in the 6 hazard ratios for the NIV and FVC less than 1 litre outcomes in the model
- scenario 2: applied alternative acceleration factors when estimating givinostat median values for NIV and FVC less than 1 litre (this resulted in even larger treatment effects across the 2 milestones than scenario 1).

  The EAG only explored scenarios extending treatment effect to NIV. This is because their clinical experts considered that although an ongoing direct effect was plausible, it was very uncertain whether it would be seen in the late stages of the disease because of accumulating fibrosis. The EAG also noted that the median ages at which people stopped givinostat in the model were 22.58 years in the company base case and 21.92 years in the EAG base case. This is lower than median age at NIV (26.96 years in the company base

case and 24.15 years in the EAG base case). The EAG explained that direct treatment effect is not possible after stopping treatment and only a carryover effect would be possible. It added that the majority of people on NIV would have stopped treatment. So, applying the full treatment effect to NIV would bias the model towards givinostat because the modelled treatment discontinuation reduces costs with no reduction in efficacy. The EAG would have preferred a model that could apply different treatment effects to people on and off treatment. In the absence of such a model, the EAG's 2 scenarios were:

- scenario 1: assuming 50% of treatment effect on LOA for NIV (no effect on FVC less than 1 litre), and
- scenario 2: assuming 100% of treatment effect on LOA for NIV (no effect on FVC less than 1 litre).

The committee recalled that company's base case applied a constant treatment effect to everyone across all milestones, regardless of discontinuation, while the EAG's preferred base case applied treatment effect only to LOA (see section 3.24). It did not think either of these approaches were appropriate for decision making. It also noted that in all scenarios givinostat extended time in every health state except health state 8, where it reduced time. The committee thought this was counterintuitive, especially given the discussions about the ongoing direct and carryover treatment effects. This contributed to uncertainty in the modelling. The committee felt that the second EAG scenario, which applies 100% of the treatment effect of LOA to the delay to NIV, was preferable for decision making. This was because it reflected the potential for an ongoing direct treatment effect and a carryover treatment effect as noted by the clinical experts. But, it noted that in the presence of relatively high discontinuation in the model, this scenario could overestimate the effectiveness of givinostat and so was also associated with uncertainty. The company, EAG and committee-preferred medians for the key milestones are summarised in table 1. Overall, the committee concluded that the second EAG scenario should be used for decision making, despite the associated uncertainties.

Patient health-related quality of life

Patient utilities

3.27 At the first meeting, the company used utility values from a recent US study by Audhya et al. (2023), which collected EQ-5D-5L data directly from people with Duchenne muscular dystrophy (n=63). This was because the health-related quality-of-life data in EPIDYS and the OLE study was collected using the Pediatric Outcomes Data Collection Instrument (PODCI) and the Pediatric Quality of Life Inventory (PedsQL). But there was no validated mapping algorithm for PODCI and the company had concerns about the uncertainty introduced by mapping from PedsQL. Audhya et al. used a US population and value set but was mostly based on self-reported data (76%) and used the EQ-5D instrument preferred by NICE (albeit the 5L version rather than the 3L). The company also included a scenario based on Landfeldt et al. (2017). Landfeldt and colleagues wrote a number of publications based on a large, cross-sectional, observational study of people with Duchenne muscular dystrophy from Germany, Italy, the UK and the US (n=770). The EAG preferred to use data from the UK-based burden-of-illness (BOI) study (n=24), done under Project HERCULES. This study used the Duchenne Muscular Dystrophy Quality of Life (DMD-QoL) instrument and was 100% self-reported. The EAG thought that it was more relevant to the NHS setting and was the only study aligned with the health states used in the economic model. The EAG highlighted that the BOI study was the only source to distinguish between night-time ventilation and full-time ventilation (health states 7 and 8), an important clinical distinction.

