NICE National Institute for Health and Care Excellence

Highly Specialised Technology (HST) Evaluation

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY (HST) EVALUATION

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from BioMarin**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Rare Disease Research Partners
   b. The MPS Society – Sophie Thomas
   c. The MPS Society – Katy Brown
   d. Birmingham Women's and Children's NHS Foundation Trust
   e. Great Ormond Street Hospital
   f. University College London NHS Foundation Trust

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Company factual accuracy check**

6. **Evidence Review Group – factual accuracy check response**

7. **Evidence Review Group – addendum following second committee meeting**

8. **Evidence Review Group – further addendum following second committee meeting**

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

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2)

Highly specialised technology (HST) evaluation

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	BioMarin International Limited	The Committee notes in the ECD that ***'the Managed Access Agreement (MAA) period has been extended twice to allow the company more time for its submission. Despite this, there were still issues with the company's analysis and modelling'*** **(section 3.3, page 6).** The company appreciates the collaboration with NICE and NHS England to the challenges on what has been a very complex process due to lack of early alignment on multiple issues which are captured below, and we hope provide learnings for future reappraisals of MAAs: • **Lack of alignment early on with ERG/Nice Technical Team with regards to the analysis plan meeting the objectives of the scope.** The focus of all parties has not considered the actual scope of this re-submission, which is focused on future treatment-naïve patients, who are predominantly newly diagnosed patients. These newly diagnosed patients are likely to have notably different phenotype or characteristics compared with the previously treated MAA cohort. For example, the newly diagnosed cohort would be expected, to be younger, have a lower weight and less disease manifestation at the time of initiating treatment. These factors would be expected to positively influence the clinical and cost-effectiveness estimates for elosulfase alfa as we describe in this response document. However, most of the evidence considered by the NICE Committee to date has been based on the overall MAA cohort, most had significant morbidity upon starting treatment. In this response, we provide additional evidence on a cohort from the MAA that is likely to be more reflective of the scope. • **Lack of alignment on a core dataset prior to starting the analysis plan which meets the scope.** Not all sources of data were aligned and shared prior to starting analysis (i.e., clinical data from treatment centres, patient-reported outcomes data from Rare Disease Research Partners (RD-RP), and notes on missing data and treatment decisions data from the NICE oversight committee). This created confusion and incoherency in the data. However, there have been multiple engagements and a strong collaboration between NICE, RD-RP and the	Thank you for your comments. At the second meeting, the appraisal committee discussed the company's new evidence. After the second committee meeting, elosulfase alfa was recommended for treating mucopolysaccharidosis type 4A (MPS 4A) in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			company during technical engagement (post first technical report in April 2021), which helped in creating a harmonised dataset. • **Lack of alignment on how to manage missing data and prioritise the analysis plan.** Following collaboration on finalising a core dataset with shared understanding there was alignment on priorities for analysis to meet the needs of the evidence review group (ERG). These also explored handling missing data, imputations where applied had minimal impact on results and given the nature of missing data (i.e., tests not conducted for various clinical reasons) it was agreed that imputation did not make sense to prioritise. • **Lack of alignment on analysis methods and approaches.** Given the missing data in the core dataset **t**here remained uncertainty around very low sample size with complete core data (particularly with a complete case analysis or CCA approach) and interpretation of results from this analysis versus MOR001. *[CCA is a statistical analysis that only includes study participants for which we have no missing data on the variables of interest].* Lack of an aligned analysis plan led to different perspectives on methods on how to approach the uncertainty support the questions asked in the scope. • **Unrealistic expectations on the real-world evidence based MAA.** The ERG expectation for data collection and management, was more in-line with one that would ordinarily consider for a prospective clinical study. This MAA/coverage with evidence was real world observational data captured by experts and not designed to align to clinical study standards. As a real-world evidence, the MAA has a high quality of data capture vs. registries and other approaches which is a testament to the efforts of the community. Misaligned expectations from the data resulted in a lot of work to answer questions which the data is not structured to answer, thereby limiting time for more relevant analyses. The issues highlighted above in terms of clarity of remit for revaluation and handling of data collection process in the MAA is a potential learning opportunity for all stakeholders and the company feels that these are important to address for future MAA processes and the ongoing Innovative Medicines Fund consultation. Some of the issues in the HST2 process are described in more details below and relate to the further responses in this document. • The original MAA and commercial agreement had different specifications on the subsequent evaluation which had been raised during the MAA oversight committee meetings. A clear	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			pathway for the re-evaluation for elosulfase alfa was not agreed until September 2020 and formally shared with the company on 10th November 2020, for a submission of evidence for the Highly Specialised Technologies Evaluation by 11th December 2020. Whilst the Company had the submission from February 2020 in place with the latest clinical evidence (but no cost-effectiveness)), the whole MAA population and subsequent modelling had to be re-analysed following the new agreement with NICE and NHSE to reflect 2017 changes to the NICE's process for HST and updated scope, with minimal time to align with experts. • We appreciated NICE's efforts to try to secure an ERG in 2020. However, the delay in securing the ERG combined with the ERG not having been involved in the 2015 submission led to the ERG having an expectation for a more complete set of evidence than that realistic in a MAA. There was a considerably higher number of clarification questions (68 questions) than what we would have expected for a re-submission. The company believes these questions have not considered the disease characteristics and dataset limitations (i.e., ultra-rare heterogenous disease, real-world dataset, existing natural history data) or informed the scope on future naïve patients treated in England. The lack of alignment with the NICE technical team on scope of analysis also related to less direction to the ERG on the key questions. • Several questions regarding gaps and missing data were raised during ERG's review of the MAA dataset. However, as mentioned above, there was a strong collaboration with NICE, RD-RP and treatment sites to create an aligned dataset. The Company requested a 6-month period for data verification and analysis but was granted only 3 months which allowed only for prioritised analyses as requested by the ERG. These requests were driven by focus on finding a comparable population like a clinical trial rather than considering key questions and areas of uncertainties such as starting severity e.g., baseline 6MWT, treatment benefit in future naïve patients, relevance of long-term outcomes and accounting for heterogeneity. • During the technical engagement, analysis was prioritised due to the limited timeframe with the NICE technical team and ERG. Concerns were raised by the Company to the NICE technical team and NHSE on the approach focusing on re-creating comparative data for the first two years of treatment, which already is captured within clinical studies. More importantly, it was highlighted that reducing the data to 1 or 2 years with the complete case analysis (CCA) approach would lead to losing the attention on the long-term data. Having to conduct the CCA left limited time for more relevant analysis and restricted the sample size,	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			which was not controlled for confounders such as age of starting treatment. Despite these limitations, NICE technical committee recommended that the company deliver on the priority CCA analyses requested by the ERG. All parties were time-limited and focused but maybe the relevance and limitations were not completely discussed.	
2	Company	BioMarin International Limited	On the **relevant data sources for decision-making (section 3.4, pages 6-8)**, the Committee notes in the ECD that *'some people in the clinical trial may have had elosulfase alfa every other week, and that this may have underestimated the treatment benefit. It was concerned that, by excluding people who had had treatment, some valuable long-term data was disregarded. The committee concluded that both the company's and ERG's preferred data sources were relevant for decision making'.* In response to this point, the company would raise the issue that the scope of the NICE HST2 review is treatment-naïve patients moving forward. Clinical opinion supports the case that future patients will be newly diagnosed patients who are expected to be around the ages of 2-3 years. In the MAA data, treatment-naïve patients who started under the age of 6 have an average age of 3.6 years. In addition, there is the potential that non-classical patients, diagnosed at a later age, may present very occasionally. Sibling studies (Frigeni et al. 2021, Ficicioglu et al. 2020, Barak et al. 2020) in MPS IVA have highlighted meaningful differences in long-term disease progression with early diagnosis and early treatment, indicative of expected potential outcomes for newly diagnosed patients in England due to increased efforts in diagnostic efforts, including nationally available genetic testing. Therefore, to align with the future population, the company looked at data in patients treated under the age of 6 and focused on this population in the model. The Company's submission in December 2020 focussed on the longer-term data, and responses to the initial clarification questions showed comparisons between the natural history cohort and long-term data which showed sustained clinical efficacy in wheelchair use, 6MWT, and FVC. However, following the initial clarification questions, the focus of the ERG was solely on prioritising the first two-year CCA comparison from the MAA to MOR-001 (Morquio A natural history study), which limited resources for continuing the analysis of the long-term data. The Company has discussed that patients, receiving lower doses of elosulfase alfa during the clinical trial were switched to the approved dose and the longer-term data would indicate their response on	Comment noted. At the second meeting, the appraisal committee discussed the baseline age of patients who have not previously had elosulfase alfa. The committee agreed that this group would be younger and healthier at baseline. See section 3.5 in the final evaluation document (FED). After the second committee meeting, elosulfase alfa was recommended for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the approved dose. The lower dose was found in the MOR-004 clinical study to offer less efficacy and this may underestimate the efficacy in the long-term data. The Company has included this data as relevant and important, and the propensity scored analysis or PSM (i.e., statistical method to construct an artificial control group by matching each treated patient with a non-treated patient of similar characteristics) in the clarification questions (ID1643 clarification letter from ERG 150121 IA ACIC_v4_22022021) showed consistent benefits for treatment vs MOR-001 over the long-term data in ex-trial patients. The Company would highlight that the overall MAA data does not represent the relevant future population and as such it would be critical to extrapolate outcomes in the relevant dataset representing early diagnosed and early treated patients. BioMarin in this response shared an approach to model this relevant population's outcomes (see issue 14 below). The data is more limited in this population but has greater relevance to the scope.	
3	Company	BioMarin International Limited	Regarding **data analyses issues (section 3.5, page 8)**, the Committee notes in the ECD that it was *'disappointed that the company did not provide more robust analyses in its submission, given the burden put on healthcare staff, people with MPS 4A and their families. This was particularly so given the additional time afforded to the company to try to address the data issues.'* The Company would highlight the MAA process was the first in England and has encountered many changes and challenges over the years of implementation. Initially the MAA data was to be reconciled and managed by NHSE, but after two years this was requested to be managed by the Company. In this type of real-world data capture there was no planning from the beginning for medical monitors or data scientists as this is not a clinical study or associated funding to clinicians for data input. As such the quality of data input was down to the experts, Company, patients and associated company providing patient reported outcome data. The learnings from this MAA should be implemented into future MAAs. More robust analysis would have required more time once the scope had been finalised and more aligned guidance with the NICE technical team around an aligned statistical analysis plan. Indeed, scope of the submission was formally shared with the company on the 10th November 2020 with a submission deadline on the 11th December 2020. The NICE technical team could then have supported discussions with the ERG to avoid the heavy focus on less relevant analysis and keep the	Comment noted. NICE arranged and attended several meetings with the company and key stakeholders. The appraisal committee considered the company's new evidence and updated analyses at the second meeting. After the second committee meeting, elosulfase alfa was recommended for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			focus on answering questions in the revised HST2 scope. The focus of the ERG on trying to recreate short-term comparative clinical data from heterogenous real world data has resulted in analysis which has significant limitations versus the original clinical studies who were compared to a similarly aligned natural history cohort. As explained above in Issue 1, the underlying issue was a lack of an aligned dataset initially, no aligned statistical analysis plan and unrealistic expectations of what can be delivered with real-world data in this ultra-rare disease. Nevertheless, in the past weeks, the company analysis has been focusing on the future patients in England who will be predominately newly diagnosed patients and maybe the occasional less affected non-classical patients. This analysis focused on long-term outcomes and extrapolation has uncertainty. Much of this is not possible to resolve but should support a more relevant analysis with regards to the scope of the evaluation.	
4	Company	BioMarin International Limited	In **section 3.6 (page 9) of the ECD on the use of complete case analyses (CCA) to assess clinical effectiveness**, the Committee *'reiterated that it wanted to use as much clinical data as possible',* but *'was aware of the limitations of the CCA because it did not include people for whom some outcome data was missing*. The Committee also *'recalled that the company had not provided any alternatives using statistical methods to impute missing data'* and therefore *'concluded that both the company's and ERG's complete case analyses could be considered for decision- making. Also, it noted that it had not seen cost-effectiveness analyses using complete case analysis of data from MOR-005'.* During the technical engagement, the Company collaborated with NICE, RD-RP, and the treatment centres to reconcile and align the MAA dataset. Despite the many data gaps being addressed after this process, there were still many missing values remaining, mostly due to clinical reasons (i.e., patients moving homes, tests not being conducted at some timepoints because of young age e.g., spirometry in <5 years old, patients going through surgery). Therefore, in alignment with NICE, it was considered inappropriate to perform data imputation due to large amount of data missing and a lack of rationale/reasons for imputing data. The Company highlighted to NICE and ERG that due to the large amount of missing data and the high level of heterogeneity in the data, the CCA approach recommended by the ERG would lead to a small number of patients meeting criteria for the analysis and non-comparable populations. Nevertheless, the Company did agree to conduct the CCA as	Comment noted. At the second meeting, the appraisal committee discussed the baseline age of patients who have not previously had elosulfase alfa. The committee agreed that this group would be younger and healthier at baseline. See section 3.5 in the FED. The committee's discussion and conclusions on the complete case analysis is summarised in section 3.7 of the FED.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			requested by ERG and NICE using the reconciled MAA dataset and comparing to MorCAP1 (as natural history arm), which is a subset of MOR-001 with inclusion criteria similar to the MAA applied. Company's rationale focusing MorCAP1 instead of MOR-001 was to align the patient characteristics as much as possible between the MOR-001 and MAA patients (short of doing a formal PSM analysis). MorCAP1 was used as a more relevant comparison to MAA patients than MOR-001, as it excluded patients <5 years old (MAA did not capture much data in these patients) and removed confounders such as surgery. Also, in MOR-001, patients below the age of 5 did not have respiratory data and had limited 6MWT data; therefore, MorCAP1 provided a more complete dataset. However, following feedback from the ERG and Committee, the Company have re-conducted this analysis versus MOR-001, which is presented below. Despite the Committee's conclusion that the ERG's CCA could be considered for decision making, the company would hold that the 1-year CCA approach of the ERG is too limited. Therefore, the company submitted a 2-year CCA with relaxed assumptions of 'CCA per-variable' rather than 'CCA all variables' to maximise the available data while still addressing the missing data issues as much as possible. Overall, the Company has highlighted to the NICE technical team concerns that CCA represents a poor approach as it does not manage baseline confounding characteristics such as age or disease severity. Regarding the CCA from MOR-005 vs MOR-001, this analysis was deprioritised versus the CCA from the MAA in discussions with the ERG and NICE Technical Team due to time pressure to conduct all the analyses. However, the Company would argue that the results would not be much different from the data presented in the original 2015 HST model, which used the modified per protocol (MPP) population (i.e., excluding patients with surgeries or with less than 80% adherence to treatment) from MOR-005 QW-QW versus MorCAP 2-year follow-up study population that are highly aligned in terms of baseline characteristics to define the first 18 months of treatment. To better represent the future population of new patients in the model, the Company looked at all the data available in patients under 6 years old. The MOR-007 study, which is the study with patients under 5 years old, has several patients who would represent this future population; in addition, there are [redacted] treatment-naïve patients in the MAA who have started treatment below the age of 6. It is important, however, to note that patients below the age of 5 have limited measurements. Nevertheless, we believe that this proportion of treatment-naïve patients below the age of 6 can more	After the second committee meeting, elosulfase alfa was recommended for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			closely represent future patients. The company compared outcomes of the treatment naïve MAA population below the age of 6 with the treatment naïve MAA population 6 years and over. The company would like to re-iterate that this younger population is more relevant to the scope because the age of starting treatment is a major confounder (i.e., less disease burden at an early age). Therefore, this analysis shows a more relevant and less confounded comparison than looking at the overall MAA cohort. See below the results of the comparison between MAA treatment-naïve population under 6 versus 6 years and over. **Figure 4.1: Linear regression of change in 6MWT over time among treatment naïve MAA population: age under 6 vs. age 6 years and over** 	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Table 4.1: Linear regression of change in 6MWT over time among treatment naïve MAA population: age under 6 vs. age 6 years and over

	Under 6 years old			6 years and over		
	Coef.	Std. Err.	P-value	Coef.	Std. Err.	P-value
Time since baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observations	[redacted]			[redacted]		

A population starting treatment with elosulfase alfa under the age of 6 would gain approximately [redacted] metres per year on the 6MWT compared a population 6 years and older who would gain approximately [redacted] metres per year on the 6MWT based on linear regression using the treatment-naïve population in the MAA (**Table 4.1**). Neither complete case analysis nor imputation were performed due to small patient numbers in these subgroups (**additional file Table A.1**).

The full baseline characteristic tables with all outcomes across different age cohorts in the treatment-naïve MAA population are shared in a separate confidential file (due to small n and potentially identifiable patient level data); baseline characteristics indicate that the patient populations were similar in key characteristics except for weight (see partial table, **Table 4.2** below including age, gender, and weight), with the under 6 population weighing significantly less than the population 6 years and over (mean [redacted] vs. [redacted], $p<0.01$).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Table 4.2: Partial* baseline characteristics (only includes age, gender, weight) of treatment naïve MAA population: age under 6 vs. age 6 years and over[#]

	Under 6 years old			6 years old and over			Two-sample t-test for difference between groups (p value)
Variable	**Obs.**	**Mean**	**Std. Dev.**	**Obs.**	**Mean**	**Std. Dev.**	
Age at baseline (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (female %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**Full table with baseline characteristics for all outcomes shared confidentially with NICE due to small n and potentially identifiable patient level data*
*# patients excluded if age = missing; [a]proportion test; [b]chi-squared test ***significant at P<0.01*

The analyses presented below support clinical advice that we would expect to see **better outcomes in the newly diagnosed population** (the scope of this evaluation) than had been demonstrated in previous analysis of the overall MAA cohort and previously considered by the Committee.

They further support that **this newly diagnosed population would likely weigh less** and therefore require less drug at treatment initiation than had been demonstrated in previous analysis of the overall MAA cohort and previously considered by the Committee.

Regarding long-term outcomes, the company looked at the age bands of 5-10 years to confirm the benefit of elosulfase alfa across ages. Despite small sample sizes in some groups, there was stabilisation or improvements seen in 6MWT and FVC values across the 5 age bands (**Table 4.3, Table 4.4**) as evidenced by positive coefficients in linear regressions (with the exception of the ≥6 to <10 years old group for 6MWT and the ≥30 years old group for FVC). Therefore, **we would not expect patients to decline to wheelchair dependency if these outcomes were extrapolated over the long-term**. Neither complete case analysis nor imputation were performed due to small

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			patient numbers in these subgroups (**additional file Table A.2**). **Figure 4.2: Linear regression of change in 6MWT over time among treatment-naïve MAA population: age i) <6, ii) ≥6 to <10,iii) ≥10 to <20, iv) ≥20 to <30, v) ≥30**  **Table 4.3: Linear regression of change in 6MWT over time among treatment naïve MAA population: age i) <6, ii) ≥6 to <10, iii) ≥10 to <20, iv) ≥20 to <30, v) ≥30**	

	<6			≥6 to <10		
	Coef.	Std. Err.	P-value	Coef.	Std. Err.	P-value
Time since baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observations	[redacted]			[redacted]		

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

	≥10 to <20			≥20 to <30		
	Coef.	Std. Err.	P-value	Coef.	Std. Err.	P-value
Time since baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observations	[redacted]			[redacted]		

	≥30		
	Coef.	Std. Err.	P-value
Time since baseline	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]
Observations	[redacted]		

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 4.3: Linear regression of change in FVC over time among treatment-naïve MAA population: age i) <6, ii) ≥6 to <10,iii) ≥10 to <20, iv) ≥20 to <30, v) ≥30  **Table 4.4: Linear regression of change in FVC over time among treatment-naïve MAA population: age i) <6, ii) ≥6 to <10, iii) ≥10 to <20, iv) ≥20 to <30, v) ≥30** [redacted]	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			<table><tr><td></td><td colspan="3">≥10 to <20</td><td colspan="3">≥20 to <30</td></tr><tr><td></td><td>Coef.</td><td>Std. Err.</td><td>P-value</td><td>Coef.</td><td>Std. Err.</td><td>P-value</td></tr><tr><td>Time since baseline</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Constant</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Observations</td><td colspan="3">[redacted]</td><td colspan="3">[redacted]</td></tr></table> <table><tr><td></td><td colspan="3">≥30</td></tr><tr><td></td><td>Coef.</td><td>Std. Err.</td><td>P-value</td></tr><tr><td>Time since baseline</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Constant</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Observations</td><td colspan="3">[redacted]</td></tr></table>	
5	Company	BioMarin International Limited	**In section 3.7 (pages 10-11) on treatment benefit**, the Committee concluded that *'elosulfase alfa is clinically effective compared with standard care'*, but that *'the size of the benefit could have been underestimated'* due to the lack of comparative long-term follow up data with standard of care. Despite being aware of the *'limitations of a naive indirect comparison using different data sources that did not match baseline characteristics'*, the Committee also noted that '*the company had not captured the benefits of elosulfase alfa well in its analyses or model structure, despite extensions to the managed access agreement.*' The Company appreciates that the NICE Committee has concluded that elosulfase alfa is clinically effective compared to standard of care. We would like to re-iterate that there is long-term follow-up data for elosulfase alfa with 5+ years of MAA data; however, we acknowledge the fact that there is no long-term data in direct comparison to standard of care because most diagnosed patients who were eligible and willing to receive treatment at the time of the MAA were started on treatment when elosulfase alfa became available. The remaining patients were either too progressed or non-classical and did not want treatment, hence why the comparison cannot really be made with these patients.	Comment noted. At the second meeting, the appraisal committee discussed the most appropriate utility values (see section 3.13 of the FED). After the second committee meeting, elosulfase alfa was recommended for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			To address the issue of better capturing the benefits of elosulfase alfa, the Company analysed data from the MPS-HAQ questionnaire to understand the broader benefits from treatment and to inform additional utility benefits in patients, which are not captured in the EQ-5D. MPS HAQ scores improved in the treatment naïve population over the course of the MAA. By Month 36, Caregiver Assistance, Self-care and Mobility domains decreased from Baseline. By Month 36, Caregiver Assistance, Self-Care and Mobility score changes were -1.67, -0.74 and -1.46 (2.90 95% CI -2.91, -0.02, P=<0.05) 1.67 (12.98), -0.74 (2.86) and -1.46 respectively (lower scores indicate improvement on the MPS HAQ). Baseline data from MAA treatment naïve patients (N=23) showed moderate, significant (P<0.05) correlations between EQ-5D 5L utility and MPS HAQ Caregiver Assistance (Spearman's Rank Correlation=-0.628, Pearson's Rank Correlation=-0.642), EQ-5D 5L utility and MPS HAQ Self-Care (Spearman's Rank Correlation=-0.557, Pearson's Rank Correlation=-0.591), EQ-5D 5L utility and MPS HAQ Mobility (Spearman's Rank Correlation=-0.476, Pearson's Rank Correlation=-0.605). Quality of life as measured by the MPS HAQ improved over the course of the MAA in the treatment-naïve population. Correlation analysis showed that the EQ-5D is correlated with the MPS HAQ, but there may be domains of quality of life not captured well by the EQ-5D.	
6	Company	BioMarin International Limited	Regarding the **Committee's conclusion on the economic model (section 3.8, pages 11-12),** the Company appreciates that the Committee has accepted the wheelchair use based model and recognises certain limitations, particularly around modelling disease progression. As a reminder of why the Company has built the model around this outcome, this was because wheelchair status represented progression through the disease and remains the outcome which correlates the most with health utilities captured via the EQ-5D. Nevertheless, the company appreciates the limitations of the wheelchair measure. In fact, none of the measures (WC use, 6MWT, FVC) truly captures patients' ability to have more energy and increase function with less pain, e.g., walk longer for an hour but maybe not faster. The company also agrees with patient and clinical perspectives that wheelchair use changes with treatment where patients utilise aids to increase daily living activities and as such see the major impact in quality of life	Comment noted. At the second meeting, the appraisal committee discussed the model structure (see section 3.9 of the FED). After the second committee meeting, elosulfase alfa was recommended for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			coming with wheelchair dependency. Moreover, throughout the submission process, the Company engaged with several clinicians and the patient community and understood that some patients treated with elosulfase alfa may choose to use a wheelchair to manage energy for daily activities. However, wheelchair dependency continues to be a strong marker of disease progression and impacts quality of life negatively as patients become less independent. As noted in the ECD (page 15/24) dated November 2021, the company accepts that utility vales at baseline is the better reflection of SoC utilities. Also, as observed in the ECD (page 15/24) dated November 2021, the company used utilities at the end of 2 years in the treatment naïve subgroup (excluding ex-trial patients from the full MAA dataset) as the utilities for patients on ERT. These values for the 3 'wheelchair use' states (no WC use, some WC use, and WC dependant) for SoC were 0.54, 0.41 and 0.08 respectively. Similarly, for patients on ERT, these utilities were 0.84, 0.64 and 0.32 respectively. This is particularly relevant for newly diagnosed patients who start treatment with a lot less disease manifestation, hence their future phenotype will differ from patients with existing morbidity. As highlighted and agreed with the committee, these patients will have a delay in onset of musculoskeletal symptoms and these patients would experience a meaningful delay in wheelchair dependency versus patients with established morbidity when starting treatment with elosulfase alfa (see Issue 4). In addition, we have explored the changes in MPS-HAQ in the MAA treatment naïve population and found that there was improvement from baseline to Month 36 across domains, supporting benefits in mobility, self-care, and reduced caregiver burden (see Issue 5). Furthermore, the MPS HAQ was associated moderately with the EQ-5D in correlations at baseline.	
7	Company	BioMarin International Limited	Regarding **Committee's conclusion on 6MWT criteria to define movement between health states (Section 3.9, pages 12-13)**, the company accepts the ERG's analysed entrance and exit thresholds from the different WC categories in the model and has implemented these into the revised model as suggested in ERG addendum post ECM1, dated October 2021 (page 7/10).	Comment noted.
8	Company	BioMarin International Limited	Regarding **Committee's preferred assumptions for modelling disease progression (Section 3.10, pages 13-14)**, the company agrees with the committee observation of standard of care (SoC) patients that start in the asymptomatic state of the model are assumed to take 3 years to progress to the symptomatic state, while elosulfase alpha patients take 9 years to move from asymptomatic to	Comment noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			symptomatic (ERG addendum post ECM1, dated October 2021, page 7/10). The company also agrees with loss of 4.86 m for 6MWT to model disease progression in the standard care arm.	
9	Company	BioMarin International Limited	The company agrees with the **Committee and the ERG's approach to link survival to lung function (Section 3.11, pages 14-15)**. The company also notes that FVC improved in all MPSs with ERT over the long term. As per the previous submission, FVC improves by 26.5% in the ex-trial population in the long-term. Hence, one year benefit is not an appropriate time point as currently in the committee model. The company needs to speak to the ERG on how to implement this in the model but expects to have minimal impact on the ICER.	Comment noted.
10	Company	BioMarin International Limited	On **utility values used in the model (Section 3.12, pages 15-16)**, the committee *'recognised that the ERG's values were similar to those accepted in the original guidance. It concluded that the ERG's utility values from the treatment-naive subgroup from the managed access agreement were appropriate'*. As noted in company's response to issue 6 earlier, the company agrees with the committee that utilities at baseline are the better reflection of SoC utilities. Also, as observed in the ECD (page 15/24) dated November 2021, the company used utilities at the end of 2 years in the treatment naïve subgroup (excluding ex-trial patients from the full MAA dataset) as the utilities for patients on ERT. These values for the 3 'wheelchair use' states (no wheelchair use, some wheelchair use and wheelchair dependant) for SoC were 0.54, 0.41 and 0.08 respectively. Similarly, for patients on ERT, these utilities were 0.84, 0.64 and 0.32 respectively.	Comment noted.
11	Company	BioMarin International Limited	**For treatment costs and impact of body weight in the model (Section 3.13, page 16),** the Committee *'accepted ERG's approach based on Montano et al (2008) study > 36.7kg by 18 years old (also confirmed by clinical experts)'*. The future new patients who would be coming on to treatment will be predominantly younger, lighter patients (as mentioned in earlier comments). Thus, due to the lower starting age, we continue to consider that lower average weights are most appropriate for new patients. The weights used in this submission for patients in different health states (asymptomatic, no wheelchair use, some wheelchair use and wheelchair dependant) remain those provided by the ERG: 3.6 kg, 19.8 kg, 27.0 kg and 35.2 kg, respectively.	Comment noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
12	Company	BioMarin International Limited	Regarding the **appropriate discount rate (3.14, pages 16-17)**, the committee concluded that *'MPS 4A is progressive and still shortens life, and that elosulfase alfa is not curative'*. Therefore, *'it did not consider that elosulfase alfa restored people to full or near full health'* and concluded that a 3.5% discount rate was appropriate. The NICE Guide to the methods of technology appraisal states that in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), a discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee. MPS IVA is a devastating, progressive and life-threatening disease. Data published by Lavery et al, 2014 highlights the mean age of death as 25.3 years in the UK based on analysis of death certificates. Whilst this has improved due to greater disease awareness and management, MPS IVA remains a devastating and life-threatening disease. The introduction of elosulfase alfa has meaningfully modified the disease trajectory, particularly if patients are treated early. It is important to recognise the benefit of initiating treatment as early as possible. Sibling studies (Frigeni et al. 2021, Ficicioglu et al. 2020, Barak et al. 2020) as mentioned in section 2 have highlighted meaningful differences in long-term disease progression with early diagnosis and early treatment. As such the Company maintains that patients without treatment continue to have a significant risk of dying or severely impaired life which is one of the criteria for a 1.5% discount rate. Furthermore, long-term data from the MAA supports that elosulfase alfa offers sustained benefits over 10 years. Given the fact that the MAA included patients who started treatment with already significant impairment, newly diagnosed patients who initiate treatment early will show less progression and the benefits can be expected to continue far into patients' lives and likely to exceed 30 years and based on the modelling these future early treated patients will live longer functional lives with improved quality of life. As such, treatment with ESA complies with the requirements for a 1.5% discount rate and the Company strongly believes that the 1.5% discount rate is appropriate for this re-submission.	Comment noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
13	Company	BioMarin International Limited	The company agrees with the **committee's observation about applying QALY weighting (Section 3.15, pages 17-18)**. In addition, the company will stress the fact that all future new patients will be predominantly young patients who are diagnosed very early calls for additional QALY weighting for potentially debilitating disease prognosis for untreated young patients (patients on elosulfase alfa will have potentially far better prognosis).	Comment noted.
14	Company	BioMarin International Limited	**Cost-effectiveness estimates – Committee's preferred assumptions (Section 3.16, page 18):** *'The company's base-case results after technical engagement resulted in an ICER under £300,000 per QALY gained (that is, the maximum ICER normally considered to be a cost-effective use of NHS resources applying a the maximum QALY weight). The committee recalled that this did not account for its preferred assumptions of the committee's preferred assumptions:* • *Both the company's and the ERG's preferred data source and analysis (see sections 3.4 and 3.6). The ERG's approach included using observed 6MWT and FVC data to estimate mean values for both arms at the end of the first year in the model (see section 3.9)* • *The ERG's 6MWT criteria to define movement between the health states (see section 3.9)* • *The company's approach for modelling long-term disease progression for people having elosulfase alfa because it was an acceptable proxy for stable MPS 4A (see section 3.10)* • *The ERG's loss of 4.86 m for 6MWT to model disease progression in the standard care arm (see section 3.10)* • *Overall survival is linked to lung function (see section 3.11)* • *The ERG's utility values from the managed access data (see section 3.12)* • *Body weight changes over time and reaches 36.7 kg by 18 years (see section 3.13)* • *A discount rate of 3.5% (see section 3.14).* *The committee noted that the ERG made several changes to the company's base case. The most influential changes were assuming that:* • *6MWT and FVC losses were equal in both arms* • *alternative transitions thresholds were applied* • *body weight changes over time* **Please note that all the updates to the cost-effectiveness model were carried out on the version sent by NICE to the company on 17/11/2021. This version is ERG's version, and for**	Comment noted. At the second meeting, the appraisal committee considered updated cost-effectiveness results using its preferred assumptions (see section 3.17 in the FED). After the second committee meeting, elosulfase alfa was recommended for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			this submission, the company made updates to this model (ID1643 ERG model post ECM 1 251021 IA [ACIC].xlsm). Based on the committee's preferred assumptions (please refer to ERG addendum post ECM1, dated October 2021, page 2/10, where the NICE technical team believes that scenarios 4 and 5 are most likely to reflect committee's preferred ICER range), the company accepts the following recommendations (scenario 4 and 5): • Body weights changes over time. Since future new patients are going to be potentially younger, the body weights used in this model for different health states are Asymptomatic 3.6 kg; No WC use 19.8 kg; Some WC use 27.0 kg and WC dependant 35.2 kg. This rhymes with the age of patients' prognosis through different health states, becoming wheelchair dependant at the age of 22 and the corresponding body weight being 35.2 kg. • Annual average loss in 6MWT was accepted as per ERG recommendations of 4.86 m in the SoC arm • Assume a 4.86m and 0.1L losses in 6MWT and FVC measures, respectively, for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patient progresses per year in the ESA arm (please vide ERG addendum post ECM1, dated October 2021, page 3/10 for scenario 4 and 5) • Use the ERG's entrance and exit thresholds from the different WC categories in the model (please vide ERG addendum post ECM1, dated October 2021, page 3/10 for scenario 4 and 5) Other than implementing above mentioned points (as recommended by the ERG and NICE technical team), the company implemented several changes to reflect the scope of the evaluation, i.e., newly treated patients. The following changes were implemented: • The transition probabilities were changed in the model to reflect ERG and committee recommendations. For SOC arm the entire MOR-001 data was used (instead of MORCAP1) to calculate transition between different health states from baseline to Year1 and Year1 to Year2 • The baseline distribution of patients by wheelchair status was updated to better reflect	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the newly diagnosed cohort. The distribution of patients <6 years old in the MAA treatment naïve population was applied (see table describing baseline characteristics of MAA treatment naïve population under 6 by wheelchair status at the end of Issue 14). The distribution of patients at baseline was [redacted] and [redacted] for no wheelchair use, some wheelchair use, and wheelchair dependent, respectively. This distribution was apportioned across the 4 health states (asymptomatic, no wheelchair use, some wheelchair use, wheelchair dependent) to accommodate for [redacted] asymptomatic patients. The starting distribution is updated as follows: <u>Previous (ID1643 ERG model post ECM 1 251021 IA [ACIC].xlsm):</u> • Asymptomatic: [redacted] • No use wheelchair: [redacted] • Sometimes use wheelchair: [redacted] • Wheelchair dependent: [redacted] **<u>Updated company model:</u>** • **Asymptomatic:** [redacted] • **No use wheelchair:** [redacted] • **Sometimes use wheelchair:** [redacted] • **Wheelchair dependent:** [redacted] • The baseline age of patients by wheelchair status was updated to better reflect the newly diagnosed cohort. The distribution of patients <6 years old in the MAA treatment naïve population was applied (see table describing baseline characteristics of MAA treatment naïve population under 6 by wheelchair status at the end of Issue 14). The starting	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			distribution is updated as follows: <u>Previous (ID1643 ERG model post ECM 1 251021 IA [ACIC].xlsm):</u> • Asymptomatic: [redacted] • No use wheelchair: [redacted] • Sometimes use wheelchair: [redacted] • Wheelchair dependent: [redacted] **<u>Updated company model:</u>** • **Asymptomatic:** [redacted] • **No use wheelchair:** [redacted] • **Sometimes use wheelchair:** [redacted] • **Wheelchair dependent:** [redacted] • The utility values were updated. As noted in the ECD (page 15/24) dated November 2021, the company accepts that utility vales at baseline is the better reflection of SoC utilities. Also, as observed in the ECD (page 15/24) dated November 2021, the company used utilities at the end of 2 years in the treatment naïve MAA population as the utilities for patients on elosulfase alfa. These values for the 3 'wheelchair use' states (no wheelchair use, some wheelchair use and wheelchair dependant) for standard care and elosulfase alfa are as follows:	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Updated company model: **Standard of care:** • **No use wheelchair: 0.54** • **Sometimes use wheelchair: 0.41** • **Wheelchair dependent: 0.08** **Elosulfase alfa:** • **No use wheelchair:** [redacted] • **Sometimes use wheelchair:** [redacted] • **Wheelchair dependent:** [redacted] • Treatment administration cost was changed from £207 to £213 as recommended by ERG and accepted by the Committee (please see ERG addendum post ECM1, dated October 2021, page 8/10) • As justified above in response to Issue 12, the company has kept discount rates for both cost and QALY at 1.5% The discounted ICER, undiscounted QALY gain and discounted QALY gain after implementing the above changes in the model are ; [redacted] and [redacted] respectively. It may be noted that all the above implementations include ERG/ NICE technical team's recommendations with some additional analysis, e.g., using MOR-001 instead of MORCAP1 and using the MAA treatment naïve cohort of <6 years of age (representative of future new patients in terms of starting age, starting weight and starting disease severity). These additional analyses are appended to this response document.	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>To stay within the recommended threshold of ICER (including QALY weighting), the company agrees to give [redacted] discount on the list price, i.e., a confidential ex-factory price of [redacted] per 5 mg vial (exc. VAT)

The new discounted ICER, undiscounted QALY gain and discounted QALY gain after implementing the above changes in the model are ; [redacted] and [redacted].

Keeping everything else the same, but changing discount rates for both costs and QALYs to 3.5% results in discounted ICER, undiscounted QALY gain and discounted QALY gain after implementing the above changes in the model are ; [redacted] and [redacted]. Please note the confidential ex-factory price is kept at £[redacted] per 5 mg vial (exc. VAT).

