National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

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

Response to consultee and commentator comments on the draft remit and draft scope

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	The MPS Society	This topic is coming to the end of the MAA agreement and therefore has to be reviewed again by NICE. The current HST review is the only option currently available.	Comment noted. This re-evaluation has been scheduled into the NICE highly specialised technologies programme. No action required.
	Genetic Alliance UK	It is appropriate that this review be carried out in a timely fashion.	Comment noted. This re-evaluation has been scheduled into the NICE highly specialised technologies programme. No action required.
	Birmingham Women's and Children's Hospitals NHS Trust	The remit is mostly clear. The remit may better reflect "avoidance of disbenefit" as well as "benefits" of therapy as the unanswered questions from the original HST assessment was the long-term real life maintenance of the benefits seen in clinical trials. No additional benefits/outcomes were measured in the managed access agreement.	Thank you for your comment. The remit of the scope is kept broad and any avoidance of disbenefit is likely to be explored within the QALY calculation during the appraisal process. No changes to the scope required.

Issue date: December 2019

Section	Consultees	Comments	Action
	Great Ormond Street Hospital NHS Foundation Trust	Remit is appropriate, i.e. to evaluate benefits and costs of elosulfase alfa for treating MPS IVa, within its marketing authorisation, for national commissioning by NHS England. This should be in line with the additional evidence collected through the managed access agreement process that has "[explored] costs and benefits in routine clinical practice" (HST2 Key Conclusion).	Comment noted. This is a re-evaluation of highly specialised technology guidance 2. The committee will consider all available evidence, including the evidence submitted originally and new evidence since that time, including evidence collected through the managed access agreement (MAA). No action required.
	NHS England and NHS Improvement	This referral to the NICE HST programme is appropriate, NHS England, NICE, the drug company, the patient group and the clinical community have been engaged in a Managed Access Agreement for this drug since December 2015.	Comment noted. This re-evaluation has been scheduled into the NICE highly specialised technologies programme. No action required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	Remit is appropriate.	Comment noted. No action required.
Wording	The MPS Society	Appropriate.	Comment noted. No action required.

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	Genetic Alliance UK	The draft scope differs only very slightly from that for a new product. This is concerning, as the review of an HST decision should follow a different procedure than that to make an original decision. It is concerning that this process is being carried out without detailed planning of a protocol to carry out this work. It is not acceptable to build a process for review of products available through managed access agreements (MAAs) via the evaluation of the first. MAAs are different and have been designed differently. To develop policy during this evaluation would likely create inequities that would harm or benefit future evaluations. This could exacerbate inequities in the rare disease medicine access environment.	Thank you for your comment. This is a re-evaluation of highly specialised technology guidance 2. The committee will consider all available evidence, including the evidence submitted originally and new evidence since that time, including evidence collected through the managed access agreement (MAA). The Interim Process and Methods of the Highly Specialised Technologies Programme (2017) will be followed where appropriate. No action required.
	Birmingham Women's and Children's Hospitals NHS Trust	See above – I would recommend the remit is to "evaluate the medium-term maintenance of benefits".	Thank you for your comment. The remit of the scope is kept broad and "medium-term maintenance of benefits" is a term that may not be consistently interpreted by everyone. No changes to the scope required.
	Great Ormond Street Hospital NHS Foundation Trust	Wording is appropriate.	Comment noted. No action required.

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	NHS England and NHS Improvement	The wording in relation to the remit does reflect the clinical and cost effectiveness issues.	Comment noted. No action required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	Wording is appropriate.	Comment noted. No action required.
Timing Issues	The MPS Society	MAA and current reimbursement arrangement arrangements cease on 15 December 2020.	Thank you for your comment. This re-evaluation has been scheduled into the NICE highly specialised technologies programme. The process for a HST re-evaluation following a period of managed access has been specifically designed to produce timely guidance before the MAA expiry date. Stakeholders will be kept informed throughout this process. No action required.
	Genetic Alliance UK	This is an existing treatment. This question feels inappropriate.	Comment noted. No action required.