At the first meeting, the patient expert read out a testimony from a person having full-time ventilation. It strongly challenged the assumption that the 2 ventilation states could be assigned the same utility value. While night-time ventilation allowed for periods of independence and lower care needs, full-time ventilation needed constant supervision, with any interruption posing a life-threatening risk. The patient expert explained that full-time ventilation is associated with a significant increase in anxiety, loss of privacy, and an inability to be left alone. It is also associated with a substantial rise in care costs and a marked decline in quality of life. They highlighted the emotional and practical burdens of managing complex care needs and the impact on daily activities and social interactions. The testimony conveyed a strong desire to return to the night-time ventilation stage,

even briefly. The patient experts also raised concerns about the plausibility of the BOI utility values, noting that in some cases the values suggested improvements in quality of life as the disease progressed. For example, the BOI utility set used a lower utility value for health state 2 (late ambulatory, 0.49) than for health state 7 (no hand-to-mouth function, night-time ventilation, 0.52), which completely lacked face validity. The committee was concerned about face validity of the values reported in the studies and how reported utility values were assigned to model health states. It wanted to ensure that the model reflects the increasing impact on people as the condition progresses. So, it asked for patient health-related quality-of-life modelling and assumptions to be further explored during its call for additional evidence.

Additional evidence: patient utilities

3.28 In response to a call for additional evidence, the company added a scenario using Crossnohere et al. (2021). This study included 263 people (74 from the UK) and used EQ-5D-3L with some self-reporting (23%) but applied a US tariff. But, the company maintained that Audhya et al. (2023) is the most appropriate source because it collected EQ-5D-5L data directly from people with Duchenne muscular dystrophy (76% self-reports). The EAG acknowledged limitations of the BOI study. It highlighted that because the company did not use the trial data, all available options have methodological and plausibility limitations. The EAG felt that the BOI study is still the most appropriate source given it was done as part of the HERCULES project and was used in TA1031. The BOI study, although aligned with the model, had incomplete and limited data for individual disease stages. A patient expert explained that despite being part of the HERCULES project, the BOI study has a number of methodological issues. These include difficulties matching responses with health states and a small sample size. As a result, it is not a reliable source for the patient utilities. The other patient expert had strong concerns about the BOI values. They again highlighted that the values lack face validity because it does not make sense that in a severe progressive disease, quality of life would decline and then go up again.

The patient experts also noted the limitations of using EQ-5D in Duchenne muscular dystrophy. For example, the EQ-5D focuses a lot on 'usual activities' and while many people with Duchenne muscular dystrophy can do their usual

activities, they cannot do a range of other things. Also, it is very difficult to estimate quality of life in children. The committee acknowledged the challenges of collecting patient health-related quality-of-life data in rare, progressive diseases, and especially in those that affect children, such as Duchenne muscular dystrophy. It recognised the limitations associated with each data set but noted that quality of life is a fundamental component of cost-effectiveness analysis and that it would have to select a utility set for decision making. The committee heard the clear evidence from the patient experts, and so considered that the BOI study was not a reliable source. It said that trial data would have been preferred but understood that it was not available. From the options available, the committee concluded that the Audhya et al. (2023) utility set, with a multiplier from Landfeldt et al. (2017) to differentiate between state 7 and 8, is suitable for decision making.

Carer health-related quality of life

Carer utilities

3.29 At the first meeting, the committee discussed challenges in the modelling in 4 areas:

- Carer utility value data: the company used utility values from a UK vignette study and the EAG used Landfeldt et al. (2016).
- Number of carers modelled: the company modelled 2 carers in all health states (including state 9). The EAG modelled 1 carer per person in the ambulatory health states (health states 1 to 3) and 2 carers per person in the non-ambulatory states (health states 4 to 8), and no carers in state 9.
- Modelling approach: the company used an 'increment relative to midway approach', which calculated an increment relative to health state 4 and applied that increment to the life years gained for givinostat for each carer. The EAG used a 'disutility approach', which calculated decrements by subtracting the utility value for each health state from health state 1.
- Life-extension benefit: the company modelled a decrement of -0.56 (calculated from a utility of 0 for carers in state 9) to the negative incremental

life years in state 9 for each carer (multiplying these 2 negatives gave a positive carer quality-adjusted life year [QALY] gain, which the company explained as an 'extension-to-life benefit for carers'). The EAG did not model any carers in state 9, and so there was no direct effect of life extension modelled on carers.