Table 14.1: Baseline characteristics of treatment naïve MAA population <6 years old by wheelchair status#
<table>
<tr><td></td><td>Overall</td><td>No WC use</td><td>Some WC use</td><td>WC-dependant</td></tr>
<tr><td>n</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Proportion, %</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Age, years (SD)</td><td></td><td></td><td></td><td></td></tr>
</table>
patients excluded if age = missing, or walking status = missing</td><td></td></tr>
<tr><td>15</td><td>Clinical Expert</td><td>Rare Disease Research Partners</td><td>Has all of the relevant evidence been taken into account?
No
Much of the evidence has been ignored and discounted for the cost effectiveness decision making. The ERG preferred to use only one year out of four years of MAA data and exclude around one third of MAA patients (those previously treated on a clinical trial). The company used only 2 years of MAA data.

It is difficult to see how this is a fair assessment of the additional data collected to resolve uncertainties from the first NICE review. It is especially concerning that patients who have been on treatment for 10 years and remained stable are excluded from the ERG data set.</td><td>Comment noted. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			At the committee meeting there was a clear disconnect between the ERG and company's presentation and analysis of the data and the committee expectations on what was to be included and reviewed. It is concerning that expectations of the committee appear to have not been factored in or discussed between NICE, the ERG and the company prior to the meeting. Had this taken place an alternative model may have been agreed and implemented before committee. There has been limited use of the HRQOL collected through the MAA. Therefore, the full impact of ERT has not be captured and interpreted with many parameters not referenced, which would have given a richness and completeness to the data and narrative from the patients. Whilst NICE acknowledged the wealth of information collected and presented by the clinicians and patient organisations, there is little evidence that this information has been considered. The reliance on modelling for decision making would seem to make it impossible for this type of evidence to be truly taken into account. It appears that not all the data has been submitted/analysed and this raises concern over whether data collection / transference of data has failed at some point. Data gaps trigger uncertainty and this was clearly the case during this review.	
16	Clinical Expert	Rare Disease Research Partners	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No Much of the clinical data was not included in the analysis, e.g. 'The committee was concerned that the company had not appropriately analysed valuable long-term data from people who started elosulfase alfa as part of a clinical trial.' 'The committee noted that the innovative nature of elosulfase alfa would be captured in the modelling if the data was measured and analysed appropriately.' The amount of evidence excluded from the analysis, including that from clinical trials, the MAA, patient and clinical expert input, meant that the size of benefit of elosulfase alfa was underestimated, and this was noted by the committee. The cost effectiveness model did not provide a reasonable interpretation of the evidence as it used very little evidence and relied heavily on assumption. The approach taken for this re-evaluation is inappropriate for extremely rare complex conditions where patient numbers are exceptionally small. In addition, they have been further discriminated against by the reduction in patient numbers to fit into an insufficient model.	Comment noted. After the second committee meeting, elosulfase alfa was recommended for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Many issues with the model were raised during the committee meeting, therefore the resultant cost-effectiveness estimates cannot be considered as a reasonable interpretation of the evidence. Not having a predefined statistical analysis plan in place for this re-evaluation has resulted in a flawed process with no defined parameters or clarity on expectations.	
17	Clinical Expert	Rare Disease Research Partners	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? No The recommendations were based on a flawed model and did not take into account all the evidence presented, therefore they cannot be considered as suitable. The evidence showed clinical and quality of life benefits and the committee noted that these had been underestimated. However, the focus of the review appeared to be totally price driven, using a model that the committee considered as inappropriate and flawed. It is still unclear why NICE have decided to only give a recommendation for new patients not currently treated under the MAA, and what impact their decision will have on those currently on treatment. If NICE's final decision is a no for newly diagnosed patients, then they would potentially be denying a population that would gain the most benefit.	Comment noted. After the second committee meeting, elosulfase alfa was recommended for treating MPS 4A in people of any age.
18	Clinical Expert	Birmingham Women's & Children's NHS Foundation Trust	At the outset I must state that we welcome the committee's conclusion (ECD 1.2) that the clinical trial evidence and the MAA data indeed suggest that elosulfase alfa is efficacious and leads to stabilisation of disease for patients with MPS IVa. This is the only disease modifying treatment available for MPS IVa and therefore having accepted effectiveness the focus of this re-evaluation must then be the cost-effectiveness of this intervention which we accept is a difficult but necessary analysis for NICE to undertake. It is, therefore, especially important that this analysis is done with the best possible data and assumptions which is perhaps less of an issue where the effectiveness of the intervention itself is in question. From that standpoint, we are concerned that the economic conclusions in this analysis are based on a model that does not take all the reported and observed benefits of this treatment into account and is based on extrapolation of short term conclusions from a different observed population to that intended for the intervention after routine commissioning. As such the cost-effectiveness analysis cannot be said to be a robust basis for final guidance on routine NHS commissioning and it is important that a more appropriate model is developed urgently to address this.	Comment noted. The appraisal committee agreed that the model structure was limited (see section 3.9 in the FED) and that some benefits may not be captured (see section 3.8 in the FED). The committee took this into account when making its recommendations. After the second committee meeting,

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				elosulfase alfa was for treating MPS 4A in people of any age.
19	Clinical Expert	Birmingham Women's & Children's NHS Foundation Trust	My main concern is that the recommendation does not take into account that the target population of this treatment after routine commissioning would be vastly different to the population studied in clinical trials and in the managed access agreement, upon which these recommendations are based. ECD **Section 3.3** states *"The committee also noted that this review would only focus on people newly diagnosed with MPS 4A. This was because continued access to elosulfase alfa for people with MPS 4A already having treatment will be discussed separately by the company and NHS England. The committee concluded that it would consider the newly diagnosed population who had not had treatment under its previous recommendations."* The corollary of this is to accept that: • The existing population of MPS IVa patients in England have all been offered elosulfase alfa already and either: o Are currently receiving and benefiting from treatment o Are no longer on treatment due to lack of benefit and/or unacceptable burden of treatment o Never commenced treatment which has been offered to them These patients are those with the greatest pre-treatment disease burden in whom the capacity to benefit is likely to be lowest. They are also the very same patients who have been studied so intensely during the development of elosulfase alfa. The largest clinical trials (MOR004/005) had an age of 5 years as a minimum eligibility criterion and such patients would already have a significant skeletal disease burden which cannot be expected to improve and would significantly limit any benefit from treatment. That a significant effect was able to be appreciated (and accepted by NICE) in this population does indeed underscore the significance of that effect. It follows that any patients offered treatment under this decision would therefore be either: • Newly diagnosed paediatric patients, some of whom may have severe disease • Newly diagnosed attenuated adult patients The age at which new paediatric patients are diagnosed has been falling consistently over the last decade and of the cohort recruited to the MAA at Birmingham Children's Hospital, all new patients have been under the age of 3 years, with one child as young as 18 months diagnosed and started on treatment shortly afterwards. These patients will have little (or no in the case of siblings prospectively diagnosed at birth) pre-treatment disease burden and consequently a far greater capacity to benefit	Comment noted. At the second meeting, the appraisal committee discussed the baseline age of patients who have not previously had elosulfase alfa. The committee agreed that this group would be younger and healthier at baseline. See section 3.5 in the FED.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			from elosulfase alfa than any patient enrolled in the MOR004/005 trials and indeed most of the patients enrolled in the MAA. The MAA has not provided the means to meaningfully assess treatment effect in these youngest patients who will have only had treatment for up to 4 years – we will only know the magnitude of the effect in those patients with much longer treatment exposure, probably in the order of 8-10 years by which time historically such patients would have achieved their final adult height but may with elosulfase alfa be continuing to grow. There may be sufficient patients in the MAA and in the MOR007 study who started treatment under the age of 2-3 years to provide some guidance to the committee on the likely effectiveness of the drug in the target population but there may not be. Either way it stands to reason that the effectiveness of this drug ***in the target paediatric population*** can only be better than in the studied population and as the target population is likely to be significantly younger and smaller than the studied population the initial cost of a weight-based drug will also be lower. ***Therefore whilst the exact cost-effectiveness of this intervention in the target paediatric population is not known it stands to reason it can ONLY be better than the conclusion reached in this re-analysis*** Similarly in adults with attenuated disease: all adults who are "grown up severe paediatric patients" have already been offered treatment. Therefore the target population of this recommendation in adults will be treatment-naïve attenuated patients who by their very nature will have the greatest capacity to respond to treatment (perhaps even better than severe children). Indeed some adults with the most attenuated disease may not even wish to start treatment as their treatment burden may exceed the burden of their disease – this has been noted in some patients recruited to the MAA. Again the studied population will have included adults of all severities and we argue it stands to reason that the effectiveness of this drug ***in the target adult population*** can only be better than in the studied population. The cost may not be different however but ***whilst the exact cost-effectiveness of this intervention in the target adult population is not known it stands to reason it can ONLY be better than the conclusion reached in this re-analysis*** As such I am deeply concerned that this analysis is inadequate to robustly inform a decision on routine commissioning on the NHS for elosulfase alfa and a cost-effectiveness model that focuses on the intended target population urgently needs to be developed.	
20	Clinical Expert	Birmingham Women's & Children's NHS Foundation Trust	We are concerned that the evaluation has focussed solely on the data measured on the MAA and analysed these in a similar way to how those parameters were analysed in the pivotal clinical trials. The MAA data were not intended to be trial outcome measures – but rather reliable and measurable outcomes that would identify patients who were NOT responding to treatment and therefore enable an evidence-based decision to stop treatment in some patients. They were not chosen to be outcomes that could measure the degree of benefit which is how they have been erroneously analysed. In my opinion the only valid analysis of the MAA data should be the proportion of patients	Comment noted. The committee noted that the detailed criteria included in the managed access agreement no longer apply and have been

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			who continued to meet the criteria – as published in Cleary et al 2021 *[Orphanet J Rare Dis . 2021 Jan 21;16(1):38. doi: 10.1186/s13023-021-01675-x.]* That the overwhelming majority of patients continued on the MAA despite their significant treatment burden is testament to its effectiveness and the value placed on that by patients and their families. The flipside of this however is not factored into the analysis. A small number of patients who recruited to the MAA did indeed come off treatment and a greater number of patients who participated in the clinical trials chose not to continue with treatment on the MAA in the first place. These are patients with significant (or rarely very minimal) disease burden who did not feel that the treatment was benefiting them and that the treatment burden was outweighing the perceived benefit. Whilst this was mandated on the MAA, this was in all cases a decision reached primarily by the patients and families themselves and there is no reason to expect this not to continue to be the case should elosulfase alfa be routinely commissioned. We do not expect patients who are not benefiting to want to continue treatment long term – and this is now routinely embedded in paediatric practice with other lysosomal storage disorders with routinely commissioned enzyme replacement therapies. We do not see this having been factored into the cost-effectiveness model – ***essentially those paediatric patients who will receive long term therapy (at higher long term cost because of their greater size) will ONLY be those who are clearly responding and feeling benefit.***	be simplified for routine clinical practice. See section 3.24 of the FED.
21	Clinical Expert	Birmingham Women's & Children's NHS Foundation Trust	Further to comment 3 – we would also point out that the chosen measured outcomes on the MAA are not the most appropriate to assess the magnitude of a response in the target paediatric population. These youngest patients cannot perform spirometry reliably and invariably have no or inaccurate baseline data – and their capacities will continue to increase with growth. Cardiac ejection fraction is almost universally normal in this age group and whilst easily measurable does not capture the benefits of treatment on the cardiovascular system in children. Even the six minute walk test is subject to variability in this age group where the youngest patients may still be learning how to walk steadily independently when they start treatment. The health-related quality of life data completed by parents is likely to have the greatest relevance to this target population but this does not appear to have been focussed on in this analysis.	Comment noted. These limitations were discussed by the appraisal committee at the second meeting (see sections 3.5 and 3.9 in the FED).
22	Clinical Expert	Birmingham Women's & Children's NHS Foundation Trust	We have concerns that the focus on a "wheelchair-use model" is wrong. The health state "Sometimes uses wheelchair" is perceived to indicate a worsening health state compared to "no use of wheelchair" whereas in fact we see in real life that many patients choose to use a wheelchair for some activities (particularly longer distance mobility) in order to preserve energy for other activities and the use of a wheelchair actually represents an *improvement* in health state. Whereas previously a patient may have opted to simply reduce activity, a patient who is responding positively to treatment may wish to stretch their potential achievements and do more than they previously would	Comment noted. The appraisal committee agreed that the model structure was limited (see section 3.9 in the FED)

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			have – and to maximise their independence in doing so, they make a positive choice to use a wheelchair some of the time. This was highlighted by clinical and patient experts at the meeting but this does not seem to have altered the analysis. A “wheelchair-dependence” model might be more appropriate – but as stated above, a meaningful assessment of this could only be achieved by following (and treating) target population patients at least until they would have been expected to become wheelchair dependent which is much longer than the follow-up currently available.	
23	Clinical Expert	Birmingham Women’s & Children’s NHS Foundation Trust	A further variable in the cost-effectiveness analysis is the expectation of families to administer infusions independently. This was not stated in the managed access agreement but over the life of the MAA the expectation of treating centres has become that families will learn to administer infusions themselves at home when it is safe and appropriate to do so. This reduces the non-drug costs of administering the treatment (be that hospital beds or home care nursing costs). If this has been factored into the analysis then this should be clarified. If not, then it should be considered.	Comment noted. The health economic model includes an assumption that 90% of patients would have home administration of elosulfase alfa (50% by self or carer, 50% nurse supervised)
24	Clinical Expert	Birmingham Women’s & Children’s NHS Foundation Trust	We are concerned that this recommendation, if implemented in the face of an agreement by NHS England to continue treatment for patients already signed up to the MAA, would place families, centres and the NHS in an ethical conflict with patients being effectively discriminated against based on their date of diagnosis. It places a family in the position of having a child with severe disease on long term treatment receiving some, but perhaps limited, benefit whilst a newly diagnosed newborn sibling, with far greater capacity to benefit from the treatment long term, unable to access treatment. This would seem to go against the principles of the NHS in ensuring an equitable access to treatments for all.	Thank you for your comments. At the second meeting, the appraisal committee discussed the baseline age of newly diagnosed patients(see section 3.5 in the FED. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age
25	Clinical Expert	The MPS Society	Whilst we accept that commercial negotiations may require separate discussions, it is still unclear why NICE have decided to only give a recommendation for new patients not currently treated under the MAA.	Comment noted. The recommendation in the FED applies to all patients in the full marketing authorisation for elosulfase alfa. See

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				section 3.3 for details of why separate discussions took place between the company and NHS England.
26	Clinical Expert	The MPS Society	NICE appears to have ignored or at best not fully taken account of a) the patient evidence b) the data from the MAA. There is an apparent disconnect in stakeholders understanding / direction of the data to be included and analysed versus the committee expectations on what was to be included and reviewed. The committee voiced their great shame that the model did not include longer term data and felt that focusing on new patients was wrong and off target. It is concerning that expectations of the committee appear to have not been factored in or discussed between NICE, the ERG and the company prior to the meeting. Had this taken place an alternative model may have been agreed and implemented before committee.	Comment noted. The appraisal committee discussed the various sources of data (see section 3.4 in the FED). The committee were also concerned that the company had not used long-term data in its model.
27	Clinical Expert	The MPS Society	We are concerned that not all the data appears to have been submitted and this raises concern over whether data collection / transference of data has failed at some point. Data gaps trigger uncertainty and this was clearly the case during this review. In addition to this, patient and clinical communities are concerned that the full impact of ERT has not be captured and interpreted with many parameters not referenced, which would have given a richness and completeness to the data and narrative being told by the clinicians and patients. Specifically the modelling has not captured all the benefits seen in clinical practice and reported directly by the patients, parent / carers. In our view there has been limited use of the HRQOL collected through the MAA and this was noted by the committee also.	Comment noted. The appraisal committee discussed the various sources of data (see section 3.4 in the FED) and that some benefits may not be captured (see section 3.8 in the FED). The committee took this into account when making its recommendations.
28	Clinical Expert	The MPS Society	We are concerned that if NICE's final decision is a no for newly diagnosed patients then they would potentially be denying a population that would gain the most benefit. We know from experience that patients treated early in their disease have better outcomes and reduced disease morbidity. Sadly this has led to a number of older patients asking whether they should give up their effective treatment, so that young patients have an opportunity to benefit from the positive effects they have experienced. How do you explain that this would not be the case and how do we managed their wellbeing and the guilt if this is in fact the final outcome? It is also concerning that NICE still do not have a solid understanding of tiny populations or the	Comment noted. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.

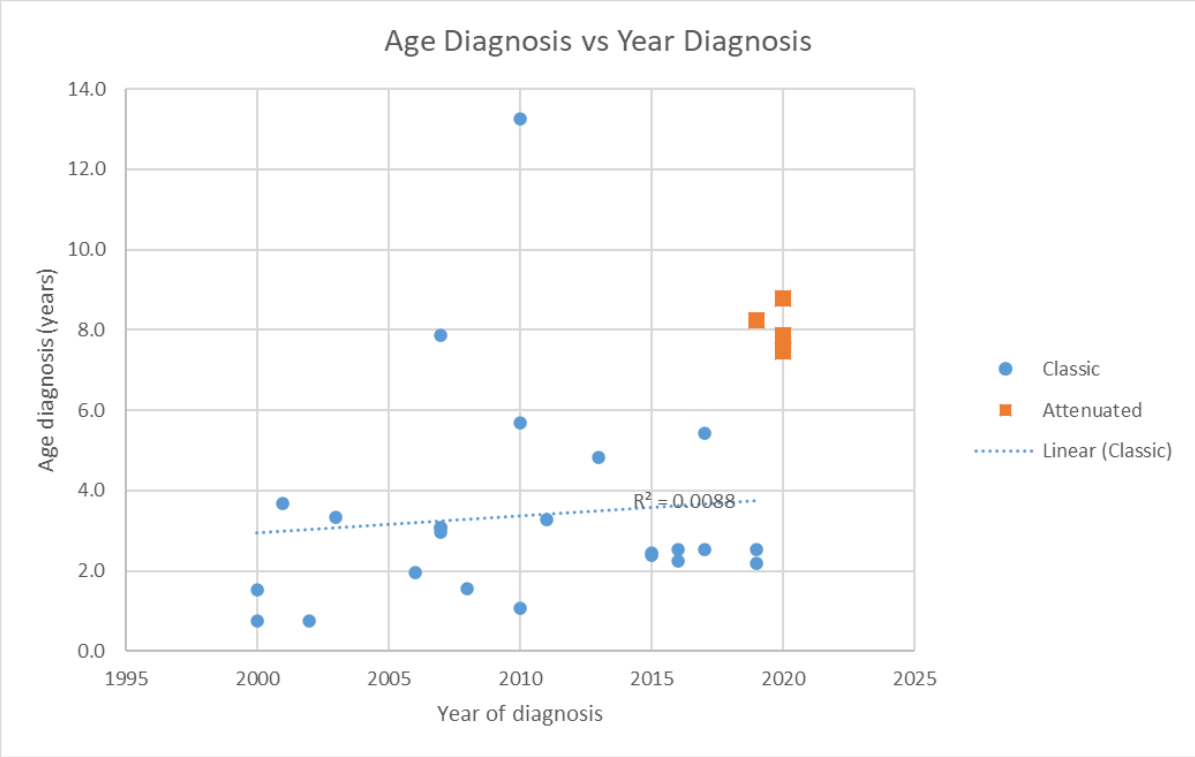
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			effects that any decision will have on this community.	
29	Clinical Expert	The MPS Society	The current model is not appropriate to determine whether elosulfase alfa is cost effective for a naïve population as it is using data from a wide range of participants with varying degrees of pathology, many of whose baseline were not captured in the MAA if already on established treatment. Whist the wheelchair model used by the company in the 2015 evaluation was accepted by the committee, they stated in the 2021 re-evaluation meeting that they did not like it and were expecting a different approach to be taken. Was this messaging conveyed to the company? In this respect, we believe the model to be flawed and an alternative model should be used.	Comment noted. The appraisal committee agreed that the model structure was limited (see section 3.9 in the FED). After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.
30	Clinical Expert	The MPS Society	Whilst NICE has acknowledged the wealth of information collected and presented by the clinicians and patient organisations, there is little evidence that this information has been considered. Participants and observers were left feeling that the focus of the review was totally price driven and not based on clinical efficacy. Q of L reports have been proven to be credible measure of the true impact of treatment for patients. This was why there was such emphasis on the collection of this data as part of the MAA. Treating these as secondary importance, in effect “anecdotal evidence”, discredits the involvement, value and commitment of the patients, families’ clinicians and the patient organisation.	Comment noted. The appraisal committee noted the valuable data submitted from patient organisations on the outcomes that matter to people with MPS 4A and the benefits of elosulfase alfa. The committee was disappointed that the company had not used this data to inform its model structure (see section 3.9 in the FED).
31	Clinical Expert	The MPS Society	Not having a predefined statistical analysis plan in place for this re-evaluation has resulted in a flawed process with no defined parameters or clarity on expectations. This is disappointing as clinical and patient organisations raised this exact point in 2018.	Comment noted. The appraisal committee noted its concerns in section 3.6 in the FED.
32	Clinical Expert	The MPS Society	We believe the summaries contained within the ECD woefully underestimate the benefit to patients from this therapy. This is disappointing given the depth of information submitted by patient organisations.	Comment noted. The appraisal committee noted that some benefits may not be

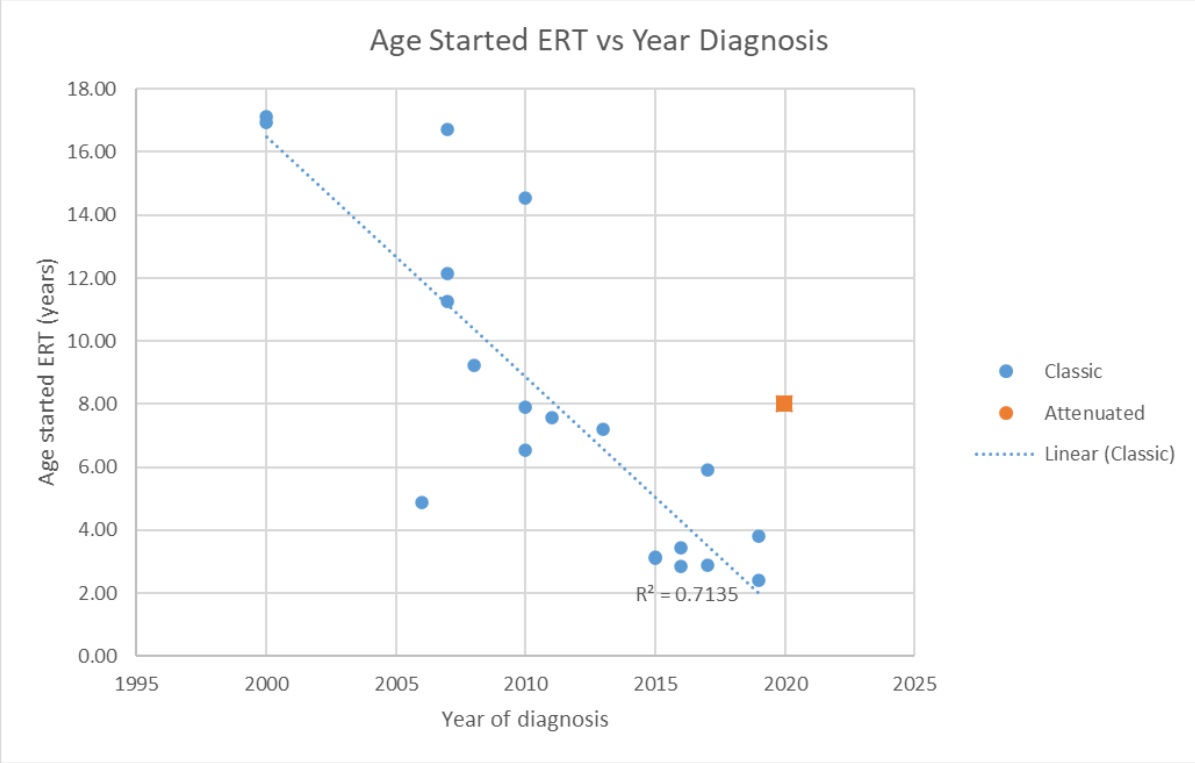
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				fully captured in the model (see section 3.8 in the FED). The committee took this into account when making its recommendations.
33	Clinical Expert	The MPS Society	The process used by NICE has exclude people, especially those with the protected characteristic of Disability, from fully contributing to this consultation and as such this current recommendation in our view is discriminatory. Additionally the recommendation itself is discriminatory as the approach that NICE has taken shows an unwillingness to use appropriate methodologies for the consideration of data related to very small populations.	Comment noted. NICE was not informed of issues with documents or asked to make adjustments during the consultation period.
34	Clinical Expert	The MPS Society	Clinical and patient reports highlight improvements in both 6MWT and lung function with all patient sub groups showing sustained and improved endurance or stability. Due to the rigorous assessments and reviews as part of the MAA, patients who were failing their assessment tests were monitored for a period of time and if deterioration continued they would be at risk of treatment being stopped. Stabilisation is an important criteria in progressive conditions and a good outcome measure. This uncertainty leads to questioning why NICE still do not have clearly defined outcome measures for treatments under review and why the same irrelevant measures are being used. In our view these should have been defined before the re-evaluation took place.	Comment noted. This is something we will feedback for future reviews
35	Clinical Expert	The MPS Society	This process is as complex and extremely frustrating for patients as it was six years ago. It has caused a huge amount of uncertainty and anxiety for patients and families, particularly those patients treated through the MAA. The wellbeing of patients remains a long way down the priority list for NICE, NHSEI and the company. Patients have complied with all requirements and expectations but feel their efforts and data has been excluded when it matters. The process for them has felt cold, demeaning and data led, with the primary focus centred on cost effectiveness and assumptions. This is extremely disappointing given the investment by patients and clinical colleagues. In our view the approach taken for this re-evaluation is inappropriate for extremely rare complex conditions where patient numbers are exceptionally small. In addition they have been further discriminated against by the reduction in patient numbers to fit into an insufficient model.	Comment noted. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.
36	Clinical Expert	University College	We are concerned that the data and population used in the modelling does not appropriately represent the characteristics and likely response to treatment of the intended target patient	Comment noted. At the second meeting,

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		London NHS Foundation Trust	population. ECD **Section 3.3** states *"The committee also noted that this review would only focus on people newly diagnosed with MPS 4A. This was because continued access to elosulfase alfa for people with MPS 4A already having treatment will be discussed separately by the company and NHS England. The committee concluded that it would consider the newly diagnosed population who had not had treatment under its previous recommendations."* However, the analysis undertaken is based on a patient population of which the majority are not newly-diagnosed but have been diagnosed and living with MPS IVa for years before this treatment was available. These patients will already have some or significant disease-related morbidity. In contrast, the majority of newly diagnosed patients in future will be younger, with a lower disease burden and are expected to derive much greater benefit from treatment started at younger age. Data from paediatric centres has shown that the median age for starting treatment for classical MPS IVa is now around 3 years. We believe the model should be adjusted to examine this intended newly-diagnosed population group separately, with a cost-effectiveness analysis undertaken for this group.	the appraisal committee discussed the baseline age of patients who have not previously had elosulfase alfa. The committee agreed that this group would be younger and healthier at baseline. See section 3.5 in the final evaluation document (FED).
37	Clinical Expert	University College London NHS Foundation Trust	We believe that the evaluation process has missed the opportunity to include and evaluate data from the MPS IVa disease registry that was required of the MAH by the European Medicines Agency.	Comment noted. The appraisal committee discussed the limitations of the data sources (see section 3.4 in the FED). The company did not include data from the disease registry in its model.
38	Clinical Expert	University College London NHS Foundation Trust	We feel that a number of important issues need to be considered / clarified in the model: • Increased use of a wheelchair has been assumed to represent a worsening health state – whereas, as discussed, this may in fact reflect increased independence of young adults. • Important clinical outcomes such as improved healing after surgery, reduction in number and severity of respiratory tract infections have not been captured in the model used.	Comment noted. The appraisal committee agreed that the model structure was limited (see section 3.9 in the FED) and that some benefits may not be fully captured in the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				model (see section 3.8 in the FED). The committee took this into account when making its recommendations.
39	Clinical Expert	University College London NHS Foundation Trust	Given that the committee recognises that the data generally show stable outcomes over time for elosulfase-treated patients in the MAA, if future review of the guidance is recommended then we would request that a comprehensive clear plan be provided to clinicians and stakeholders in advance as to what new information needs to be gathered and how this will be analysed to provide a robust outcome.	Comment noted.
40	Clinical Expert	Great Ormond Street Hospital	We are deeply concerned about the ongoing uncertainty and anxiety for patients with MPS 4A and their families about provision of elosulfase alfa that has resulted from the protracted process for reviewing this technology. Patients who have been receiving treatment under the Managed Access Agreement (MAA) and who have borne the very significant burden placed on them to undertake the associated assessments still do not have clarity about whether they will be able to continue treatment after the end of the MAA. Section 1.2 of the ECD states that "This recommendation is not intended to affect treatment with elosulfase alfa that was started in the NHS before this guidance was published."	Comment noted. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age
41	Clinical Expert	Great Ormond Street Hospital	We are concerned that the conclusions from the re-evaluation are based on what is considered by the committee to be a deeply flawed and inadequate economic model that does not take into account all the observed benefits of the technology, and is based on assumptions rather than observed data. The committee thus acknowledges that the model does not take account of the relevant evidence that is available and is not suitable to determine if the technology is cost-effective. Therefore the recommendations made are not a sound and suitable basis for the final guidance to the NHS. An alternative model that does take into account the available evidence should be used.	Comment noted. The appraisal committee agreed that the model structure was limited (see section 3.9 in the FED) and that some benefits may not be captured (see section 3.8 in the FED). The committee took this into account when making its recommendations.
42	Clinical Expert	Great Ormond Street Hospital	**We are concerned that the data and population used in the modelling do not represent correctly the characteristics and likely response to treatment of the "target population".** ECD **Section 3.3** states *"The committee also noted that this review would <u>only focus on people</u>*	Comment noted. At the second meeting, the appraisal committee discussed

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			newly diagnosed with MPS 4A. This was because continued access to elosulfase alfa for people with MPS 4A already having treatment will be discussed separately by the company and NHS England. The committee concluded that it would consider the newly diagnosed population who had not had treatment under its previous recommendations." However, the analysis undertaken is based on a patient population of which the majority are not newly-diagnosed but are "older" and have lived with a diagnosis of MPS IVa for years but before treatment was available. This applies to both the MAA treatment naïve and ex-MOR trial patients, and to the MOR-005 patient population. All of these patients will have accrued disease-related "damage" and have established pathology before treatment is started. Prospectively going forwards, newly diagnosed patients will be younger and will have accrued less disease-damage pathology and are expected to derive much greater benefit from treatment started at younger age. [See below GOSH cohort data that shows median age diagnosis is 2.5years for classic MPS IVa and 8.0yrs for paediatric attenuated MPS IVa, with no significant change in age of diagnosis over the last 20 years. Since 2015, median age starting treatment for classical MPS IVa = 3.1years] The modelling based the distribution of patients across the health states in the Markov model based on the MAA cohort, whereas "newly diagnosed paediatric patients" prospectively would be expected to be all in the first health state at the time of diagnosis. A simple manipulation of the economic model provided for the purposes of review of the ECD adjusting the baseline distribution such that all patients were in the asymptomatic category at start of the model does indeed lead to altered ICER estimates. Similarly, newly-diagnosed adult patients are likely to have much milder disease and may stand to benefit from treatment or be too mild to derive benefit. In essence, the analysis undertaken appears to be assessing the impact of the technology on the current cohort of patients distributed across a wide age range and most of whom already have established pathology, but this is not an appropriate analysis population to determine whether elosulfase alfa is cost effective when applied to a cohort of "newly diagnosed" treatment-naïve patients, and therefore this is not a suitable basis for making recommendations to the NHS on this technology. **An analysis on the likely cost-effectiveness for the target population needs to be completed.**	the baseline age of patients who have not previously had elosulfase alfa. The committee agreed that this group would be younger and healthier at baseline. See section 3.5 in the final evaluation document (FED).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
43	Clinical Expert	Great Ormond Street Hospital	**GOSH Paediatric MPS IVa cohort: age diagnosis vs year diagnosis:**  **GOSH Paediatric MPS IVa cohort: age started ERT vs year diagnosis:**	Thank you, your comments have been noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				
44	Clinical Expert	Great Ormond Street Hospital	We are concerned that the evaluation process has focussed heavily on the data generated from the MAA and treated this as a quasi-trial evidence. The parameters measured in the MAA were selected to identify “Responders” to elosulfase alfa to determine if they could continue to receive treatment, setting specific thresholds to determine Responders, and were not primarily established as the best parameters for measuring the nuances in how the disease affects children. For example the MAA parameter for Cardiac disease was the Ejection Fraction, but this is only one aspect of cardiac function and does not capture well the effect of treatment on cardiac disease. Respiratory function was assessed using FVC and FEV1 but did not take into account more detailed information from polysomnography, use of non-invasive ventilation etc. The parameters were also difficult to obtain reliably (if at all) in the younger patients (<5yrs) who are the very “target cohort” that the evaluation is aiming to assess clinical-effectiveness for. The original MAA also specified that a disease registry would be established and that this would be	Comment noted. The appraisal committee discussed the limitations of the data sources (see section 3.4 in the FED). The company did not include data from the disease registry in its model. I

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the primary source of information that would be made available to NHSE to assess the effectiveness of treatment. (MAA Section 5.2) "*5.2 The MAH has been asked by the European Medicines Agency to enroll all patients into a 12 year disease registry to continue to gather information about this ultra-rare condition. The purposes of this registry are to: (i) characterise and describe the MPS IVA population as a whole, including the heterogeneity, progression and natural history of MPS IVA; (ii) to evaluate the long-term effectiveness and safety of Vimizim (elosulfase alfa): (iii) to help the MPS IVA medical community with the development of recommendations for monitoring subjects and reports on subject outcomes to optimise subject care; (iv) to collect data on other treatment paradigms, evaluate the prevalence of their use and their effectiveness; (v) to characterise the effects of 5 years of elosulfase alfa treatment in subjects under 5 years of age; and (vi) to collect additional data to: (a) help broaden knowledge of identified and potential risks of elosulfase alfa, as well as increase the size of the safety database and possibly provide new information on use in identified subgroups (pregnancy, hepatic and renal impairment, cardiac impairment); and (b) to help evaluate long-term effectiveness of elosulfase alfa. The MAH will provide access for NHS England to this database to assist it in assessing the clinical impact of elosulfase alfa on this disease. As part of this Managed Access Agreement the MAH agrees to NHS England appointing a representative to sit on the registry advisory board."* We are concerned that this data [from the disease registry] has not been used in the evaluation process, which would have provided a much richer range of outcome measures rather than purely limiting analysis to the 6MWT.	
45	Clinical Expert	Great Ormond Street Hospital	We welcome the committee's conclusion (ECD 1.2) that the clinical trial evidence and the MAA data suggest that elosulfase alfa is efficacious and leads to stabilisation of disease for patients with MPS IVa. We agree that the health and quality of life benefits of elosulfase alfa are substantial. We are concerned that the evaluation is then based on a model that does not capture many of these acknowledged benefits.	Comment noted. The appraisal committee noted that some benefits may not be fully captured in the model (see section 3.8 in the FED). The committee took this into account when making its recommendations.
46	Clinical Expert	Great Ormond Street Hospital	ECD 3.4 (data sources). We are concerned that the analysis and incorporation of the available outcome measures do not appropriately take in to account the expected changes in growing paediatric patients, for example the impact on growth on FVC/FEV1/6MWT.	Comment noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
47	Clinical Expert	Great Ormond Street Hospital	ECD 3.4 (data sources). The committee acknowledges that it is important to not exclude ex-MOR trial patients from analysis in order to maximise data available. Ex-MOR trial patients may have had lower dosing or less-frequent dosing with elosulfase alfa during the clinical trial but this would lead to an underestimate of effect (not overestimate) and so the long-term data should be used to maximise reliability of the model.	Comment noted.
48	Clinical Expert	Great Ormond Street Hospital	ECD 3.5 (Data analysis issues) We agree with the committee that *"a predefined statistical analysis plan is important for all treatments that are recommended as part of a managed access agreement"* and this is of paramount importance for any future MAA for other technologies. However, this was not implemented in this evaluation to the detriment of the process. We also agree with the committee that there was significant effort from patients, families and clinical teams in gathering the required data and submitting this regularly. It is deeply regrettable that the data collection and analysis process was not robust, and that there was not a predefined plan for analysis.	Comment noted.
49	Clinical Expert	Great Ormond Street Hospital	ECD 3.6 (Complete case analysis) We share the committee's concern that the approach taken by ERG and the company has resulted in limited short-term outcome data being used to inform the models. It is clearly imperative that as much reliable outcome data as possible is used to inform the modelling so that the model can be considered to be reliable and a valid means of assessing cost-effectiveness. Given the chronic slow-changing nature of the disorder and need to evaluate the long-term response to treatment every effort must be made to ensure that robust long-term data is used in this process. We are concerned that the ERG and company approach has limited this.	Comment noted. The committee's discussion and conclusions on long-term outcomes is summarised in section 3.11 of the FED
50	Clinical Expert	Great Ormond Street Hospital	ECD 3.7 (Treatment benefit) The committee concludes that all the data from MAA and MOR-005 show generally stable outcomes over time, including for 6MWT, lung function, and health-related quality of life. We also agree with committee that additional benefit including skeletal outcomes, and response to surgery, are not fully captured. We agree that *"elosulfase alfa is clinically effective compared with standard of care, and the size of the benefit could have been underestimated*." We remain concerned that the modelling has not captured all the benefits seen, and the modelling has been limited to a small subset of the available outcome data parameters. In particular, little attention has been given to the nuanced and useful qualitative data captured in the HRQL data in the MAA, and has not been taken into account in the model.	Comment noted. The appraisal committee noted the valuable data submitted from patient organisations on the outcomes that matter to people with MPS 4A and the benefits of elosulfase alfa. The committee was disappointed that the company had not used this data to inform its model structure (see section 3.9 in the FED).
51	Clinical Expert	Great Ormond	ECD 3.9 (Wheelchair based model.) We share concerns that the model used does not accurately represent the disease progression. There are concerns that the model assumes that "Sometimes	Comment noted. The appraisal committee

