National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Human alpha 1-proteinase inhibitor for treating emphysema

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	CSL Behring	Yes. A NICE HST process is the most appropriate mechanism to assess human alpha1-proteinase inhibitor (Respreeza) as a maintenance treatment for emphysema in patients with severe alpha1-proteinase inhibitor (A1PI) deficiency for the following reasons: 1. CSL Behring believes Respreeza as a therapeutic protein should be subject to an appropriate appraisal for its use within the NHS 2. The NICE HST process is the most effective mechanism to assess therapeutic proteins such as Respreeza. The manufacturing costs for Respreeza are very high, making it expensive to produce, not only due to being a protein, rather than a small molecule, but also as grams of protein, rather than milligrams, are required 3. The NICE HST process is an adequate mechanism to assess medicines for small patient populations/orphan diseases because: • Respreeza represents a step change in significantly reducing the irreversible loss of lung tissue and slowing the progression of emphysema. It is the only licensed therapy to demonstrate	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		disease-modifying effect in patients with A1PI deficiency • To slow the progression of irreversible damage to the lungs, it is important to treat this disease early, which means survival benefits accrue later in life and are heavily discounted, significantly reducing their value in today's terms 4. Respreeza meets all seven of the criteria for appraisal using the NICE HST process: • The target patient group is small enough that treatment will be concentrated in very few specialised centres • The target patient group is distinct for clinical reasons in that they have documented severe A1PI deficiency and evidence of progressive lung disease • The condition is chronic and severely disabling as it is progressive and ultimately leads to death or lung transplantation • The technology is expected to be used exclusively in the context of a highly specialised service – which is currently under development by NHS England • The technology is likely to have a very high acquisition cost due to being a protein and required in large quantities • The technology has the potential for life long use because this disease is a long term condition based on patients' missing a protein inhibitor of a destructive enzyme, and should be treated in the same way as enzyme replacement therapies (ERTs) The need for national commissioning is significant due to the specialised nature and limited expertise	Comment noted. No action required.
	Alpha-1 UK Support Group	Yes, we consider it appropriate to refer "Human alpha1-proteinase inhibitor for treating emphysema" to NICE Highly Specialised Technologies	Comment noted. No action required.

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		Evaluation.	
	Association of Respiratory Nurse Specialists	Yes, this is an under researched area that would benefit from further evaluation although it is worth noting it effects a small number of people and it is unclear at what stage treatment would be considered, alongside how this population will be identified.	Comment noted. No action required.
	Birmingham University	Yes highly and important for a rare disease where it is the only Internationally recognised specific therapy	Comment noted. No action required.
	British Thoracic Society	*It is important that appropriate topics are referred to NICE to ensure that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would it be appropriate to refer this topic to NICE for evaluation?* Yes	Comment noted. No action required.
	Royal College of Physicians	It is appropriate to refer this topic for assessment under the NICE Highly Specialised Technologies Evaluation.	Comment noted. No action required.
Wording	CSL Behring	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* Yes	Comment noted. No action required.
	Alpha-1 UK Support Group	Yes, although the following suggested wording would be more specific: "To appraise the clinical and cost effectiveness of human alpha1-proteinase inhibitor within its marketing authorisation for slowing the progression of emphysema secondary to severe alpha1-antitrypsin deficiency."	Thank you for your comment. The wording of the remit has been agreed.
	Association of	*Does the wording of the remit reflect the issue(s) of clinical and cost*	Comment noted. No

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	Respiratory Nurse Specialists	*effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* Yes	action required.
	Birmingham University	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* Fine	Comment noted. No action required.
	British Thoracic Society	The wording is very clear. Minor changes in specific sections suggested below.	Comment noted. No action required.
	Royal College of Physicians	The wording of the remit is appropriate.	Comment noted. No action required.
Timing Issues	CSL Behring	In the context of NHS England developing a highly specialised service in time for April 2019, Respreeza should be reviewed based on the best available evidence and aligned to the highly specialised service. Access to optimal diagnosis and management in this patient population is urgent as there are currently no available treatments that slow the underlying cause of this progressive disease where life expectancy is significantly reduced in comparison with general population.	Comment noted. No action required.
	Alpha-1 UK Support Group	The only treatments currently available to patients with alpha-1 antitrypsin deficiency (AATD) in England are for symptomatic relief only. No disease-modifying treatments are available in the UK that slow or halt the progression of AATD-associated emphysema. The therapy under consideration is the only licensed therapy with the potential to modify the course of AATD, and UK patients continue to die prematurely in the absence of any effective treatment options – since the	Comment noted. No action required.