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	Birmingham Women's and Children's Hospitals NHS Trust	This review needs to be completed as planned by December 2020. Patients are currently in receipt of ERT and in paediatrics this is often through central venous catheters. The planning of placing/replacing such catheters will be highly dependent on the likelihood of continued need for them (it would be unethical to put a child through a general anaesthetic for a defunct port if a drug were to be withheld. Some of this cohort of patients have already experienced delays in negotiations between Biomarin and NHS England (leading to suspension of treatment for a while) and a repeat of this very poor experience must be avoided.	Thank you for your comment. This re-evaluation has been scheduled into the NICE highly specialised technologies programme. The process for a HST re-evaluation following a period of managed access has been specifically designed to produce timely guidance before the MAA expiry date. Stakeholders will be kept informed throughout this process. No action required.
	Great Ormond Street Hospital NHS Foundation Trust	Patients are currently receiving regular elosulfase alfa infusions and many have long term indwelling central venous access devices to facilitate this. It is imperative that guidance is concluded in a timely manner so that patients, carers and families, and healthcare professionals, know whether treatment will continue beyond the end of the MAA in December 2020. If cost-negotiations with the company are expected there must be time in the process to account for this, and if this will not be concluded by December 2020 there must be an interim agreement and process by which treatment can continue.	Thank you for your comment. This re-evaluation has been scheduled into the NICE highly specialised technologies programme. The process for a HST re-evaluation following a period of managed access has been specifically designed to produce timely guidance before the MAA expiry date. Stakeholders will be kept informed throughout this process. No action required.

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	NHS England and NHS Improvement	This is an urgent evaluation, the current MAA is due to expire in December 2020.	Thank you for your comment. This re-evaluation has been scheduled into the NICE highly specialised technologies programme. The process for a HST re-evaluation following a period of managed access has been specifically designed to produce timely guidance before the MAA expiry date. Stakeholders will be kept informed throughout this process. No action required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	Patients are currently receiving regular elosulfase alfa infusions and many (in particular children and adolescents) have long term indwelling central venous access devices to facilitate this. It is imperative that guidance is concluded in a timely manner so that patients, carers and families, and healthcare professionals, know whether or not treatment will continue beyond the end of the MAA in December 2020. If cost-negotiations with the company are expected there must be time in the process to account for this, and if this will not be concluded by December 2020 there should be an interim agreement and process by which treatment can continue, while a final decision is awaited. If delays occur, then regular updates should be communicated to all stakeholders.	Thank you for your comment. This re-evaluation has been scheduled into the NICE highly specialised technologies programme. The process for a HST re-evaluation following a period of managed access has been specifically designed to produce timely guidance before the MAA expiry date. Stakeholders will be kept informed throughout this process. No action required.

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Additional comments on the draft remit	The MPS Society	We have concerns over the current scheduling timelines. The proposed date of the committee decision is November 2020. This gives very little time should the result be negative or if it is to be referred to a 2nd committee. What is the mitigation plan should discussions be ongoing post the 15 December 2020?	Thank you for your comment. This re-evaluation has been scheduled into the NICE highly specialised technologies programme. The process for a HST re-evaluation following a period of managed access has been specifically designed to produce timely guidance before the MAA expiry date. Stakeholders will be kept informed throughout this process. No action required.

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	Genetic Alliance UK	This consultation appears to be happening before detailed plans have been made as to how it might be delivered – as evidenced by the lack of bespoke consultation materials. The review of HST decisions (with or without MAAs) will be become a part of the work of NICE in the future. It is only fair to the whole rare disease community that this process be designed in consultation with the whole community. It is unfair to the mucopolysaccharidosis type IVa community to treat this evaluation as a pilot. We propose that this planning be done so that there is a transparent pathway, process and method for reviews. This should be developed with the multistakeholder community, and should include: - timelines for review so that patient communities with existing MAAs can begin to plan for the assessment. - clear rules about where new evidence might be included – we would suggest a broad scope for this - under what circumstances a change to the existing decision might be made It would then be fair to issue a bespoke scoping document that is built to gather evidence for an established decision-making pathway.	Thank you for your comment. This is a re-evaluation of highly specialised technology guidance 2. The committee will consider all available evidence, including the evidence submitted originally and new evidence since that time, including evidence collected through the managed access agreement (MAA). The Interim Process and Methods of the Highly Specialised Technologies Programme (2017) will be followed where appropriate. No action required.
	Birmingham Women's and Children's Hospitals NHS Trust	No comment.	No action required.