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		Street Hospital	uses wheelchair" is a worse quality of life than "no use of wheelchair" whereas this may represent a positive change as detailed by the Patient Experts and acknowledged by the committee. We remain concerned that the model is not appropriate and that recommendations have been based on a model that is acknowledged to have significant and serious limitations.	agreed that the model structure was limited (see section 3.9 in the FED)
52	Clinical Expert	Great Ormond Street Hospital	ECD 3.11 (Overall survival). We agree that even with elosulfase alfa that treated patients will have higher morbidity and likely higher mortality than the general population, even if treatment is started from a very young age. However modelling this is difficult and still based on assumptions, and linking mortality purely to change in FVC is also likely to be inaccurate.	Comment noted.
53	Clinical Expert	Great Ormond Street Hospital	ECD 3.13 (Body weight). It is appropriate in modelling to take into account the expected weight gain for paediatric patients as they grow, and to base this on Montano et al 2008. Internal data review at GOSH suggests the MAA cohort from our centre are distributed within the range suggested by Montano. It is reasonable to assume stable weight once final height is obtained and that this is lower than the general population. This should be very straightforward to incorporate into the modelling.	Comment noted.
54	Clinical Expert	[Great Ormond Street Hospital	ECD 3.16 (Cost effectiveness estimates). It is not clear which of the committee's preferred assumptions were subsequently incorporated into the modelling to derive the ICER. With regard to changes in body weight over time it should be clarified how this was applied to patients in the modelling. As per point (3) above, if the modelling is based on an initial young, newly-diagnosed treatment-naïve population then a reasonable assumption about growth and weight gain would be based on following the 50th centile growth charts (Montano et al 2008).	Comment noted. The committee's preferred assumptions are summarised in section 3.17 in the FED
55	Clinical Expert	Great Ormond Street Hospital	ECD 3.17 (Indirect benefits). We welcome that the committee recognises the very significant and important benefits of treatment to patients with MPS 4A. However, these are not reflected in the evaluation model.	Comment noted.
56	Clinical Expert	Great Ormond Street Hospital	ECD 3.18 (Home infusions). The vast majority of patients treated in the MAA already receive infusion at home and some are able to self-administer these independently without nursing input, reducing administration costs further. Has this been accounted for in the modelling?	Comment noted. The health economic model includes an assumption that 90% of patients would have home administration of elosulfase alfa (50% by self or carer, 50% nurse supervised)
57	Clinical Expert	Great Ormond Street Hospital	ECD 3.21 (Long term benefits). The Committee agreed that there are likely to be long term benefits with elosulfase alfa, and the model does not capture all of these. The committee acknowledged that the company's analyses were not robust and that an alternative model could capture the benefits better. It must be noted that a significant burden was placed on patients and their families in getting	Comment noted. The appraisal committee noted the valuable data submitted from

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the data. We are concerned the process of interaction between ERG, company and NICE committee has not resulted in an acceptable alternative model being derived.	patient organisations on the outcomes that matter to people with MPS 4A and the benefits of elosulfase alfa. The committee was disappointed that the company had not used this data to inform its model structure (see section 3.9 in the FED).
58	Clinical Expert	Great Ormond Street Hospital	ECD 3.22 (Recommendation). The modelling did not demonstrate cost effectiveness, but we are concerned that the committee conclusion is based on what the committee considers to be a flawed model.	Comment noted. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.
59	Clinical Expert	Great Ormond Street Hospital	ECD 4.1 (Review of Guidance). We note that a review of the guidance by the guidance executive after 3 years is recommended and that the guidance executive will decide whether the technology should be reviewed based on information gathered by NICE and in consultation with consultees and commentators. We remain concerned about the uncertainty about provision of on-going treatment for those patients who have been receiving treatment under the MAA during this period of time. We are also concerned that there is no defined further process during this 3 year period for what new information should be sought or made available. A clear plan must be put in place and recommended otherwise the same cycle of events with non-informative outcome will result, to the detriment of a cohort of patients with a rare disease for which an acknowledged effective treatment exists.	Comment noted. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.
60	Website		**Has all of the relevant evidence been taken into account?** No: a. The combined long term benefits of persons who have been on Elosulphase alpha since early trial phases (>10 years) has not been collated, presented or considered. b. The fact that the slowing of disease progression has allowed patients to be fit enough to undertake surgical interventions to address some of the effects of the disease not fully managed by the ERT provides additional and significant benefit. This factor has not been taken into account in the	Thank you for your comment. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			ERGs revised forecast of life expectancy (having rejected the company's forecast as 'implausible'). c. The QALYs do not adequately take into account the significant benefits to patients of other factors such as increased patient height, less degradation in hearing/sight loss, stamina improvements, leading to increased fitness/muscle tone/mental wellbeing, when compared with patients on standard care. Much of this data was gathered during the MAA. d. The Qalys do not take into account the fact that (based on the experience of our affected family members) any issues requiring intervention are more spread out over time, degradation is slower and there tend to be only one issue that needs resolution at a time rather than multiple interrelated issues. This gives time for proper planning of treatment and significant windows between recoveries. The possibility of surgery or other medical intervention to resolve specific areas of degeneration means that transition through the health states (whether modelled by wheelchair use or any other marker) is not always a straight line. Our experience shows that since being on elosuphase alfa, our children have been well enough to undergo major surgery which has significantly improved their pain, mobility, breathing, energy and overall well-being, including mental health. Prior to surgery in both cases (double hip replacement for one child at age 15/16) and tracheal resection for the other at 18) the affected individuals were very depressed, unable to engage easily with friends, family or school work and suffering varying degrees of pain, reduced mobility and fatigue. A big part of helping them manage this time whilst waiting for decisions regarding surgery, coping with the surgery and the effort required to for rehabilitation post-surgery, was the knowledge that elosulphase alfa was still supporting their overall condition: they were dealing with a specific health problem with a specific treatment available – they were not staring into the black hole of "Morquio degeneration" with no prospect of ever improving. In both cases, the surgery was successful with the specific problem areas alleviated and they have both been able to pursue their studies at college and university and get on with their lives. e. There is no assessment or consideration of the potential detrimental impacts of withdrawing (or not providing) the treatment (physical and mental wellbeing). One of our children now lives away form home and manages his own ERT infusions semi-independently with only minor nursing support. This is a big commitment for him to fit around his studies and all aspects of learning to live independently. How would we expect him to feel when it is determined that this has all been as waste of time and he cannot have the treatment any more. When our children were first diagnosed we were told that there was no treatment available for this condition and when the opportunity came along a few years later to participate in the clinical trial for the drug now known as elosulphase alfa, we took the decision to allow our children to take part – partly, obviously, in the hope that they would gain some benefit from the treatment, but also so that in the future no parents would have to be told on diagnosis of their child that there is still no treatment. It will be heart-breaking for new parents to have to be told that yes there is a treatment but because it failed some arbitrary threshold for cost effectiveness it cannot be given to your child.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No: a. The ERG assertion that 6MWT results are 'implausible' on the basis that they were higher for partial wheelchair users is flawed. In my experience, partial wheelchair users use their wheelchairs to conserve their limited reserves of energy/stamina to be able to deploy it when required (i.e on the 6MWT rather than on getting to the wards in the first place) b. The EQ 5D 5L only attributes utility gains for increases in 6MWT/FVC. Recognising MPSIV is a degenerative condition, and Elosulfase alfa delays the effects, rather than restores any losses/damage already incurred, the utility gains should be based on 'what is not lost' compared with those on standard care. This gives considerably higher figures. c. The model also needs to account for the cumulative effects of these 'gains' over time. Data currently only considers the QALY gained over 1 year of treatment i.e The 'value' of the second year of treatment is the sum of the Year 1 and Year 2 i. (nominally double the 'value' for only a slight 'weight affected' increase in cost) d. The majority of data collected to date has been on the existing MPSIV population, which covers a range of ages. These patients already had some level of degenerative impact prior to commencement of treatment. There is no recognition within the QALYs that treatment of newly diagnosed (usually young) patients will gain even more quality of life gains from the treatment, as any pre-treatment degeneration will be minimised e. The committee acknowledge that the trial evidence and MAA data suggest that treatment with elosuphase alfa provides stability to the condition for MPS IVA patients in the long term. We agree – this has been the experience for our affected family members. We do not feel that enough weight is given to the benefit of stabilisation in what is otherwise a degenerative condition. When energy levels and stamina regularly fluctuate and general health frequently varies, it is impossible to plan your life from one day or week to the next, never mind looking ahead at future studying or career options, which is what young adults with MPS IVA want to do, the same as everyone else. Stabilisation of the condition means that someone can reasonably assume that their current pattern of energy use/pain management and required recovery time will continue at least over the next few months or years. This enables them to get maximum use out of their current state of health without fear of overdoing it, which in turn leads to better physical and mental health and the ability to plan for the future. The associated well-being gains are immense. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No: a. Request for better comparison group data for ultra-rare conditions to have been gathered over the 5 year MAA period was naïve (as any newly diagnosed but non-treatmented cohort was always going to be minimal). Given the small numbers affected with the condition and the significant	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			differences in the way individuals are affected by the condition then any attempt to model effectiveness and put a numerical value on quality of life gained from treatment is going to be extremely difficult, bordering on impossible. A different approach entirely should be considered for conditions of this nature. b. It is recognised by NICE that the process for evaluating Highly Specialised Technologies are not appropriate (as they are currently under review by NICE). I believe that the threshold prices used in evaluation are based on 'Very rare' conditions – which equates to around 10,000 cases across UK. MPSIVa has cases in the UK in the low hundreds. As such it is discriminatory for the 'price per patient' is not proportionately higher to account for this order of magnitude difference. c. Elosulphase alfa was the first treatment to be managed via a MAA. The findings of this review have identified that the process, and subsequent results/outcomes at the end of the 5 year period have significant areas for improvement. However, the patients involved in this first MAA should not be penalised for the failings/shortfalls of the existing processes. d. The criticism of the selected assessment criteria should be directed as much at the NICE committee who granted the MAA, as well as the company. Both should have established/agreed effective criteria for successful re-evaluation, during rather than at the end of the process. NOTE This point was made during consultation on the original findings. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Yes: a. The costing model is discriminatory against the positive effect of the drug on MPSIV patients . In essence, the more effective the treatment is in allowing patients to grow during childhood/adolescence, the less cost effective the treatment is – because you need more of the drug to treat that patient. b. The paper implies that newly diagnosed patients will be treated differently to existing patients. As the significant benefits have been recognised by the committee, this is discriminatory between these two cohorts. c. We believe that the threshold prices used in evaluation are based on 'Very rare' conditions – which equates to around 10,000 cases across UK. MPSIVa has cases in the UK in the low hundreds. As such it is discriminatory for the 'price per patient' is not proportionately higher to factor in the fact that development/production costs etc are shared across a smaller cohort of patients	
61	Website		**Has all of the relevant evidence been taken into account?** Example responses may include:	Thank you for your comment. After the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• No, NICE have not taken into account the patient evidence and data from the MAA, because: only newly treated patient data has been included and only two years of data from the MAA was presented. Much of the data from the MAA was not shared or presented • No, it appears that NICE have ignored or at best not fully take account of a) the patient evidence b) the data from the MAA • Disconnect in the data requested and committee expectations. Committee were expecting long-term data from clinical trial pts but focus from ERG is on naïve patients only. It is concerning that the prior communications between NICE, ERG and the company has not led to an acceptable, alternative model being agreed and implemented. • The modelling has not captured all the benefits seen in clinical practice and reported directly by the patients, parent / carers. There has been limited use of the HRQOL collected through the MAA • Whist committee accepted the W/C model last time they did not like it. Was this conveyed to company? • Whilst NICE has acknowledged the wealth of information collected and presented by the clinicians and patient organisations, there is little evidence that this information has been considered and participants and observers were left feeling that the focus of the review was totally price driven and not based on clinical efficacy. • We are concerned that not all the data appears to have been submitted and this raises concern over whether data collection / transference of data has failed at some point. Data gaps trigger uncertainty. Patient and clinical communities are concerned that the full impact of ERT has not be captured and interpreted with many parameters not referenced, which would have given a richness and completeness to the data and narrative being told by the clinicians and patients • Not having a predefined statistical analysis plan in place for this re-evaluation has resulted in a flawed process with no defined parameters or clarity on expectations. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** • No, the summaries do not fully capture the benefits to patients from receiving this treatment. Share information on personal experience / benefits • No, the summaries woefully underestimate the benefit to patient from this therapy • No, the model is flawed and an alternative model should be used **Are the recommendations sound and a suitable basis for guidance to the NHS?** • It was evident, there was no clear process on how to review treatments coming out of a MAA. • Recommendations were flawed due to lack of data and clarity on the areas of focus for the review • Bring in your personal view and how you feel about being part of this process and part of the ongoing assessments and data collection for the MAA.	second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• No, it does not appear as if NICE has a solid understanding of this tiny population of people or the effect that any decision will have on this community • The current model is not appropriate to determine whether elosulfase alfa is cost effective for a naïve population as it is using data from a wide range of participants with varying degrees of pathology, many of whose baseline were not captured in the MAA if already on established treatment **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** • Yes, the process has discriminated against me as it has failed to use appropriate approaches in reviewing data from small patient populations. • Review of data for specific disease groups was excluded • Longer term data was excluded as pre-treated patients were not included in the review. • It is still unclear why NICE have decided to review existing and new patients separately. • Yes, the process used by NICE has exclude people, especially those with the protected characteristic of Disability, from fully contributing to this consultation and as such this current recommendation is discriminatory. Additionally the recommendation itself is discriminatory as the approach that NICE has taken shows an unwillingness to use appropriate methodologies for the consideration of data related to very small populations • Process has cause ongoing uncertainty and anxiety for patients and families, particularly for those patients treated through the clinical trial • Patients have complied with all requirements and expectations but it appears their efforts and data has been excluded when it matters • Main point of MAA was to capture long term data to respond / answer the uncertainties raised by the committee. Currently this has not been reflected in this process. • If NICE's decision is a no for newly diagnosed patients then they will be denying a population that would gain the most benefit. We know from experience that patients treated early in their disease have better outcomes and reduced disease morbidity. This process has resulted in older patients asking whether they should give up their effective treatment, so that young patients have an opportunity to glean the benefits they have experienced through this treatment out of pure guilt.	
62	Website		**General comments:** I am aware of someone who takes this drug and it has been a life changer for her. It relieves her pain, so she can get out of bed and be able to go to work.	Thank you for your comment.
63	Website		**Has all of the relevant evidence been taken into account?**	Thank you for your

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Yes, but more emphasis should be placed on the substantial impact it has on improving quality of life **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No. Vimizim causes substantial improvement in patients symptoms and greatly increases their quality of life - the differences you can see in patients from before they start treatment to now are clear. Such beneficial impact is undoubtedly cost effective, and should be available to newly diagnosed patients too. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No. These recommendations are plunging newly diagnosed patients into a life where they cannot receive adequate treatment and will not have the same quality of life as those with this treatment. This guidance is giving a basis for guidance to the NHS that people with extremely rare disabilities are not entitled to life changing care, which is unacceptable. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Yes. The individuals receiving this treatment have one of the rarest disabilities in the UK, and these recommendations are saying that these people aren't entitled to life changing treatment for their disability.	comment. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.
64	Website		**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The costs incurred to take care of people with Morquio A without this drug will be far greater than the cost of the drug itself. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** This is directly discriminating against people with a very specific disability. This decision to not distribute a life altering drug is effectively signing the death certificate of those who need it. People who rely on this medication will have no quality of life and will not be able to function. I know someone with Morquio A and she will not be able to have a life without this medication.	Thank you for your comment. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
65	Website		**Has all of the relevant evidence been taken into account?** No. As a colleague of someone currently taking elosulfase alfa I don't think it has at all. During covid her treatment was paused for a considerable amount of months and during this time her health has decreased considerably. Since restarting treatment she has seen markable improvements in her quality of life and is much more able to live a less debilitating life. I do not think NICE has gone far enough to gather real life data that clearly shows elosulfase alfa addresses the underlying cause of Morquio A syndrome.	Thank you for your comment. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.
66	Website		**Has all of the relevant evidence been taken into account?** No. A significant proportion of the data from the managed access scheme was not taken into consideration. Despite the Managed Access Scheme running for over 5 years, only 2 years' of data was included, which is inexplicable given the whole purpose of the Managed Access Scheme was to collect evidence of benefits over a longer term period of time. The data presented only included newly treated patients, this in itself automatically excluded evidence from patients who have been on treatment for a longer period of time (due to being part of the clinical trial for a number of years before that). I also do not feel that the extensive quality of life benefits and broader patient evidence about the real life benefits of Vimizim has been properly considered or factored into the decision making process. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No. Broader patient benefits have not been appropriately interpreted or captured. My son Sam has been receiving Vimizim for almost 10 years. He does not suffer with fatigue. He does not routinely have any pain. He is 13 but is still very mobile and independent. Vimizim has had an incredible impact on his life, his quality of life and his independence. The evidence from clinicians and other patients is totally aligned to our experience, yet this is not fully reflected or given sufficient weight or importance in this recommendation. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No. It is blatantly obvious that NICE do not have a robust process in place to assess treatment following a Managed Access Scheme. This is entirely unacceptable - there has been a six year period to plan and prepare for this, yet the process is both confused and fundamentally flawed. As a result of incompetence in designing an appropriate process, patients yet again are left in limbo, causing unnecessary stress, anxiety and suffering in lives that are already incredibly challenging. This is unforgivable. It is also entirely unacceptable for the challenges with data to not be resolved before this point. Areas	Thank you for your comment. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			of focus for the review have not been clear throughout. Both NICE and the company have access to the data, its is perplexing therefore to be in this situation right now. Having been part of the Managed Access Scheme for 6 years. diligently committing to reviews and hospital visits, 2 hours away from home, going through the excruciating waiting for "exam results" every year to find out if treatment will continue is soul destroying, and has impacted my mental health, that of my family and my son particularly. To commit to all of that as a family, then to find that data has not been properly used, and the benefits not fully represented is an absolute travesty. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Yes. This process is directly discriminatory to my son. He and all other Morquio patients fall under the protected characteristic of disability, and the only reason that this cost effectiveness guidance is being given is because he is unfortunate enough to be born with a condition that only affects a very small patient population. This is entirely beyond his control. The process does not fully take this into account and therefore is structurally discriminatory. This is also evidenced by the fact that NICE openly admits the benefits and positive impacts of Vimizim, yet still says no. The exclusion of longer term data is also discriminatory because it clouds decision making and holds valuable evidence back. This is unacceptable given the rarity of the condition and the inherent challenges involved in collecting the data. It is both discriminatory and negligent. Splitting the decision making process between new and existing patients creates concern also, especially given there is zero visibility of when and how a decision will be made for existing patients. Whilst I understand that this decision sits with NHSE, it is unacceptable for NICE to wash their hands of this situation; from a patient perspective, it should not matter who the decision maker is, the approach needs to be transparent. It is not, and again, patients are left stuck in the middle, uncertain, anxious and afraid. This is no way to treat disabled children and adults who are disadvantaged daily because of the condition they have and the way society treats them.	
67	Website		**General comments:** While recognising the heavy demand on NHS resources and funding it seems contradictory to deny treatment to desperate patients who will make high financial care demands if denied treatment by this medication. Apart from the fact that the pain isolation and suffering these patients endure even with the treatment surely the NHS has the duty to ensure for them a quality of life that is above the	Thank you for your comment. After the second committee meeting, elosulfase alfa was for treating

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			bare essential minimum of existence.	MPS 4A in people of any age.
68	Website		**Has all of the relevant evidence been taken into account?** No, NICE have not taken into account the patient evidence and data from the MMA, because only newly treated patient data has been included and only two years of data from the MAA was presented. Much of the data from the MAA was not shared or presented. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No, the summaries do not fully capture the benefits to patients from receiving this treatment. I am a patient with Morquio. Prior to receiving Vimizim I had no expectations about my future and quality of life. I was in pain all the time and relied on painkillers. My joints were stiff and my mobility very restricted. I had to have knee braces prescribed. I relied on cabs or others to get to places and back and be helped in out of cars etc. My wrists were very laxed and hurt and that meant carrying a simple mug of tea was very difficult, wringing a cloth was impossible. My upper core strength was noticeably getting worse and it affected my posture making walking harder. My energy level was low and so too my stamina – simple things like having a shower meant I had to rest straight afterwards as I knew I would be very tired. I planned my day limiting to what I could do so that I could rest My hearing began to deteriorate much more as I got older – having to get more powerful hearing aids with each passing years. In the last few years prior to starting Vimizim, people would approach me to ask how I was as they could see my breathing was heavy even though I did not realise and that was a huge worry. My skin was taut, sore and I had adult acne and no medication, specialist treatment helped. As there was no treatment for this disease, I had to accept all these health issues as part of my life. When I first heard about the new ERT Vimizim for Morquio in 2015, I immediately asked my GP to refer me to a specialist centre (previous I was under many different Consultants but none were Morquio specific) and was allowed to join the MAA and started Vimizim in May 2015. I was 47 years old. I did not want to build my hopes up as I was an older patient and thought that the deterioration was far too great for the treatment to be effective but I felt that I was given a chance to try to improve my health and the quality of my life and would do everything that the MAA required to allow me to try this new drug. I first noticed an improvement after a couple of months when I realised I was wringing my wash cloth with ease – I saw that my wrists were much less laxed and no longer had that lingering pain and strength was improving in my arms. From there, I noticed that I could carry from one room to another a mug of tea on my own. I could lift a 4 pint milk carton! Using the handrail to climb a step was so much easier as I had the improved upper core strength to push me up. Washing my hair, getting in and out of the shower was easier etc. The pain in my joints greatly reduced and did not have to take painkillers. I can shower and get on with my day without having to allocate time to rest as had much	Thank you for your comment. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			more stamina. My sleep has improved so I wake up with much more energy. Family and friends have commented that I have become more sociable. I am able to help with housework which had not been possible before and had to rely on others. I still have to wear knee braces but I notice I wear them more when I am out and much less at home as I am more stable standing and walking. My posture improved greatly helping my back pain to ease alot. During this time my hearing remained stable and I did not have to get more powerful aids. My skin improved so much that I no longer have to use any treatment. Based on assessments my 6MWT improved showing I can walk further without exertion and my lung capacity has improved too and no longer get comments about being out of breath. Although all the above maybe considered anecdotal, they all point towards just how much Vimizim has helped me physically and mentally, even as an older patient. It has given me hope for the first time. With the pandemic in March 2020, and the fact that I was severely at risk from Covid complications, I felt I had no choice but to take a pause in treatment as it requires a face to face contact on a weekly basis. After a couple of months, I started to notice all the previous symptoms returning bit by bit. My joints started to hurt and again affecting my mobility, the strength in my legs and upper core body weakened and my wrists became laxed again and sore. I had to start using my knee braces indoors again as they became less stable. Sleep has been affected and my stamina and energy reverted to its old levels so I was again finding myself having to rest a lot more. I notice my hearing worsened and testing revealed it had so now need more powerful hearing aids. The pause in treatment has proven just how Vimizim has benefited me illustrating a before and after scenario and this is not included in the evidence. **Are the recommendations sound and a suitable basis for guidance to the NHS?** It was evident that there was no clear process on how to review treatments coming out off a MAA. Recommendations were flawed due to lack of data and clarity on the areas of focus for the review. I made every effort, and at a financial and time cost to both myself and my family, to help provide all the evidence needed for the MAA in the last 6 years. It took up a lot of time but I felt that it was something I needed to commit to in order to show just how vital Vimizim is to all Morquio patients. It is upsetting to see that all the evidence and hard work from all patients, Clinicians and the MPS Society has not been used. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Yes, the process has discriminated against me as it has not used appropriate approaches in reviewing data from small patient population. Morquio is an ultra rare disease and it is unfair that I have to follow such a long drawn out process to access the only drug that has proven to help me	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			have a better quality of life, slow down the progression of the disease and prolong my life. . Also, longer term data was excluded as pre-treated patients were not included in the review. It is not clear why NICE decided to review existing and new patients separately.	
69	Website		**Has all of the relevant evidence been taken into account?** No, NICE have not taken into account the patient evidence and data from the MAA, because: only newly treated patient data has been included and only two years of data from the MAA was presented. Much of the data from the MAA was not shared or presented. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No, the summaries do not fully capture the benefits to patients from receiving this treatment. I am a patient with Morquio who is currently receiving Vimizim on the MAA. Prior to starting treatment, I was in constant pain, suffered from extreme fatigue and my mobility was very poor due to stiff and painful joints. The effort required to walk made it feel like walking through treacle. I could only manage to walk very short distances before becoming tired, breathless, and experiencing increased pain in my joints. Travel was limited to cars or taxis, I'd have to be taken door to door to limit the amount I would need to walk. I was taking ibuprofen on a daily basis to manage the constant underlying pain I had in my joints. I suffered from fatigue and lack of stamina: I had to limit my daily activities and make sure I had plenty of rest in between to manage pain and fatigue. Simply having a shower would wear me out and I would need to rest before continuing my day. A simple shopping trip would mean I would be bedridden the following day. I suffered from brain fog: I had difficulty concentrating for long periods of time or focusing on a long conversation. My poor mobility lead to an unhealthy weight gain - I needed to lose weight but found it impossible to do so. I had breathing issues - my breathing was shallow and I easily became short of breath. I had to constantly face upwards to keep my airways open. I suffered from sleep apnea and daytime sleepiness - I used a CPAP machine at night to combat this. I had weakness in my arms and legs and lax wrists I found carrying anything from a mug of tea to a bag difficult and cumbersome. I had skin problems and suffered from painful adult acne. These symptoms would get progressively worse over time. No treatment and no cure meant that I had no choice but to suffer and tolerate them. I had to accept these symptoms as part of the problem. I started Vimizim treatment under the MAA in April 2015, aged 42. I had low expectations thinking that the damage had already been done by Morquio, so I was overwhelmed when I began to notice the benefits of Vimizim. My mobility improved: I was able to walk further without the need to stop and rest - this was evidenced by the 6MWT I had to do as part of the MAA which showed I could walk more than twice the distance with fewer rest breaks while on treatment. My breathing improved and is no longer shallow. I can speak a whole sentence without stopping to catch my breath. My posture has changed - I no longer have to hold head facing upwards to keep my airways open. This was evidenced by the lung function tests I did as part of the MAA - my lung capacity increased by 50%.	Thank you for your comment. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			These are the benefits where I have provided clinical evidence, but there are plenty of other benefits which are considered anecdotal, but have made a significant immeasurable improvement to my quality of life. I experienced a decrease in joint pain and stiffness - any pain I do have easier to manage without the need to take pain killers. I have thrown away boxes of unused ibuprofen that had expired as I don't need to take them on a regular basis any more. My joints are no longer stiff: simple things like turning around and getting out of bed or getting in and out of shower are so much easier. My body feels lighter and I no longer feel like I am walking through treacle. I experience less fatigue and more stamina. I can get more activities done during the day without feeling tired, and less need for breaks in between each activity. The brain fog disappeared - friends have commented on how much more alert and "bright" I am, more "with it" - I can hold and follow a conversation without fading. I can concentrate for longer. have an Increased upper body strength - carrying things like mugs of tea and bags are no longer an issue and I am more stable on my feet. I am able to open bottles and jars with less effort. My sleep disturbances improved and I was taken off CPAP after 20 months of Vimizim. My new found mobility and energy helped me achieve my weight loss goals - I lost a quarter of my body weight (13kg). The condition of my skin improved - it is softer and I finally got rid of my painful adult acne without the need for any additional skin treatment! I am brighter, more sociable and independent - and happier. None of these positive improvements can be quantified or were captured as evidence for clinical and cost effectiveness At the beginning of the pandemic, my risk of severe complications of covid were high, so I took a pause in treatment. Within a less than a month of not having Vimizim, my old symptoms returned, most noticeably the pain, fatigue and breathing difficulties. This was also not captured as evidence for clinical and cost effectiveness **Are the recommendations sound and a suitable basis for guidance to the NHS?** It was evident there was no clear process on how to review treatments coming out of a MAA. Recommendations were flawed due to lack of data and clarity on the areas of focus for the review. I put in a lot of time, money and effort to provide as much evidence of the benefits of Vimizim through the ongoing assessments and data collection for the MAA for 6 years. It was repetitive, tiresome and intrusive but I was more than happy tolerate the burden to provide this evidence, not only to be able to continue receiving treatment, but also because it was the only way I could prove the effectiveness of the drug which would then make the drug accessible to all patients with Morquio. It is incredibly frustrating to see that the data collected from all patients by clinicians and the MPS Society was not used properly when making this recommendation. **Are there any aspects of the recommendations that need particular consideration to ensure**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? The process has discriminated against me and my disability as it has failed to use appropriate approaches in reviewing data from small patient populations. It has discriminated against me due to my disability being caused by an ultra rare disease which means I have to go through a long drawn out process to get access to a drug which has been proven to significantly improve my quality of life and prolong my life. Having benefitted from treatment and providing continuous clinical evidence of this benefit for 6 years, it would be unethical to withdraw it from me now. Longer term data was excluded as pre-treated patients were not included in the review. It is still unclear why NICE have decided to review existing and new patients separately. **General comments:** I wholeheartedly do NOT agree with this recommendation. It is unclear why NICE is only considering access for new patients and NHSE will consider those already on treatment. What is the reason behind this? Surely all data should be considered. Why was valuable long term data from those on the clinical trial discarded? I find everything in this paragraph a huge concern. It was a huge burden to provide all the data required for the MAA and it is disconcerting that this data has not been analysed and used correctly by the company. I agree that the wheelchair based economic model is flawed. Prior to Vimizim, much of my time was spent indoors with no wheelchair use as I was too tired or in too much pain to leave the house. Quite often I would be bedridden. Vimizim has given me a new lease of life and I now have the energy and stamina for outdoor activities. I use a mobility scooter outdoors but I do not see this transition from "no wheelchair use" to "wheelchair use sometimes" as a negative thing. I now have the energy to use a wheelchair more often, and that can only be construed as a positive thing. I have more independence, can use public transport, can go to concerts, the theatre, museums, travel independently, visit friends and family, that I couldn't do before treatment	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Vimizim has had an immense impact on my life beyond the direct health benefits. Not only has my physical health improved but so has my mental health - it's only with hindsight that I appreciate this impact. I feel much more in control of my life and more optimistic about making future plans as I know activities will no longer have to be cancelled due to pain and fatigue. I am more independent and no longer have to rely on others for help. My social life has improved as I can engage better with friends and family and I can enjoy my time with them more. Having infusions that take a whole day out of my week is a huge burden especially when having to travel to a specialist centre each time. Home infusions dramatically reduce this burden.	
70	Website		**Has all of the relevant evidence been taken into account?** NO, NICE have not taken into account the patient evidence and data from the MAA, only newly treated patient data has been included and only two years of data from the MAA was presented. Much of the data from the MAA was not shared or presented. Why should this be removed when you recognise the long term benefits of elosulfase alfa? **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries do not fully capture the benefits to patients from receiving this treatment. We have noticed that our daughter's energy levels are a lot better, before treatment started she was unable to complete a school week, without being tired on the Friday evening after school. She was slow to walk upstairs, stepping one step at a time. After treatment she seems to have much more energy, but the biggest difference is how happier she is. She is singing and dancing much more than she ever did. **Are the recommendations sound and a suitable basis for guidance to the NHS?** It was evident there was no clear process on how to review treatments coming out of a MAA. The recommendations are flawed due to lack of data and clarity on the areas of focus for the review. We have only had our diagnoses for about five months, we were devastated with the news that our beautiful little girl had a life limiting disease. We know that nothing will change our daughters condition but this treatment, as we understand, slows the downward progression of the disease. I can't believe it is right or moral to remove a treatment which is proven to extend a 6 year old life and possible give her a better quality of life. The stress of the threat of this treatment being removed is too much to bear. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender,**	Thank you for your comment. After the second committee meeting, elosulfase alfa was for treating MPS 4A in people of any age.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Yes, the process has discriminated against us as it has failed to use appropriate approaches in reviewing data from small patient populations. Longer term data was excluded as pre-treated patients were not included in the review. It is still unclear why NICE have decided to review existing and new patients separately.	

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	BioMarin International Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No link to the tobacco industry.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

Name of commentator person completing form:	Mohit Jain

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The Committee notes in the ECD that ***'the Managed Access Agreement (MAA) period has been extended twice to allow the company more time for its submission. Despite this, there were still issues with the company's analysis and modelling'*** **(section 3.3, page 6).** The company appreciates the collaboration with NICE and NHS England to the challenges on what has been a very complex process due to lack of early alignment on multiple issues which are captured below, and we hope provide learnings for future reappraisals of MAAs: • **Lack of alignment early on with ERG/Nice Technical Team with regards to the analysis plan meeting the objectives of the scope.** The focus of all parties has not considered the actual scope of this re-submission, which is focused on future treatment-naïve patients, who are predominantly newly diagnosed patients. These newly diagnosed patients are likely to have notably different phenotype or characteristics compared with the previously treated MAA cohort. For example, the newly diagnosed cohort would be expected, to be younger, have a lower weight and less disease manifestation at the time of initiating treatment. These factors would be expected to positively influence the clinical and cost-effectiveness estimates for elosulfase alfa as we describe in this response document. However, most of the evidence considered by the NICE Committee to date has been based on the overall MAA cohort, most had significant morbidity upon starting treatment. In this response, we provide additional evidence on a cohort from the MAA that is likely to be more reflective of the scope. • **Lack of alignment on a core dataset prior to starting the analysis plan which meets the scope.** Not all sources of data were aligned and shared prior to starting analysis (i.e., clinical data from treatment centres, patient-reported outcomes data from Rare Disease Research Partners (RD-RP), and notes on missing data and treatment decisions data from the NICE oversight committee). This created confusion and incoherency in the data. However, there have been multiple engagements and a strong collaboration between NICE, RD-RP and the company during technical engagement (post first technical report in April 2021), which helped in creating a harmonised dataset. • **Lack of alignment on how to manage missing data and prioritise the analysis plan.** Following collaboration on finalising a core dataset with shared understanding there was alignment on priorities for analysis to meet the needs of the evidence review group (ERG). These also explored handling missing data, imputations where applied

had minimal impact on results and given the nature of missing data (i.e., tests not conducted for various clinical reasons) it was agreed that imputation did not make sense to prioritise.

- **Lack of alignment on analysis methods and approaches.** Given the missing data in the core dataset **t**here remained uncertainty around very low sample size with complete core data (particularly with a complete case analysis or CCA approach) and interpretation of results from this analysis versus MOR001. *[CCA is a statistical analysis that only includes study participants for which we have no missing data on the variables of interest].* Lack of an aligned analysis plan led to different perspectives on methods on how to approach the uncertainty support the questions asked in the scope.

- **Unrealistic expectations on the real-world evidence based MAA.** The ERG expectation for data collection and management, was more in-line with one that would ordinarily consider for a prospective clinical study. This MAA/coverage with evidence was real world observational data captured by experts and not designed to align to clinical study standards. As a real-world evidence, the MAA has a high quality of data capture vs. registries and other approaches which is a testament to the efforts of the community. Misaligned expectations from the data resulted in a lot of work to answer questions which the data is not structured to answer, thereby limiting time for more relevant analyses.

The issues highlighted above in terms of clarity of remit for revaluation and handling of data collection process in the MAA is a potential learning opportunity for all stakeholders and the company feels that these are important to address for future MAA processes and the ongoing Innovative Medicines Fund consultation. Some of the issues in the HST2 process are described in more details below and relate to the further responses in this document.

- The original MAA and commercial agreement had different specifications on the subsequent evaluation which had been raised during the MAA oversight committee meetings. A clear pathway for the re-evaluation for elosulfase alfa was not agreed until September 2020 and formally shared with the company on 10th November 2020, for a submission of evidence for the Highly Specialised Technologies Evaluation by 11th December 2020. Whilst the Company had the submission from February 2020 in place with the latest clinical evidence (but no cost-effectiveness)), the whole MAA population and subsequent modelling had to be re-analysed following the new agreement with NICE and NHSE to reflect 2017 changes to the NICE's process for HST and updated scope, with minimal time to align with experts.

- We appreciated NICE's efforts to try to secure an ERG in 2020. However, the delay in securing the ERG combined with the ERG not having been involved in the 2015 submission led to the ERG having an expectation for a more complete set of evidence than that realistic in a MAA. There was a considerably higher number of clarification questions (68 questions) than what we would have expected for a re-submission. The company believes these questions have not considered the disease characteristics and dataset limitations (i.e., ultra-rare heterogenous disease, real-world dataset, existing natural history data) or informed the scope on future naïve patients treated in England.