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		previous scoping of human alpha1-proteinase inhibitor for evaluation under NICE's STA programme in September 2015, 28 members of our patient charity have died, with an average age at death of 58 years (and 4 of these were below the age of 50). In addition, patients with severe AATD have for many years had access to human alpha1-proteinase inhibitor in many European countries in the EU (incl. Germany, Italy, Spain, Austria, Portugal, Belgium, Switzerland etc.) and in the US, and comparison studies have shown improved clinical outcomes in patients treated with human alpha1-proteinase inhibitor compared to patients treated with standard therapy. Patients in England therefore strongly feel that this technology should be considered by NICE as a matter of urgency in order to enable timely patient access to this therapy, if deemed appropriate, and to reduce the inequality of access to this therapy across Europe.	
	Association of Respiratory Nurse Specialists	Low urgency, this relates to a relatively small number of people rather than large groups who would benefit, but could have a significant impact on their quality of life.	Comment noted. No action required.
	Birmingham University	An important issue that has been outstanding for years and at variance with the EU directive on rare diseases, clinical practice in many European and American countries as well as professional strategy documents and guidelines.It should be addressed as soon as possible to permit National commissioning to proceed and support for specialist centres again in line with International guidelines and strategies.	Comment noted. No action required.
	British Thoracic Society	The evaluation is timely.	Comment noted. No action required.

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	Royal College of Physicians	Patients with severe alpha1-antitrypsin deficiency (AATD) in England receive only symptomatic treatment for the partial alleviation of the symptom of breathlessness. However, this approach does not influence the natural history of disease, which is that of inexorable progression. Consequently, patients are currently subject to the deleterious effects of faster disease progression than they would otherwise experience if they had access to a disease-modifying treatment that would retard or halt disease progression. In addition, there continues to be a clear disparity in available treatment options between patients with AATD in England and those in other European countries. Patients in other European countries (eg Spain, Portugal, Italy, Austria, Germany, Switzerland) and in the US and Canada, receive human alpha1-proteinase inhibitor with the intention of reducing the rate of disease progression. Studies which have compared the clinical outcomes in countries where augmentation therapy is available with those where no human alpha1-proteinase inhibitor is available (eg Seersholm et al. ERJ. 1997: 10:2260-3: The Alpha-1-Antitrypsin Deficiency Registry Study Group. AJRCCM. 1998: 158:49-59: Wenker et al. Chest. 2001:119:737-744) demonstrate superior outcomes in those countries where human alpha1-proteinase inhibitor is available. (Since the standard of care for AATD in these countries is otherwise very similar, these studies provide some supportive clinical evidence of treatment efficacy of human alpha1-proteinase inhibitor.) This disparity and inequality across different countries, particularly within Europe, is not only considered unacceptable by patients, who believe that they are subject to discrimination, but by their physicians who wish to have the option of prescribing the same therapy that is available to specialists in other countries. There exists a high unmet need for a disease-modifying therapy for AATD. An appraisal of this technology by NICE that could facilitates timely patient access to this therapy is therefore of the essence.	Comment noted. No action required.

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Additional comments on the draft remit	Association of Respiratory Nurse Specialists	no	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	CSL Behring	It is stated that people with A1PI deficiency who smoke can have COPD symptoms in their 20s. However, it is important to note that most people are diagnosed in their 40s. The mean age of patients included in the pivotal study for Respreeza was 51 years.	Thank you for your comment. The background section of the scope includes the typical age of onset of symptoms in non-smokers.
	Alpha-1 UK Support Group	It should be noted that the epidemiology, disease characteristics and disease progression of emphyema in patients with AATD are different from in usual COPD. Consequently, it is inappropriate to include AATD within the umbrella of what is generally termed 'usual' COPD. We therefore disagree with the suggested grouping of AATD-associated emphysema with emphysema due to usual COPD. AATD causes a different type of emphysema with early onset, more rapid decline, and more frequent and severe exacerbations. The NICE clinical guideline 101 (section 1.1.3.3.) recommends that patients identified as having AATD should be offered the opportunity to be referred to a specialist centre to discuss the clinical management of this condition. This recommendation is obviously based on the recognition that AATD and COPD require different management, which contrasts with the suggestion that	Comment noted. The background section of the scope has been updated.