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	Great Ormond Street Hospital NHS Foundation Trust	No comment.	No action required.
	NHS England and NHS Improvement	No comment.	No action required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	No comments.	No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	The MPS Society	Total number known to the MPS Society is 120.	Thank you for your comment. The background section of the scope has been updated to reflect this value.
	Genetic Alliance UK	No comment.	No action required.
	Birmingham Women's and Children's Hospitals NHS Trust	The background information is mostly accurate. It might be more complete to add that in the most severe cases, surgery (especially to the neck) is essential to decelerate the progression of the disease and without it, four limb paralysis with complete dependence is expected. Surgery will be required even in those receiving other forms of treatment, and surgeries tend to be at	Thank you for your comment. The background section of the scope is intended to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive.

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		higher risk of complications due to the multisystem and multi-level nature of the disease. Exceptionally families may choose palliative care for their child (especially if diagnosis is late with established long term complications). I would also highlight that the progressiveness of the disorder means that even in attenuated cases, loss of mobility over time is not unexpected and wheelchair use at some point in the disease course is the norm.	No changes to the scope required.
	Great Ormond Street Hospital NHS Foundation Trust	The background information is accurate in its description of the disorder, the epidemiology and multidisciplinary treatment including with elosulfase alfa.	Comment noted. No action required.
	NHS England and NHS Improvement	The background information is accurate. Additional information on the heterogeneity of the condition and mortality rates would be a useful addition.	Thank you for your comment. The background section of the scope is intended to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive. No changes to the scope required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	The background is accurate.	Comment noted. No action required.
The technology/ intervention	The MPS Society	Appropriate.	Comment noted. No action required.
	Genetic Alliance UK	No comment.	No action required.
	Birmingham Women's and Children's	The description is accurate. I would mention that the drug is administered by IV infusion, lasting approximately 4hrs, every	Comment noted. The technology section aims to

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	Hospitals NHS Trust	week (because other enzyme therapies are administered fortnightly and clinical trials established firmly that fortnightly treatment with elosulfase alfa was ineffective. Also some enzyme therapies are able to be infused much more quickly). It may or may not be necessary to add that infusion may be through peripheral or indwelling central venous catheters (the latter more likely in children and bringing with them additional complications and burdens).	provide a brief overview of the technology and does not include information about dose frequency. No changes to the scope required.
	Great Ormond Street Hospital NHS Foundation Trust	The description is accurate. It may be helpful to mention that treatment is be weekly intravenous infusion and treatment would be expected to be life-long.	Thank you for your comment. The technology section aims to provide a brief overview of the technology and does not include information about dose frequency and duration of treatment. No changes to scope required.
	NHS England and NHS Improvement	This information is accurate.	No action needed.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	The description is accurate.	No action needed.
Population	The MPS Society	Appropriate	No action needed.
	Genetic Alliance UK	No comment	No action needed.
	Birmingham Women's and Children's Hospitals NHS Trust	Yes. Elosulfase alfa is used for all people with MPS IVa. It is true of most enzyme therapies that the greatest benefit is	Thank you for your comments. The other considerations section of the scope has been updated to include subgroup