	The lack of alignment with the NICE technical team on scope of analysis also related to less direction to the ERG on the key questions. • Several questions regarding gaps and missing data were raised during ERG's review of the MAA dataset. However, as mentioned above, there was a strong collaboration with NICE, RD-RP and treatment sites to create an aligned dataset. The Company requested a 6-month period for data verification and analysis but was granted only 3 months which allowed only for prioritised analyses as requested by the ERG. These requests were driven by focus on finding a comparable population like a clinical trial rather than considering key questions and areas of uncertainties such as starting severity e.g., baseline 6MWT, treatment benefit in future naïve patients, relevance of long-term outcomes and accounting for heterogeneity. • During the technical engagement, analysis was prioritised due to the limited timeframe with the NICE technical team and ERG. Concerns were raised by the Company to the NICE technical team and NHSE on the approach focusing on re-creating comparative data for the first two years of treatment, which already is captured within clinical studies. More importantly, it was highlighted that reducing the data to 1 or 2 years with the complete case analysis (CCA) approach would lead to losing the attention on the long-term data. Having to conduct the CCA left limited time for more relevant analysis and restricted the sample size, which was not controlled for confounders such as age of starting treatment. Despite these limitations, NICE technical committee recommended that the company deliver on the priority CCA analyses requested by the ERG. All parties were time-limited and focused but maybe the relevance and limitations were not completely discussed.
2	On the **relevant data sources for decision-making (section 3.4, pages 6-8)**, the Committee notes in the ECD that *'some people in the clinical trial may have had elosulfase alfa every other week, and that this may have underestimated the treatment benefit. It was concerned that, by excluding people who had had treatment, some valuable long-term data was disregarded. The committee concluded that both the company's and ERG's preferred data sources were relevant for decision making'.* In response to this point, the company would raise the issue that the scope of the NICE HST2 review is treatment-naïve patients moving forward. Clinical opinion supports the case that future patients will be newly diagnosed patients who are expected to be around the ages of 2-3 years. In the MAA data, treatment-naïve patients who started under the age of 6 have an average age of 3.6 years. In addition, there is the potential that non-classical patients, diagnosed at a later age, may present very occasionally. Sibling studies (Frigeni et al. 2021, Ficicioglu et al. 2020, Barak et al. 2020) in MPS IVA have highlighted meaningful differences in long-term disease progression with early diagnosis and early treatment, indicative of expected potential outcomes for newly diagnosed patients in England due to increased efforts in diagnostic efforts, including nationally available genetic testing. Therefore, to align with the future population, the company looked at data in patients treated under the age of 6 and focused on this population in the model. The Company's submission in December 2020 focussed on the longer-term data, and responses to the initial clarification questions showed comparisons between the natural history cohort and long-term data which showed sustained clinical efficacy in wheelchair use, 6MWT,

	and FVC. However, following the initial clarification questions, the focus of the ERG was solely on prioritising the first two-year CCA comparison from the MAA to MOR-001 (Morquio A natural history study), which limited resources for continuing the analysis of the long-term data. The Company has discussed that patients, receiving lower doses of elosulfase alfa during the clinical trial were switched to the approved dose and the longer-term data would indicate their response on the approved dose. The lower dose was found in the MOR-004 clinical study to offer less efficacy and this may underestimate the efficacy in the long-term data. The Company has included this data as relevant and important, and the propensity scored analysis or PSM (i.e., statistical method to construct an artificial control group by matching each treated patient with a non-treated patient of similar characteristics) in the clarification questions (ID1643 clarification letter from ERG 150121 IA ACIC_v4_22022021) showed consistent benefits for treatment vs MOR-001 over the long-term data in ex-trial patients. The Company would highlight that the overall MAA data does not represent the relevant future population and as such it would be critical to extrapolate outcomes in the relevant dataset representing early diagnosed and early treated patients. BioMarin in this response shared an approach to model this relevant population's outcomes (see issue 14 below). The data is more limited in this population but has greater relevance to the scope.
3	Regarding **data analyses issues (section 3.5, page 8)**, the Committee notes in the ECD that it was *'disappointed that the company did not provide more robust analyses in its submission, given the burden put on healthcare staff, people with MPS 4A and their families. This was particularly so given the additional time afforded to the company to try to address the data issues.'* The Company would highlight the MAA process was the first in England and has encountered many changes and challenges over the years of implementation. Initially the MAA data was to be reconciled and managed by NHSE, but after two years this was requested to be managed by the Company. In this type of real-world data capture there was no planning from the beginning for medical monitors or data scientists as this is not a clinical study or associated funding to clinicians for data input. As such the quality of data input was down to the experts, Company, patients and associated company providing patient reported outcome data. The learnings from this MAA should be implemented into future MAAs. More robust analysis would have required more time once the scope had been finalised and more aligned guidance with the NICE technical team around an aligned statistical analysis plan. Indeed, scope of the submission was formally shared with the company on the 10th November 2020 with a submission deadline on the 11th December 2020. The NICE technical team could then have supported discussions with the ERG to avoid the heavy focus on less relevant analysis and keep the focus on answering questions in the revised HST2 scope. The focus of the ERG on trying to recreate short-term comparative clinical data from heterogenous real world data has resulted in analysis which has significant limitations versus the original clinical studies who were compared to a similarly aligned natural history cohort. As explained above in Issue 1, the underlying issue was a lack of an aligned dataset initially, no aligned statistical analysis plan and unrealistic expectations of what can be delivered with real-world data in this ultra-rare disease.

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	Nevertheless, in the past weeks, the company analysis has been focusing on the future patients in England who will be predominately newly diagnosed patients and maybe the occasional less affected non-classical patients. This analysis focused on long-term outcomes and extrapolation has uncertainty. Much of this is not possible to resolve but should support a more relevant analysis with regards to the scope of the evaluation.
4	In **section 3.6 (page 9) of the ECD on the use of complete case analyses (CCA) to assess clinical effectiveness**, the Committee *'reiterated that it wanted to use as much clinical data as possible',* but *'was aware of the limitations of the CCA because it did not include people for whom some outcome data was missing*. The Committee also *'recalled that the company had not provided any alternatives using statistical methods to impute missing data'* and therefore *'concluded that both the company's and ERG's complete case analyses could be considered for decision- making. Also, it noted that it had not seen cost-effectiveness analyses using complete case analysis of data from MOR-005'.* During the technical engagement, the Company collaborated with NICE, RD-RP, and the treatment centres to reconcile and align the MAA dataset. Despite the many data gaps being addressed after this process, there were still many missing values remaining, mostly due to clinical reasons (i.e., patients moving homes, tests not being conducted at some timepoints because of young age e.g., spirometry in <5 years old, patients going through surgery). Therefore, in alignment with NICE, it was considered inappropriate to perform data imputation due to large amount of data missing and a lack of rationale/reasons for imputing data. The Company highlighted to NICE and ERG that due to the large amount of missing data and the high level of heterogeneity in the data, the CCA approach recommended by the ERG would lead to a small number of patients meeting criteria for the analysis and non-comparable populations. Nevertheless, the Company did agree to conduct the CCA as requested by ERG and NICE using the reconciled MAA dataset and comparing to MorCAP1 (as natural history arm), which is a subset of MOR-001 with inclusion criteria similar to the MAA applied. Company's rationale focusing MorCAP1 instead of MOR-001 was to align the patient characteristics as much as possible between the MOR-001 and MAA patients (short of doing a formal PSM analysis). MorCAP1 was used as a more relevant comparison to MAA patients than MOR-001, as it excluded patients <5 years old (MAA did not capture much data in these patients) and removed confounders such as surgery. Also, in MOR-001, patients below the age of 5 did not have respiratory data and had limited 6MWT data; therefore, MorCAP1 provided a more complete dataset. However, following feedback from the ERG and Committee, the Company have re-conducted this analysis versus MOR-001, which is presented below. Despite the Committee's conclusion that the ERG's CCA could be considered for decision making, the company would hold that the 1-year CCA approach of the ERG is too limited. Therefore, the company submitted a 2-year CCA with relaxed assumptions of 'CCA per-variable' rather than 'CCA all variables' to maximise the available data while still addressing the missing data issues as much as possible. Overall, the Company has highlighted to the NICE technical team concerns that CCA represents a poor approach as it does not manage baseline confounding characteristics such as age or disease severity. Regarding the CCA from MOR-005 vs MOR-001, this analysis was deprioritised versus the CCA from the MAA in discussions with the ERG and NICE Technical Team due to time pressure to

conduct all the analyses. However, the Company would argue that the results would not be much different from the data presented in the original 2015 HST model, which used the modified per protocol (MPP) population (i.e., excluding patients with surgeries or with less than 80% adherence to treatment) from MOR-005 QW-QW versus MorCAP 2-year follow-up study population that are highly aligned in terms of baseline characteristics to define the first 18 months of treatment.

To better represent the future population of new patients in the model, the Company looked at all the data available in patients under 6 years old. The MOR-007 study, which is the study with patients under 5 years old, has several patients who would represent this future population; in addition, there are *[academic / commercial in confidence information removed]* treatment-naïve patients in the MAA who have started treatment below the age of 6. It is important, however, to note that patients below the age of 5 have limited measurements. Nevertheless, we believe that this proportion of treatment-naïve patients below the age of 6 can more closely represent future patients.

The company compared outcomes of the treatment naïve MAA population below the age of 6 with the treatment naïve MAA population 6 years and over. The company would like to re-iterate that this younger population is more relevant to the scope because the age of starting treatment is a major confounder (i.e., less disease burden at an early age). Therefore, this analysis shows a more relevant and less confounded comparison than looking at the overall MAA cohort.

See below the results of the comparison between MAA treatment-naïve population under 6 versus 6 years and over.

Figure 4.1: Linear regression of change in 6MWT over time among treatment naïve MAA population: age under 6 vs. age 6 years and over
[academic / commercial in confidence information removed]

Table 4.1: Linear regression of change in 6MWT over time among treatment naïve MAA population: age under 6 vs. age 6 years and over
[academic / commercial in confidence information removed]

A population starting treatment with elosulfase alfa under the age of 6 would gain approximately *[academic / commercial in confidence information removed]* metres per year on the 6MWT compared a population 6 years and older who would gain approximately *[academic / commercial in confidence information removed]* metres per year on the 6MWT based on linear regression using the treatment-naïve population in the MAA (**Table 4.1**). Neither complete case analysis nor imputation were performed due to small patient numbers in these subgroups (**additional file Table A.1**).

The full baseline characteristic tables with all outcomes across different age cohorts in the treatment-naïve MAA population are shared in a separate confidential file (due to small n and potentially identifiable patient level data); baseline characteristics indicate that the patient populations were similar in key characteristics except for weight (see partial table, **Table 4.2** below including age, gender, and weight), with the under 6 population weighing significantly less than the population 6 years and over (mean *[academic / commercial in confidence information removed]* vs. *[academic / commercial in confidence information removed]*, $p<0.01$).

	Table 4.2: Partial* baseline characteristics (only includes age, gender, weight) of treatment naïve MAA population: age under 6 vs. age 6 years and over# *[academic / commercial in confidence information removed]* The analyses presented below support clinical advice that we would expect to see **better outcomes in the newly diagnosed population** (the scope of this evaluation) than had been demonstrated in previous analysis of the overall MAA cohort and previously considered by the Committee. They further support that **this newly diagnosed population would likely weigh less** and therefore require less drug at treatment initiation than had been demonstrated in previous analysis of the overall MAA cohort and previously considered by the Committee. Regarding long-term outcomes, the company looked at the age bands of 5-10 years to confirm the benefit of elosulfase alfa across ages. Despite small sample sizes in some groups, there was stabilisation or improvements seen in 6MWT and FVC values across the 5 age bands (**Table 4.3, Table 4.4**) as evidenced by positive coefficients in linear regressions (with the exception of the ≥6 to <10 years old group for 6MWT and the ≥30 years old group for FVC). Therefore, **we would not expect patients to decline to wheelchair dependency if these outcomes were extrapolated over the long-term**. Neither complete case analysis nor imputation were performed due to small patient numbers in these subgroups (**additional file Table A.2**). **Figure 4.2: Linear regression of change in 6MWT over time among treatment-naïve MAA population: age i) <6, ii) ≥6 to <10, iii) ≥10 to <20, iv) ≥20 to <30, v) ≥30** *[academic / commercial in confidence information removed]* **Table 4.3: Linear regression of change in 6MWT over time among treatment naïve MAA population: age i) <6, ii) ≥6 to <10, iii) ≥10 to <20, iv) ≥20 to <30, v) ≥30** *[academic / commercial in confidence information removed]* **Figure 4.3: Linear regression of change in FVC over time among treatment-naïve MAA population: age i) <6, ii) ≥6 to <10, iii) ≥10 to <20, iv) ≥20 to <30, v) ≥30** *[academic / commercial in confidence information removed]* **Table 4.4: Linear regression of change in FVC over time among treatment naïve MAA population: age i) <6, ii) ≥6 to <10, iii) ≥10 to <20, iv) ≥20 to <30, v) ≥30** *[academic / commercial in confidence information removed]*
5	**In section 3.7 (pages 10-11) on treatment benefit**, the Committee concluded that *'elosulfase alfa is clinically effective compared with standard care'*, but that *'the size of the benefit could have been underestimated'* due to the lack of comparative long-term follow up data with standard of care. Despite being aware of the *'limitations of a naive indirect comparison using different data sources that did not match baseline characteristics'*, the Committee also noted that

	'*the company had not captured the benefits of elosulfase alfa well in its analyses or model structure, despite extensions to the managed access agreement.*' The Company appreciates that the NICE Committee has concluded that elosulfase alfa is clinically effective compared to standard of care. We would like to re-iterate that there is long-term follow-up data for elosulfase alfa with 5+ years of MAA data; however, we acknowledge the fact that there is no long-term data in direct comparison to standard of care because most diagnosed patients who were eligible and willing to receive treatment at the time of the MAA were started on treatment when elosulfase alfa became available. The remaining patients were either too progressed or non-classical and did not want treatment, hence why the comparison cannot really be made with these patients. To address the issue of better capturing the benefits of elosulfase alfa, the Company analysed data from the MPS-HAQ questionnaire to understand the broader benefits from treatment and to inform additional utility benefits in patients, which are not captured in the EQ-5D. MPS HAQ scores improved in the treatment naïve population over the course of the MAA. By Month 36, Caregiver Assistance, Self-care and Mobility domains decreased from Baseline. By Month 36, Caregiver Assistance, Self-Care and Mobility score changes were -1.67, -0.74 and -1.46 (2.90 95% CI -2.91, -0.02, P=<0.05) 1.67 (12.98), -0.74 (2.86) and -1.46 respectively (lower scores indicate improvement on the MPS HAQ). Baseline data from MAA treatment naïve patients (N=23) showed moderate, significant (P<0.05) correlations between EQ-5D 5L utility and MPS HAQ Caregiver Assistance (Spearman's Rank Correlation=-0.628, Pearson's Rank Correlation=-0.642), EQ-5D 5L utility and MPS HAQ Self-Care (Spearman's Rank Correlation=-0.557, Pearson's Rank Correlation=-0.591), EQ-5D 5L utility and MPS HAQ Mobility (Spearman's Rank Correlation=-0.476, Pearson's Rank Correlation=-0.605). Quality of life as measured by the MPS HAQ improved over the course of the MAA in the treatment-naïve population. Correlation analysis showed that the EQ-5D is correlated with the MPS HAQ, but there may be domains of quality of life not captured well by the EQ-5D.
6	Regarding the **Committee's conclusion on the economic model (section 3.8, pages 11-12),** the Company appreciates that the Committee has accepted the wheelchair use based model and recognises certain limitations, particularly around modelling disease progression. As a reminder of why the Company has built the model around this outcome, this was because wheelchair status represented progression through the disease and remains the outcome which correlates the most with health utilities captured via the EQ-5D. Nevertheless, the company appreciates the limitations of the wheelchair measure. In fact, none of the measures (WC use, 6MWT, FVC) truly captures patients' ability to have more energy and increase function with less pain, e.g., walk longer for an hour but maybe not faster. The company also agrees with patient and clinical perspectives that wheelchair use changes with treatment where patients utilise aids to increase daily living activities and as such see the major impact in quality of life coming with wheelchair dependency.

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	Moreover, throughout the submission process, the Company engaged with several clinicians and the patient community and understood that some patients treated with elosulfase alfa may choose to use a wheelchair to manage energy for daily activities. However, wheelchair dependency continues to be a strong marker of disease progression and impacts quality of life negatively as patients become less independent. As noted in the ECD (page 15/24) dated November 2021, the company accepts that utility vales at baseline is the better reflection of SoC utilities. Also, as observed in the ECD (page 15/24) dated November 2021, the company used utilities at the end of 2 years in the treatment naïve subgroup (excluding ex-trial patients from the full MAA dataset) as the utilities for patients on ERT. These values for the 3 'wheelchair use' states (no WC use, some WC use, and WC dependant) for SoC were 0.54, 0.41 and 0.08 respectively. Similarly, for patients on ERT, these utilities were 0.84, 0.64 and 0.32 respectively. This is particularly relevant for newly diagnosed patients who start treatment with a lot less disease manifestation, hence their future phenotype will differ from patients with existing morbidity. As highlighted and agreed with the committee, these patients will have a delay in onset of musculoskeletal symptoms and these patients would experience a meaningful delay in wheelchair dependency versus patients with established morbidity when starting treatment with elosulfase alfa (see Issue 4). In addition, we have explored the changes in MPS-HAQ in the MAA treatment naïve population and found that there was improvement from baseline to Month 36 across domains, supporting benefits in mobility, self-care, and reduced caregiver burden (see Issue 5). Furthermore, the MPS HAQ was associated moderately with the EQ-5D in correlations at baseline.
7	Regarding **Committee's conclusion on 6MWT criteria to define movement between health states (Section 3.9, pages 12-13)**, the company accepts the ERG's analysed entrance and exit thresholds from the different WC categories in the model and has implemented these into the revised model as suggested in ERG addendum post ECM1, dated October 2021 (page 7/10).
8	Regarding **Committee's preferred assumptions for modelling disease progression (Section 3.10, pages 13-14)**, the company agrees with the committee observation of standard of care (SoC) patients that start in the asymptomatic state of the model are assumed to take 3 years to progress to the symptomatic state, while elosulfase alpha patients take 9 years to move from asymptomatic to symptomatic (ERG addendum post ECM1, dated October 2021, page 7/10). The company also agrees with loss of 4.86 m for 6MWT to model disease progression in the standard care arm.
9	The company agrees with the **Committee and the ERG's approach to link survival to lung function (Section 3.11, pages 14-15)**. The company also notes that FVC improved in all MPSs with ERT over the long term.
10	On **utility values used in the model (Section 3.12, pages 15-16)**, the committee *'recognised that the ERG's values were similar to those accepted in the original guidance. It concluded that the ERG's utility values from the treatment-naive subgroup from the managed access agreement were appropriate'*.

Please return to: **NICE DOCS**

	As noted in company's response to issue 6 earlier, the company agrees with the committee that utilities at baseline are the better reflection of SoC utilities. Also, as observed in the ECD (page 15/24) dated November 2021, the company used utilities at the end of 2 years in the treatment naïve subgroup (excluding ex-trial patients from the full MAA dataset) as the utilities for patients on ERT. These values for the 3 'wheelchair use' states (no wheelchair use, some wheelchair use and wheelchair dependant) for SoC were 0.54, 0.41 and 0.08 respectively. Similarly, for patients on ERT, these utilities were 0.84, 0.64 and 0.32 respectively.
11	**For treatment costs and impact of body weight in the model (Section 3.13, page 16),** the Committee *'accepted ERG's approach based on Montano et al (2008) study > 36.7kg by 18 years old (also confirmed by clinical experts)'*. The future new patients who would be coming on to treatment will be predominantly younger, lighter patients (as mentioned in earlier comments). Thus, due to the lower starting age, we continue to consider that lower average weights are most appropriate for new patients. The weights used in this submission for patients in different health states (asymptomatic, no wheelchair use, some wheelchair use and wheelchair dependant) remain those provided by the ERG: 3.6 kg, 19.8 kg, 27.0 kg and 35.2 kg, respectively.
12	Regarding the **appropriate discount rate (3.14, pages 16-17)**, the committee concluded that *'MPS 4A is progressive and still shortens life, and that elosulfase alfa is not curative'*. Therefore, *'it did not consider that elosulfase alfa restored people to full or near full health'* and concluded that a 3.5% discount rate was appropriate. The NICE Guide to the methods of technology appraisal states that in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), a discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee. MPS IVA is a devastating, progressive and life-threatening disease. Data published by Lavery et al, 2014 highlights the mean age of death as 25.3 years in the UK based on analysis of death certificates. Whilst this has improved due to greater disease awareness and management, MPS IVA remains a devastating and life-threatening disease. The introduction of elosulfase alfa has meaningfully modified the disease trajectory, particularly if patients are treated early. It is important to recognise the benefit of initiating treatment as early as possible. Sibling studies (Frigeni et al. 2021, Ficicioglu et al. 2020, Barak et al. 2020) as mentioned in section 2 have highlighted meaningful differences in long-term disease progression with early diagnosis and early treatment. As such the Company maintains that patients without treatment continue to have a significant risk of dying or severely impaired life which is one of the criteria for a 1.5% discount rate. Furthermore, long-term data from the MAA supports that elosulfase alfa offers sustained benefits over 10 years. Given the fact that the MAA included patients who started treatment with already significant impairment, newly diagnosed patients who initiate treatment early will show less progression and the benefits can be expected to continue far into patients' lives and likely to

	exceed 30 years and based on the modelling these future early treated patients will live longer functional lives with improved quality of life. As such, treatment with ESA complies with the requirements for a 1.5% discount rate and the Company strongly believes that the 1.5% discount rate is appropriate for this re-submission.
13	The company agrees with the **committee's observation about applying QALY weighting (Section 3.15, pages 17-18)**. In addition, the company will stress the fact that all future new patients will be predominantly young patients who are diagnosed very early calls for additional QALY weighting for potentially debilitating disease prognosis for untreated young patients (patients on elosulfase alfa will have potentially far better prognosis).
14	**Cost-effectiveness estimates – Committee's preferred assumptions (Section 3.16, page 18):** *'The company's base-case results after technical engagement resulted in an ICER under £300,000 per QALY gained (that is, the maximum ICER normally considered to be a cost-effective use of NHS resources applying a the maximum QALY weight). The committee recalled that this did not* *account for its preferred assumptions of the committee's preferred assumptions:* • *Both the company's and the ERG's preferred data source and analysis (see sections 3.4 and 3.6). The ERG's approach included using observed 6MWT and FVC data to estimate mean values for both arms at the end of the first year in the model (see section 3.9)* • *The ERG's 6MWT criteria to define movement between the health states (see section 3.9)* • *The company's approach for modelling long-term disease progression for people having elosulfase alfa because it was an acceptable proxy for stable MPS 4A (see section 3.10)* • *The ERG's loss of 4.86 m for 6MWT to model disease progression in the standard care arm (see section 3.10)* • *Overall survival is linked to lung function (see section 3.11)* • *The ERG's utility values from the managed access data (see section 3.12)* • *Body weight changes over time and reaches 36.7 kg by 18 years (see section 3.13)* • *A discount rate of 3.5% (see section 3.14).* *The committee noted that the ERG made several changes to the company's base case. The most influential changes were assuming that:* • *6MWT and FVC losses were equal in both arms* • *alternative transitions thresholds were applied* • *body weight changes over time* **Please note that all the updates to the cost-effectiveness model were carried out on the version sent by NICE to the company on 17/11/2021. This version is ERG's version, and for this submission, the company made updates to this model (ID1643 ERG model post ECM 1 251021 IA [ACIC].xlsm).** Based on the committee's preferred assumptions (please refer to ERG addendum post ECM1, dated October 2021, page 2/10, where the NICE technical team believes that scenarios 4 and 5

	are most likely to reflect committee's preferred ICER range), the company accepts the following recommendations (scenario 4 and 5): • Body weights changes over time. Since future new patients are going to be potentially younger, the body weights used in this model for different health states are Asymptomatic 3.6 kg; No WC use 19.8 kg; Some WC use 27.0 kg and WC dependant 35.2 kg. This rhymes with the age of patients' prognosis through different health states, becoming wheelchair dependant at the age of 22 and the corresponding body weight being 35.2 kg. • Annual average loss in 6MWT was accepted as per ERG recommendations of 4.86 m in the SoC arm • Assume a 4.86m and 0.1L losses in 6MWT and FVC measures, respectively, for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patient progresses per year in the ESA arm (please vide ERG addendum post ECM1, dated October 2021, page 3/10 for scenario 4 and 5) • Use the ERG's entrance and exit thresholds from the different WC categories in the model (please vide ERG addendum post ECM1, dated October 2021, page 3/10 for scenario 4 and 5) Other than implementing above mentioned points (as recommended by the ERG and NICE technical team), the company implemented several changes to reflect the scope of the evaluation, i.e., newly treated patients. The following changes were implemented: • The transition probabilities were changed in the model to reflect ERG and committee recommendations. For SOC arm the entire MOR-001 data was used (instead of MORCAP1) to calculate transition between different health states from baseline to Year1 and Year1 to Year2 • The baseline distribution of patients by wheelchair status was updated to better reflect the newly diagnosed cohort. The distribution of patients <6 years old in the MAA treatment naïve population was applied (see table describing baseline characteristics of MAA treatment naïve population under 6 by wheelchair status at the end of Issue 14). The distribution of patients at baseline was *[academic / commercial in confidence information removed]* for no wheelchair use, some wheelchair use, and wheelchair dependent, respectively. This distribution was apportioned across the 4 health states (asymptomatic, no wheelchair use, some wheelchair use, wheelchair dependent) to accommodate for *[academic / commercial in confidence information removed]* asymptomatic patients. The starting distribution is updated as follows: <u>Previous (ID1643 ERG model post ECM 1 251021 IA [ACIC].xlsm):</u> • Asymptomatic: *[academic / commercial in confidence information removed]* • No use wheelchair: *[academic / commercial in confidence information removed]*

	• Sometimes use wheelchair: *[academic / commercial in confidence information removed]* • Wheelchair dependent: *[academic / commercial in confidence information removed]* **<u>Updated company model:</u>** • **Asymptomatic: *[academic / commercial in confidence information removed]*** • **No use wheelchair: *[academic / commercial in confidence information removed]*** • **Sometimes use wheelchair: *[academic / commercial in confidence information removed]*** • **Wheelchair dependent: *[academic / commercial in confidence information removed]*** • The baseline age of patients by wheelchair status was updated to better reflect the newly diagnosed cohort. The distribution of patients <6 years old in the MAA treatment naïve population was applied (see table describing baseline characteristics of MAA treatment naïve population under 6 by wheelchair status at the end of Issue 14). The starting distribution is updated as follows: <u>Previous (ID1643 ERG model post ECM 1 251021 IA [ACIC].xlsm):</u> • Asymptomatic: *[academic / commercial in confidence information removed]* • No use wheelchair: *[academic / commercial in confidence information removed]* • Sometimes use wheelchair: *[academic / commercial in confidence information removed]* • Wheelchair dependent: *[academic / commercial in confidence information removed]* **<u>Updated company model:</u>** • **Asymptomatic: *[academic / commercial in confidence information removed]*** • **No use wheelchair: *[academic / commercial in confidence information removed]*** • **Sometimes use wheelchair: *[academic / commercial in confidence information removed]*** • **Wheelchair dependent: *[academic / commercial in confidence information removed]***

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

- The utility values were updated. As noted in the ECD (page 15/24) dated November 2021, the company accepts that utility vales at baseline is the better reflection of SoC utilities. Also, as observed in the ECD (page 15/24) dated November 2021, the company used utilities at the end of 2 years in the treatment naïve MAA population as the utilities for patients on elosulfase alfa. These values for the 3 'wheelchair use' states (no wheelchair use, some wheelchair use and wheelchair dependant) for standard care and elosulfase alfa are as follows:

  Updated company model:

  Standard of care:

  - **No use wheelchair: 0.54**
  - **Sometimes use wheelchair: 0.41**
  - **Wheelchair dependent: 0.08**

  Elosulfase alfa:

  - **No use wheelchair: *[academic / commercial in confidence information removed]***
  - **Sometimes use wheelchair: *[academic / commercial in confidence information removed]***
  - **Wheelchair dependent: *[academic / commercial in confidence information removed]***

- Treatment administration cost was changed from £207 to £213 as recommended by ERG and accepted by the Committee (please see ERG addendum post ECM1, dated October 2021, page 8/10)
- As justified above in response to Issue 12, the company has kept discount rates for both cost and QALY at 1.5%

The discounted ICER, undiscounted QALY gain and discounted QALY gain after implementing the above changes in the model are *[academic / commercial in confidence information removed]* respectively.

It may be noted that all the above implementations include ERG/ NICE technical team's recommendations with some additional analysis, e.g., using MOR-001 instead of MORCAP1 and using the MAA treatment naïve cohort of <6 years of age (representative of future new patients in terms of starting age, starting weight and starting disease severity). These additional analyses are appended to this response document.

To stay within the recommended threshold of ICER (including QALY weighting), the company agrees to give *[academic / commercial in confidence information removed]* discount on the list price, i.e., a confidential ex-factory price of *[academic / commercial in confidence information removed]* per 5 mg vial (exc. VAT)

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	The new discounted ICER, undiscounted QALY gain and discounted QALY gain after implementing the above changes in the model are *[academic / commercial in confidence information removed]*. Keeping everything else the same but changing discount rates for both costs and QALYs to 3.5% results in discounted ICER, undiscounted QALY gain and discounted QALY gain after implementing the above changes in the model are *[academic / commercial in confidence information removed]*. Please note the confidential ex-factory price is kept at *[academic / commercial in confidence information removed]* per 5 mg vial (exc. VAT). **Table 14.1: Baseline characteristics of treatment naïve MAA population <6 years old by wheelchair status#** *[academic / commercial in confidence information removed]*

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Sophie Thomas The MPS Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Sophie Thomas

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Whilst we accept that commercial negotiations may require separate discussions, it is still unclear why NICE have decided to only give a recommendation for new patients not currently treated under the MAA.
2	NICE appears to have ignored or at best not fully taken account of a) the patient evidence b) the data from the MAA. There is an apparent disconnect in stakeholders understanding / direction of the data to be included and analysed versus the committee expectations on what was to be included and reviewed. The committee voiced their great shame that the model did not include longer term data and felt that focusing on new patients was wrong and off target. It is concerning that expectations of the committee appear to have not been factored in or discussed between NICE, the ERG and the company prior to the meeting. Had this taken place an alternative model may have been agreed and implemented before committee.
3	We are concerned that not all the data appears to have been submitted and this raises concern over whether data collection / transference of data has failed at some point. Data gaps trigger uncertainty and this was clearly the case during this review. In addition to this, patient and clinical communities are concerned that the full impact of ERT has not be captured and interpreted with many parameters not referenced, which would have given a richness and completeness to the data and narrative being told by the clinicians and patients. Specifically the modelling has not captured all the benefits seen in clinical practice and reported directly by the patients, parent / carers. In our view there has been limited use of the HRQOL collected through the MAA and this was noted by the committee also.
4	We are concerned that if NICE's final decision is a no for newly diagnosed patients then they would potentially be denying a population that would gain the most benefit. We know from experience that patients treated early in their disease have better outcomes and reduced disease morbidity. Sadly this has led to a number of older patients asking whether they should give up their effective treatment, so that young patients have an opportunity to benefit from the positive effects they have experienced. How do you explain that this would not be the case and how do we managed their wellbeing and the guilt if this is in fact

	the final outcome? It is also concerning that NICE still do not have a solid understanding of tiny populations or the effects that any decision will have on this community.
5	The current model is not appropriate to determine whether elosulfase alfa is cost effective for a naïve population as it is using data from a wide range of participants with varying degrees of pathology, many of whose baseline were not captured in the MAA if already on established treatment. Whist the wheelchair model used by the company in the 2015 evaluation was accepted by the committee, they stated in the 2021 re-evaluation meeting that they did not like it and were expecting a different approach to be taken. Was this messaging conveyed to the company? In this respect, we believe the model to be flawed and an alternative model should be used.
6	Whilst NICE has acknowledged the wealth of information collected and presented by the clinicians and patient organisations, there is little evidence that this information has been considered. Participants and observers were left feeling that the focus of the review was totally price driven and not based on clinical efficacy. Q of L reports have been proven to be credible measure of the true impact of treatment for patients. This was why there was such emphasis on the collection of this data as part of the MAA. Treating these as secondary importance, in effect "anecdotal evidence", discredits the involvement, value and commitment of the patients, families' clinicians and the patient organisation.
7	Not having a predefined statistical analysis plan in place for this re-evaluation has resulted in a flawed process with no defined parameters or clarity on expectations. This is disappointing as clinical and patient organisations raised this exact point in 2018.
8	We believe the summaries contained within the ECD woefully underestimate the benefit to patients from this therapy. This is disappointing given the depth of information submitted by patient organisations.
9	The process used by NICE has exclude people, especially those with the protected characteristic of Disability, from fully contributing to this consultation and as such this current recommendation in our view is discriminatory. Additionally the recommendation itself is discriminatory as the approach that NICE has taken shows an unwillingness to use appropriate methodologies for the consideration of data related to very small populations.
10	Clinical and patient reports highlight improvements in both 6MWT and lung function with all patient sub groups showing sustained and improved endurance or stability. Due to the rigorous assessments and reviews as part of the MAA, patients who were failing their assessment tests were monitored for a period of time and if deterioration continued they would be at risk of treatment being stopped. Stabilisation is an important criteria in

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	progressive conditions and a good outcome measure. This uncertainty leads to questioning why NICE still do not have clearly defined outcome measures for treatments under review and why the same irrelevant measures are being used. In our view these should have been defined before the re-evaluation took place.
11	This process is as complex and extremely frustrating for patients as it was six years ago. It has caused a huge amount of uncertainty and anxiety for patients and families, particularly those patients treated through the MAA. The wellbeing of patients remains a long way down the priority list for NICE, NHSEI and the company. Patients have complied with all requirements and expectations but feel their efforts and data has been excluded when it matters. The process for them has felt cold, demeaning and data led, with the primary focus centred on cost effectiveness and assumptions. This is extremely disappointing given the investment by patients and clinical colleagues. In our view the approach taken for this re-evaluation is inappropriate for extremely rare complex conditions where patient numbers are exceptionally small. In addition they have been further discriminated against by the reduction in patient numbers to fit into an insufficient model.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Katy Brown The MPS Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Katy Brown

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Has all of the relevant evidence been taken into account? No. A significant proportion of the data from the managed access scheme was not taken into consideration. Despite the Managed Access Scheme running for over 5 years, only 2 years' of data was included, which is inexplicable given the whole purpose of the Managed Access Scheme was to collect evidence of benefits over a longer term period of time. The data presented only included newly treated patients, this in itself automatically excluded evidence from patients who have been on treatment for a longer period of time (due to being part of the clinical trial for a number of years before that). I also do not feel that the extensive quality of life benefits and broader patient evidence about the real life benefits of Vimizim has been properly considered or factored into the decision making process.
2	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. Broader patient benefits have not been appropriately interpreted or captured. My son Sam has been receiving Vimizim for almost 10 years. He does not suffer with fatigue. He does not routinely have any pain. He is 13 but is still very mobile and independent. Vimizim has had an incredible impact on his life, his quality of life and his independence. The evidence from clinicians and other patients is totally aligned to our experience, yet this is not fully reflected or given sufficient weight or importance in this recommendation.
3	Are the recommendations sound and a suitable basis for guidance to the NHS? No. It is blatantly obvious that NICE do not have a robust process in place to assess treatment following a Managed Access Scheme. This is entirely unacceptable - there has been a six year period to plan and prepare for this, yet the process is both confused and fundamentally flawed. As a result of incompetence in designing an appropriate process, patients yet again are left in limbo, causing unnecessary stress, anxiety and suffering in lives that are already incredibly challenging. This is unforgivable.