The EAG thought that using the vignette study was not appropriate because direct measurements were available. It explained that Landfeldt et al. (2016) collected EQ-5D-3L, which is preferred by NICE. The committee acknowledged the limitations of all sources of carer utilities. It was concerned about the face validity of the values reported in the studies, how reported utility values were assigned to model health states, and the lack of evidence on number of carers. The EAG's preferred base case still resulted in a carer QALY gain with givinostat, but the gain was much smaller than in the company's base case. The EAG's approach captured an increasing impact of Duchenne muscular dystrophy on carers as the disease progresses. Because extending the time in each health state extends the duration of that impact, it leads to a prediction that extending life in Duchenne muscular dystrophy worsens carer quality of life. Patient experts also raised that the EAG's approach implied that extending the life of people with Duchenne muscular dystrophy worsens carer QALYs. The patient experts said that this was the exact opposite of their experience, which is that extending the life of people with Duchenne muscular dystrophy would improve carer QALYs. One patient expert explained that there is a physical burden of care that would no longer apply after the death of the patient (in state 9). But they said this would be completely outweighed by the emotional anguish of losing a child. They said that it was unreasonable to think that there would be no negative effect of losing a child on health-related quality of life. The committee understood why the EAG's modelling approach created the predictions it did, but it clearly heard the testimony of the patient experts and considered that the EAG's approach was not appropriate for decision making. But it also thought that the company's approach of using of the -0.56 decrement lacked clear justification, evidence and face validity. This approach modelled a QALY gain of 0.56 for each carer for each year of life extension for the patient having givinostat treatment. The committee did not consider this plausible. It concluded that carer health-related quality of life needs to be captured appropriately, but neither the company's nor the EAG's approaches to quantify this had done so. The committee acknowledged the sensitivity and

critical importance of this issue for people with Duchenne muscular dystrophy and their families, and the substantial technical challenges associated with it. So, it concluded that further information and modelling was needed and requested further exploration of this in the call for additional evidence.

Additional evidence: carer utilities

Source of carer utilities

3.30 In response to the call for additional evidence, the company shared interim results from an unpublished study from the Sheffield Centre for Health and Related Research (from here, the Sheffield study). The Sheffield study collected data from parents or people with parental responsibility. The results are confidential and cannot be reported here. The company and EAG both used the Sheffield study in their updated base cases. It reported values for ambulatory states 1 and 2 combined, with values for other states available. Because only a small number of responses were available for the later stages, the company used the average value from the non-ambulatory health states for all non-ambulatory health states (states 4 to 8). The EAG considered that the number of responses for health state 4 was reasonable. So, it used the specific value for that health state and an average value (weighted by sample size) for non-ambulatory health states 5 to 8. There were 3 versions of the Sheffield utility data available:

- Sheffield 1: company approach where health states 4 to 8 all have the same average value
- Sheffield 2: original data from the study, which has separate values for each health state but very low samples in the later health states and some counterintuitive results
- Sheffield 3: EAG approach where health states 1 to 4 have specific values but health states 5 to 8 use an average value weighted by sample size.

The patient and clinical experts supported this evidence, but noted that neither the company nor EAG approach differentiated between health states 7 and 8. The committee noted the lack of evidence on carer health-related

quality of life in general. It also specifically noted the challenges in collecting reliable evidence in rare, progressive diseases like Duchenne muscular dystrophy and so it welcomed this new data. The committee noted that the Sheffield 1 data did not distinguish between health state 4 and the subsequent health states. This meant that when used with the company's base-case approach (see section 3.32), the model assumed a carer QALY gain associated with ambulatory states. But, the model assumed no effect on carers (either positive or negative) of life extension in later health states (health states 4 to 8). The committee thought that progression would have an increasing impact on carer health-related quality of life and that the utility values should reflect this as much as possible. It thought that the EAG's approach used the available granularity of the data better. The committee concluded that using the Sheffield 3 dataset was appropriate for decision making.