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		achieved when treatment is started early and this is particularly true for conditions involving the skeletal system. However the majority of patients in the pivotal clinical trials were older (with age of 5yrs being a minimum inclusion criterion by which time skeletal disease was well established in many patients). The effect of treatment in patients starting before the age of 5yrs has been published in only a small number of patients on defined substudies with limited follow-up (eg Jones et al Pediatr Res. 2015 Dec; 78(6): 717–722.) Therefore, the longer- term follow-up of patients starting treatment early (before the age of 5yrs) is a group that merits separate analysis and comment. It is also well recognised that patients with MPS IVa lie on a clinical spectrum but that this spectrum is not a uniform continuum of severities. Founder genetic effects have led to discrete subpopulations of patients with particularly severe (eg homozygous for G116V) and unusually attenuated phenotypes in certain ethnicities. Whilst the review might not be robust enough to analyse such groups separately it would be a worthwhile exploratory aim to see if these subgroups.	analysis by age if evidence allows.
	Great Ormond Street Hospital NHS Foundation Trust	Elosulfase alfa would be considered for all people with MPS IVa. Treatment initiated earlier (i.e. at a younger age) is expected to derive greater benefit (Akyol et al Orphanet J Rare Dis 2019;14:137) and in considering evidence of efficacy it would be appropriate to consider if evidence from younger cohorts of patients is available.	Thank you for your comments. The other considerations section of the scope has been updated to include subgroup analysis by age if evidence allows.
	NHS England and NHS Improvement	The population is appropriately defined.	Comment noted. No action required.
	University College	Elosulfase alfa would be considered for all individuals with MPS	Thank you for your comments.

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	London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	IVa. Treatment initiated earlier (i.e. at a younger age) is expected to derive greater benefit (Akyol et al Orphanet J Rare Dis 2019;14:137) and in considering evidence of efficacy it would be appropriate to consider if evidence from younger cohorts of patients is available.	The other considerations section of the scope has been updated to include subgroup analysis by age if evidence allows.
Comparators	The MPS Society	Yes.	Comment noted. No action required.
	Genetic Alliance UK	No comment.	No action required.
	Birmingham Women's and Children's Hospitals NHS Trust	The comparator for elosulfase alfa is indeed established clinical management without elosulfase alfa. This is, however, not so easy to define. Currently the majority of children with MPS IVa in England are being treated with elosulfase alfa. The untreated patients comprise patients with more severe disease burdens who were deemed not appropriate to treat, and patients who had already attempted treatment on clinical trials and had withdrawn due to adverse events or failure of efficacy. These patients are not, therefore, an appropriate comparator. However historical outcomes before the introduction of elosulfase alfa (such as those described by Harmatz et al Molecular Genetics and Metabolism Volume 109, Issue 1, May 2013, 54-61) may be more appropriate.	Thank you for your comments. Following the consultation exercise, it was concluded that established clinical management is the appropriate comparator. No changes to the scope required.
	Great Ormond Street Hospital NHS Foundation Trust	The appropriate comparator for elosulfase alfa is, as stated, established clinical management without elosulfase alfa. However, in the paediatric population the majority of patients are now treated with elosulfase alfa and those who are not treated with elosulfase alfa usually have much more advanced disease and have therefore declined treatment due to lack of expected benefit.	Thank you for your comments. No changes to the scope required.

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	NHS England and NHS Improvement	The comparator is appropriate.	Comment noted. No action required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	The appropriate comparator for elosulfase alfa is established clinical management without elosulfase alfa. However, the majority of patients are now treated with elosulfase alfa and those who are not treated with elosulfase alfa usually have much more advanced disease and have therefore declined treatment due to lack of expected benefit.	Thank you for your comments. No changes to the scope required.
Outcomes	The MPS Society	The current list was taken from the clinical trial data. Not all of this data was collected within the MAA. Some may have been collected through MARS **Measures monitored through MAA** Endurance and mobility – captured through 6MWT or 25ft ambulation test Respiratory and cardiac function Growth –weight Pain Health related Q of L (both patient and carer reported) **Not collected through MAA** Development Fatigue (only anecdotal) Adverse effects of treatment – only those relating to patients coming off treatment are discussed at MAA meetings **Potentially through MARS** Vision and hearing Sleep apnoea Adverse events	Thank you for comments. This is a re-evaluation of highly specialised technology guidance 2. The committee will consider all available evidence, including the evidence submitted originally and new evidence since that time, including evidence collected through the managed access agreement (MAA). The outcomes section of the scope has been updated to include the other outcomes collected in the managed access agreement, in addition to those already included in the scope: neutralising antibodies and urinary keratan sulfate.