Please return to: **NICE DOCS**

	It is also entirely unacceptable for the challenges with data to not be resolved before this point. Areas of focus for the review have not been clear throughout. Both NICE and the company have access to the data, its is perplexing therefore to be in this situation right now. Having been part of the Managed Access Scheme for 6 years. diligently committing to reviews and hospital visits, 2 hours away from home, going through the excruciating waiting for "exam results" every year to find out if treatment will continue is soul destroying, and has impacted my mental health, that of my family and my son particularly. To commit to all of that as a family, then to find that data has not been properly used, and the benefits not fully represented is an absolute travesty.
4	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Yes. This process is directly discriminatory to my son. He and all other Morquio patients fall under the protected characteristic of disability, and the only reason that this cost effectiveness guidance is being given is because he is unfortunate enough to be born with a condition that only affects a very small patient population. This is entirely beyond his control. The process does not fully take this into account and therefore is structurally discriminatory. This is also evidenced by the fact that NICE openly admits the benefits and positive impacts of Vimizim, yet still says no. The exclusion of longer term data is also discriminatory because it clouds decision making and holds valuable evidence back. This is unacceptable given the rarity of the condition and the inherent challenges involved in collecting the data. It is both discriminatory and negligent. Splitting the decision making process between new and existing patients creates concern also, especially given there is zero visibility of when and how a decision will be made for existing patients. Whilst I understand that this decision sits with NHSE, it is unacceptable for

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	NICE to wash their hands of this situation; from a patient perspective, it should not matter who the decision maker is, the approach needs to be transparent. It is not, and again, patients are left stuck in the middle, uncertain, anxious and afraid. This is no way to treat disabled children and adults who are disadvantaged daily because of the condition they have and the way society treats them.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Rare Disease Research Partners**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Alex Morrison

Comment number	**Comments**

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that …….. • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS?
	Has all of the relevant evidence been taken into account?
1	No
2	Much of the evidence has been ignored and discounted for the cost effectiveness decision making. The ERG preferred to use only one year out of four years of MAA data and exclude around one third of MAA patients (those previously treated on a clinical trial). The company used only 2 years of MAA data. It is difficult to see how this is a fair assessment of the additional data collected to resolve uncertainties from the first NICE review. It is especially concerning that patients who have been on treatment for 10 years and remained stable are excluded from the ERG data set.
3	At the committee meeting there was a clear disconnect between the ERG and company's presentation and analysis of the data and the committee expectations on what was to be included and reviewed. It is concerning that expectations of the committee appear to have not been factored in or discussed between NICE, the ERG and the company prior to the meeting. Had this taken place an alternative model may have been agreed and implemented before committee.
4	There has been limited use of the HRQOL collected through the MAA. Therefore, the full impact of ERT has not be captured and interpreted with many parameters not referenced, which would have given a richness and completeness to the data and narrative from the patients.
5	Whilst NICE acknowledged the wealth of information collected and presented by the clinicians and patient organisations, there is little evidence that this information has been considered. The reliance on modelling for decision making would seem to make it impossible for this type of evidence to be truly taken into account.
6	It appears that not all the data has been submitted/analysed and this raises concern over whether data collection / transference of data has failed at some point. Data gaps trigger uncertainty and this was clearly the case during this review.
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
7	No
8	Much of the clinical data was not included in the analysis, e.g. '*The committee was concerned that the company had not appropriately analysed valuable long-term data from people who started elosulfase alfa as part of a clinical trial*.' *'The committee noted that the innovative nature of elosulfase alfa would be captured in the modelling if the data was measured and analysed appropriately.'*
9	The amount of evidence excluded from the analysis, including that from clinical trials, the MAA, patient and clinical expert input, meant that the size of benefit of elosulfase alfa was underestimated, and this was noted by the committee.
10	The cost effectiveness model did not provide a reasonable interpretation of the evidence as it used very little evidence and relied heavily on assumption. The approach taken for this re-evaluation is

Please return to: **NICE DOCS**

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	inappropriate for extremely rare complex conditions where patient numbers are exceptionally small. In addition, they have been further discriminated against by the reduction in patient numbers to fit into an insufficient model.
11	Many issues with the model were raised during the committee meeting, therefore the resultant cost-effectiveness estimates cannot be considered as a reasonable interpretation of the evidence.
12	Not having a predefined statistical analysis plan in place for this re-evaluation has resulted in a flawed process with no defined parameters or clarity on expectations.
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
13	No
14	The recommendations were based on a flawed model and did not take into account all the evidence presented, therefore they cannot be considered as suitable.
15	The evidence showed clinical and quality of life benefits and the committee noted that these had been underestimated. However, the focus of the review appeared to be totally price driven, using a model that the committee considered as inappropriate and flawed.
16	It is still unclear why NICE have decided to only give a recommendation for new patients not currently treated under the MAA, and what impact their decision will have on those currently on treatment.
17	If NICE's final decision is a no for newly diagnosed patients, then they would potentially be denying a population that would gain the most benefit.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and

transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Saikat Santra (Clinical Expert)/ **Birmingham Women's & Children's NHS Foundation Trust**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[No links to the tobacco industry to disclose]
Name of commentator person completing form:	[**Saikat Santra]**

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	At the outset I must state that we welcome the committee's conclusion (ECD 1.2) that the clinical trial evidence and the MAA data indeed suggest that elosulfase alfa is efficacious and leads to stabilisation of disease for patients with MPS IVa. This is the only disease modifying treatment available for MPS IVa and therefore having accepted effectiveness the focus of this re-evaluation must then be the cost-effectiveness of this intervention which we accept is a difficult but necessary analysis for NICE to undertake. It is, therefore, especially important that this analysis is done with the best possible data and assumptions which is perhaps less of an issue where the effectiveness of the intervention itself is in question. From that standpoint, we are concerned that the economic conclusions in this analysis are based on a model that does not take all the reported and observed benefits of this treatment into account and is based on extrapolation of short term conclusions from a different observed population to that intended for the intervention after routine commissioning. As such the cost-effectiveness analysis cannot be said to be a robust basis for final guidance on routine NHS commissioning and it is important that a more appropriate model is developed urgently to address this.

2	My main concern is that the recommendation does not take into account that the target population of this treatment after routine commissioning would be vastly different to the population studied in clinical trials and in the managed access agreement, upon which these recommendations are based.
	
	ECD **Section 3.3** states *"The committee also noted that this review would only focus on people newly diagnosed with MPS 4A. This was because continued access to elosulfase alfa for people with MPS 4A already having treatment will be discussed separately by the company and NHS England. The committee concluded that it would consider the newly diagnosed population who had not had treatment under its previous recommendations."*
	
	The corollary of this is to accept that:
	• The existing population of MPS IVa patients in England have all been offered elosulfase alfa already and either:
	  ○ Are currently receiving and benefiting from treatment
	  ○ Are no longer on treatment due to lack of benefit and/or unacceptable burden of treatment
	  ○ Never commenced treatment which has been offered to them
	
	These patients are those with the greatest pre-treatment disease burden in whom the capacity to benefit is likely to be lowest. They are also the very same patients who have been studied so intensely during the development of elosulfase alfa. The largest clinical trials (MOR004/005) had an age of 5 years as a minimum eligibility criterion and such patients would already have a significant skeletal disease burden which cannot be expected to improve and would significantly limit any benefit from treatment. That a significant effect was able to be appreciated (and accepted by NICE) in this population does indeed underscore the significance of that effect.
	
	It follows that any patients offered treatment under this decision would therefore be either:
	• Newly diagnosed paediatric patients, some of whom may have severe disease
	• Newly diagnosed attenuated adult patients
	
	The age at which new paediatric patients are diagnosed has been falling consistently over the last decade and of the cohort recruited to the MAA at Birmingham Children's Hospital, all new patients have been under the age of 3 years, with one child as young as 18 months diagnosed and started on treatment shortly afterwards. These patients will have little (or no in the case of siblings prospectively diagnosed at birth) pre-treatment disease burden and consequently a far greater capacity to benefit

Please return to: **NICE DOCS**

	from elosulfase alfa than any patient enrolled in the MOR004/005 trials and indeed most of the patients enrolled in the MAA. The MAA has not provided the means to meaningfully assess treatment effect in these youngest patients who will have only had treatment for up to 4 years – we will only know the magnitude of the effect in those patients with much longer treatment exposure, probably in the order of 8-10 years by which time historically such patients would have achieved their final adult height but may with elosulfase alfa be continuing to grow. There may be sufficient patients in the MAA and in the MOR007 study who started treatment under the age of 2-3 years to provide some guidance to the committee on the likely effectiveness of the drug in the target population but there may not be. Either way it stands to reason that the effectiveness of this drug ***in the target paediatric population*** can only be better than in the studied population and as the target population is likely to be significantly younger and smaller than the studied population the initial cost of a weight-based drug will also be lower. ***Therefore whilst the exact cost-effectiveness of this intervention in the target paediatric population is not known it stands to reason it can ONLY be better than the conclusion reached in this re-analysis*** Similarly in adults with attenuated disease: all adults who are "grown up severe paediatric patients" have already been offered treatment. Therefore the target population of this recommendation in adults will be treatment-naïve attenuated patients who by their very nature will have the greatest capacity to respond to treatment (perhaps even better than severe children). Indeed some adults with the most attenuated disease may not even wish to start treatment as their treatment burden may exceed the burden of their disease – this has been noted in some patients recruited to the MAA. Again the studied population will have included adults of all severities and we argue it stands to reason that the effectiveness of this drug ***in the target adult population*** can only be better than in the studied population. The cost may not be different however but ***whilst the exact cost-effectiveness of this intervention in the target adult population is not known it stands to reason it can ONLY be better than the conclusion reached in this re-analysis*** As such I am deeply concerned that this analysis is inadequate to robustly inform a decision on routine commissioning on the NHS for elosulfase alfa and a cost-effectiveness model that focuses on the intended target population urgently needs to be developed.
3	We are concerned that the evaluation has focussed solely on the data measured on the MAA and analysed these in a similar way to how those parameters were analysed in the pivotal clinical trials. The MAA data were not intended to be trial outcome measures – but rather reliable and measurable outcomes that would identify patients who were NOT responding to treatment and therefore enable an evidence-based decision to stop treatment in some patients. They were not chosen to be outcomes that could measure the degree of benefit which is how they have been erroneously analysed. In my opinion the only valid analysis of the MAA data should be the proportion of patients who continued to meet the criteria – as published in Cleary et al 2021 *[Orphanet J Rare Dis . 2021 Jan 21;16(1):38. doi: 10.1186/s13023-021-01675-x.]* That the overwhelming majority of patients continued on the MAA despite their significant treatment burden is testament to its effectiveness and the value placed on that by patients and their families. The flipside of this however is not factored into the analysis. A small number of patients who recruited to the MAA did indeed come off treatment and a greater number of patients who participated in the clinical trials chose not to continue with treatment on the MAA in the first place. These are patients with significant (or rarely very minimal) disease burden who did not feel that the treatment was benefiting them and that the treatment burden was outweighing the perceived benefit. Whilst this was mandated on the MAA, this was in all cases a decision reached primarily by the patients and families themselves and there is no reason to expect this not to continue to be the case should elosulfase alfa be routinely commissioned. We do not expect patients who are not benefiting to want to continue treatment long term – and this is now routinely embedded in paediatric practice with other lysosomal storage disorders with routinely commissioned enzyme replacement therapies. We do not see this having been factored into the cost-effectiveness model – ***essentially those paediatric patients who***

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	will receive long term therapy (at higher long term cost because of their greater size) will ONLY be those who are clearly responding and feeling benefit.
4	Further to comment 3 – we would also point out that the chosen measured outcomes on the MAA are not the most appropriate to assess the magnitude of a response in the target paediatric population. These youngest patients cannot perform spirometry reliably and invariably have no or inaccurate baseline data – and their capacities will continue to increase with growth. Cardiac ejection fraction is almost universally normal in this age group and whilst easily measurable does not capture the benefits of treatment on the cardiovascular system in children. Even the six minute walk test is subject to variability in this age group where the youngest patients may still be learning how to walk steadily independently when they start treatment. The health-related quality of life data completed by parents is likely to have the greatest relevance to this target population but this does not appear to have been focussed on in this analysis.
5.	We have concerns that the focus on a "wheelchair-use model" is wrong. The health state "Sometimes uses wheelchair" is perceived to indicate a worsening health state compared to "no use of wheelchair" whereas in fact we see in real life that many patients choose to use a wheelchair for some activities (particularly longer distance mobility) in order to preserve energy for other activities and the use of a wheelchair actually represents an *improvement* in health state. Whereas previously a patient may have opted to simply reduce activity, a patient who is responding positively to treatment may wish to stretch their potential achievements and do more than they previously would have – and to maximise their independence in doing so, they make a positive choice to use a wheelchair some of the time. This was highlighted by clinical and patient experts at the meeting but this does not seem to have altered the analysis. A "wheelchair-dependence" model might be more appropriate – but as stated above, a meaningful assessment of this could only be achieved by following (and treating) target population patients at least until they would have been expected to become wheelchair dependent which is much longer than the follow-up currently available.
6.	A further variable in the cost-effectiveness analysis is the expectation of families to administer infusions independently. This was not stated in the managed access agreement but over the life of the MAA the expectation of treating centres has become that families will learn to administer infusions themselves at home when it is safe and appropriate to do so. This reduces the non-drug costs of administering the treatment (be that hospital beds or home care nursing costs). If this has been factored into the analysis then this should be clarified. If not, then it should be considered.
7	We are concerned that this recommendation, if implemented in the face of an agreement by NHS England to continue treatment for patients already signed up to the MAA, would place families, centres and the NHS in an ethical conflict with patients being effectively discriminated against based on their date of diagnosis. It places a family in the position of having a child with severe disease on long term treatment receiving some, but perhaps limited, benefit whilst a newly diagnosed newborn sibling, with far greater capacity to benefit from the treatment long term, unable to access treatment. This would seem to go against the principles of the NHS in ensuring an equitable access to treatments for all.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See

Please return to: **NICE DOCS**

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[James Davison (Clinical Expert)/ **Great Ormond Street Hospital**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[No links to the tobacco industry to disclose]
Name of commentator person completing form:	[**James Davison**]

Please return to: **NICE DOCS**

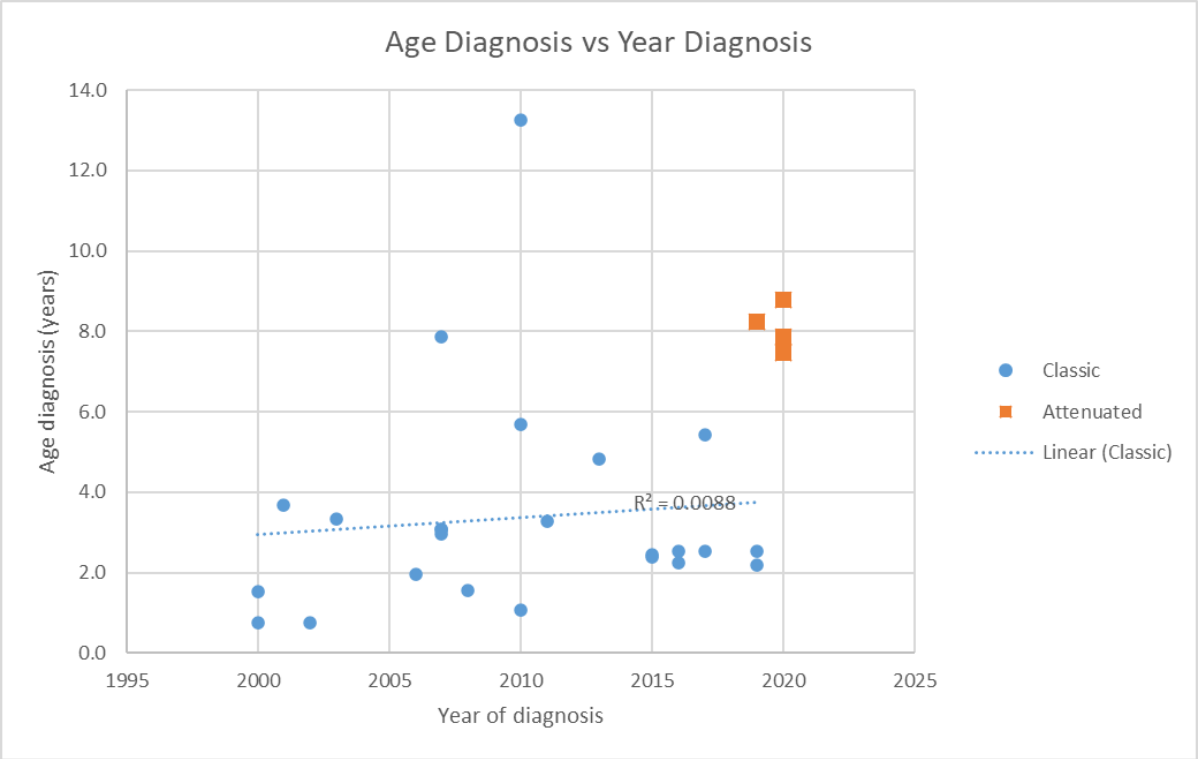
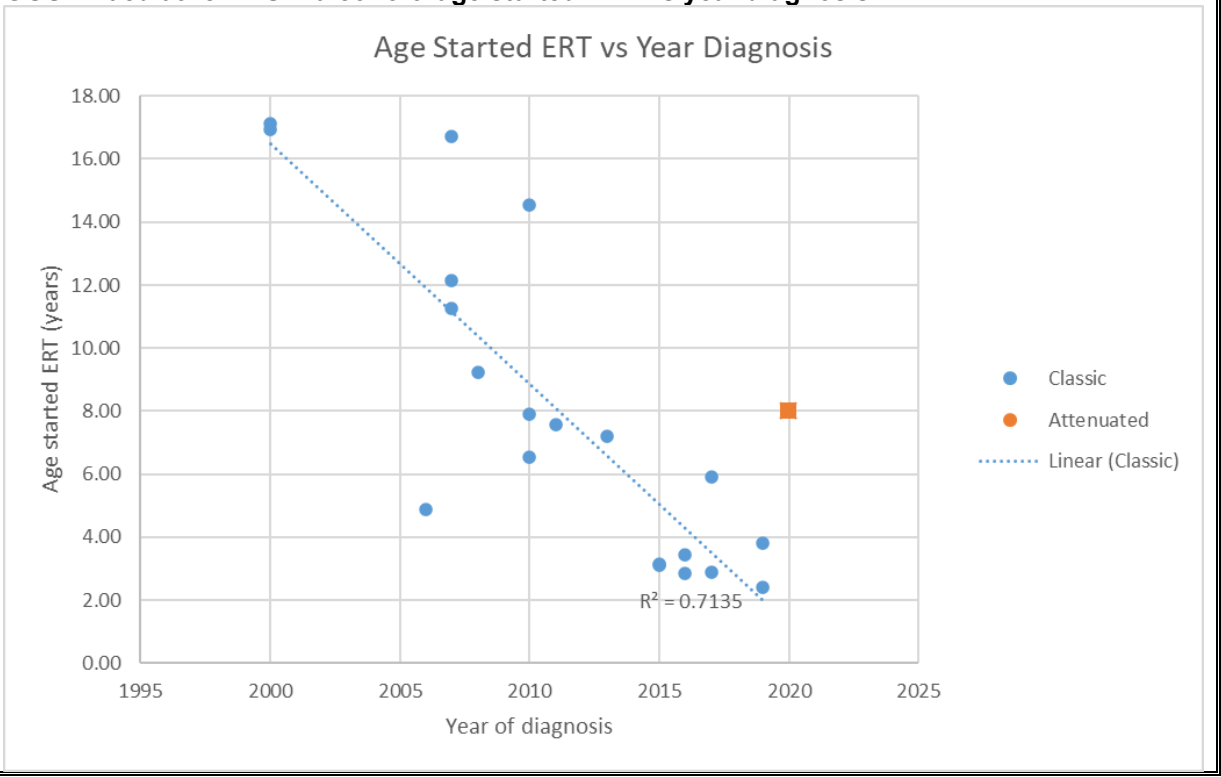
NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are deeply concerned about the ongoing uncertainty and anxiety for patients with MPS 4A and their families about provision of elosulfase alfa that has resulted from the protracted process for reviewing this technology. Patients who have been receiving treatment under the Managed Access Agreement (MAA) and who have borne the very significant burden placed on them to undertake the associated assessments still do not have clarity about whether they will be able to continue treatment after the end of the MAA. **Section 1.2** of the ECD states that "*This recommendation is not intended to affect treatment with elosulfase alfa that was started in the NHS before this guidance was published*."
2	We are concerned that the conclusions from the re-evaluation are based on what is considered by the committee to be a deeply flawed and inadequate economic model that does not take into account all the observed benefits of the technology, and is based on assumptions rather than observed data. The committee thus acknowledges that the model does not take account of the relevant evidence that is available and is not suitable to determine if the technology is cost-effective. Therefore the recommendations made are not a sound and suitable basis for the final guidance to the NHS. An alternative model that does take into account the available evidence should be used.
3	**We are concerned that the data and population used in the modelling do not represent correctly the characteristics and likely response to treatment of the "target population".** ECD **Section 3.3** states *"The committee also noted that this review would only focus on people newly diagnosed with MPS 4A. This was because continued access to elosulfase alfa for people with MPS 4A already having treatment will be discussed separately by the company and NHS England. The committee concluded that it would consider the newly diagnosed population who had not had treatment under its previous recommendations."* However, the analysis undertaken is based on a patient population of which the majority are not newly-diagnosed but are "older" and have lived with a diagnosis of MPS IVa for years but before treatment was available. This applies to both the MAA treatment naïve and ex-MOR trial patients, and to the MOR-005 patient population. All of these patients will have accrued disease-related "damage" and have established pathology before treatment is started. Prospectively going forwards, newly diagnosed patients will be younger and will have accrued less disease-damage pathology and are expected to derive much greater benefit from treatment started at younger age. [See below GOSH cohort data that shows median age diagnosis is 2.5years for classic MPS IVa and 8.0yrs for paediatric attenuated MPS IVa, with no significant change in age of diagnosis over the last 20 years. Since 2015, median age starting treatment for classical MPS IVa = 3.1years] The modelling based the distribution of patients across the health states in the Markov model based on the MAA cohort, whereas "newly diagnosed paediatric patients" prospectively would be expected to be all in the first health state at the time of diagnosis. A simple manipulation of the economic model provided for the purposes of review of the ECD adjusting the baseline distribution such that all patients were in the asymptomatic category at start of the model does indeed lead to altered ICER estimates. Similarly, newly-diagnosed adult patients are likely to have much milder disease and may stand to benefit from treatment or be too mild to derive benefit. In essence, the analysis undertaken appears to be assessing the impact of the technology on the current cohort of patients distributed across a wide age range and most of whom already have established pathology, but this is not an appropriate analysis population to determine whether elosulfase alfa is cost effective when applied to a cohort of "newly diagnosed" treatment-naïve

Please return to: **NICE DOCS**

	patients, and therefore this is not a suitable basis for making recommendations to the NHS on this technology. **An analysis on the likely cost-effectiveness for the target population needs to be completed.**
	GOSH Paediatric MPS IVa cohort: age diagnosis vs year diagnosis:  **GOSH Paediatric MPS IVa cohort: age started ERT vs year diagnosis:** 

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

4	We are concerned that the evaluation process has focussed heavily on the data generated from the MAA and treated this as a quasi-trial evidence. The parameters measured in the MAA were selected to identify "Responders" to elosulfase alfa to determine if they could continue to receive treatment, setting specific thresholds to determine Responders, and were not primarily established as the best parameters for measuring the nuances in how the disease affects children. For example the MAA parameter for Cardiac disease was the Ejection Fraction, but this is only one aspect of cardiac function and does not capture well the effect of treatment on cardiac disease. Respiratory function was assessed using FVC and FEV1 but did not take into account more detailed information from polysomnography, use of non-invasive ventilation etc. The parameters were also difficult to obtain reliably (if at all) in the younger patients (<5yrs) who are the very "target cohort" that the evaluation is aiming to assess clinical-effectiveness for. The original MAA also specified that a disease registry would be established and that this would be the primary source of information that would be made available to NHSE to assess the effectiveness of treatment. (MAA Section 5.2) "*5.2 The MAH has been asked by the European Medicines Agency to enroll all patients into a 12 year disease registry to continue to gather information about this ultra-rare condition. The purposes of this registry are to: (i) characterise and describe the MPS IVA population as a whole, including the heterogeneity, progression and natural history of MPS IVA; (ii) to evaluate the long-term effectiveness and safety of Vimizim (elosulfase alfa): (iii) to help the MPS IVA medical community with the development of recommendations for monitoring subjects and reports on subject outcomes to optimise subject care; (iv) to collect data on other treatment paradigms, evaluate the prevalence of their use and their effectiveness; (v) to characterise the effects of 5 years of elosulfase alfa treatment in subjects under 5 years of age; and (vi) to collect additional data to: (a) help broaden knowledge of identified and potential risks of elosulfase alfa, as well as increase the size of the safety database and possibly provide new information on use in identified subgroups (pregnancy, hepatic and renal impairment, cardiac impairment); and (b) to help evaluate long-term effectiveness of elosulfase alfa. The MAH will provide access for NHS England to this database to assist it in assessing the clinical impact of elosulfase alfa on this disease. As part of this Managed Access Agreement the MAH agrees to NHS England appointing a representative to sit on the registry advisory board."* We are concerned that this data [from the disease registry] has not been used in the evaluation process, which would have provided a much richer range of outcome measures rather than purely limiting analysis to the 6MWT.
5	We welcome the committee's conclusion (ECD 1.2) that the clinical trial evidence and the MAA data suggest that elosulfase alfa is efficacious and leads to stabilisation of disease for patients with MPS IVa. We agree that the health and quality of life benefits of elosulfase alfa are substantial. We are concerned that the evaluation is then based on a model that does not capture many of these acknowledged benefits.
6	ECD 3.4 (data sources). We are concerned that the analysis and incorporation of the available outcome measures do not appropriately take in to account the expected changes in growing paediatric patients, for example the impact on growth on FVC/FEV1/6MWT.
7.	ECD 3.4 (data sources). The committee acknowledges that it is important to not exclude ex-MOR trial patients from analysis in order to maximise data available. Ex-MOR trial patients may have had lower dosing or less-frequent dosing with elosulfase alfa during the clinical trial but this would lead to an underestimate of effect (not overestimate) and so the long-term data should be used to maximise reliability of the model.
8.	ECD 3.5 (Data analysis issues) We agree with the committee that *"a predefined statistical analysis plan is important for all treatments that are recommended as part of a managed access agreement"* and this is of paramount importance for any future MAA for other technologies. However, this was not implemented in this evaluation to the detriment of the process. We also agree with the committee that there was significant effort from patients, families and clinical teams in gathering the required data and submitting this regularly. It is deeply regrettable that the data collection and analysis process was not robust, and that there was not a predefined plan for analysis.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

9.	ECD 3.6 (Complete case analysis) We share the committee's concern that the approach taken by ERG and the company has resulted in limited short-term outcome data being used to inform the models. It is clearly imperative that as much reliable outcome data as possible is used to inform the modelling so that the model can be considered to be reliable and a valid means of assessing cost-effectiveness. Given the chronic slow-changing nature of the disorder and need to evaluate the long-term response to treatment every effort must be made to ensure that robust long-term data is used in this process. We are concerned that the ERG and company approach has limited this.
10.	ECD 3.7 (Treatment benefit) The committee concludes that all the data from MAA and MOR-005 show generally stable outcomes over time, including for 6MWT, lung function, and health-related quality of life. We also agree with committee that additional benefit including skeletal outcomes, and response to surgery, are not fully captured. We agree that *"elosulfase alfa is clinically effective compared with standard of care, and the size of the benefit could have been underestimated*." We remain concerned that the modelling has not captured all the benefits seen, and the modelling has been limited to a small subset of the available outcome data parameters. In particular, little attention has been given to the nuanced and useful qualitative data captured in the HRQL data in the MAA, and has not been taken into account in the model.
11.	ECD 3.9 (Wheelchair based model.) We share concerns that the model used does not accurately represent the disease progression. There are concerns that the model assumes that "Sometimes uses wheelchair" is a worse quality of life than "no use of wheelchair" whereas this may represent a positive change as detailed by the Patient Experts and acknowledged by the committee. We remain concerned that the model is not appropriate and that recommendations have been based on a model that is acknowledged to have significant and serious limitations.
12.	ECD 3.11 (Overall survival). We agree that even with elosulfase alfa that treated patients will have higher morbidity and likely higher mortality than the general population, even if treatment is started from a very young age. However modelling this is difficult and still based on assumptions, and linking mortality purely to change in FVC is also likely to be inaccurate.
13	ECD 3.13 (Body weight). It is appropriate in modelling to take into account the expected weight gain for paediatric patients as they grow, and to base this on Montano et al 2008. Internal data review at GOSH suggests the MAA cohort from our centre are distributed within the range suggested by Montano. It is reasonable to assume stable weight once final height is obtained and that this is lower than the general population. This should be very straightforward to incorporate into the modelling.
14.	ECD 3.16 (Cost effectiveness estimates). It is not clear which of the committee's preferred assumptions were subsequently incorporated into the modelling to derive the ICER. With regard to changes in body weight over time it should be clarified how this was applied to patients in the modelling. As per point (3) above, if the modelling is based on an initial young, newly-diagnosed treatment-naïve population then a reasonable assumption about growth and weight gain would be based on following the 50th centile growth charts (Montano et al 2008).
15.	ECD 3.17 (Indirect benefits). We welcome that the committee recognises the very significant and important benefits of treatment to patients with MPS 4A. However, these are not reflected in the evaluation model.
16.	ECD 3.18 (Home infusions). The vast majority of patients treated in the MAA already receive infusion at home and some are able to self-administer these independently without nursing input, reducing administration costs further. Has this been accounted for in the modelling?
17.	ECD 3.21 (Long term benefits). The Committee agreed that there are likely to be long term benefits with elosulfase alfa, and the model does not capture all of these. The committee acknowledged that the company's analyses were not robust and that an alternative model could capture the benefits better. It must be noted that a significant burden was placed on patients and their families in getting the data. We are concerned the process of interaction between ERG, company and NICE committee has not resulted in an acceptable alternative model being derived.
18.	ECD 3.22 (Recommendation). The modelling did not demonstrate cost effectiveness, but we are concerned that the committee conclusion is based on what the committee considers to be a flawed model.
19.	ECD 4.1 (Review of Guidance). We note that a review of the guidance by the guidance executive after 3 years is recommended and that the guidance executive will decide whether the technology

Please return to: **NICE DOCS**

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	should be reviewed based on information gathered by NICE and in consultation with consultees and commentators. We remain concerned about the uncertainty about provision of on-going treatment for those patients who have been receiving treatment under the MAA during this period of time. We are also concerned that there is no defined further process during this 3 year period for what new information should be sought or made available. A clear plan must be put in place and recommended otherwise the same cycle of events with non-informative outcome will result, to the detriment of a cohort of patients with a rare disease for which an acknowledged effective treatment exists.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	University College London NHS Foundation Trust
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links to the tobacco industry to disclose
Name of commentator person completing form:	Elaine Murphy

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**We are concerned that the data and population used in the modelling does not appropriately represent the characteristics and likely response to treatment of the intended target patient population.** ECD **Section 3.3** states *"The committee also noted that this review would only focus on people newly diagnosed with MPS 4A. This was because continued access to elosulfase alfa for people with MPS 4A already having treatment will be discussed separately by the company and NHS England. The committee concluded that it would consider the newly diagnosed population who had not had treatment under its previous recommendations."* However, the analysis undertaken is based on a patient population of which the majority are not newly-diagnosed but have been diagnosed and living with MPS IVa for years before this treatment was available. These patients will already have some or significant disease-related morbidity. In contrast, the majority of newly diagnosed patients in future will be younger, with a lower disease burden and are expected to derive much greater benefit from treatment started at younger age. Data from paediatric centres has shown that the median age for starting treatment for classical MPS IVa is now around 3 years. We believe the model should be adjusted to examine this intended newly-diagnosed population group separately, with a cost-effectiveness analysis undertaken for this group.
2	**We believe that the evaluation process has missed the opportunity to include and evaluate data from the MPS IVa disease registry that was required of the MAH by the European Medicines Agency.**
3	**We feel that a number of important issues need to be considered / clarified in the model:** • Increased use of a wheelchair has been assumed to represent a worsening health state – whereas, as discussed, this may in fact reflect increased independence of young adults. • Important clinical outcomes such as improved healing after surgery, reduction in number and severity of respiratory tract infections have not been captured in the model used.
4	**Given that the committee recognises that the data generally show stable outcomes over time for elosulfase-treated patients in the MAA, if future review of the guidance is recommended then we would request that a comprehensive clear plan be provided to clinicians and stakeholders in advance as to what new information needs to be gathered and how this will be analysed to provide a robust outcome.**

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 3 December 2021. Please submit via NICE Docs.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

Comments on the ECD received from the public through the NICE Website

Name	[redacted]
Comments on the ECD:	

Has all of the relevant evidence been taken into account?

No:

a. The combined long term benefits of persons who have been on Elosulphase alpha since early trial phases (>10 years) has not been collated, presented or considered.

b. The fact that the slowing of disease progression has allowed patients to be fit enough to undertake surgical interventions to address some of the effects of the disease not fully managed by the ERT provides additional and significant benefit. This factor has not been taken into account in the ERGs revised forecast of life expectancy (having rejected the company's forecast as 'implausible').

c. The QALYs do not adequately take into account the significant benefits to patients of other factors such as increased patient height, less degradation in hearing/sight loss, stamina improvements, leading to increased fitness/muscle tone/mental wellbeing, when compared with patients on standard care. Much of this data was gathered during the MAA.

d. The Qalys do not take into account the fact that (based on the experience of our affected family members) any issues requiring intervention are more spread out over time, degradation is slower and there tend to be only one issue that needs resolution at a time rather than multiple interrelated issues. This gives time for proper planning of treatment and significant windows between recoveries. The possibility of surgery or other medical intervention to resolve specific areas of degeneration means that transition through the health states (whether modelled by wheelchair use or any other marker) is not always a straight line. Our experience shows that since being on elosuphase alfa, our children have been well enough to undergo major surgery which has significantly improved their pain, mobility, breathing, energy and overall well-being, including mental health. Prior to surgery in both cases (double hip replacement for one child at age 15/16) and tracheal resection for the other at 18) the affected individuals were very depressed, unable to engage easily with friends, family or school work and suffering varying degrees of pain, reduced mobility and fatigue. A big part of helping them manage this time whilst waiting for decisions regarding surgery, coping with the surgery and the effort required to for rehabilitation post-surgery, was the knowledge that elosulphase alfa was still supporting their overall condition: they were dealing with a specific health problem with a specific treatment available – they were not staring into the black hole of "Morquio degeneration" with no prospect of ever improving. In both cases, the surgery was successful with the specific problem areas alleviated and they have both been able to pursue their studies at college and university and get on with their lives.

e. There is no assessment or consideration of the potential detrimental impacts of withdrawing (or not providing) the treatment (physical and mental wellbeing). One of our children now lives away form home and manages

his own ERT infusions semi-independently with only minor nursing support. This is a big commitment for him to fit around his studies and all aspects of learning to live independently. How would we expect him to feel when it is determined that this has all been as waste of time and he cannot have the treatment any more. When our children were first diagnosed we were told that there was no treatment available for this condition and when the opportunity came along a few years later to participate in the clinical trial for the drug now known as elosulphase alfa, we took the decision to allow our children to take part – partly, obviously, in the hope that they would gain some benefit from the treatment, but also so that in the future no parents would have to be told on diagnosis of their child that there is still no treatment. It will be heart-breaking for new parents to have to be told that yes there is a treatment but because it failed some arbitrary threshold for cost effectiveness it cannot be given to your child.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No:

a. The ERG assertion that 6MWT results are 'implausible' on the basis that they were higher for partial wheelchair users is flawed. In my experience, partial wheelchair users use their wheelchairs to conserve their limited reserves of energy/stamina to be able to deploy it when required (i.e on the 6MWT rather than on getting to the wards in the first place)

b. The EQ 5D 5L only attributes utility gains for increases in 6MWT/FVC. Recognising MPSIV is a degenerative condition, and Elosulfase alfa delays the effects, rather than restores any losses/damage already incurred, the utility gains should be based on 'what is not lost' compared with those on standard care. This gives considerably higher figures.

c. The model also needs to account for the cumulative effects of these 'gains' over time. Data currently only considers the QALY gained over 1 year of treatment i.e The 'value' of the second year of treatment is the sum of the Year 1 and Year 2

i. (nominally double the 'value' for only a slight 'weight affected' increase in cost)

d. The majority of data collected to date has been on the existing MPSIV population, which covers a range of ages. These patients already had some level of degenerative impact prior to commencement of treatment. There is no recognition within the QALYs that treatment of newly diagnosed (usually young) patients will gain even more quality of life gains from the treatment, as any pre-treatment degeneration will be minimised

e. The committee acknowledge that the trial evidence and MAA data suggest that treatment with elosuphase alfa provides stability to the condition for MPS IVA patients in the long term. We agree – this has been the experience for our affected family members. We do not feel that enough weight is given to the benefit of stabilisation in what is otherwise a degenerative condition. When energy levels and stamina regularly fluctuate and general health frequently varies, it is impossible to plan your life from one day or week to the next, never mind looking ahead at future studying or career options, which is what young adults with MPS IVA want to do, the

same as everyone else. Stabilisation of the condition means that someone can reasonably assume that their current pattern of energy use/pain management and required recovery time will continue at least over the next few months or years. This enables them to get maximum use out of their current state of health without fear of overdoing it, which in turn leads to better physical and mental health and the ability to plan for the future. The associated well-being gains are immense.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No:

a. Request for better comparison group data for ultra-rare conditions to have been gathered over the 5 year MAA period was naïve (as any newly diagnosed but non-treatmented cohort was always going to be minimal). Given the small numbers affected with the condition and the significant differences in the way individuals are affected by the condition then any attempt to model effectiveness and put a numerical value on quality of life gained from treatment is going to be extremely difficult, bordering on impossible. A different approach entirely should be considered for conditions of this nature.

b. It is recognised by NICE that the process for evaluating Highly Specialised Technologies are not appropriate (as they are currently under review by NICE). I believe that the threshold prices used in evaluation are based on 'Very rare' conditions – which equates to around 10,000 cases across UK. MPSIVa has cases in the UK in the low hundreds. As such it is discriminatory for the 'price per patient' is not proportionately higher to account for this order of magnitude difference.

c. Elosulphase alfa was the first treatment to be managed via a MAA. The findings of this review have identified that the process, and subsequent results/outcomes at the end of the 5 year period have significant areas for improvement. However, the patients involved in this first MAA should not be penalised for the failings/shortfalls of the existing processes.

d. The criticism of the selected assessment criteria should be directed as much at the NICE committee who granted the MAA, as well as the company. Both should have established/agreed effective criteria for successful re-evaluation, during rather than at the end of the process. NOTE This point was made during consultation on the original findings.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes:

a. The costing model is discriminatory against the positive effect of the drug on MPSIV patients . In essence, the more effective the treatment is in allowing patients to grow during childhood/adolescence, the less cost effective the treatment is – because you need more of the drug to treat that patient.

b. The paper implies that newly diagnosed patients will be treated differently to existing patients. As the significant benefits have been recognised by the committee, this is discriminatory between these two cohorts.
c. We believe that the threshold prices used in evaluation are based on 'Very rare' conditions – which equates to around 10,000 cases across UK. MPSIVa has cases in the UK in the low hundreds. As such it is discriminatory for the 'price per patient' is not proportionately higher to factor in the fact that development/production costs etc are shared across a smaller cohort of patients

Name	[redacted]
Comments on the ECD:	

Has all of the relevant evidence been taken into account?
Example responses may include:
- No, NICE have not taken into account the patient evidence and data from the MAA, because: only newly treated patient data has been included and only two years of data from the MAA was presented. Much of the data from the MAA was not shared or presented
- No, it appears that NICE have ignored or at best not fully take account of a) the patient evidence b) the data from the MAA
- Disconnect in the data requested and committee expectations. Committee were expecting long-term data from clinical trial pts but focus from ERG is on naïve patients only. It is concerning that the prior communications between NICE, ERG and the company has not led to an acceptable, alternative model being agreed and implemented.
- The modelling has not captured all the benefits seen in clinical practice and reported directly by the patients, parent / carers. There has been limited use of the HRQOL collected through the MAA
- Whist committee accepted the W/C model last time they did not like it. Was this conveyed to company?
- Whilst NICE has acknowledged the wealth of information collected and presented by the clinicians and patient organisations, there is little evidence that this information has been considered and participants and observers were left feeling that the focus of the review was totally price driven and not based on clinical efficacy.
- We are concerned that not all the data appears to have been submitted and this raises concern over whether data collection / transference of data has failed at some point. Data gaps trigger uncertainty. Patient and clinical communities are concerned that the full impact of ERT has not be captured and interpreted with many parameters not referenced, which would have given a richness and completeness to the data and narrative being told by the clinicians and patients
- Not having a predefined statistical analysis plan in place for this re-evaluation has resulted in a flawed process with no defined parameters or clarity on expectations.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

- No, the summaries do not fully capture the benefits to patients from receiving this treatment. Share information on personal experience / benefits
- No, the summaries woefully underestimate the benefit to patient from this therapy
- No, the model is flawed and an alternative model should be used

Are the recommendations sound and a suitable basis for guidance to the NHS?