Number of carers

3.31 Based on the confidential results from the Sheffield study (see section 3.30), the company updated the number of carers needed in each model state. It modelled:

- 2 carers per person in the ambulatory health states (health states 1 to 3)
- 3 carers per person in the non-ambulatory states (health states 4 to 8), and
- 3 carers in state 9 (see section 3.33).

The EAG did not update its approach to modelling, retaining 1 carer in the ambulatory states and 2 in subsequent states. It acknowledged that Duchenne muscular dystrophy affects all carers but retained its approach because:

- it interpreted the model as accounting for average full-time informal carers, and it thought that it was unclear if all of the carers recorded in the Sheffield study would be full time, and
- the utility values from the Sheffield study were specifically from parents or those with parental responsibility and it was unclear how generalisable these values would be to non-parent carers.

The patient expert highlighted that it is important not to conflate physical burden of caring with the wider health-related quality of life of carers. They explained that the impact on health-related quality of life goes well beyond carer burden. The impact on mental and social wellbeing of carers, including parents, siblings, grandparents and wider family and friends, is felt well before the physical burden of care. Then, as the physical impact increases, the impact on carers increases. The other patient expert agreed and noted that the concept of 'full-time care' is unclear. If full-time care (equivalent to continuous, day-and-night care) was calculated, the number of carers would be much higher than what is currently included in the company model. As an example, in 1 week, 2 parents will often provide care that might require a team of 9 paid carers. Those 9 carers would all be considered to be working full time. The patient and clinical experts highlighted 2 aspects of caring:

- first, the physical impact (sometimes referred to as a burden) of caring for a family member with Duchenne muscular dystrophy
- second, the profound impact on carer's mental and social wellbeing of a family member having Duchenne muscular dystrophy.

The committee agreed with the patient and clinical experts and did not think that assuming 1 carer in the ambulatory health states and 2 carers in the non-ambulatory health states was realistic. It noted that there was some uncertainty around whether the utility values from the Sheffield study would apply to non-parent carers. But from the options available, it felt that the company's approach was a good compromise. It concluded that the company approach of assuming 2 carers per person in the ambulatory health states and 3 carers per person in the non-ambulatory states is appropriate for decision making.

Modelling approach

3.32 The company retained the 'increments relative to midway' approach to calculating carer QALYs. This calculated an increment relative to health state 4 and applied that increment to the life years gained for givinostat in each health state. But, the company base case was updated using the Sheffield 1 data (see section 3.30).

The updated company's base case resulted in 0.58 incremental carer QALYs acquired over the 8 health states and a total of 10.51 incremental carer QALYs when the extension-to-life benefit is applied (see section 3.33).

The EAG acknowledged the committee's concerns around its previous modelling of carer quality of life using the disutilities approach (see section 3.29) and updated its modelling by using a utility approach. This method actively models carers by applying health-state utilities directly in the model and calculating the absolute QALYs of each carer. The EAG applied this approach with the Sheffield 3 data (see section 3.30). This approach results in 7.83 givinostat incremental carer QALYs (acquired over the 8 health states) when used with the other parameters from the company base case and 7 incremental carer QALYs in the EAG base case. The EAG explained that it preferred the utilities approach because it:

- implies that an extension-to-life of the patient results in increased carer QALYs, and
- already implicitly incorporates an extension-to-life benefit, so the additional modelling used in the company base case is not needed (see section 3.33).

The committee recalled hearing about the impact of caring for a family member with Duchenne muscular dystrophy and its profound impact on carers' mental and social wellbeing (see section 3.3). It noted the lack of consensus in modelling carer health-related quality of life. It further noted that the company's approach using health state 4 as an anchor point to calculate increments was an arbitrary decision and did not reflect the disease progression. It thought that the EAG's approach was simple, intuitive and avoided contradicting the experiences reported by the patient experts regarding the effect of life extension on carers. It noted that both company and EAG base cases resulted in very large incremental carer QALYs for givinostat. The committee concluded that the utility approach to modelling carers' health-related quality of life is appropriate for decision making.