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		Not included within suggested outcomes, but collected during the MAA are: UGAGs Antibodies **Additional information to be considered:** In conjunction with the MAA Q of L data, MPS Commercial have been collating PRO data. This should be considered when reviewing the above clinical and Q of L data.	
	Genetic Alliance UK	No comment.	No action required.
	Birmingham Women's and Children's Hospitals NHS Trust	The list of outcome measures are all relevant to MPS IVa but the review will be constrained by the fact that the managed access agreement specified only a limited number of outcome measures for routine collection and therefore a complete data set will only be achieved for those measures. These included: • 6-minute walk test (for endurance) • FEV1 and FVC for respiratory function • Ejection fraction for cardiac function • Urine keratan sulfate • Quality of life scores including the MPS-HAQ, Beck Depression Score and BRIEF Pain Inventory Some patients may have been recruited to the MARS registry and additional data on some of these measures (such as vision, hearing, sleep apnoea, growth) may be available for those patients but this will be incomplete. Some of the listed outcome measures (such as development and fatigue) were not specifically measured/captured in either setting and therefore cannot be assessed in a meaningful way from this cohort.	Thank you for comments. This is a re-evaluation of highly specialised technology guidance 2. The committee will consider all available evidence, including the evidence submitted originally and new evidence since that time, including evidence collected through the managed access agreement (MAA). The outcomes section of the scope has been updated to include the other outcomes collected in the managed access agreement, in addition to those already included in the scope: neutralising antibodies and urinary keratan sulfate.

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		The specific choice of outcome measures was made based on those used for clinical trials and not necessarily because they were the most appropriate clinical outcome measure for this disease. The review should make allowances for an assessment of the validity of those measures and for professional opinion regarding their validity. For example cardiac ejection fraction may not be the most appropriate indicator of "cardiac function" in these patients.	
	Great Ormond Street Hospital NHS Foundation Trust	The outcome measures suggested are broadly appropriate for assessing disease progression in patients with MPS IVa, however: (a) not all the outcome measures listed were included in the Managed Access Agreement as specific measures to be assessed and so the MAA process in itself will not have generated additional information about these domains, (b) not all of the outcome measures would be expected to be significantly changed by enzyme replacement therapy (from wider experience in other MPS disorders treated with Enzyme Replacement Therapy, e.g. vision, or established cardiac valvular disease), and (c) some of the measures suggested are not tightly defined (e.g. "cardiac function" rather than a specific measure of cardiac function). The managed access agreement defined specific measures to be assessed as markers of treatment efficacy (i.e. Ejection Fraction for cardiac function, Forced Vital Capacity and Forced Expired Volume in 1 second (FEV1) for respiratory function, 6Minute walk test for endurance/overall function, urine keratan sulfate concentration together with quality of life measures) and for each	Thank you for comments. This is a re-evaluation of highly specialised technology guidance 2. The committee will consider all available evidence, including the evidence submitted originally and new evidence since that time, including evidence collected through the managed access agreement (MAA). The outcomes section of the scope has been updated to include the other outcomes collected in the managed access agreement, in addition to those already included in the scope: neutralising antibodies and urinary keratan sulfate.

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		outcome measure a defined “success criterion”. It will be important that these measures (amongst others) are reviewed, and whether patients achieved the treatment success targets and specified under the managed access agreement to demonstrate efficacy of treatment “in routine clinical practice”. Again, the managed access agreement parameters did **not** include measures for all the Outcomes specified in the draft Scope document (I,e, growth and development, vision, hearing) and was limited in the parameters being collated for some of the other outcome domains (e.g. pain assessment).	
	NHS England and NHS Improvement	The outcomes measures reflect those measure in the clinical trials and the MAA.	Thank you for your comment. No action required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	The outcome measures suggested are broadly appropriate for assessing disease progression in patients with MPS Iva and the managed access agreement also defined specific measures to be assessed to demonstrate efficacy of treatment “in routine clinical practice”. It is worth noting that: (a) not all the outcome measures listed were included in the Managed Access Agreement as specific measures to be assessed and so the MAA process in itself will not have generated additional information about these domains. Examples of measures not included in the MAA include: vision, hearing, growth, development, and sleep apnoea. (b) not all of the outcome measures would be expected to be significantly changed by enzyme replacement therapy (e.g. vision, or established cardiac valvular disease).	Thank you for comments. This is a re-evaluation of highly specialised technology guidance 2. The committee will consider all available evidence, including the evidence submitted originally and new evidence since that time, including evidence collected through the managed access agreement (MAA). The outcomes section of the scope has been updated to include the other outcomes collected in the managed access agreement, in addition to those already