- It was evident, there was no clear process on how to review treatments coming out of a MAA.
- Recommendations were flawed due to lack of data and clarity on the areas of focus for the review
- Bring in your personal view and how you feel about being part of this process and part of the ongoing assessments and data collection for the MAA.
- No, it does not appear as if NICE has a solid understanding of this tiny population of people or the effect that any decision will have on this community
- The current model is not appropriate to determine whether elosulfase alfa is cost effective for a naïve population as it is using data from a wide range of participants with varying degrees of pathology, many of whose baseline were not captured in the MAA if already on established treatment

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

- Yes, the process has discriminated against me as it has failed to use appropriate approaches in reviewing data from small patient populations.
- Review of data for specific disease groups was excluded
- Longer term data was excluded as pre-treated patients were not included in the review.
- It is still unclear why NICE have decided to review existing and new patients separately.
- Yes, the process used by NICE has exclude people, especially those with the protected characteristic of Disability, from fully contributing to this consultation and as such this current recommendation is discriminatory. Additionally the recommendation itself is discriminatory as the approach that NICE has taken shows an unwillingness to use appropriate methodologies for the consideration of data related to very small populations
- Process has cause ongoing uncertainty and anxiety for patients and families, particularly for those patients treated through the clinical trial
- Patients have complied with all requirements and expectations but it appears their efforts and data has been excluded when it matters

• Main point of MAA was to capture long term data to respond / answer the uncertainties raised by the committee. Currently this has not been reflected in this process. • If NICE's decision is a no for newly diagnosed patients then they will be denying a population that would gain the most benefit. We know from experience that patients treated early in their disease have better outcomes and reduced disease morbidity. This process has resulted in older patients asking whether they should give up their effective treatment, so that young patients have an opportunity to glean the benefits they have experienced through this treatment out of pure guilt.

Name	[redacted]
Comments on the ECD:	
General comments: I am aware of someone who takes this drug and it has been a life changer for her. It relieves her pain, so she can get out of bed and be able to go to work.	

Name	[redacted]
Comments on the ECD:	
Has all of the relevant evidence been taken into account? Yes, but more emphasis should be placed on the substantial impact it has on improving quality of life **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No. Vimizim causes substantial improvement in patients symptoms and greatly increases their quality of life - the differences you can see in patients from before they start treatment to now are clear. Such beneficial impact is undoubtedly cost effective, and should be available to newly diagnosed patients too. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No. These recommendations are plunging newly diagnosed patients into a life where they cannot receive adequate treatment and will not have the same quality of life as those with this treatment. This guidance is giving a basis for guidance to the NHS that people with extremely rare disabilities are not entitled to life changing care, which is unacceptable.	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Yes. The individuals receiving this treatment have one of the rarest disabilities in the UK, and these recommendations are saying that these people aren't entitled to life changing treatment for their disability.

Name	[redacted]
Comments on the ECD:	

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The costs incurred to take care of people with Morquio A without this drug will be far greater than the cost of the drug itself.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
This is directly discriminating against people with a very specific disability. This decision to not distribute a life altering drug is effectively signing the death certificate of those who need it. People who rely on this medication will have no quality of life and will not be able to function.
I know someone with Morquio A and she will not be able to have a life without this medication.

Name	[redacted]
Comments on the ECD:	

Has all of the relevant evidence been taken into account?
No. As a colleague of someone currently taking elosulfase alfa I don't think it has at all. During covid her treatment was paused for a considerable amount of months and during this time her health has decreased considerably. Since restarting treatment she has seen markable improvements in her quality of life and is much more able to live a less debilitating life. I do not think NICE has gone far enough to gather real life data that clearly shows elosulfase alfa
addresses the underlying cause of Morquio A syndrome.

Name	[redacted]
Comments on the ECD:	

Has all of the relevant evidence been taken into account?
No. A significant proportion of the data from the managed access scheme was not taken into consideration. Despite the Managed Access Scheme running for over 5 years, only 2 years' of data was included, which is inexplicable given the whole purpose of the Managed Access Scheme was to collect evidence of benefits over a longer term period of time. The data presented only included newly treated patients, this in itself automatically excluded evidence from patients who have been on treatment for a longer period of time (due to being part of the clinical trial for a number of years before that). I also do not feel that the extensive quality of life benefits and broader patient evidence about the real life benefits of Vimizim has been properly considered or factored into the decision making process.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No. Broader patient benefits have not been appropriately interpreted or captured. My son Sam has been receiving Vimizim for almost 10 years. He does not suffer with fatigue. He does not routinely have any pain. He is 13 but is still very mobile and independent. Vimizim has had an incredible impact on his life, his quality of life and his independence. The evidence from clinicians and other patients is totally aligned to our experience, yet this is not fully reflected or given sufficient weight or importance in this recommendation.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No.
It is blatantly obvious that NICE do not have a robust process in place to assess treatment following a Managed Access Scheme. This is entirely unacceptable - there has been a six year period to plan and prepare for this, yet the process is both confused and fundamentally flawed. As a result of incompetence in designing an appropriate process, patients yet again are left in limbo, causing unnecessary stress, anxiety and suffering in lives that are already incredibly challenging. This is unforgivable.

It is also entirely unacceptable for the challenges with data to not be resolved before this point. Areas of focus for the review have not been clear throughout. Both NICE and the company have access to the data, its is perplexing therefore to be in this situation right now.

Having been part of the Managed Access Scheme for 6 years. diligently committing to reviews and hospital visits, 2 hours away from home, going through the excruciating waiting for "exam results" every year to find out if treatment will continue is soul destroying, and has impacted my mental health, that of my family and my son particularly. To commit to all of that as a family, then to find that data has not been properly used, and the benefits not fully represented is an absolute travesty.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Yes.
This process is directly discriminatory to my son. He and all other Morquio patients fall under the protected characteristic of disability, and the only reason that this cost effectiveness guidance is being given is because he is unfortunate enough to be born with a condition that only affects a very small patient population. This is entirely beyond his control. The process does not fully take this into account and therefore is structurally discriminatory. This is also evidenced by the fact that NICE openly admits the benefits and positive impacts of Vimizim, yet still says no.

The exclusion of longer term data is also discriminatory because it clouds decision making and holds valuable evidence back. This is unacceptable given the rarity of the condition and the inherent challenges involved in collecting the data. It is both discriminatory and negligent.

Splitting the decision making process between new and existing patients creates concern also, especially given there is zero visibility of when and how a decision will be made for existing patients. Whilst I understand that this decision sits with NHSE, it is unacceptable for NICE to wash their hands of this situation; from a patient perspective, it should not matter who the decision maker is, the approach needs to be transparent. It is not, and again, patients are left stuck in the middle, uncertain, anxious and afraid. This is no way to treat disabled children and adults who are disadvantaged daily because of the condition they have and the way society treats them.

Name	[redacted]
Comments on the ECD:	

General comments:
While recognising the heavy demand on NHS resources and funding it seems contradictory to deny treatment to desperate patients who will make high financial care demands if denied treatment by this medication. Apart from the fact that the pain isolation and suffering these patients endure even with the treatment surely the NHS has the duty to ensure for them a quality of life that is above the bare essential minimum of existence.

Name	[redacted]
Comments on the ECD:	

Has all of the relevant evidence been taken into account?

No, NICE have not taken into account the patient evidence and data from the MMA, because only newly treated patient data has been included and only two years of data from the MAA was presented. Much of the data from the MAA was not shared or presented.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, the summaries do not fully capture the benefits to patients from receiving this treatment.

I am a patient with Morquio. Prior to receiving Vimizim I had no expectations about my future and quality of life. I was in pain all the time and relied on painkillers. My joints were stiff and my mobility very restricted. I had to have knee braces prescribed. I relied on cabs or others to get to places and back and be helped in out of cars etc. My wrists were very laxed and hurt and that meant carrying a simple mug of tea was very difficult, wringing a cloth was impossible. My upper core strength was noticeably getting worse and it affected my posture making walking harder. My energy level was low and so too my stamina – simple things like having a shower meant I had to rest straight afterwards as I knew I would be very tired. I planned my day limiting to what I could do so that I could rest My hearing began to deteriorate much more as I got older – having to get more powerful hearing aids with each passing years. In the last few years prior to starting Vimizim, people would approach me to ask how I was as they could see my breathing was heavy even though I did not realise and that was a huge worry. My skin was taut, sore and I had adult acne and no medication, specialist treatment helped. As there was no treatment for this disease, I had to accept all these health issues as part of my life.

When I first heard about the new ERT Vimizim for Morquio in 2015, I immediately asked my GP to refer me to a specialist centre (previous I was under many different Consultants but none were Morquio specific) and was allowed to join the MAA and started Vimizim in May 2015. I was 47 years old. I did not want to build my hopes up as I was an older patient and thought that the deterioration was far too great for the treatment to be effective but I felt that I was given a chance to try to improve my health and the quality of my life and would do everything that the MAA required to allow me to try this new drug.

I first noticed an improvement after a couple of months when I realised I was wringing my wash cloth with ease – I saw that my wrists were much less laxed and no longer had that lingering pain and strength was improving in my arms. From there, I noticed that I could carry from one room to another a mug of tea on my own. I could lift a 4 pint milk carton! Using the handrail to climb a step was so much easier as I had the improved upper core strength to push me up. Washing my hair, getting in and out of the shower was easier etc. The pain in my joints greatly reduced and did not have to take painkillers. I can shower and get on with my day without having to allocate time to rest as had much more stamina. My sleep has improved so I wake up with much more energy. Family and friends have commented that I have become more sociable. I am able to help with housework which had not been possible before and had to rely on others. I still have to wear knee braces but I notice I wear them more when I am out and much less at

home as I am more stable standing and walking. My posture improved greatly helping my back pain to ease alot. During this time my hearing remained stable and I did not have to get more powerful aids. My skin improved so much that I no longer have to use any treatment. Based on assessments my 6MWT improved showing I can walk further without exertion and my lung capacity has improved too and no longer get comments about being out of breath. Although all the above maybe considered anecdotal, they all point towards just how much Vimizim has helped me physically and mentally, even as an older patient. It has given me hope for the first time.
With the pandemic in March 2020, and the fact that I was severely at risk from Covid complications, I felt I had no choice but to take a pause in treatment as it requires a face to face contact on a weekly basis. After a couple of months, I started to notice all the previous symptoms returning bit by bit. My joints started to hurt and again affecting my mobility, the strength in my legs and upper core body weakened and my wrists became laxed again and sore. I had to start using my knee braces indoors again as they became less stable. Sleep has been affected and my stamina and energy reverted to its old levels so I was again finding myself having to rest a lot more. I notice my hearing worsened and testing revealed it had so now need more powerful hearing aids.
The pause in treatment has proven just how Vimizim has benefited me illustrating a before and after scenario and this is not included in the evidence.

Are the recommendations sound and a suitable basis for guidance to the NHS?
It was evident that there was no clear process on how to review treatments coming out off a MAA.
Recommendations were flawed due to lack of data and clarity on the areas of focus for the review.
I made every effort, and at a financial and time cost to both myself and my family, to help provide all the evidence needed for the MAA in the last 6 years. It took up a lot of time but I felt that it was something I needed to commit to in order to show just how vital Vimizim is to all Morquio patients. It is upsetting to see that all the evidence and hard work from all patients, Clinicians and the MPS Society has not been used.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Yes, the process has discriminated against me as it has not used appropriate approaches in reviewing data from small patient population. Morquio is an ultra rare disease and it is unfair that I have to follow such a long drawn out process to access the only drug that has proven to help me have a better quality of life, slow down the progression of the disease and prolong my life. .

Also, longer term data was excluded as pre-treated patients were not included in the review.
It is not clear why NICE decided to review existing and new patients separately.

Name	[redacted]
Comments on the ECD:	

Has all of the relevant evidence been taken into account?
No, NICE have not taken into account the patient evidence and data from the MAA, because: only newly treated patient data has been included and only two years of data from the MAA was presented. Much of the data from the MAA was not shared or presented.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No, the summaries do not fully capture the benefits to patients from receiving this treatment. I am a patient with Morquio who is currently receiving Vimizim on the MAA. Prior to starting treatment, I was in constant pain, suffered from extreme fatigue and my mobility was very poor due to stiff and painful joints. The effort required to walk made it feel like walking through treacle. I could only manage to walk very short distances before becoming tired, breathless, and experiencing increased pain in my joints. Travel was limited to cars or taxis, I'd have to be taken door to door to limit the amount I would need to walk. I was taking ibuprofen on a daily basis to manage the constant underlying pain I had in my joints. I suffered from fatigue and lack of stamina: I had to limit my daily activities and make sure I had plenty of rest in between to manage pain and fatigue. Simply having a shower would wear me out and I would need to rest before continuing my day. A simple shopping trip would mean I would be bedridden the following day. I suffered from brain fog: I had difficulty concentrating for long periods of time or focusing on a long conversation. My poor mobility lead to an unhealthy weight gain - I needed to lose weight but found it impossible to do so. I had breathing issues - my breathing was shallow and I easily became short of breath. I had to constantly face upwards to keep my airways open. I suffered from sleep apnea and daytime sleepiness - I used a CPAP machine at night to combat this. I had weakness in my arms and legs and lax wrists I found carrying anything from a mug of tea to a bag difficult and cumbersome. I had skin problems and suffered from painful adult acne. These symptoms would get progressively worse over time. No treatment and no cure meant that I had no choice but to suffer and tolerate them. I had to accept these symptoms as part of the problem.

I started Vimizim treatment under the MAA in April 2015, aged 42. I had low expectations thinking that the damage had already been done by Morquio, so I was overwhelmed when I began to notice the benefits of Vimizim. My mobility improved: I was able to walk further without the need to stop and rest - this was evidenced by the 6MWT I had to do as part of the MAA which showed I could walk more than twice the distance with fewer rest breaks

while on treatment. My breathing improved and is no longer shallow. I can speak a whole sentence without stopping to catch my breath. My posture has changed - I no longer have to hold head facing upwards to keep my airways open. This was evidenced by the lung function tests I did as part of the MAA - my lung capacity increased by 50%.
These are the benefits where I have provided clinical evidence, but there are plenty of other benefits which are considered anecdotal, but have made a significant immeasurable improvement to my quality of life. I experienced a decrease in joint pain and stiffness - any pain I do have easier to manage without the need to take pain killers. I have thrown away boxes of unused ibuprofen that had expired as I don't need to take them on a regular basis any more. My joints are no longer stiff: simple things like turning around and getting out of bed or getting in and out of shower are so much easier. My body feels lighter and I no longer feel like I am walking through treacle. I experience less fatigue and more stamina. I can get more activities done during the day without feeling tired, and less need for breaks in between each activity. The brain fog disappeared - friends have commented on how much more alert and "bright" I am, more "with it" - I can hold and follow a conversation without fading. I can concentrate for longer. have an Increased upper body strength - carrying things like mugs of tea and bags are no longer an issue and I am more stable on my feet. I am able to open bottles and jars with less effort. My sleep disturbances improved and I was taken off CPAP after 20 months of Vimizim. My new found mobility and energy helped me achieve my weight loss goals - I lost a quarter of my body weight (13kg). The condition of my skin improved - it is softer and I finally got rid of my painful adult acne without the need for any additional skin treatment! I am brighter, more sociable and independent - and happier. None of these positive improvements can be quantified or were captured as evidence for clinical and cost effectiveness

At the beginning of the pandemic, my risk of severe complications of covid were high, so I took a pause in treatment. Within a less than a month of not having Vimizim, my old symptoms returned, most noticeably the pain, fatigue and breathing difficulties. This was also not captured as evidence for clinical and cost effectiveness

Are the recommendations sound and a suitable basis for guidance to the NHS?
It was evident there was no clear process on how to review treatments coming out of a MAA.

Recommendations were flawed due to lack of data and clarity on the areas of focus for the review.

I put in a lot of time, money and effort to provide as much evidence of the benefits of Vimizim through the ongoing assessments and data collection for the MAA for 6 years. It was repetitive, tiresome and intrusive but I was more than happy tolerate the burden to provide this evidence, not only to be able to continue receiving treatment, but also because it was the only way I could prove the effectiveness of the drug which would then make the drug

accessible to all patients with Morquio. It is incredibly frustrating to see that the data collected from all patients by clinicians and the MPS Society was not used properly when making this recommendation.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
The process has discriminated against me and my disability as it has failed to use appropriate approaches in reviewing data from small patient populations.

It has discriminated against me due to my disability being caused by an ultra rare disease which means I have to go through a long drawn out process to get access to a drug which has been proven to significantly improve my quality of life and prolong my life. Having benefitted from treatment and providing continuous clinical evidence of this benefit for 6 years, it would be unethical to withdraw it from me now.

Longer term data was excluded as pre-treated patients were not included in the review.

It is still unclear why NICE have decided to review existing and new patients separately.

General comments:

I wholeheartedly do NOT agree with this recommendation.

It is unclear why NICE is only considering access for new patients and NHSE will consider those already on treatment. What is the reason behind this?

Surely all data should be considered. Why was valuable long term data from those on the clinical trial discarded?

I find everything in this paragraph a huge concern. It was a huge burden to provide all the data required for the MAA and it is disconcerting that this data has not been analysed and used correctly by the company.

I agree that the wheelchair based economic model is flawed. Prior to Vimizim, much of my time was spent indoors with no wheelchair use as I was too tired or in too much pain to leave the house. Quite often I would be bedridden. Vimizim has given me a new lease of life and I now have the energy and stamina for outdoor activities. I use a mobility scooter outdoors but I do not see this transition from "no wheelchair use" to "wheelchair use sometimes" as a negative thing. I now have the energy to use a wheelchair more often, and that can only be construed as a positive thing. I have more independence, can use public transport, can go to concerts, the theatre,

museums, travel independently, visit friends and family, that I couldn't do before treatment

Vimizim has had an immense impact on my life beyond the direct health benefits. Not only has my physical health improved but so has my mental health - it's only with hindsight that I appreciate this impact. I feel much more in control of my life and more optimistic about making future plans as I know activities will no longer have to be cancelled due to pain and fatigue. I am more independent and no longer have to rely on others for help. My social life has improved as I can engage better with friends and family and I can enjoy my time with them more.

Having infusions that take a whole day out of my week is a huge burden especially when having to travel to a specialist centre each time. Home infusions dramatically reduce this burden.

Name	[redacted]

Comments on the ECD:

Has all of the relevant evidence been taken into account?
NO, NICE have not taken into account the patient evidence and data from the MAA, only newly treated patient data has been included and only two years of data from the MAA was presented. Much of the data from the MAA was not shared or presented.

Why should this be removed when you recognise the long term benefits of elosulfase alfa?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The summaries do not fully capture the benefits to patients from receiving this treatment. We have noticed that our daughter's energy levels are a lot better, before treatment started she was unable to complete a school week, without being tired on the Friday evening after school. She was slow to walk upstairs, stepping one step at a time. After treatment she seems to have much more energy, but the biggest difference is how happier she is. She is singing and dancing much more than she ever did.

Are the recommendations sound and a suitable basis for guidance to the NHS?
It was evident there was no clear process on how to review treatments coming out of a MAA. The recommendations are flawed due to lack of data and clarity on the areas of focus for the review. We have only had our diagnoses for about five months, we were devastated with the news that our beautiful little girl had a life limiting disease. We know that nothing will change our daughters condition but this treatment, as we understand, slows

the downward progression of the disease. I can't believe it is right or moral to remove a treatment which is proven to extend a 6 year old life and possible give her a better quality of life. The stress of the threat of this treatment being removed is too much to bear.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes, the process has discriminated against us as it has failed to use appropriate approaches in reviewing data from small patient populations. Longer term data was excluded as pre-treated patients were not included in the review. It is still unclear why NICE have decided to review existing and new patients separately.

BMJ TAG

Elosulfase alfa for treating mucopolysaccharidosis type IVA (re-evaluation of highly specialised technologies guidance 2)

ERG review of company's response to the ECD

December 2021

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/08/34T.

1 Introduction

This document provides the evidence review group's (ERG's) response in relation to the company's comments and additional data presented as a response to the evaluation consultation document (ECD).

2 ERG review of comments

2.1 Comment 1: The Managed Access Agreement process

The ERG considers this an issue for The National Institute for Health and Care Excellence (NICE).

2.2 Comment 2: Relevant data sources for decision-making

In their response to the ECD, the company highlighted that the scope of the NICE HST2 review is enzyme replacement therapy naïve (ERT-naïve) patients and that their clinical experts consider that future patients commencing treatment with elosulfase alfa (ESA) will be newly diagnosed patients of approximately age 2-3 years old. The company also reported that in the managed access agreement (MAA) data, ERT-naïve patients who started ESA under the age of 6 had an average age of 3.6 years, although they also highlighted that occasionally some patients may be diagnosed at an older age.

The company reported that sibling studies (Frigeni *et al.* 2021[1], Ficicioglu *et al.* 2020[2], Barak *et al.* 2020[3]) in mucopolysaccharidosis type IVA (MPS IVA) have highlighted meaningful differences in long-term disease progression with early diagnosis and early treatment, although due to time constraints the evidence review group (ERG) has been unable to review the papers cited by the company to validate these claims. Nevertheless, the ERG notes that the company considers these studies to be indicative of expected potential outcomes for newly diagnosed patients in England due to advancements in early diagnosis. The company reported that they have therefore now focused on using data from patients aged under 6 years old in the economic model to align with the anticipated population in clinical practice. The ERG's clinical experts reported that they would expect the patients with the most severe symptoms to be diagnosed by the age of 3, although patients with milder symptoms may still be diagnosed at a later age. The ERG notes that this is consistent with the findings of the International Morquio A Registry reported by Montaño *et al.*[4], where mean age of recognition of initial symptoms was 2.1 years and mean age at diagnosis was 4.7 years. The ERG is unsure why the company selected a threshold of under 6 years, but the ERG understands the value of running a scenario analysis where patients are younger and healthier at baseline (see Section 2.8).

However, the ERG is concerned about the robustness of the data in this population due to the small number of patients in the MAA and limited data collection on lung function in patients aged under 5 years. The ERG considers that the MAA ERT-naïve cohort of patients is of more relevance to the NICE final scope for this review than the ex-trial cohort due to the use of the baseline being the start of the MAA rather than the start of their original trials for the ex-trial patients. However, the ERG also considers the data from the ex-trial cohort could have been utilised to provide information on the long-term effects of ESA and, if baseline data were available from the start of the original trials, then the data from the MAA ex-trial patients could also provide important data that is as relevant as that of the MAA ERT-naïve cohort.

The ERG notes that there is clinical heterogeneity among patients with MPS IVA and therefore considered a complete case analysis (CCA) to be the most reliable use of the data from the MAA to inform the economic model. Unfortunately it is not clear to the ERG how to interpret all of the raw data in the MAA data file provided by the company, in particular the ex-trial patient data. For example, the ERG considers it to be unclear what patients baseline data were in their original trials as the MAA ex-trial data provided are reported only as [redacted] Additionally, the ERG is concerned [redacted] The ERG has thus been limited in the analyses it can undertake, and for the ex-trial MAA patients has only been able to use data from the MAA baseline in the CCAs. Nevertheless, the ERG has conducted an exploratory 3-year CCA using the MAA ex-trial patients to explore the long-term impact of ESA on 6-minute walk test (6MWT) and the results of this exploratory analysis are discussed in Section 2.4.

2.3 Comment 3: Data analysis issues

Unfortunately there is a lack of direct comparative study data for standard of care (SoC) versus ESA and so alternative methods are required to enable a comparison. The ERG is concerned that a naïve comparison between the ESA data from the managed access agreement (MAA) and SoC from the MOR-001 trial is subject to clinical heterogeneity. However, the ERG also considers the propensity score matching (PSM) results reported by the company in their clarification question response to be unreliable due to flaws in the coding and analysis of the patient level data that were discussed in detail in the ERG report.

The ERG was particularly concerned that MPS IVA comprises a heterogenous patient population and so individual patients could have markedly different baselines and treatment responses. The ERG noted that not all patients had baseline and follow-up data at each time point in the company's

analyses. The company's previous approach of comparing the mean estimates of all patients observed at each time point, does not therefore account for the fact that these represent different cohorts of patients with potentially very different outcomes. Additionally, it was not possible to assess the direction of the resulting bias from the company's approach. The ERG therefore considered it important that the company instead conduct CCAs, where the same cohort of patients are followed from baseline to each subsequent timepoint.

Following technical engagement, the ERG conducted an exploratory 1-year CCA using the full MOR-001 population and the MAA ERT-naïve population because [redacted] As discussed in Section 2.2, the ERG is concerned that the company may not have fully utilised the data from the MAA ex-trial patients and, due to a lack of clarity in the data provided by the company, the ERG has been limited in what further analyses it can conduct. The ERG considers the MAA ex-trial data should at a minimum be able to help inform the longer-term outcomes for ESA. The ERG has thus conducted an exploratory 3-year CCA for 6MWT using the MAA ex-trial data from the MAA baseline which is discussed further in Section 2.4.

2.4 Comment 4: Use of complete case analysis

The company argues that the CCA approach recommended by the ERG would lead to a small number of patients meeting the criteria for the analysis and non-comparable populations. The ERG agrees that it results in a much smaller population but considers it a more reliable method for assessing changes over time in outcomes with ESA treatment. This is because of the clinical heterogeneity in the patient population and thus the ERG considers it most appropriate to ensure the same cohort of patients are followed up for outcomes and each timepoint to ensure any changes from baseline accurately reflect the patients in the analysis. The ERG acknowledges that the CCA approach does not account for differences in baseline characteristics between the studies (e.g. MAA and MOR-001) but due to the small patient numbers in the analyses, as agreed by the company, it is not possible to perform any matching such as propensity score matching. It is thus a limitation of the analysis and the ERG considers the CCA approach to more robust than the use of naïve comparisons presented in the December 2020 company submission.

As discussed in the ERG report following technical engagement, the ERG considers the full MOR-001 population to be the most appropriate source of data for the CCA of SoC as the MAA includes patients aged <5 years old. The company reported that, *"following feedback from the ERG and*

Committee, the Company have re-conducted this analysis versus MOR-001, which is presented below" but the ERG was unable to find any new CCA results in the company response to the ECD. The company also reported that the results of a CCA of MOR-005 vs MOR-001, "*would not be much different from the data presented in the original 2015 HST model, which used the modified per protocol (MPP) population (i.e., excluding patients with surgeries or with less than 80% adherence to treatment) from MOR-005 QW-QW versus MorCAP 2-year follow-up study population that are highly aligned in terms of baseline characteristics to define the first 18 months of treatment.*" The ERG is unable to validate this conclusion as the ERG does not have access to data to conduct any CCAs for MOR-005 but the ERG does still consider that a CCA of MOR-005 and MorCAP1 would be useful to provide further evidence on the effectiveness of ESA.

The company report that, "*To better represent the future population of new patients in the model, the Company looked at all the data available in patients under 6 years old*." In the MAA ERT-naïve cohort there are [redacted] patients who started treatment below the age of 6 and the ERG notes that [redacted] MAA ex-trial patients originated from the MOR-007 study, which is a study in patients under 5 years old. However, the ERG also notes that few patients aged under 5 years had lung function assessments in the MAA. The ERG notes that the clinical data for the MAA ERT-naïve subgroup aged under 6 years are not used in the economic model and the ERG considers the data are likely to be unreliable due to the [redacted]

The company reported that they consider the [redacted] ERT-naïve MAA patients aged under 6 more closely represent patients who will be commencing ESA in the future and thus they provided subgroup analyses by age for the outcomes of 6MWT and forced vital capacity (FVC) using linear regression analyses. The ERG is concerned that the company's linear regression analyses do not use the CCA approach preferred by the ERG and for the subgroup aged under 6 years the patient numbers in the analyses are extremely low as not all [redacted] ERT-naïve MAA patients had 6MWT and FVC measures (baseline values reported by company for [redacted] patients for 6MWT, and [redacted] for FVC). [redacted] The ERG also notes that the company presented 6MWT results using age bands of 5-10 years to provide more detailed age subgroup analyses which they reported were to inform the long-term outcomes with ESA. The ERG does not consider the use of data from the MAA ERT-naïve subgroup are appropriate for informing long-term outcomes, rather they show the effect of ESA in ERT-naïve patients commencing treatment at older ages. The ERG is

concerned by the [redacted], thus the ERG does not discuss these results further.

The results of the company's linear regression of change in 6MWT over time for the ERT-naïve MAA subgroup aged under 6 years versus 6 years and over suggest [redacted] (Table 1). However, as already discussed, the ERG is concerned that these analyses do not comprise a CCA and comprise a [redacted] cohort of patients who may not be fully representative of the population who will be receiving ESA in the future.

Table 1. Linear regression of change in 6MWT over time among treatment naïve MAA population: age under 6 vs. age 6 years and over (reproduced from company response to ECD Table 4.1)

	Under 6 years old			6 years and over		
	Coef.	Std. Err.	P-value	Coef.	Std. Err.	P-value
Time since baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observations	[redacted]			[redacted]		

As discussed in Sections 2.2 and 2.3, the ERG has conducted a 3-year CCA using the ex-trial MAA data for 6MWT in an attempt to explore the long-term impact of ESA. The ERG used data from the ex-trial MAA patients who had both a baseline 6MWT result reported and a further 6MWT measurement reported at 36 months. The ERG's analysis included [redacted] patients and the mean change from baseline to 36 months was [redacted] metres. The ERG considers the findings of this analysis to demonstrate that patients on long-term ESA show [redacted] Unfortunately due to time constraints the ERG was unable to explore the long-term impact of ESA on other outcomes such as FVC.

Table 2. ERG 3-year CCA of MAA ex-trial patients 6MWT change from baseline to 36 months

Outcome by health state at baseline	MAA ex-trial		
	Mean	SD	n
6MWT at baseline (metres)	[redacted]	[redacted]	[redacted]
Mean 6MWT at 36 months (metres)	[redacted]	[redacted]	[redacted]
Mean change from baseline in 6MWT at 36 months (metres)	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute-walk test; SD, standard deviation.

2.5 Comment 5: Treatment impact on MPS-HAQ

The ERG notes that, as discussed previously in the ERG report, the data for SoC are limited and so it is not possible to conduct analyses of ESA versus SoC using the long-term ESA data. In the company response to the ECD, the company reported that to help inform the benefits of ESA they have: *"analysed data from the MPS-HAQ questionnaire to understand the broader benefits from treatment and to inform additional utility benefits in patients, which are not captured in the EQ-5D".*

The ERG notes that the MPS-HAQ (MPS Health Assessment Questionnaire) data from the MAA were presented by the company in their submission in December 2020 along with EQ-5D data. However, as discussed in Section 2.4, the ERG is concerned that these data do not comprise CCAs and thus the ERG advises caution in drawing any conclusions.

The ERG notes that the MPS-HAQ results for the MAA ERT-naïve patients reported by the company suggest an [redacted] Additionally, the ERG is unsure whether [redacted] on the MPS-HAQ would be deemed a clinically meaningful benefit for patients.

Table 3. MPS-HAQ mean change baseline versus last follow-up (adapted from company submission, Table 41)

	Mean change from baseline (lower score is an improvement)		
	Year 1	Year 2	Year 3

Mobility domain			
ERT-Naïve Patients (Mean Treatment duration, 3.6 years)	[redacted]	[redacted]	[redacted]
Ex-Trial (Mean Treatment duration, 8.0 years)	[redacted]	[redacted]	[redacted]
MOR-001 (Natural history cohort)	[redacted]	[redacted]	[redacted]
Self-care domain			
ERT-Naïve Patients (Mean Treatment duration, 3.6 years)	[redacted]	[redacted]	[redacted]
Ex-Trial (Mean Treatment duration, 8.0 years)	[redacted]	[redacted]	[redacted]
MOR-001 (Natural history cohort)	[redacted]	[redacted]	[redacted]
Caregiver domain			
ERT-Naïve Patients (Mean Treatment duration, 3.6 years)	[redacted]	[redacted]	[redacted]
Ex-Trial (Mean Treatment duration, 8.0 years)	[redacted]	[redacted]	[redacted]
MOR-001 (Natural history cohort)	[redacted]	[redacted]	[redacted]

The company also reported in their response to ECD that, "correlation analysis showed that the EQ-5D is correlated with the MPS-HAQ, but there may be domains of quality of life (QoL) not captured well by the EQ-5D." The ERG is not familiar with the MPS-HAQ and is unable to comment on the potential differences between the MPS-HAQ and the EQ-5D. However, the ERG notes that the NICE methods guide states that if the EQ-5D is considered inappropriate, empirical evidence should be provided on why the properties of the EQ-5D are not suitable for the particular patient population and that these properties may include the content validity, construct validity, responsiveness and reliability of EQ-5D.[5] The ERG does not consider the company to have provided any evidence to

suggest that the EQ-5D is not a reliable measure of QoL in this instance, and therefore the ERG considers the NICE preference for EQ-5D should be maintained.

2.6 Comment 6, 7, 8, and 9: Committee's conclusions on economic model

2.6.1 Company's modelling approach

The company states that the committee has accepted a WC based model. The ERG disagrees with the company's conclusion and notes that the ECD reports that, "*the committee was reluctant to accept the company's wheelchair model because it did not model disease progression well, and long-term benefits relied solely on assumptions rather than clinical data. It had expected the company to address the limitations of the model structure that it had set out in the original guidance. Without any alternatives, the committee concluded that the company's model could be used for decision making. However, it noted that the model added considerable uncertainty because it did not model disease progression well*."

Additionally, the stakeholders' comments on the ECD consistently raised a concern for the lack of validity of a WC-based model and its inability to accurately measure disease progression. The ECD also noted that patient experts, "*explained that people often choose to use wheelchairs to allow independent living rather than simply for mobility issues. Because people have short stature, wheelchairs make everyday activities such as pressing buttons and using public transport easier*".

The company's response to ECD was based on the same justification as that provided after the clarification and the TE stages of this evaluation, and it consists of the argument that WC use is the outcome which correlates the most with health utilities captured via the EQ-5D. Equally, the ERG's assessment of the company's justification remains the same as there is no evidence to corroborate the justification provided by the company (for more details please see the ERG's review of the company's response to TE).

Therefore, the ERG's original concerns around the lack of appropriateness of a WC-based model remain. The ERG considers that a model based around endurance and respiratory measures would have provided a better tool for decision making. Crucially, such a modelling approach would have allowed the company to use the MAA or the MOR-005, and MOR-001 data to estimate changes (increase or decrease) in 6MWT and FVC outcomes according to treatment arm, instead of relying almost solely on assumptions around disease progression. The ERG notes that WC use data from the MOR-001 and the MAA studies are only used in the first year of the economic model, while

progression in the subsequent years was based on assumptions for the ESA arm, and on 6MWT and FVC outcomes from MOR-001 for the SoC arm. Therefore, the company had to make further assumptions to link FVC and 6MWT outcomes to the WC states in the model, where the outcome data could have been directly used.