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

3.33 In response to the call for additional evidence, the company retained the decrement to the incremental years spent in state 9 (see section 3.32), but it now

modelled 3 carers in state 9 for the duration of the incremental life years (see section 3.31). The resulting decrement is confidential and cannot be reported here. But, it was larger than the decrement the company used at the first meeting (-0.56). Of the 10.51 incremental carer QALYs in the company's base case, 9.93 of them were from state 9 after the death of the person with Duchenne muscular dystrophy. Only 0.58 QALYs were acquired in health states 1 to 8. The EAG had explained that the utilities approach already incorporates an extension-to-life benefit indirectly, so no additional modelling is necessary (see section 3.32). It felt that the company approach was novel and not evidence based. In addition to the implied effects of life extension in its modelling, the EAG also presented a scenario exploring an additional effect of modelling an explicit bereavement decrement. It was based on a perinatal mortality study. This scenario applied a decrement of -0.224 in state 9 for 3 years. This resulted in 0.01 QALYs gain in state 9 after the death of the person with Duchenne muscular dystrophy and had minimal effect on the incremental cost-effectiveness ratios (ICERs). The committee noted that because bereavement ultimately occurred in both arms, the net effect of this scenario was to model only the delay in the bereavement in the givinostat arm, and so the effect was a numerically modest addition to the already captured effects of life extension. The committee recalled that it preferred the utility approach for modelling carer health-related quality of life, and understood that this captured health-related quality-of-life benefits to carers associated with extending the life of a person with Duchenne muscular dystrophy (see section 3.32). The committee was also uncertain why the company's extension-to-life-benefit approach produced more incremental carer QALYs than the EAG's utility approach. But, it thought that a bereavement adjustment should be included in the model to attempt to explicitly capture the effect of bereavement on carers, and considered that the EAG's approach was acceptable. It concluded that the effects on carers of life extension for people with Duchenne muscular dystrophy were acceptably captured by the EAG's carer utility modelling approach.

Costs

Resource use

3.34 The company selected Morgan et al. (2024) as the primary source for health-state costs in the economic model. The study was based on the Project HERCULES UK longitudinal study using the Clinical Practice Research Datalink. It included scenario analyses using other sources, including the BOI study and Landfeldt et al. (2014). The EAG initially preferred the BOI study done under Project HERCULES. But, following technical engagement, it agreed with the company that Morgan et al. is the most suitable and robust source for health-state costs. In response to clarification questions, the company included a scenario in which a multiplier was used to increase the cost in state 8. Similarly, it included a scenario using a multiplier and inflating costs to include tertiary-care and medical-aid costs. Nonetheless, the EAG maintained its view that the cost estimates in later stages of the condition, when the burden on NHS and personal social services resources increases, may be underestimated. The committee was concerned that adding tertiary-care and medical-aid costs, and differentiating between health states 7 and 8, were not fully explored. It wanted to ensure that the increasing costs as the condition progresses were reflected in the model. So, it asked for cost modelling and assumptions to be further explored during its call for additional evidence.

Additional evidence: resource use

3.35 In response to the call for additional evidence, the company made no changes to its base case and did not introduce additional scenarios. It highlighted that scenarios differentiating between health states 7 and 8 and costs for tertiary care and medical aid were already explored. The EAG reverted to using the BOI study because it does differentiate between health states 7 and 8 and because it was used in TA1031. It used annual direct medical cost used in TA1031 and applied it in its preferred base case. The committee noted that both the EAG's and the company's base-case costs, although using different sources, are similar. The patient expert explained that despite being part of the HERCULES project, the BOI study has a number of methodological issues and is not a reliable source for

the cost data. They further explained that accessing cost information is particularly challenging, especially in the later stages of the condition. The committee acknowledged challenges in collecting reliable cost data for rare, progressive diseases like Duchenne muscular dystrophy and the resulting uncertainty in the available data. It noted that the choice of cost inputs does not significantly impact the overall cost-effectiveness estimates. The committee considered patient expert testimony regarding limitations in the BOI study and concluded that Morgan et al. (2024) should be used to inform decision making.