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			included in the scope: neutralising antibodies and urinary keratan sulfate.
Equality	The MPS Society	New patients have only been reviewed and assessed by the MAA criteria, although other data may have been inputted into the MARS registry. The MAA criteria was designed to address the uncertainties of the committee and this has been rigorously collected and reviewed on a 6 monthly basis for the duration of the MAA. Any concerns or errors in data capture has been discussed with all stakeholders including NHSE and NICE and any errors or gaps in the data should have been raised at the time. Patients in receipt of treatment continue to meet the expected criteria within the MAA. It is therefore unclear what remaining uncertainties the committee will be reviewing? Without a clear understanding of the evidence required, how can the patient organisation ensure that we will provide what is needed and safeguard against the patient group being disadvantaged due to missing evidence. We have concerns around possible timescale failure resulting in patients coming off of treatment before the process review has concluded.	Thank you for comments. This is a re-evaluation of highly specialised technology guidance 2. The committee will consider all available evidence, including the evidence submitted originally and new evidence since that time, including evidence collected through the managed access agreement (MAA). The Interim Process and Methods of the Highly Specialised Technologies Programme (2017) will be followed where appropriate. The process for a HST re-evaluation following a period of managed access has been specifically designed to produce timely guidance before the MAA expiry date. Stakeholders will be kept informed throughout this process. No action required.
	Genetic Alliance UK	No comments.	No action required.

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	Birmingham Women's and Children's Hospitals NHS Trust	My only comment in this regard is that if it is proposed that subgroups of patients with MPS IVa are analysed for differences in their response to elosulfase alfa this may have a disproportionate effect on certain ethnicities. For example, patients homozygous for the G116V mutation tend to have a more severe phenotype and these patients all originate from the Kashmir area of Pakistan. Any separate consideration of this group must be careful to address this as a genotype-based analysis (which may be lawful and scientific) and not a purely ethnicity-based one (which would be unlawful).	Thank you for you comments. The committee will consider whether its recommendations could have a differential impact on people with protected chrematistics covered by equality legislation (that is patients homozygous for the G116V mutation and age). No changes to the scope required.
	Great Ormond Street Hospital NHS Foundation Trust	No specific comments.	No action required.
	NHS England and NHS Improvement	The remit meets the requirements of equality legislation.	No action required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	No specific comments.	No action required.
Other considerations	The MPS Society	It should be recognised that some patients clinical outcomes on the MAA are measured against the baseline assessments performed at the commencement of a clinical trial, whereas new patients clinical baselines were taken at entry to the MAA.	Thank you for your comments. The committee will consider all aspects of clinical data in the re-evaluation of elosulfase alfa. No changes to the scope required.
	Genetic Alliance UK	No comment.	No action required.

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	Birmingham Women's and Children's Hospitals NHS Trust	No comment.	No action required.
	Great Ormond Street Hospital NHS Foundation Trust	The scope document mentions "Extent and nature of current treatment options". It is important to note that there is no other efficacious disease modifying treatment for MPS IVa. The scope mentions "staffing and infrastructure requirements including training and planning for expertise". It should be noted that the successful delivery of the treatment has been demonstrated by the managed access agreement.	Thank you for your comments. The company submission can expand on the delivery of the treatment during the period of managed access and also the lack of other treatment options as appropriate. No changes to the scope required.
	NHS England and NHS Improvement	No comments.	No action required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	The scope document mentions "Extent and nature of current treatment options". It is important to note that there is no other specific disease modifying treatment for MPS IVa. The scope mentions "staffing and infrastructure requirements including training and planning for expertise". The successful delivery of the treatment has already been demonstrated by the managed access agreement over a number of years.	Thank you for your comments. No changes to the scope required.
Innovation	The MPS Society	Yes, the clinical data, MAA data and PRO's show the significant and substantial health benefits to patients.	Thank you for your comment. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are