2.6.2 Estimation of WC dependency in the model

2.6.2.1 Exit and entrance threshold for WC use

The ERG disagreed with the 6MWT entrance and exit thresholds used by the company to model transition between WC states as these were based on implausible results, where mean 6MWT increased when people in the model moved from NWC use to SWC use. As a scenario analysis, and to provide an alternative to the company's unsubstantiated assumptions, the ERG used the MOR-001 6MWT values at baseline to re-define the entrance and exit thresholds for each WC state in the model. The details of this analysis are further discussed in Section 3.8 of the ERG's review of the company's response to TE.

The committee agreed that the company's approach appeared counterintuitive because WC use did not appear to adequately capture disease progression. The committee also agreed with the ERG's 6MWT criteria to define movement between health states and considered it acceptable for decision making.

As a response to the ECD, the company reported that it has accepted the ERG's re-estimated entrance and exit thresholds from the different WC categories in the model and reportedly implemented these into the revised model. Nonetheless, upon inspection of the company's updated model, the ERG concluded that the thresholds were not used and that the company's original thresholds were still being used (Table 4).

Changing the thresholds in the company's updated model increased the company's updated ICER from [redacted] to [redacted] with a 1.5% discount rate, and from [redacted] to [redacted] with a 3.5% discount rate.

Table 4. Entrance and exit 6MWT thresholds

Outcome by health state at baseline	ERG's	Company's updated model
Mean 6MWT at baseline (metres)		

No wheelchair use	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]

2.6.2.2 Change in WC use in first year of the model

Given the availability of annual WC change data, the ERG did not agree with the company's approach of using the data on WC change from baseline to 72 weeks in the MAA dataset and from baseline to 2 years in the MOR-001 study, respectively, to model the transition between WC states in the first year of the model.

Therefore, after TE, the ERG replaced these in the model with the TPs from baseline to year 1 in the MAA (treatment naïve patients) and in MOR-001 using the ERG's 1-year CCA.

As a response to the ECD, the company stated that, "*The transition probabilities were changed in the model to reflect ERG and committee recommendations.*"

Table 5 and Table 8 report the TPs used in the company's original model, for ESA and SoC patients, respectively. Table 7 and Table 10 present the TPs derived from the ERG's 1-year CCA. Finally, Table 6 and Table 9 provide the TPs used in the company's updated model. The latter do not match the TPs used by the ERG in its analysis (or the company's original analysis) and describe a scenario where ESA patients had no progression in year 1 of the model (see Table 6), instead of using the observed data from the MAA.

Overall, the ERG is unclear on the source of the estimations provided by the company in their updated analysis and disagrees with the use of these TPs in the model as the source of data preferred by the ERG to model TPs in the first year of the model remains the 1-year CCA. Crucially, the ERG notes that the company's updated analysis assumes that ESA patients do not have any progression in the model (in year 1 or any subsequent year). Therefore, the ERG disagrees with the company's statement that the model was changed to reflect the ERG's and the committee's recommendations.

Results of implementing the ERG's preferred TPs in the company's updated model are provided in Section 2.11.1.

Table 5. Transition matrices for baseline to Year 1 used in the company's original model, MAA patients, treatment-naive

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair
No wheelchair use	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]
*sum of the probability of patients transitioning from the NWC state to the SWC (36%) and to the WCD (9%) states.			

Table 6. Transition matrices for baseline to Year 1 used in the company's updated model

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair
No wheelchair use	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]

Table 7. Transition matrices for baseline to year 1 used in the ERG's analysis, CAA by 1 year, MAA patients, treatment-naïve

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total number of patients (N=36)
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]

Table 8. Transition matrices for baseline to Year 1 used in the company's original model, MOR-001

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair
No wheelchair use	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]
*company's assumption			

Table 9. Transition matrices for baseline to Year 1 used in the company's updated model, MOR-001

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair
No wheelchair use	[redacted]	[redacted]	[redacted]

Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]
*company's assumption			

Table 10. Transition matrices for baseline to Year 1 used in the ERG's analysis, CCA by 1 year, MOR-001

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total number of patients (N=97)
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]

2.6.2.3 Change in WC use from year 2+ in the model

The company has assumed that only 1 in 10,000 ESA patients change WC dependency (i.e., progresses) per year. The ERG has expressed its concerns around this assumption given it has not seen any data to substantiate the company's assumption. The latter also implies that ESA patients' 6MWT and FVC values at year 1 do not change for these patients' lifetime.

The ECD reports that, "*the committee recalled longer-term clinical evidence that suggested the condition remained broadly stable over time* […]. *It considered that the company's approach may more closely capture a stabilisation of disease* […]. *It noted that the company's assumption of very little disease progression for people having elosulfase alfa was more optimistic than the longer-term managed access data, which generally showed stable MPS 4A*."

The company has not changed its original modelling approach to estimate the long-term benefit associated with ESA in the model.

For SoC patients, the company agreed with the ERG's proposed approach of assuming a loss of 4.86m for 6MWT to model disease progression and of 0.1L in their FVC measures, according to the Harmatz *et al*. study and has implemented this in the updated model.[6]

The ERG remains concerned that the assumption that that only 1 in 10,000 ESA patients progresses per year, after year 1 in the model is unsubstantiated. For example, the CCA by 2 years reported in the company's submission show that ESA patients could still progress in their WC dependency from year 1 to year 2. Additionally, the the 3-year CCA analysis undertaken by the ERG (See Section 2.4) also shows that patients on ESA suffered a decrease in their 6MWT outcomes.

Given the lack of data to substantiate any estimate of long-term effectiveness with ESA, the ERG conducted a scenario where it was assumed that after year 1 in the model, ESA patients lost [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). This assumption was based on the pooled results from the MAA and MOR-001, which show that ESA patients had an improvement of [redacted] in their 6MWT compared to SoC patients after year 1. For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 11, for ease of interpretation.

The ERG notes that this scenario assumes a life-long benefit associated with ESA, as patients take longer to progress from the all the WC states when compared to SoC patients. For example, it takes ESA patients 77 years to progress from the SWC to the WCD state, compared to 35 years in the SoC arm; and 39 years vs 14 for patients to move from the NWC to the SWC states, respectively. The ERG reiterates its preference for this scenario, as it uses observed data to estimate a long-term treatment effect with ESA, instead of relying on the assumption of no disease progression for these patients.

Table 11. Years to disease progression after year 1 in company's model and ERG's alternative estimates

Outcome by health state at baseline	SoC patients		ESA patients	
	Company's model	**ERG-preferred**	**Company's model**	**ERG-preferred**
Years taken to change from NWC to SWC	[redacted]	14	[redacted]	39
Years taken to change from SWC to WCD	[redacted]	35	[redacted]	77
Years taken to change from WCD to paraplegic	[redacted]	7.4	[redacted]	7.7

Abbreviations: ESA: elosulfase alfa; SoC: standard of care; NWC: no wheelchair; SWC: sometimes wheelchair; WCD: wheelchair dependent.

2.6.2.4 *Patients in the asymptomatic state*

The company's model assumed that SoC patients take 3 years to become symptomatic and that ESA patients take 9 years to show symptoms. The company based the SoC assumption on the Montaño *et al*. study[4] and the ESA assumption on clinical expert opinion.

The committee accepted the company's assumptions that it takes 3 years for SoC patients and 9 years for ESA patients to develop symptoms.

2.6.3 *Estimation of mortality*

In response to the ECD, the company agreed with the committee's and the ERG's approach to link survival to FVC outcomes. Nonetheless, the company disagreed with the improvement in FVC estimated by the ERG. The company stated that, "*as per the previous submission, FVC improves by 26.5% in the ex-trial population in the long-term*". The ERG is confused by the company's statement as the company's original model for this evaluation used an improvement factor of %FVC vs baseline of 16.5% over the course of 3 years of treatment with ESA (taken from the MOR-002/100 trial).

The ERG had concerns with the use of MOR-100 as the source of the %FVC improvement factor associated with ESA (see Section 3.9 in ERG's review of the company's response to TE). The ERG originally recommended that the company analysed the improvement factor in FVC over time observed in MOR-005 and apply it in the model (as this was the ERG's preferred data to be used to estimate FVC). The company did not undertake such analysis. Therefore, the ERG used the FVC improvement based on the ERG's 1-year CCA of FVC data in MOR-001 and the MAA treatment-naïve patients of [redacted]%.

Despite the company's disagreement with the use of the [redacted]% improvement factor, the company's updated model used this estimate. As the ERG maintains its view that this is the most reliable source of data provided by the company (other than MOR-005 as originally requested by the ERG), the ERG considers that the [redacted]% improvement factor should be used in the model and thus, no changes were required by the ERG.

2.7 Comment 10 and 13: Utility values used in the model

The ERG received confirmation from the company post-TE that that the utility values used to estimate the utility for SoC patients ([redacted]; [redacted]; [redacted] for NWC; SWC; and WCD, respectively) in the company's model were not based on baseline utility values from the MAA dataset. The company

confirmed that the utility values used in the SoC arm were those resulting from a, "*composite score from 3 time points (baseline, 12M and 24M), for each wheelchair state*". Therefore, as discussed by the ERG in their response to TE, the ERG disagreed with the use of these utility data in the SoC arm as these reflect the impact of treatment with ESA on patients' quality of life over 2 years. In their response to TE, the ERG reported the results of its additional investigation of the MAA treatment-naïve baseline utility data, using the maximum available baseline data (i.e. including all patients with baseline EQ-5D and WC data), and arrived at the values [redacted] for NWC; SWC; and WCD, respectively.

The ECD stated that the, "*committee concluded that the ERG's utility values from the treatment-naive subgroup from the MAA were appropriate*".

In their response to the ECD, the company accepted that baseline utility data from the MAA should be used to reflect SoC utilities. Nonetheless, the company used different utility values of [redacted] for NWC use, SWC use, and WCD, respectively. The ERG is unclear on how these values were estimated.

As a response to ECD, the company also reported changing the utility values associated with ESA, to reflect those, "*at the end of 2 years in the treatment naïve subgroup (excluding ex-trial patients from the full MAA dataset)*". The company reports using the utility values of [redacted] for NWC use, SWC use, and WCD, respectively. Nonetheless, the ERG's investigation of the model led to the conclusion that the company's updated model does not use these values. Instead, it uses the company's updated SoC utility values with the ESA-specific incremental utility added as per the ERG's calculations after TE (see Section 3.10 in the ERG's review of the company's response to TE and Table 12 below).

As requested by the committee and the NICE technical team, the ERG provided ICERs using the utilities estimated from the MAA treatment-naïve baseline utility data, using the maximum available baseline data ([redacted] for NWC; SWC; and WCD, respectively). Nonetheless, the ERG reiterates that using the Hendriksz study to estimate the utilities for the SoC arm of the model is also a relevant scenario. The utility values used in the HST2 (which in turn were taken from the Hendriksz *et al*. 2014 burden of disease study for patients with MPS IVA), were 0.85; 0.58; and 0.06 respectively, in adults (18 years or above) not using a wheelchair, using a wheelchair only when needed, and always using a wheelchair. The ERG notes that the Hendriksz *et al*. 2014 utility value for

WCD is [redacted] from that observed in the MAA analysis; however, the WCD and the SWC values in the Hendriksz study are [redacted], than those seen in the MAA. Given that the Hendriksz utilities were accepted in the HST2; and the higher number of adult patients in the published study across each WC category (4 for NWC; 12 for SWC; and 9 for WCD) when compared to the number of adults in the MAA treatment naïve patients (3 for NWC; 3 for SWC; and 2 for WCD), the ERG considers that two scenarios are warranted to estimate the utilities for the SoC arm of the model – one using the Hendriksz study; and the other using the baseline utility data collected in the MAA. The ERG provides results using both sets of utilities in Section 2.11.1.

Table 12. Model utility values

	SoC arm			Effect of ESA on 6MWT (m) or FVC (L) ~	Treatment specific increment ~	ESA arm		
Health state	Company's updated model	ERG's post-TE analysis (taken from Handriksz)	ERG's scenario analysis^			Company's updated model	ERG's post-TE analysis	ERG's scenario analysis
Asymptomatic	[redacted]	1.000	1.000	-	-	[redacted]	1.000	1.000
No wheelchair	[redacted]	0.846	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair	[redacted]	0.582	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wheelchair dependent	[redacted]	0.057	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraplegic	[redacted]	0.057*	[redacted]	-	-	[redacted]	[redacted]	[redacted]
End state	[redacted]	0.024	0.024	-	-	[redacted]	0.024	0.024

Abbreviations: SE, standard error; SOC, standard of care; ESA, elosulfase alfa
*assumed the same as the WCD state
^ using baseline MAA values for SoC utilities
~ estimated by the ERG

2.8 Comment 11: Body weight used in the model

The company agreed with the ERG's and committee's view that patients' weight in the model should increase until patients reached the weight reported in the Montaño *et al.* paper[7], according to age.

The ERG assumed that, on average, all patients would reach 36.7kg by the time they were 18 years old. This assumption was based on the Montaño *et al.* paper where it is reported that the mean

weight of males and females with MPS IVA at 18 years is 37.6 ± 13.4 kg; and 35.8 ± 14 kg; respectively.[7] The ERG weighted the mean weights by the proportion of males (52%) and females (48%) in the model and arrived at the weight of 36.7kg. The ERG then assumed that patients' weight would increase at a constant rate over the remaining years (from mean age at year 1 until they reached 18 years) and stopped when patients reached 36.7kg (see Table 13 below and Section 3.11 of the ERG review of the company's response to TE for more details).

Table 13. Weight change applied by the ERG in the model

Health state	Average age at baseline (years)	Average weight (Kg) at baseline	Average weight (Kg) at 12 months (estimated)	Increase in weight until 18 years	Weight used in long-term model
Asymptomatic	0	3.6	10.66*	26.04	36.7
No use wheelchair	16	19.8	21.0	15.7	36.7
Some use wheelchair	14	27.0	29.3	7.4	36.7
Wheelchair dependent	22	35.2	41.2	-	41.2

*taken from Montaño *et al. 2018*

Given the company's assessment that future newly diagnosed patients would be younger (see Section 2.2), the company changed the baseline age across WC categories in the model. Nonetheless, even though the company stated that due to the lower starting age, patients would also be expected to be lighter at baseline, the company did not change the baseline weights used in the ERG's analysis after TE. This resulted in a clinically implausible combination of patients' age and weight (see Table 14). For example, patients with a mean age of 4 years weigh 19.8kg in the NWC category but weight 27kg in the SWC category, when the Montaño *et al.*, paper[7] shows that 4 year old MPS IVA patients are between 14kg (females) and 15kg (males).

Therefore, the ERG disagrees with the company's approach of decreasing the baseline age of patients but using the baseline weight estimated by the ERG.

Table 14. Weight and age used in the company's updated model

Health state	Average age at baseline (years)	Average weight (Kg) at baseline	Baseline % of patients
Asymptomatic	0	3.6	5%
No use wheelchair	4	19.8	68%

Some use wheelchair	4	27.0	27%
Wheelchair dependent	22	35.2	0%

Given stakeholder comments that newly diagnosed patients will be younger and will have accrued less disease-damage pathology and thus are expected to derive much greater benefit from treatment started at younger age than treatment-naïve patients in the MAA, the ERG understands the value of running a scenario analysis where patients are younger and healthier at baseline. Stakeholder comments reported that in the GOSH cohort , median age at diagnosis is 3 years for classic MPS IVA and 8 years for paediatric attenuated MPS IVA, with no significant change in age of diagnosis over the last 20 years. The stakeholder comments also reported that since 2015, the median age for starting treatment for classical MPS IVA is 3.1 years. Therefore, the ERG has run a scenario with a baseline age of 3 years (based on classic MPS-IVA patients). The ERG caveats this scenario analysis with the fact that the treatment effectiveness data associated with ESA did not change in the model.

Table 15. Weight change applied by the ERG in scenario analysis

Health state	% of patients at baseline^	Average age at baseline (years)	Average weight (kg) at baseline*	Increase in weight until 18 years (kg)*	Weight used in long-term model (kg)*
Asymptomatic	5%	0	3.6	26.0	36.7
No use wheelchair	95%	3	13.5	23.2	36.7
Some use wheelchair	0%	-	-	-	-
Wheelchair dependent	0%	-	-	-	-

*taken from Montaño *et al.* 2018

^based on clinical expert opinion provided to the ERG

2.9 Comment 12: Discount rate used

The committee concluded that ESA is not curative and therefore, concluded that the use of a 3.5% discount rate was appropriate.

The company disagreed with the committee's assessment and noted that the use of ESA has meaningfully modified the disease trajectory, particularly if patients are treated early. The company

noted the NICE Guide to the Methods of Technology Appraisal, which states that in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), a discount rate of 1.5% for costs and benefits may be considered.

The company added that long-term data from the MAA supports that ESA offers sustained benefits over 10 years and that it is likely that ESA's benefits can be expected to continue far into patients' lives and likely to exceed 30 years.

The ERG presents results using both discount rates.

2.10 Comment 13: QALY weighting

The ERG does not have anything to add to the company's observation which is in agreement with the committee's decision that ESA meets the criteria for applying a QALY weight.

2.11 Comment 14: Company's updated cost-effectiveness results

As discussed throughout this report, the company reports implementing changes in the updated economic model which the ERG could not verify. Therefore, in this section the ERG lists the company's changes to the economic model, along with the committee and ERG preferred assumptions (see Table 16).

Table 16. Assumptions used in the company's updated model

Assumption	Committee preferred	ERG preferred	Included in company's base case updated post-ECD model	Company's approach in updated post ECD model
Use of a WC-based model	No	No	Yes	As reported in company's response to ECD
Assumption of a 4.86m (instead of a 6.84m) annual loss in 6MWT for SoC patients after year 1 in the model	Yes	Yes	Yes	As reported in company's response to ECD
ERG's entrance and exit thresholds from the different WC categories in the model	Yes	Yes	No	Upon inspection of the company's updated model, the ERG concluded that the thresholds were not used in the model and that the company's original thresholds were still used, despite the company's statement that these had been

				changed to reflect the committee's preference
Use of ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model	Yes	Yes	No	The ERG is unclear on the source/estimation methods for these new transition probabilities
Assumption that that only 1 in 10,000 patients progresses per year in the ESA arm after year 1 in the model	Yes	No	Yes	As reported in company's response to ECD
Assumption that the effect of ESA observed in the 1-year CCA would be observed for every year of treatment with ESA in the model. For this scenario, the ERG assumed that after year 1 in the model, ESA patients lost 31% less than SoC patients in their 6MWT, (i.e., 3.3m vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost 4% less than SoC patients, (i.e., 0.0957L vs 0.1L, respectively, annually).	No	Yes	No	n/a
SoC patients that start in the asymptomatic state of the model are assumed to take 3 years to progress to the symptomatic state, while elosulfase alfa (ESA) patients take 9 years to move from asymptomatic to symptomatic	Yes	No	Yes	As reported in company's response to ECD
Linking mortality to decreased %FVC predicted in the model (with ERG's 1-year complete case analysis [CCA] estimations for FVC decrease taken from the MAA and MOR-001 data)	Yes	Yes	Yes	Despite the company's disagreement in their ECD response with the use of the [redacted]% improvement factor in FVC to estimate the impact of ESA on mortality, the company's updated model used this estimate
Use the ERG-estimated baseline utility data from the MAA for SoC patients and the ERG's estimations of FVC and 6MWT gains associated with utility increments in the ESA arm	Yes	Unclear. The ERG also considers the Hendriksz *et al*. 2014 study relevant.	No	Using utility values of [redacted] for NWC use, SWC use, and WCD, respectively for SoC patients (the ERG is unclear on how these values were estimated) and adding the ERG-estimated ESA-specific incremental utility to estimate utility values in the ESA arm of the model

The ERG's assumptions for changes in patients' body weight	Yes	Yes	Partially	Allowing patients' body weight to change over time and using the ERG's proposed weight in the model. However, the company's change in baseline age resulted in clinically inconstant baseline weight for patients.
Changing the baseline age distribution to reflect a younger population	Not discussed as a required change in the model	Not discussed as a required change in the model	Yes	The company changed the baseline distribution of patients by WC status to reflect a newly diagnosed cohort. The distribution of patients at baseline in the updated model is 4.9%; 68.0; 27.1%; and 0% for no asymptomatic, NWC, SWC and WCD, respectively.
Changing the baseline WC distribution to reflect a healthier population	Not discussed as a required change in the model	Not discussed as a required change in the model	Yes	The distribution of patients' age at baseline was changed to 0; 4; 4; and 22 years for no asymptomatic, NWC, SWC and WCD, respectively.
Treatment administration cost of £213	Yes	Yes	Yes	n/a
Use of a 3.5% discount rate	Yes	Unclear	No	Use of a 1.5% discount rate
Updated patient access scheme (PAS)	n/a	n/a	Yes	As reported in company's response to ECD

The company's updated base case deterministic ICER (discounted) for ESA versus SoC is provided in Table 17, when using a discount rate of 1.5% and 3.5%. The table below also reports the undiscounted QALY gain of 28.66 associated with ESA in the company's base case results.

Table 17. Company's deterministic base case results (discounted except for undiscounted QALYs with updated PAS)

Interventions	Total Costs (£)	Total QALYs undiscounted	Total QALYs	Incremental costs (£)	Incremental QALYs undiscounted	Incremental QALYs	ICER (£/QALY)
Using a 1.5% discount rate							
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Elosulfase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Using a 3.5% discount rate							
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elosulfase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

2.11.1 ERG's analysis

2.11.1.1 Company's corrected base case analysis

Given the company's statement in the ECD response that the ERG's entrance and exit thresholds from the different WC categories in the model had been applied in the company's updated model, the ERG assumed that the company's use of its old thresholds is a modelling mistake. Therefore, the ERG corrected this in the model.

The ERG also corrected a minor utility error in the model, where the company was using a 0.08 utility value for paraplegic patients instead of a 0.00795 value.

The company's updated corrected base case deterministic ICER (discounted) for ESA versus SoC is provided in Table 18, when using a discount rate of 1.5% and 3.5%. The table below also reports the undiscounted QALY gain of 23.70 associated with ESA in the company's base case results.

Table 18. Company's deterministic base case results (discounted except for undiscounted QALYs with updated PAS)

Interventions	Total Costs (£)	Total QALYs undiscounted	Total QALYs	Incremental costs (£)	Incremental QALYs undiscounted	Incremental QALYs	ICER (£/QALY)
Using a 1.5% discount rate							
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-
Elosulfase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Using a 3.5% discount rate							

Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elosulfase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

2.11.1.2 ERG's exploratory analysis

Given the company's assessment that future newly diagnosed patients would be younger the company changed the baseline age across WC categories in the model. As discussed in Section 2.8, the ERG disagrees with the implemented changes as these resulted in a clinically implausible combination of patients' age and weight.

However, given stakeholder comments that newly diagnosed patients will be younger and will have accrued less disease-damage pathology and thus are expected to derive much greater benefit from treatment started at younger age than treatment-naïve patients in the MAA, the ERG understands the value of running a scenario analysis where patients are younger and healthier at baseline.

Therefore, the ERG presents the results of its exploratory analysis using two populations:

- A population reflecting the baseline characteristics of treatment-naïve patients in the MAA (previously used by the company and by the ERG in their analyses).
- A population with median age at diagnosis of 3 years; WC distribution at baseline of 95% of patients in the NWC category and 5% of asymptomatic patients (based on ERG's clinical expert opinion); and baseline weight of 3.6kg for asymptomatic patients and 13.5kg for NWC patients (according to Montaño *et al.* 2018). The ERG caveats this scenario analysis with the fact that the treatment effectiveness data associated with ESA did not change in the model.

In light of the ECD, the ERG's preferred assumptions common to both populations are the following:

1. Standard of care (SoC) patients that start in the asymptomatic state of the model are assumed to take 3 years to progress to the symptomatic state, while elosulfase alfa (ESA) patients take 9 years to move from asymptomatic to symptomatic – already incorporated in company's updated base case analysis;

2. Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients.
3. Using the entrance and exit thresholds estimated by the ERG – already incorporated in company's updated corrected base case analysis;
4. ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data;
5. Assumption of a 4.86m (instead of a 6.84m) annual loss in 6MWT for SoC patients after year 1 in the model – already incorporated in company's updated base case analysis;
6. Estimating mortality linking changes in FVC predicted to survival. The ERG calculated the %FVC predicted values in MOR-001 and assumed an improvement of FVC of [redacted]% associated with ESA as estimated in the ERG's 1-year CCA of FVC data in MOR-001 and the MAA treatment-naïve patients – already incorporated in company's updated base case analysis;
7. Using the ERG's assumptions for changes in patients' body weight – already incorporated in company's updated base case analysis for the MAA population;
8. Replacing the £207 treatments administration cost in the model with the updated £213 estimate – already incorporated in company's updated base case analysis.

In addition to these, the ERG explored the following alternative scenarios:

a) Assuming that after year 1 in the model, ESA patients lose [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). This assumption was based on the pooled results from the MAA and MOR-001, which show that ESA patients had an improvement of [redacted] in their 6MWT compared to SoC patients after year 1. For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 11, for ease of interpretation. Alternatively;
b) Assuming that only 1 in 10,000 ESA patients change WC dependency (i.e., progresses in 6MWT or FVC outcomes) per year (company's base case assumption).
c) Using the utilities reported in the Hendriksz for SoC patients and applying the utility increments for the NWC and the SWC utilities for the ESA arm, associated with the 6MWT increase of [redacted] and [redacted] (estimated by the ERG to be the increase in 6MWT results for NWC and SWC patients with ESA, respectively, from the MAA). For the WCD state, the

ERG did not apply any utility increments in the ESA arm, as there was no FVC increase observed for ESA patients in the ERG's analysis.

Alternatively;

d) Using the MAA treatment-naïve utility values to estimate utility in the SoC arm of the model and estimating utility increments for the NWC and the SWC utilities for the ESA arm, associated with the 6MWT increase of [redacted] and [redacted] (estimated by the ERG to be the increase in 6MWT results for NWC and SWC patients with ESA, respectively. For the WCD state, the ERG did not apply any utility increments in the ESA arm, as there was no FVC increase observed for ESA patients in the ERG's analysis.

Scenarios 1; 3; 4; 5; and b have been incorporated in the company's updated corrected base case ICERs, reported in Table 18.

Table 19 and Table 20 include the results of the ERG's analysis using the MAA treatment-naïve patients, with a 3.5% and 1.5% discount rate, respectively. Table 21 and Table 22 provide the equivalent results for the younger, less severe population.

For the 3.5% discount rate, the ERG's exploratory ICERs for the MAA treatment-naïve population vary between [redacted] (using the Hendriksz utility values) and [redacted] (using the MAA baseline utility values), when it is assumed that only 1 in 10,000 ESA patients has deterioration in 6MWT or FVC socres per year, after year 1 in the model. When it is assumed that after year 1 in the model, ESA patients lose [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually) and [redacted] less in their FVC, the equivalent ICERs increase to [redacted] and [redacted], depending on the source of utility used. The ERG notes that the [redacted] and [redacted] ICERs assume a life-long benefit associated with ESA, as patients take longer to progress from the all the WC states when compared to SoC patients. For example, as reported in Table 11, it takes ESA patients 77 years to progress from the SWC to the WCD state, compared to 35 years in the SoC arm; and 39 years vs 14 for patients to move from the NWC to the SWC states, respectively.

The equivalent ICERs using a 1.5% discount rate amount to [redacted] (using the Hendriksz utility values) and [redacted] (using the MAA baseline utility values), when it is assumed that only 1 in 10,000 ESA patients progresses. When it is assumed that after year 1 in the model, ESA patients lose [redacted] less than SoC patients in their 6MWT, and [redacted] less in their FVC, the equivalent ICERs increase to [redacted] and [redacted].

The ERG's exploratory ICERs for the younger population (using a 3.5% discount rate) vary between [redacted] (using the Hendriksz utility values) and [redacted] (using the MAA baseline utility values), when it is assumed that only 1 in 10,000 ESA patients progresses per year, after year 1 in the model. When it is assumed that after year 1 in the model, ESA patients lose [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually) and [redacted] less in their FVC, the equivalent ICERs increase to [redacted] and [redacted], depending on the source of utility used.

The ERG notes that the exploratory analysis using a younger population is based on the assumptions that 100% of patients start the model in the NWC (or asymptomatic) categories. When combined with the assumption that only 1 in 10,000 ESA patients progresses in the model, this reflects a very optimistic scenario, where the majority of ESA patients spend their lifetime not using a wheelchair, with only 11% of ESA patients progressing to sometimes using a wheelchair in the model. This compared to ~40% of ESA patients at some point in the model needing a wheelchair sometimes when it is assumed that ESA patients lose [redacted] less than SoC patients in their 6MWT and [redacted] less in their FVC.

The equivalent ICERs using a 1.5% discount rate amount to [redacted] (using the Hendriksz utility values) and [redacted] (using the MAA baseline utility values), when it is assumed that only 1 in 10,000 ESA patients change WC dependency. When it is assumed that after year 1 in the model, ESA patients lose [redacted] less than SoC patients in their 6MWT, and [redacted] less in their FVC, the equivalent ICERs increase to [redacted] and [redacted].

In conclusion, due to the paramount uncertainty in the clinical data, the ERG does not have a preferred ICER, and instead presented several ICERs including different permutations of assumptions to aid decision making. The ERG also considers that the discount rate used in the analysis should match the assumption made for the long-term effectiveness of ESA. If committee's preferred assumptions include treating young (and so by definition asymptomatic patients) and assuming the drug prevents disease progression for patients' entire lifetimes, this lends itself to using a 1.5% discount rate. However, the ERG notes, again, that all the scenarios including the latter assumption (i.e., that only 1 in 10,000 ESA patients progress in their 6MWT or FVC outcomes) translates a potentially clinically implausible scenario where all patients have a "perfect" response to ESA throughout their lifetimes.

Table 19. Deterministic results (discounted except for undiscounted QALYs) using a 3.5% discount rate, MAA treatment-naïve patients

Scenario		Incremental costs	Incremental QALYs	ICER	Undiscounted incremental QALYs
0	Company's corrected updated base case, which includes scenarios 1; 3; 5; 6; 7; 8 and b	[redacted]	[redacted]	[redacted]	[redacted]
Population	MAA treatment-naïve patients	[redacted]	[redacted]	[redacted]	[redacted]
0+2	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+c	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the utilities reported in the Hendriksz for SoC patients and applying utility increments for the NWC and the SWC utilities for the ESA arm	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+d	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data	[redacted]	[redacted]	[redacted]	[redacted]

	Using the MAA treatment-naïve utility values to estimate utility in the SoC arm of the model and estimating utility increments for the NWC and the SWC utilities for the ESA arm				
0+2+4+c+a	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the utilities reported in the Hendriksz for SoC patients and applying utility increments for the NWC and the SWC utilities for the ESA arm Assuming that after year 1 in the model, ESA patients lose [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 11, for ease of interpretation	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+d+a	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the MAA treatment-naïve utility values to estimate utility in the SoC arm of the model and estimating utility increments for the NWC and the SWC utilities for the ESA arm Assuming that after year 1 in the model, ESA patients lose [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 11, for ease of interpretation	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 20. Deterministic results (discounted except for undiscounted QALYs) using a 1.5% discount rate, MAA treatment-naïve patients

Scenario		Incremental costs	Incremental QALYs	ICER	Undiscounted incremental QALYs
0	Company's corrected updated base case, which includes scenarios 1; 3; 5; 6; 7; 8 and b	[redacted]	[redacted]	[redacted]	[redacted]
Population	MAA treatment-naïve patients	[redacted]	[redacted]	[redacted]	[redacted]
0+2	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+c	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the utilities reported in the Hendriksz for SoC patients and applying utility increments for the NWC and the SWC utilities for the ESA arm	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+d	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data	[redacted]	[redacted]	[redacted]	[redacted]

	Using the MAA treatment-naïve utility values to estimate utility in the SoC arm of the model and estimating utility increments for the NWC and the SWC utilities for the ESA arm				
0+2+4+c+a	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the utilities reported in the Hendriksz for SoC patients and applying utility increments for the NWC and the SWC utilities for the ESA arm Assuming that after year 1 in the model, ESA patients lose [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 11, for ease of interpretation	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+d+a	MAA treatment-naïve patients Scenarios 1; 3; 5; 6; 7; 8 Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the MAA treatment-naïve utility values to estimate utility in the SoC arm of the model and estimating utility increments for the NWC and the SWC utilities for the ESA arm Assuming that after year 1 in the model, ESA patients lose [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 11, for ease of interpretation	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 21. Deterministic results (discounted except for undiscounted QALYs) using a 3.5% discount rate, younger patients

Scenario		Incremental costs	Incremental QALYs	ICER	Undiscounted incremental QALYs
0	Company's corrected updated base case, which includes scenarios 1; 3; 5; 6; 7; 8 and b	[redacted]	[redacted]	[redacted]	[redacted]
Population	Younger patients	[redacted]	[redacted]	[redacted]	[redacted]
0+2	Younger patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4	Younger patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+c	Younger patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the utilities reported in the Hendriksz for SoC patients and applying utility increments for the NWC and the SWC utilities for the ESA arm	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+d	Younger patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data	[redacted]	[redacted]	[redacted]	[redacted]

	Using the MAA treatment-naïve utility values to estimate utility in the SoC arm of the model and estimating utility increments for the NWC and the SWC utilities for the ESA arm				
0+2+4+c+a	Younger patients Scenarios 1; 3; 5; 6; 7; 8 Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the utilities reported in the Hendriksz for SoC patients and applying utility increments for the NWC and the SWC utilities for the ESA arm Assuming that after year 1 in the model, ESA patients lose [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 11, for ease of interpretation	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+d+a	Younger patients Scenarios 1; 3; 5; 6; 7; 8 Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the MAA treatment-naïve utility values to estimate utility in the SoC arm of the model and estimating utility increments for the NWC and the SWC utilities for the ESA arm Assuming that after year 1 in the model, ESA patients lose [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 11, for ease of interpretation	[redacted]	[redacted]	[redacted]	[redacted]

Table 22. Deterministic results (discounted except for undiscounted QALYs) using a 1.5% discount rate, younger patients

Scenario		Incremental costs	Incremental QALYs	ICER	Undiscounted incremental QALYs
0	Company's corrected updated base case, which includes scenarios 1; 3; 5; 6; 7; 8 and b	[redacted]	[redacted]	[redacted]	[redacted]
Population	Younger patients	[redacted]	[redacted]	[redacted]	[redacted]
0+2	Younger patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4	Younger patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+c	Younger patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the utilities reported in the Hendriksz for SoC patients and applying utility increments for the NWC and the SWC utilities for the ESA arm	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+d	Younger patients Scenarios 1; 3; 5; 6; 7; 8 and b Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data	[redacted]	[redacted]	[redacted]	[redacted]

	Using the MAA treatment-naïve utility values to estimate utility in the SoC arm of the model and estimating utility increments for the NWC and the SWC utilities for the ESA arm				
0+2+4+c+a	Younger patients Scenarios 1; 3; 5; 6; 7; 8 Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the utilities reported in the Hendriksz for SoC patients and applying utility increments for the NWC and the SWC utilities for the ESA arm Assuming that after year 1 in the model, ESA patients loose [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 11, for ease of interpretation	[redacted]	[redacted]	[redacted]	[redacted]
0+2+4+d+a	Younger patients Scenarios 1; 3; 5; 6; 7; 8 Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data Using the MAA treatment-naïve utility values to estimate utility in the SoC arm of the model and estimating utility increments for the NWC and the SWC utilities for the ESA arm Assuming that after year 1 in the model, ESA patients loose [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 11, for ease of interpretation	[redacted]	[redacted]	[redacted]	[redacted]

3 References

1. Frigeni M, Rodriguez-Buritica DF, Saavedra H, Gunther KA, Hillman PR, Balaguru D, et al. The youngest pair of siblings with Mucopolysaccharidosis type IVA to receive enzyme replacement therapy to date: A case report. *Am J Med Genet A* 2021; **185**: 3510-6.
2. Ficicioglu C, Matalon DR, Luongo N, Menello C, Kornafel T, Degnan AJ. Diagnostic journey and impact of enzyme replacement therapy for mucopolysaccharidosis IVA: a sibling control study. *Orphanet J Rare Dis* 2020; **15**: 336.
3. Barak S, Anikster Y, Sarouk I, Stern E, Eisenstein E, Yissar T, et al. Long-Term Outcomes of Early Enzyme Replacement Therapy for Mucopolysaccharidosis IV: Clinical Case Studies of Two Siblings. *Diagnostics (Basel)* 2020; **10**.
4. Montaño AM, Tomatsu S, Gottesman GS, Smith M, Orii T. International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. *J Inherit Metab Dis* 2007; **30**: 165-74.
5. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013 (Process and methods [PMG9]). 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Date accessed: 17 Dec 2021.
6. Harmatz PR, Mengel KE, Giugliani R, Valayannopoulos V, Lin SP, Parini R, et al. Longitudinal analysis of endurance and respiratory function from a natural history study of Morquio A syndrome. *Mol Genet Metab* 2015; **114**: 186-94.
7. Montaño AM, Tomatsu S, Brusius A, Smith M, Orii T. Growth charts for patients affected with Morquio A disease. *Am J Med Genet A* 2008; **146A**: 1286-95.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 24 December** using the below comments table.