Resource use: uncaptured costs

3.36 The committee discussed the Morgan et al. (2024) cost set and considered costs that might be missing from the estimates. The patient expert had explained there are barriers to access even basic medical care for people with Duchene muscular dystrophy. This is because even simple procedures require additional support. For example, a 1-week hospital stay and specialist team care was needed for their son to have a colonoscopy. The more disabled a person is, the more specialist care is needed. These additional costs would not be captured, but are all relevant. The patient testimonies also estimated that the annual cost of care could be between £40,000 to £100,000 for people having night ventilation and between £250,000 and £380,000 for people in full ventilation stages. Another patient expert explained that the cost can be even higher, when people with Duchenne muscular dystrophy or their carers are not managing their care themselves, and using agencies instead. They noted that cost can be up to £500,000 per year. The clinical experts agreed that the costs included in the company's and EAG's base case are too low, especially for the later stages of the disease. Several multipliers were proposed by the company and EAG to explore uncertainties in the cost set:

- 1.57-times multiplier based on the UK BOI study to explore adding tertiary-care and medical-aid costs
- 3.05-times multiplier based on Landfeldt et al. (2014) to explore adding tertiary-care and medical-aid costs
- 30-times multiplier based on patient testimony to explore adding costs of social care borne by local authorities or the NHS

- 1.30-times multiplier based on the BOI study to differentiate between health states 7 and 8.

  The EAG explained that only the exploratory 30-times multiplier scenario based on a patient testimony has a substantial effect on the resulting cost effectiveness of givinostat. But it also noted that givinostat (compared with ECM) increases time spent in all health states, except for health state 8 (see section 3.20). As a result, in the exploratory 30-times scenario, the costs in health state 8 are lower in givinostat than in ECM. This has large influence on total cost, making the difference in cost between the 2 treatments much smaller, with givinostat appearing much cheaper. The EAG was concerned because treatments that slow disease progression are normally more costly as people are being treated for longer. It was unsure whether the reduced time in health state 8 for givinostat compared with ECM was plausible and, if it was not, then applying this modifier might bias the model in favour of givinostat. The committee agreed with the EAG. It concluded that it would not apply this modifier but acknowledged that this meant that potentially very high additional costs (such as those borne by local authorities to provide care) were not captured in the model. It thought that this was associated with substantial uncertainty but that the true effect of incorporating these costs on the ICERs was unclear. The committee thought that the costs should differentiate between health states 7 and 8 and should reflect the high costs that the patient experts had spoken about. The committee concluded that the approach most able to do this, and that is therefore appropriate for decision making, was using Morgan et al. (2024) with:

- the company's 1.30-times multiplier differentiating between health states 7 and 8, and
- the 3.05-times multiplier increasing costs to include tertiary-care and medical-aid costs.

Severity

1.7 severity multiplier

3.37 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs, called a severity modifier, if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's manual on technology appraisal and highly specialised technologies guidance. The company assumed a starting age of 6 years based on the age in the marketing authorisation. The company base case resulted in a severity modifier of 1.7. Applying the committee's preferred assumptions (see section 3.38) also resulted in a severity modifier of 1.7. The committee understood that Duchene muscular dystrophy is a severe, progressive and fatal disease that arises in childhood and causes significant effects on health-related quality of life. So, the committee concluded that the severity weight of 1.7 applied to the QALYs was appropriate.