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			unlikely to be included in the QALY calculation during assessment. No action required.
	Genetic Alliance UK	No comment.	No action required.
	Birmingham Women's and Children's Hospitals NHS Trust	I do consider elosulfase alfa to be an innovative "Step Change" in the management of MPS IVa. It is the only successful disease modifying therapy – all existing treatment options are symptomatic only. HSCT has not proven widely effective in this condition.	Thank you for your comment. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during assessment and how it might improve the way that current need is met. No action required.
	Great Ormond Street Hospital NHS Foundation Trust	This is a Step-change treatment in the management of MPS IVa, and is the first (and currently only) specific disease modifying treatment that aims to correct the underlying biochemical defect in this disorder.	Thank you for your comment. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during assessment and how it might improve the way that current

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			need is met. No action required.
	NHS England and NHS Improvement	The technology is innovative. Current treatment for this patient group is best supportive care.	Thank you for your comment. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during assessment and how it might improve the way that current need is met. No action required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	This is the first (and currently only) specific disease modifying treatment that aims to correct the underlying biochemical defect and improve long-term outcome in this disorder.	Thank you for your comment. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during assessment and how it might improve the way that current need is met. No action required.
Questions for	The MPS Society	What weight will be given to MAA data compared to clinical trial	Thank you for your comment.

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consultation: Have there been any changes to the management of mucopolysaccharidosis type IVA or the commissioning of services that would affect the proposed scope for this evaluation? • Have all relevant comparators for elosulfase alfa been included in the scope? How is established clinical management without elosulfase alfa defined? • Are the outcomes listed appropriate? • Are there any subgroups of people in whom		data and other evidence reviewed during the first HST? Patients currently enrolled on the MAA are responding and meeting the expected outcomes of the MAA. The MAA outcomes are not indicating that there are any sub groups showing greater or lesser benefit.	This is a re-evaluation of highly specialised technology guidance 2. The committee will consider all available evidence, including the evidence submitted originally and new evidence since that time, including evidence collected through the managed access agreement (MAA). The other considerations section of the scope has been updated to include subgroup analysis by genotype and age should be considered if evidence allows.
	Genetic Alliance UK	No comments.	No action required.
	Birmingham Women's and Children's Hospitals NHS Trust	***Q:*** *Have there been any changes to the management of mucopolysaccharidosis type IVA or the commissioning of services that would affect the proposed scope for this evaluation?* **A:** No – other than the widespread acceptance of elosulfase alfa for nationally/insurance funded therapy in many parts of the World. ***Q:*** *Have all relevant comparators for elosulfase alfa been included in the scope? How is established clinical management without elosulfase alfa defined?* **A:** See above in comparator section for comments on this. Historical published cohorts probably give the best numerical	Comment noted. No change to scope required. Comment noted. No changes to the scope required.

Section	Consultees	Comments	Action
elosulfase alfa is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?		data for a comparative analysis. The definition of established clinical management in England would be that patients are managed in one of the designated centres for Lysosomal Storage Disorders in England. ***Q:*** *Are the outcomes listed appropriate?* **A:** See above. **Q:** *Are there any subgroups of people in whom elosulfase alfa is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?* **A**: See above.	No action required. No action required.
	Great Ormond Street Hospital NHS Foundation Trust	***Q:*** *Have there been any changes to the management of mucopolysaccharidosis type IVA or the commissioning of services that would affect the proposed scope for this evaluation?* **A:** No. ***Q:*** *Have all relevant comparators for elosulfase alfa been included in the scope? How is established clinical management without elosulfase alfa defined?* **A:** Comparison to those not treated with elosulfase alfa but receiving standard of care is the relevant comparator, but within the managed access agreement the vast majority of patients eligible for elosulfase alfa have opted to receive this. Data from patients who have discontinued treatment would also be important to consider.	Comment noted. No changes to the scope required. Thank you for your comments. No changes to the scope required.