All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

1) Clarified rationale for choosing a threshold of under 6 years old patients in treatment naïve MAA patients

Description of problem	Description of proposed amendment	Justification for amendment
Comment 2 (page 2) – *'The ERG is unsure why the company selected a threshold of under 6 years, but the ERG understands the value of running a scenario analysis where patients are younger and healthier at baseline'.*	The company would like to clarify the rationale for selecting a threshold of under 6 years old treatment naïve MAA patients in their analyses submitted on the 3rd December 2021. The age cut-off of 6 years old was chosen for the following two reasons: i. Clinical plausibility: Clinical advice received by both the company and ERG highlighted that future patients commencing treatment with elosulfase alfa (ESA) will be newly diagnosed patients of approximately age 2-3 years old. Potentially, very occasionally, mildly affected adult patient may be diagnosed later in life, but it is unclear whether these patients would want to take treatment. ii. Analytical purposes: The 6-year cut-off was chosen because this would reflect the future patients coming on treatment on ERT, and in the MAA dataset the sample size (n=11) was considered a good sample size on which to base meaningful analysis. A younger age group would have lowered the sample size (n=11) further and limited the feasibility of analysis. The MAA ERT-naïve patients who started ESA under the age of 6 had an average age of 3.6 years with a standard deviation of 0.9.	The company agrees that the rationale was not well described in their 3rd December 2021 submission and would like to clarify this in their ECD response.

2) Baseline data of MAA ex-trial patients

Description of problem	Description of proposed amendment	Justification for amendment
Comment 2 (page 3) – *'ERG considers it to be unclear what patients baseline data were in their original trials as the MAA ex-trial data provided are reported only as trial 12, 24, 36 or 48 months. Additionally, the ERG is concerned there maybe errors within the data set.'*	True baseline of MAA ex-trial patients has been confirmed and re-programmed in line with the clinical trial baseline data. However, due to time constraints, the interim data points between the true baseline, clinical trial, and MAA baseline have not been checked and confirmed. Please see the dataset attached to this response (shared as AIC).	*AIC Removed These corrections allowed for the analysis of the ex-trial patients to support the extrapolation of patients under 6 years. EQ-5D was not performed in ESA clinical trials therefore these pre-treatment baseline measures are not available. EQ-5D and MPS HAQ baseline are defined as the measure at the first MAA visit (at 4months). Due to the absence of MAA baseline clinical measurements in these ex-trial patients (except for MOR-004), the EQ-5D scores at 'MAA baseline' were aligned with the first MAA visit (4 months).

3) Use of MAA ex-trial data in the model

Description of problem	Description of proposed amendment	Justification for amendment
Comment 3 (page 4) – *'The ERG considers the MAA ex-trial data should at a minimum be able to help inform the longer-term outcomes for ESA.* […] *ERG also notes that the company presented 6MWT results using age bands of 5-10 years to provide more detailed age subgroup analyses which they reported were to inform the long-term outcomes with ESA. The ERG does not consider the*	The company agrees that ex-trial cohort from MAA should be able to define the long-term outcomes and inform longer-term extrapolations. However, given that there is no long-term data beyond 10 years from the MAA or MARS, hence the consideration was to use extrapolation based on regression curves: this is common to almost all conditions where we are extrapolating long-term outcomes from short-term trials. In this case we have cohorts of patients treated on average for between 6-9 years.	As stated in the ECD, the treatment naïve cohort is a relevant population for decision making and therefore the company has focused much of its analyses on this group, while providing supporting evidence using the ex-trial population for longer term outcomes and these perspectives are supported with the MARS registry. These data sets are the strongest evidence sets in a heterogenous, complex and ultra-rare condition where these is inherent variability,

use of data from the MAA ERT-naïve subgroup are appropriate for informing long-term outcomes, rather they show the effect of ESA in ERT-naïve patients commencing treatment at older ages'	Extrapolation using the naïve comparison data maximises the evidence used and does not create a false comparison versus the MOR-001 (natural history) cohort. By extrapolating across available data at different age cohorts and accounting for the exit health states by age cohort, a logical extrapolation can be made for the younger under 6 years cohort. Given that there is no perfect comparable approach, we focused our analysis on a naïve comparison. The company rejects the idea of using the CCA methodology as the two cohorts have different baseline ages and severities. This minimises data and creates knowingly incorrect confounded analyses. PSM analysis would be the best pathway forward; however, we do agree that the dataset is too small, and time was not available to explore different PSM approaches for cohorts.	but the totality of evidence is supportive of the conclusions drawn from the treatment-naïve cohort and extrapolations in terms of the long-term effects of elosulfase alfa.

4) Updated CCA results from 3rd December ECD consultation response

Description of problem	Description of proposed amendment	Justification for amendment
Comment 4 (page 5): 1) *'The ERG was unable to find any new CCA results in the company response to the ECD.'* 2) *'The ERG notes that the clinical data for the MAA ERT-naïve subgroup aged under 6 years are not used in the economic model […].'* *3) 'The ERG is concerned that the company's linear regression*	Please find below a response to each issue/comment highlighted by the ERG: 1) Please see the updated CCA results attached to this response (Excel workbook). Results of these analyses informed the 2-year data in the model (based on MOR-001 and treatment-naïve MAA cohort by age group ≥6Y and <6Y). 2) The updated economic model attached to this FAC response uses clinical data for the MAA ERT-naïve subgroup aged under 6 years. The workbook (2021-11-15_Final_Flat_File_Analysis) attached contains the flat file and analysis that was performed and used in the	1) N/A 2) N/A 3) Justification for amendment provided in the proposed amendment comment.

*analyses do not use the CCA approach preferred by the ERG and for the subgroup aged under 6 years the patient numbers in the analyses are extremely low as not all *AIC removed ERT-naïve MAA patients had 6MWT and FVC measures (baseline values reported by company for *CIC removed patients for 6MWT, and *CIC removed patient for FVC). *CIC removed.'*	economic model. The workbook contains worksheets (Analysis 1 to Analysis 8) that include: ▪ Analysis 1: Baseline EQ5D utilities for ≥6Y and <6Y for MAA treatment-naïve cohort ▪ Analysis 2: 1Y & 2Y EQ5D utilities for ≥6Y and <6Y for MAA treatment-naïve cohort ▪ Analysis 3: Baseline weight in treatment-naïve MAA cohort and MOR-001 for ≥6Y and <6Y ▪ Analysis 4: baseline, 1Y and 2Y 6MWT for treatment-naïve MAA cohort and MOR-001 for ≥6Y and <6Y ▪ Analysis 5: 1Y and 2Y FVC for treatment-naïve MAA cohort and MOR-001 for ≥6Y and <6Y ▪ Analysis 6: same as Analysis 4, but presented for visualisation of change at the 3 timepoints (baseline, 1Y & 2Y) for ⩾6Y and <6Y for both MAA treatment-naïve and MOR-001 ▪ Analysis 7: same as Analysis 5, but presented for visualisation of change at the 3 timepoints (baseline, 1Y & 2Y) for ≥6Y and <6Y for both MAA treatment-naïve and MOR-001 ▪ Analysis 8: Transition probabilities from baseline to 1Y and 1Y to 2Y in treatment-naïve MAA cohort and MOR-001 for ≥6Y and <6Y 3) As flagged on several occasions during the technical engagement and in the company's ECD response dated	

	3rd December 2021, the company believes that complete case analysis is not feasible for several analyses that are most important for decision making, namely i) analyses that look at long-term follow-up, and ii) analyses that look at a younger cohort where, as the ERG acknowledges, the sample size is already small. CCA would place further restrictions on sample size as timepoints are extended across multiple years in a small sample of ultra-rare disease patients. The company would argue that it is to be expected that treatments will come to market with trial data collected over a relatively short timeframe that requires extrapolation, and therefore methods such as regression analysis and health state transition models, supplemented and supported by clinical expert opinion, are invariably required to support decision making which takes into account the long-term costs and benefits of treatment. Further details of the regression analysis are as follows: **AIC removed.* Therefore, the company believes that it is preferable to present a linear regression using all available data in this younger population most relevant for decision making to estimate a rate of change (regression coefficient), rather than presenting no analysis for the sake of adhering to CCA methods.	

5) Implementation of ERG's entry and exit thresholds in the updated model

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th></tr>
<tr>
<td>Comments 6, 7, 8, and 9 – 2.6.2. Estimation of WC dependency in the model (pages 10/11):
1) Page 10: 'Nonetheless, upon inspection of the company's updated model, the ERG concluded that the thresholds were not used and that the company's original thresholds were still being used.'
2) Page 11: 'The [TPs used in company's updated model, i.e., ECD response] do not match the TPs used by the ERG in its analysis (or the company's original analysis) and describe a scenario where ESA patients had no progression in year 1 of the model (see Table 6), instead of using the observed data from the MAA. Overall, the ERG is unclear on the source of the estimations provided by the company in their updated analysis […].'</td>
<td>Please find below a response to each issue/comment highlighted by the ERG:
1) As suggested by ERG, the entrance and exit criteria have been changed in the model attached to this response as shown in Table 4 below (as per the ERG review of company's response to the ECD dated 3rd December 2021)
Table 4. Entrance and exit 6MWT thresholds
<table>
<tr><th>Outcome by health state at baseline</th><th>ERG's</th><th>Company's updated model</th></tr>
<tr><td colspan="3">Mean 6MWT at baseline (metres)</td></tr>
<tr><td>No wheelchair use</td><td>*CIC removed</td><td>*CIC removed</td></tr>
<tr><td>Some wheelchair use</td><td>*CIC removed</td><td>*CIC removed</td></tr>
<tr><td>Always use wheelchair</td><td>*CIC removed</td><td>*CIC removed</td></tr>
</table>
2) As stated in the company response dated 3rd December 2021, the transition probabilities in the SOC arm were changed to full MOR-001 dataset (instead of MORCAP1). This was based on the ERG's suggestion of using full MOR-001 dataset, and not MORCAP1. Please see in the updated model attached to this response. The raw data underpinning these transition probabilities are shared as a separate file. It may be noted that there were no patients with transition probabilities for <6Y in the MOR-001, hence transition probability for ≥6Y was used, and the raw</td>
<td>As per ERG's highlighted issues, the company submitted an updated version of the model with the changes implemented. See a summary of all changes implemented in the updated version of the model in comment #9 below.</td>
</tr>
</table>

	data from baseline to Y1 are presented in the table below: *AIC Removed Raw data for transition probabilities from Y1 to Y2 in MOR-001 are: *AIC Removed Similarly, since there were no patients in 'wheelchair dependant' state at baseline in <6Y cohort of MAA Tx-naïve, transition probability for ≥6Y was used, and the raw data from baseline to Y1 is presented in the table below: *AIC Removed All the analysis underpinning the transition probabilities from both MOR-001 and MAA Tx-naive are shown in a separate workbook attached to this response.	

6) Estimation of mortality in the model

Description of problem	Description of proposed amendment	Justification for amendment
Comments 6, 7, 8, and 9 – 2.6.3. Estimation of mortality (page 15): • *'The company stated that, "as per the previous submission, FVC improves by 26.5% in the ex-trial population in the long-term". The ERG is confused by the company's statement as the*	The company has not changed the conservative suggestion of the ERG of 4.23% FVC improvement factor in the model. However, we would highlight that the 4-year clinical trial data MOR-002/100 showed a 16.5% improvement versus baseline over 3 years and all ERTs have shown considerable improvement in FVC.	The company disagrees with the ERG assumption of 4.23% benefit as it only considers 1 year of benefit. All ERTs in MPSs showed continued long-term improvement in FVC, hence the 1-year assumption should be highlighted as knowingly incorrect.

company's original model for this evaluation used an improvement factor of % FVC vs baseline of 16.5% over the course of 3 years of treatment with ESA (taken from the MOR-002/100 trial).' • *'Despite the company's disagreement with the use of the 4.23% improvement factor, the company's updated model used this estimate.'*	The MAA publication from Cleary et al. 2021 showed consistent changes in FVC from baseline of around 16%. *AIC Removed of FVC in the MAA ex-trial cohort presented in the original submission from 11th December 2020. Further analysis could provide more insight on the long-term FVC benefits, but all data shows at least 16% benefit. However, as stated, the model attached with this submission uses 4.23% improvement in FVC, as suggested by ERG.	

7) Utility values used in the model

Description of problem	Description of proposed amendment	Justification for amendment
Comments 10 & 13 (page 16): 1) *'In their response to the ECD, the company accepted that baseline utility data from the MAA should be used to reflect SoC utilities. Nonetheless, the company used different utility values of 0.54, 0.41 and 0.08 for NWC use, SWC use, and WCD, respectively. The ERG is unclear on how these values were estimated.'* 2) *'The company reports using the utility values of 0.84, 0.64 and 0.32 for NWC use, SWC use, and WCD, respectively. Nonetheless,*	Please find below a response to each issue/comment highlighted by the ERG: 1) The analysis underpinning the utility values at baseline from MAA treatment-naïve patients are presented as a separate workbook attached to this response. It may be noted that these values have been taken for ≥6Y olds as no data was available for wheelchair dependant state (please see the separate flat file attached). As suggested in the company submission dated 3rd December 2021, the utility values used in the model (see model attached to this response) for SOC arm (baseline utilities from MAA treatment-naïve) cohort are presented in the table below:	The company has corrected utility values in the attached model to this response as per indicated in the ECD response dated 3rd December 2021. See a summary of all changes implemented in the updated version of the model in comment #9 below.

the ERG's investigation of the model led to the conclusion that the company's updated model does not use these values. Instead, it uses the company's updated SoC utility values with the ESA-specific incremental utility added as per the ERG's calculations after TE.'	*CIC Removed 2) For the ERT arm, the utilities have been updated in the attached model based on utilities for MAA treatment-naïve ≥6Y olds. The analysis underpinning these new utilities are presented as a separate file, and are presented below: *CIC Removed	

8) Body weight used in the model

Description of problem	Description of proposed amendment	Justification for amendment
Comment 11 (page 18): *'Nonetheless, even though the company stated that due to the lower starting age, patients would also be expected to be lighter at baseline, the company did not change the baseline weights used in the ERG's analysis after TE. This resulted in a clinically implausible combination of patients' age and weight (see Table 14). For example, patients with a mean age of 4 years weigh 19.8kg in the NWC category but weight 27kg in the SWC category, when the Montaño et al., paper shows that 4-year-old MPS IVA patients are between 14kg (females) and 15kg (males).'*	The updated weights of 3.6kg, 19.8kg, 27.0kg and 35.2kg have been updated in the attached model to this response for asymptomatic, NWC, SWC and WCD states respectively. Please find a summary of the model changes implemented in this FAC response in comment #9.	The company rechecked the weights for different health states (asymptomatic, NWC, SWC and WCD) in the MAA. And the analysis underpinning these weights are attached. The ERG in its response to the company submission on 3rd December 2021 (ERG review of company's response to the ECD dated December 2021) states on page 18 of 36, table 13 that the weights applied in the model are:

Health state	Avg. age (Y) at baseline	Avg. weight (Kg) at baseline
Asymptomatic	0	3.6

NWC	16	19.8
SWC	14	27.0
WCS	22	35.2
*taken from Montano et al. 2018		

In the same report (ERG review of company's response to the ECD dtd. December 2021) on page 24 of 36, ERG states that:

Therefore, the ERG presents the results of its exploratory analysis using two populations:

- *A population reflecting the baseline characteristics of treatment-naïve patients in the MAA (previously used by the company and by the ERG in their analyses).*

A population with median age at diagnosis of 3 years; WC distribution at baseline of 95% of patients in the NWC category and 5% of asymptomatic patients (based on ERG's clinical expert opinion); and baseline weight of 3.6kg for asymptomatic patients and 13.5kg for NWC patients (according to Montaño et al. 2018). The ERG caveats this scenario analysis with the fact that the treatment effectiveness data associated with ESA did not change in the model.

9) Summary of the new updates done in the attached model to this FAC response (vs. model submitted with the ECD response on 3rd December 2021):

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th></tr>
<tr>
<td>Relates to ERG's highlighted discrepancies/issues in the model from 3rd December 2021.</td>
<td>Please see below a summary of the updates made in the attached model to this FAC check form submission:
1) Use of under 6 years subgroup, wherever possible. Please see the excel workbook for all the analysis by age cohorts (<6Y and ≥6Y)
2) The entry and exit criteria updated to ERG suggested values of 269.04, 210.64 and 27.50 m for NWC, SWC and WCD, respectively
3) The transition probabilities in SOC arm for baseline to Y1 and Y1 to Y2 has been updated based on full MOR-001 dataset
4) The transition probabilities for ERT arm for baseline to Y1 has been updated based on ⩾ 6Y olds (no WCD patients in <6Y at baseline)
5) The utility values have been updated for SOC arm (baseline MAA treatment-naïve) and ERT arm (utility values at 2Y in MAA treatment-naïve)
6) The baseline weights for 4 states (asymptomatic, NWC, SWC and WCD) have been updated to 3.6kg, 19.8kg, 27.0kg and</td>
<td>The company has corrected issues highlighted by the ERG in the attached model to this FAC response form.
For the bullet 6 in the 'Description of proposed amendment' column, we rechecked the weights for different health states (asymptomatic, NWC, SWC and WCD).
The ERG in its response to the company submission on 3rd December 2021 (ERG review of company's response to the ECD dated 3rd December 2021) states on page 18 of 36, table 13 that the weights applied by the ERG in the model are:
<table>
<tr><th>Health state</th><th>Avg. age (Y) at baseline</th><th>Avg. weight (Kg) at baseline</th></tr>
<tr><td>Asymptomatic</td><td>0</td><td>3.6</td></tr>
<tr><td>NWC</td><td>16</td><td>19.8</td></tr>
<tr><td>SWC</td><td>14</td><td>27.0</td></tr>
<tr><td>WCS</td><td>22</td><td>35.2</td></tr>
</table>
</td>
</tr>
</table>

	35.2kg, respectively, representing the actual treatment naïve MAA cohort data **Based on these updates the discounted ICER, undiscounted QALY gain and discounted QALY gain after implementing the above changes in the model are *CIC Removed; *CIC Removed and *CIC Removed respectively at 1.5% discount rates for costs and QALYs.** **The discounted ICER, undiscounted QALY gain and discounted QALY gain after implementing the above changes in the model, and at 3.5% discount rates for costs and QALYs are *CIC Removed; *CIC Removed and *CIC Removed respectively.** **These differences in the ICER vs ERG are driven by:** - **Transition probabilities for SOC (from Y0 to Y1 and Y1 to Y2), as detailed in the response to issue 5 above** - **Transition probabilities for ESA arm (Y0 to Y1), as detailed in the response to issue 5 above** - **Utilities for both SOC and ERT arms, as detailed in the response to issue 7 above** - **The ERG suggested entry and exit criteria of 6MWT have been stayed with in this model** - **The FVC % improvement as suggested by ERG has been stayed with in this model**	*taken from Montano et al. 2018 In the same report (ERG review of company's response to the ECD dated 3rd December 2021) on page 24 of 36, ERG states that: *Therefore, the ERG presents the results of its exploratory analysis using two populations:* ▪ *A population reflecting the baseline characteristics of treatment-naïve patients in the MAA (previously used by the company and by the ERG in their analyses).* ▪ *A population with median age at diagnosis of 3 years; WC distribution at baseline of 95% of patients in the NWC category and 5% of asymptomatic patients (based on ERG's clinical expert opinion); and baseline weight of 3.6kg for asymptomatic patients and 13.5kg for NWC patients (according to Montaño et al. 2018). The ERG caveats this scenario analysis with the fact that the treatment effectiveness data associated with ESA did not change in the model.*

	- **The starting age and weights in different health states have been changed as detailed in the response to issue 8 and 9 above**	

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.

(Please add further lines to the table as necessary)

BMJ TAG

Elosulfase alfa for treating mucopolysaccharidosis type IVA (re-evaluation of highly specialised technologies guidance 2)

ERG addendum post factual accuracy check

January 2022

1 Introduction

This document provides the Evidence Review Group's (ERG's) addendum after the company's factual accuracy check (FAC). The ERG notes that the FAC produced by the company did not report any factual errors on the ERG's report after the first ECD, but instead provided new analyses undertaken by the company and an updated post-FAC economic model.

2 Issues raised by the company

2.1 Comment 2: Relevant data sources for decision-making

2.1.1 Threshold of under 6 years

The company has now provided detail on their rationale for selecting a threshold of age under 6 years old treatment naïve MAA patients in their analyses submitted on 3 December 2021. The company report that the age cut-off of 6 years old was chosen for the following two reasons:

1) Clinical plausibility: The clinical advice the company received suggested that future patients commencing treatment with elosulfase alfa (ESA) will be mostly newly diagnosed patients aged approximately 2-3 years old.
2) Analytical purposes: The company considered the 6-year cut-off in the MAA dataset resulted in, "*a good sample size on which to base meaningful analysis*"; the ERG notes the sample size from the MAA ERT-naïve under 6 years age subgroup is n=[redacted].

The company reported that using a younger age group from the MAA would have lowered the sample size further and limited the feasibility of analysis. Additionally, they highlighted that the MAA ERT-naïve patients who started ESA under the age of 6 had an average age of 3.6 years (standard deviation 0.9). However, the ERG notes that FVC wasn't consistently measured in patients under 5 years and so clinical outcome data for the age subgroup are limited. In addition, the ERG is concerned that the company's analysis of the age subgroups does not comprise complete case analysis (CCA), although the ERG also notes that that it is not feasible to conduct a CCA on the under 6 years age subgroup due to the low number of patients.

2.1.2 Ex-trial patients baseline

The ERG notes that the company [redacted] in the MAA dataset:

- [redacted];
- [redacted]

In summary, [redacted]

The ERG also notes that the company has reported that, "*due to time constraints, the interim data points between the true baseline, clinical trial, and MAA baseline have not been checked and confirmed*". The ERG has been unable to further review the revised dataset due to time constraints. The ERG does, however, note that the company reports that "*These corrections allowed for the analysis of the ex-trial patients to support the extrapolation of patients under 6 years.*", but no further detail is provided as to what this means and from the additional files supplied by the company the ERG is unable to identify where and how the corrected ex-trial patient data has been utilised.

The company reported that EQ-5D was not performed in the ESA clinical trials (with the exception of MOR-004) and that the EQ-5D and MPS HAQ baseline for MAA ex-trial patients are defined as the measure at the first MAA visit which is 4 months. The ERG notes this is a potentially significant discrepancy, for example, if data for baseline 6MWT is used from timepoint 0 months when the wheelchair status assessment is based on MPS HAQ data from 4 months (post-MAA baseline). However, as discussed above, the ERG is unclear how the revised MAA ex-trial patient data has been used by the company.

2.2 Comment 3: Data analysis issues

No additional new data were supplied in response to this issue. The ERG maintains its preference for CCAs, where the same cohort of patients are followed from baseline to each subsequent timepoint. Additionally, the ERG notes that due to the low patient numbers it is not feasible to conduct propensity score matching in addition to using the CCA approach, and so the comparisons between ESA and SoC using the CCA data are limited to naïve comparisons.

2.3 Comment 4: Use of complete case analysis

In the company response to FAC, the company reported that they had supplied updated CCA results, although the ERG notes that the results are supplied only within an Excel data file and that there is limited supporting narrative to explain the analyses. The company reported that the results of the analyses: "*inform the 2-year data in the model (based on MOR-001 and treatment-naïve MAA cohort by age group ≥6Y and <6Y)*". The company also reported that: "*The updated economic model attached to this [the company] FAC response uses clinical data for the MAA ERT-naïve subgroup aged under 6 years.*" The ERG notes that the data analyses provided by the company are as follows:

- Analysis 1: Baseline EQ5D utilities for ≥6Y and <6Y for MAA treatment-naïve cohort;
- Analysis 2: 1Y & 2Y EQ5D utilities for ≥6Y and <6Y for MAA treatment-naïve cohort;
- Analysis 3: Baseline weight in treatment-naïve MAA cohort and MOR-001 for ≥6Y and <6Y;
- Analysis 4: baseline, 1Y and 2Y 6MWT for treatment-naïve MAA cohort and MOR-001 for ≥6Y and <6Y;
- Analysis 5: 1Y and 2Y FVC for treatment-naïve MAA cohort and MOR-001 for ≥6Y and <6Y;
- Analysis 6: same as Analysis 4, but presented for visualisation of change at the 3 timepoints (baseline, 1Y & 2Y) for ≥6Y and <6Y for both MAA treatment-naïve and MOR-001;
- Analysis 7: same as Analysis 5, but presented for visualisation of change at the 3 timepoints (baseline, 1Y & 2Y) for ≥6Y and <6Y for both MAA treatment-naïve and MOR-001; and
- Analysis 8: Transition probabilities from baseline to 1Y and 1Y to 2Y in treatment-naïve MAA cohort and MOR-001 for ≥6Y and <6Y.

The analyses for utilities are discussed further in Section 2.5 but the ERG considers it important to flag that [redacted] and thus the ERG is concerned about the reliability of the results presented by the company. Unfortunately, due to time constraints the ERG has been unable to fully review the data and analyses, but the ERG maintains its view that the ERG 1 year CCA is the most robust analysis given the low number of patients and the absence of patients in some baseline wheelchair categories when a 2 year CCA is used.

The company also provided further details and justification for the regression analysis they conducted in their response to the ECD. The company reported that [redacted] patients were excluded from the analyses due to

[redacted] In the ERG's review of the company's response to the ECD, the ERG conducted a 3-year CCA using the ex-trial MAA data for 6MWT in an attempt to explore the long-term impact of ESA. The ERG used data from the ex-trial MAA patients who had both a baseline 6MWT result reported and a further 6MWT measurement reported at 36 months. However, following review of the amended data for the ex-trial MAA patients provided by the company as part of their FAC response, the ERG has established that the ERG's 3-year CCA results are now flawed. The amended data from the company shows that the baseline values for some of the ex-trial patients was previously incorrectly reported. [redacted] The results of the ERG's 3-year CCA are thus no longer valid and the ERG is also concerned about how the MAA ex-trial patient data is being utilised by the company. The ERG notes there is a statement in the company FAC response to say that the corrections to the ex-trial patient baselines, "*allowed for the analysis of the ex-trial patients to support the extrapolation of patients under 6 years*" but no further detail is provided as to what this means and from the additional files supplied by the company the ERG is unable to identify where and how the ex-trial patient data has been utilised.

The ERG notes that the linear regression analysis files supplied with the company's response to the FAC relate to analyses of the MAA treatment naïve population age under 6 years subgroup and age 6 years and over subgroup. The results presented remain the same as those previously presented by the company in their response to the ECD and discussed by the ERG in the ERG review of the company's response to the ECD (December 2021).

2.4 Comment 6, 7, 8, and 9: Committee's conclusions on economic model

2.4.1.1 Exit and entrance threshold for WC use

As a response to the ECD, the company reported that it had accepted the ERG's estimated entrance and exit thresholds from the different WC categories in the model and reportedly implemented these into the revised model. Nonetheless, upon inspection of the company's updated model, the ERG concluded that the thresholds were not used and that the company's original thresholds were still being used.

In their FAC, the company reported that the model was updated to include the ERG's entrance and exit thresholds. The ERG still found errors in the implementation of the thresholds in the model, therefore, has corrected these in the updated model. The impact of the corrections on the company's updated ICER was negligible and changed the ICERs from [redacted].

2.4.1.2 Change in WC use in first year of the model

The company has not implemented any changes to their post-FAC model with regards to the transition probabilities (TPs) used in the model. However, after the FAC, the ERG understands that the difference between the ERG-preferred TPs and those used by the company in their post-ECD model to be the use of a 1-year CCA or the 2-year CCA, respectively.

The ERG maintains its view that the 1-year CCA TPs derived by the ERG are the most robust source of data to be used in the model (Section 2.3).

2.5 Comment 10 and 13: Utility values used in the model

In their response to TE, the ERG reported the results of its additional investigation of the MAA treatment-naïve baseline utility data, using the maximum available baseline data (i.e. including all patients with baseline EQ-5D and WC data), and arrived at the values [redacted] for NWC; SWC; and WCD, respectively.

The ECD stated that the, "*committee concluded that the ERG's utility values from the treatment-naive subgroup from the MAA were appropriate*".

In their response to the ECD, the company accepted that baseline utility data from the MAA should be used to reflect SoC utilities. Nonetheless, the company used different utility values of

[redacted] for NWC use, SWC use, and WCD, respectively. The ERG was unclear on how these values were estimated.

After the FAC, the company provided the ERG with an Excel file containing the estimation of the utility values used by the company. Upon investigation of the file, the ERG concluded that the [redacted] utilities used by the company for NWC, SWC, and WCD, respectively, were derived by taking a subgroup of patients from the MAA treatment-naïve patients with baseline utility data. This subgroup consisted of patients with an age of 6 years (or older) and patients with a 2-year CCA for EQ-5D data.

The ERG is unclear why the company would exclude patients younger than 6 years from the QoL analysis, although it notes that adding these patients to the analysis has a small impact and generates utilities of [redacted] for NWC, SWC, and WCD, respectively.

Crucially, the need to only include patients with 2-year CCA QoL data is only relevant if the source of data for estimating the utilities in the ESA arm is the MAA dataset. In the limited time available to the ERG to investigate the company's Excel file, the ERG found several inconsistencies in the way the company analysed the data for the ESA arm. For example,
[redacted] (as discussed in Section 2.3) – as an example, the ERG looked at the company's 2-years CCA included in the Excel file, where the company has estimated an utility value for ESA patients in the WCD state of [redacted].
[redacted] This illustrates two key issues in the company's approach: 1) the company's model structure does not allow for the effect of ESA on patients' QoL to be disentangled from the change in WC status. Only an individual patient-level data model would have allowed patients' change in QoL and change in WC status to be followed individually; 2) crucially, the company's approach shows (once more) the lack of a robust relationship between WC use and any of the relevant clinical outcomes for this appraisal.
[redacted] which is in complete conformity with the patient experts' view raised

during the first committee meeting that a WC-based model is not able to accurately measure disease progression and that patients, "*often choose to use wheelchairs to allow independent living rather than simply for mobility issues.*".

Given this, the ERG does not consider that the company's 2-year CCA for the MAA treatment naïve patients is robust enough to inform the utility of life for ESA patients, thus, the ERG preference is to use the more complete baseline utility data in the MAA dataset (as originally done by the ERG) to estimate the utility values for SoC patients, and to estimate the utility for ESA patients by linking the changes in FVC and 6MWT observed in the MAA to the gain in QoL (also included in the ERG's original approach).

Table 1. Patients in the WC category for the QoL analysis of the MAA treatment-naïve population

Patients	Baseline	12 months	24 months
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Average utility ([redacted] patients)	[redacted]	[redacted]	[redacted]

Abbreviations: WC, wheelchair.

Even though the company updated their post-FAC model to include the utility values of [redacted] for NWC use, SWC use, and WCD, respectively, (thus confirming these were the values intended to be used by the company), the ERG disagrees with the use of these values.

2.6 Comment 11: Body weight used in the model

The company has not implemented any changes to their post FAC model with regards to estimating patients' body weight compared to their post ECD model.

2.7 Company's updated cost-effectiveness results

The company reported undertaking several changes to their post-FAC model. The ERG summarised these changes below, together with the validation undertaken for assessing the implementation of the changes in the model (Table 2).

The updated ICERs reported by the company of [redacted] (1.5% discount rate) and [redacted] (3.5% discount rate) corrected to [redacted] and [redacted], respectively (after the ERG correction in the entrance and exit thresholds) only includes two changes: the change in the entrance and exit thresholds to those preferred by the ERG (and the committee) and the change in the utility values used in the ESA arm of the model (which the ERG disagrees with).

Table 2. Changes in the company's post-FAC model

Change reported by the company	Has the change been implemented?	Does the ERG agree with the change?
Use of under 6 years subgroup, wherever possible	As far as the ERG can tell, no subgroup data on clinical outcomes have been implemented in the post FAC model	n/a
The entry and exit criteria were updated to ERG suggested values	Partially. The ERG found an error in the company's implementation of the thresholds in the model, therefore, has corrected this in the updated model. The impact of the correction on the company's updated ICER was negligible	Yes (after the ERG correction)
The TP between WC states in the ESA and SoC arm from baseline to Y1 and Y1 to Y2 have been updated based on the full MOR-001 dataset	Not a change compared to the company's post-ECD model	As discussed in Section 2.5, the ERG disagrees with the use of the company's 2-year CCA of the MAA TP data
The utility values have been updated for the SoC arm and the ERT arm	Partially. Compared to the post-ECD model, the company has only changed the utility values used in the ESA arm (while the utility values for the SoC arm remained unchanged)	No. As discussed in Section 2.5, the ERG disagrees with using the company's MAA 2-year CCA to estimate the utility values for the ESA arm
The baseline weights for asymptomatic, NWC, SWC and WCD have been updated to 3.6kg, 19.8kg, 27.0kg and 35.2kg, respectively, representing the actual treatment naïve MAA cohort data	Not a change compared to the company's post-ECD model	No (see Section 2.8 in the ERG's review of the company's response to ECD)

BMJ TAG

Elosulfase alfa for treating mucopolysaccharidosis type IVA (re-evaluation of highly specialised technologies guidance 2)

ERG addendum post ECM2

January 2022

1 Introduction

This document provides the Evidence Review Group's (ERG's) addendum after the second committee meeting. The analyses provided in this addendum were requested by the NICE technical team.

2 Additional analyses requested by NICE

The NICE technical team requested ICERs that include the committee's preferred assumptions. All the analyses requested by the NICE technical team include the following assumptions:

- Standard of care (SoC) patients that start in the asymptomatic state of the model are assumed to take 3 years to progress to the symptomatic state, while elosulfase alpha (ESA) patients take 9 years to move from asymptomatic to symptomatic;
- Use the ERG's scenario analysis linking mortality to decreased %FVC predicted in the model (with ERG's 1-year complete case analysis [CCA] estimations for FVC decrease taken from the MAA and MOR-001 data);
- The ERG's entrance and exit thresholds from WC categories;
- The ERG's 1-year CCA to estimate transition probabilities;
- The ERG's assumptions for changes in patients' body weight;
- Baseline age of 3 years (based on classic MPS-IVA patients) and baseline distribution of patients across WC categories is 95% in the NWC and 5% are asymptomatic. The ERG caveats this scenario analysis with the fact that the treatment effectiveness data associated with ESA did not change in the model.
- Use a 3.5% discount rate.

The different scenarios requested by NICE (incorporating the assumptions described above) consist of the following:

Scenario 1:

- ESA long term benefit: ERG alternative scenario using MAA data (31% reduction in 6MWT & 4% in FVC compared with SoC)
- Utility source: company utility analysis from the MAA

Scenario 2:

- ESA long term benefit: ERG alternative scenario using MAA data (31% reduction in 6MWT & 4% in FVC compared with SoC)
- Utility source: ERG's utility analysis from the MAA

Scenario 3:

- ESA long term benefit: ERG alternative scenario using MAA data (31% reduction in 6MWT & 4% in FVC compared with SoC)
- Utility source: Hendriksz *et al*. 2014

Table 1. Deterministic results (discounted except for life years gained)

Scenario	Incremental costs	Incremental QALYs	ICER	Undiscounted incremental QALYs
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]

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

The ERG reiterates its concerns around the use of the company's analysis of the utility MAA data and considers that these values are based on incorrect methods of analysis:

- The ERG found several inconsistencies in the way the company analysed the data for the ESA arm:
  - For example, company did not "anchor" their CCA on patients' WC baseline status, but instead on patients' WC status at 2 years– as an example, the ERG looked at the company's 2-years CCA included in the Excel file, where the company has estimated an utility value for ESA patients in the WCD state of [redacted]. The company included 3 patients in their analysis for the WCD state and the fact that the analysis was "anchored" on patients' WC status at 2 years meant that one patient (i.e. 33% of patients) who was in the SWC category at baseline was included in the analysis.
  - The ERG could not replicate the utility value estimated by the company for the SWC category ([redacted]);
  - The company seems to have excluded one patient from the analysis for the NWC state. The company's estimated value is of [redacted] however the ERG estimated the value of [redacted] when all patients are included in the analysis.

- The company's analysis shows the lack of a robust relationship between WC use and any of the relevant clinical outcomes for this appraisal. For several patients in the company's MAA analysis, QoL increased while patients' WC use also increased. Nonetheless, the company's model is centred around having the increase in WC use linked to a decrease in patients' QoL.
- The company's model structure does not allow for the effect of ESA on patients' QoL to be disentangled from the change in WC status if the MAA data are used. Only an individual patient-level data model would have allowed patients' change in QoL and change in WC status to be followed individually.

3 References

1. National Institute for Health and Care Excellence. Final evaluation determination: Elosulfase alfa for treating mucopolysaccharidosis type IVa [HST 2], 2015. Available from: https://www.nice.org.uk/guidance/hst2/documents/final-evaluation-determination-document. Date accessed: 23 Sept 2021.
2. Hendriksz CJ, Lavery C, Coker M, Ucar SK, Jain M, Bell L, et al. Burden of disease in patients with Morquio A syndrome: results from an international patient-reported outcomes survey. *Orphanet J Rare Dis* 2014; **9**: 32.
3. Harmatz PR, Mengel KE, Giugliani R, Valayannopoulos V, Lin SP, Parini R, et al. Longitudinal analysis of endurance and respiratory function from a natural history study of Morquio A syndrome. *Mol Genet Metab* 2015; **114**: 186-94.
4. Montaño AM, Tomatsu S, Gottesman GS, Smith M, Orii T. International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. *J Inherit Metab Dis* 2007; **30**: 165-74.
5. Neas LM, Schwartz J. Pulmonary function levels as predictors of mortality in a national sample of US adults. *Am J Epidemiol* 1998; **147**: 1011-8.
6. Montaño AM, Tomatsu S, Brusius A, Smith M, Orii T. Growth charts for patients affected with Morquio A disease. *Am J Med Genet A* 2008; **146A**: 1286-95.