Cost-effectiveness estimates

Committee's preferred assumptions and ICER

3.38 The committee recalled its preferred assumptions, which were to:

- use ECM based on treatment regimens used in EPIDYS as a comparator (see section 3.5)
- use the UK real-world dataset as a source for ECM data in the unanchored MAIC (see section 3.14)
- use the full givinostat population from EPIDYS and the OLE study as a source of givinostat data for the unanchored MAIC (see section 3.15)
- use the reference-case discount rate of 3.5% for outcomes and costs (see section 3.18)

- use the company's updated natural history model (see section 3.19)
- use SOLVER to apply treatment effect to the model (see section 3.23)
- use the EAG scenario of modelling treatment effect beyond LOA as 100% of treatment effect on LOA for NIV (see section 3.26)
- use Audhya et al. (2023) to model patient utilities (see section 3.28)
- use the 1.7 severity modifier (see section 3.37)
- use Sheffield 3 data as a source for carer health-related quality of life (see section 3.30)
- assume 2 carers per person in the ambulatory health states, and 3 carers per person in the non-ambulatory health states (see section 3.31)
- use the EAG's utility approach to modelling carer health-related quality of life (see section 3.32)
- include the EAG's bereavement disutility scenario (see section 3.33)
- use Morgan et al. (2024) with the company's 1.30-times multiplier differentiating between health states 7 and 8, and the 3.05-times multiplier increasing costs to include tertiary-care and medical-aid costs (see section 3.35 and section 3.36).

  When taking into account how severe Duchene muscular dystrophy is and how it affects both quality and length of life, the committee's preferred ICER was marginally higher than £35,000 per QALY gained. Because there is a confidential discount for givinostat, the exact ICER cannot be reported here.

Committee's view on the ICER

3.39 NICE's manual on technology appraisal and highly specialised technologies guidance notes that, above a most plausible ICER of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER, aspects that relate to uncaptured benefits and non-health factors, and aspects that relate

to health inequalities. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also be mindful that there are certain circumstances in which evidence generation is particularly difficult. The committee understood that above a most plausible ICER of £35,000 per QALY gained, it would need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources.

The committee noted the high level of uncertainty, specifically the:

- lack of adjustment of potential prognostic factors in the MAIC (see section 3.14)
- overestimation of the tails of survival probabilities by the updated natural history model (see section 3.19)
- inability to use the MAIC hazard ratios directly in the model without generating implausible results (see section 3.22)
- need for SOLVER to estimate model transitions (see section 3.23)
- immaturity of the trial data and requirement to approximate givinostat age at NIV and FVC less than 1 litre data (see section 3.16)
- face validity concerns about why givinostat reduces time in health state 8 despite extending time in all other health states (see section 3.36)
- application of givinostat treatment effect in the model in the context of discontinuation (see section 3.26)
- patient health-related quality-of-life assumptions (see section 3.28)
- carer health-related quality-of-life assumptions (see section 3.30 to 3.33)
- exclusion of local authority or NHS care costs from the model (see section 3.36).

The committee noted the considerable challenges in generating robust evidence for a rare, progressive childhood condition with a long-term disease course such as Duchenne muscular dystrophy. It recognised that long-term outcomes are difficult to capture within feasible study timeframes. Evidence generation is also further constrained by limited sample sizes, heterogeneity

in disease progression, and the challenges and complexities of involving children and young people in clinical trials. Together, these factors restrict the availability of high-quality evidence and increase the degree of uncertainty, leading to greater reliance on modelling assumptions. The committee understood that the NICE's manual on technology appraisal and highly specialised technologies guidance specifies that it can make recommendations accepting a higher degree of uncertainty in specific circumstances where evidence generation is particularly difficult. The committee recognised that the difficulties in collecting evidence in Duchenne muscular dystrophy meant that a greater tolerance for uncertainty than usual was appropriate. Moreover, it recognised the significant attempts to mitigate uncertainty in Duchenne muscular dystrophy through Project HERCULES. It considered the other factors that it should take into account in its decision making, and noted in particular the impact of disease progression, and of delaying disease progression, at key stages in young people's lives. Taking all these considerations into account, and considering the full range of evidence and the specific circumstances of this appraisal, it concluded that there was a sufficient case to conclude that givinostat would represent an effective use of NHS resources.