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		"Established clinical management without elosulfase alfa" is defined by the multidisciplinary management provided at specialist paediatric or adult centres through the Highly Specialised LSD Service in England. Recent international consensus guidelines on management including use of elosulfase alfa have been recently published (Akyol et al, Orphanet J Rare Dis 2019;14:137). ***Q**: Are the outcomes listed appropriate?* **A:** See comments above. ***Q:** Are there any subgroups of people in whom elosulfase alfa is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?* **A:** As discussed above, greater clinical benefit is expected if treatment is initiated at a younger age (Akyol et al, Orphanet J Rare Dis 2019;14:137) although evidence shows it is of benefit in older patients as well. There are some subgroups with most severe forms or most advanced disease in whom benefit may be less.	No action required. Thank you for your comments. The other considerations section of the scope has been updated to include subgroup analysis by genotype and age should be considered if evidence allows.
	NHS England and NHS Improvement	No comment.	No action required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	***Q:** Have there been any changes to the management of mucopolysaccharidosis type IVA or the commissioning of services that would affect the proposed scope for this evaluation?* **A:** No ***Q**: Have all relevant comparators for elosulfase alfa been*	No action required. Thank your comments. No

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		included in the scope? How is established clinical management without elosulfase alfa defined? **A:** Comparison to those not treated with elosulfase alfa but receiving standard of care is the relevant comparator, but within the managed access agreement the vast majority of patients eligible for elosulfase alfa have opted to receive this. Data from the small number of patients who have discontinued treatment would also be important to consider. "Established clinical management without elosulfase alfa" is defined by the multidisciplinary management provided at specialist paediatric or adult centres through the Highly Specialised LSD Service in England. Recent international consensus guidelines on management including use of elosulfase alfa have been recently published (Akyol et al, Orphanet J Rare Dis 2019;14:137). ***Q:** Are the outcomes listed appropriate?* **A:** See comments above ***Q:** Are there any subgroups of people in whom elosulfase alfa is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?* **A:** Greater clinical benefit is expected if treatment is initiated at a younger age (Akyol et al, Orphanet J Rare Dis 2019;14:137) although evidence shows it is of benefit in older patients as well. There are some subgroups with most severe forms or most advanced disease in whom the benefit may be less.	changes to the scope required. No action required. Thank you for your comments. The other considerations section of the scope has been updated to include subgroup analysis by genotype and age should be considered if evidence allows. No changes to the scope required.
Additional	The MPS Society	The review process is still unclear with conflicting advice being	Thank you for comments. This

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comments on the draft scope		given on how the process will be conducted and how and what evidence is to be reviewed. What is the risk assessment and management plan for this review? It is not a typical HST review. When do we expect to receive the terms of engagement document? We are still awaiting information on what the contingency plan will be if a decision is not met by the 15 December 2020.	is a re-evaluation of highly specialised technology guidance 2. The committee will consider all available evidence, including the evidence submitted originally and new evidence since that time, including evidence collected through the managed access agreement (MAA). The Interim Process and Methods of the Highly Specialised Technologies Programme (2017) will be followed where appropriate. The process for a HST re-evaluation following a period of managed access has been specifically designed to produce timely guidance before the MAA expiry date. Stakeholders will be kept informed throughout this process. No action required.
	Genetic Alliance UK	No comment.	No action required.
	Birmingham Women's and Children's Hospitals NHS Trust	No comment.	No action required.
	Great Ormond Street	No comment.	No action required.

Section	Consultees	Comments	Action
	Hospital NHS Foundation Trust		
	NHS England and NHS Improvement	No comment.	No action required.
	University College London Hospitals NHS Foundation Trust – Charles Dent Metabolic Unit	No comments.	No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None