Equality

3.40 The committee noted that Duchenne muscular dystrophy affects children and young adults and that presentation in girls is very rare. Age and sex are protected characteristics under the Equality Act 2010. It was aware that some people with Duchenne muscular dystrophy have learning or behavioural difficulties, ADHD, autism, or pre-existing psychiatric difficulties. It noted that a significant proportion of people with these issues cannot take corticosteroids and may find assessments and tests difficult. It also heard that some people with Duchenne muscular dystrophy can struggle to access specialist treatment centres because of location, mobility or transport issues. In response to the call for additional evidence, stakeholders noted a number of additional potential equality issues. They highlighted that rare diseases disproportionately affect disabled and paediatric populations. For example, they raised concerns about:

- issues with measures of carer's health-related quality of life

- limitations with paediatric health-related quality-of-life measures
- inappropriate standards for paediatric disability
- the requirement for restoring to full health for the non-reference 1.5% rate for cost and health effects, and
- the exclusion of social care costs.

Stakeholders also:

- noted that NICE processes do not account for living with a severe disability or for those who will become wheelchair users (disabled people have worse health outcomes, raising questions about health inequalities)
- felt that NICE's methods guide fails to operationalise flexibility, which could breach NICE's duty to consider equity and long-term societal impact
- thought that limiting any recommendation to an ambulant starting population would constitute discrimination
- suggested that the Medicines for Children Policy could apply
- noted potential health inequalities and associative discrimination in employment of parent carers, further highlighting that parent carers suffer poor health outcomes and are predominantly female, and
- explained the intersectionality of protected characteristics, including age, disability, sex, and pregnancy or maternity characteristics under the Equality Act 2010, and the compounded disadvantage these characteristics can have on carers.

The committee was aware that collecting any evidence in rare and progressive diseases starting in childhood such as Duchenne muscular dystrophy is very difficult. The NICE's manual on technology appraisal and highly specialised technologies guidance includes flexibility to appropriately consider evidence in such rare diseases, and the committee considered these flexibilities throughout its deliberations. It recalled that it had considered each of the following potential issues in detail:

- patient health-related quality of life (see section 3.28)

- carer health-related quality of life (see sections 3.29 to 3.33), and
- social care cost (see section 3.35).

The committee thought that there were no further potential equality issues beyond its consideration of those issues.

The committee discussed the other equality issues that were raised. It explained that the Medicines for Children Policy is not within the remit of NICE. NHS England can apply this policy to treatments that are already recommended in adults. It recalled its careful consideration of the non-ambulant starting population (see section 3.8) and non-reference-case discounting (see section 3.18), including the equality issues. It considered that the equality issues had been addressed. The committee carefully considered all potential health inequalities relating to disability and carers. The committee concluded that there are no further equality issues that could be addressed in a technology appraisal or further steps or adjustments needed in light of its equalities duties.

Conclusion

Recommendation

3.41 The committee understood the nature of Duchenne muscular dystrophy and its profound impact on people with the condition and their carers and families. It recognised the importance of effective treatments that could delay progression, and noted the clinical effectiveness evidence for givinostat. When taking into account how severe Duchenne muscular dystrophy is, and how it affects both quality and length of life, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources (see section 3.39). So, givinostat can be used routinely in the NHS to treat Duchenne muscular dystrophy in people 6 years and over who are ambulant (able to walk or stand, with or without support) at the start of treatment (see section 3.8).

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Section 4 of The Innovative Medicines Fund Principles states that a discretionary source of early funding (from the overall Innovative Medicines Fund budget) is available for certain medicines recommended by NICE. In this instance, interim funding has been agreed for givinostat. Interim funding will end 90 days after positive final guidance is published at which point funding will switch to routine commissioning budgets.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has Duchenne muscular dystrophy and the healthcare professional responsible for their care thinks that givinostat is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

This topic was evaluated as a single technology evaluation by the highly specialised technologies evaluation committee. Because of this, some members of the technology evaluation committees were brought in to provide additional expertise to the committee. The highly specialised technologies evaluation committee and the 4 technology evaluation committees are standing advisory committees of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Iolo Doull
Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

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