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		patients with AATD constitute merely a sub-group of the usual COPD population. It should be noted that the NICE clinical guideline 101, which does not recommend human alpha1-proteinase inhibitor for people with AATD, was issued without consideration of the evidence presented in recent years in several landmark studies, demonstrating that human alpha1-proteinase inhibitor slows the progression of AATD-related emphysema (Dirksen et al. Eur Repir J. 2009; 33:1345-53; Stockley et al. Respir Res. 2010; 11(1):136; Chapman et al. Lancet. 2015;386(9991):360-8), particularly in the lung bases, where emphysema is usually located in AATD patients (Parr et al. Respir Res. 2009; 10:750). We note that the NICE guideline 101 is currently under review, and we would expect that appropriate consideration will be given in this review to all available evidence on clinical efficacy of human alpha1-proteinase inhibitor augmentation therapy.	
	Association of Respiratory Nurse Specialists	Easy to read, it is clear there is a low incidence	Comment noted. No action required.
	Birmingham University	The information provided is brief and does not reflect all of the available information although that should emerge as part of the consultation	Comment noted. The comments received during consultation have been considered and incorporated into the final scope where appropriate.
	British Thoracic	For completeness consider adding:	Comment noted. The

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	Society	P1 last paragraph after smoking cessation: avoidance of other environmental risk factors. P2, paragraph 1 prior to transplantation: endoscopic lung volume reduction (insertion of endobronchial valves or coils) and lung volume reduction surgery.	background section of the scope has been updated.
	Royal College of Physicians	The information included in the Background of the draft scope is largely correct. However, it is inaccurate to include AATD within the umbrella term COPD because of the recognised pathological diferences between AATD-associated emphysema and usual COPD; AATD is associated primarily with the development of early onset, panlobular emphysema which predominantly affects the lower parts of the lung, whereas patients with usual COPD and emphysema usually develop centrilobular emphysema which affects the upper parts of the lung (and it should be appreciated that many patients who have usual COPD have no emphysema). The emphysema associated with AATD typically progresses at a faster rate than the emphysema associated with usual COPD. Depsite these differences, the management of emphysema associated with AATD currently does not differ from that of usual COPD in England. Current management strategies for usual COPD continue to be based on the use of inhaled therapies that were developed initially for the treatment of asthma (and which are efficacious for the treatment of asthma), but with the recognition that airways obstruction in COPD is not reversible and that there are no treatments, other than smoking cessation, that are proven to modify the natural history of usual COPD. The approach adopted in the NICE clinical guideline 101 does not depart from this nihilistic (but realistic) view of COPD management, however, given the phenotypic differences between usual COPD and AATD, these guidelines are not a suitable reference for optimal clinical management for AATD. Furthermore, significant evidence has been published since the publication of the NICE guideline 101 that does support the efficacy of AAT augmentation	Comment noted. The background section of the scope has been updated. Comment noted. The background section of the scope has been updated.

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		therapy (Dirksen et al. Eur Repir J. 2009; 33:1345-53; Stockley et al. Respir Res. 2010; 11(1):136; Chapman et al. Lancet. 2015;386(9991):360-8). In particular, there is also evidence that the retardation of CT lung density loss is specifically observed in those areas where panlobular emphysema is distributed but not in those areas where centrilobular emphysema is distributed (Parr et al. Respir Res. 2009; 10:750); this serves to emphasise the fundamental difference between AATD (which has predominantly panlobular emphysema) and usual COPD (which has predominantly centrilobular emphysema).	
The technology/ intervention	CSL Behring	Yes. It should be noted that, while the brand name for the intervention being considered is Respreeza, other equivalent brands of A1PI are licensed outside of the UK. Where single studies cannot be expected to demonstrate significant differences in all outcomes, meta-analysis of clinical trials that have evaluated A1PIs can be very informative in the interpretation of the limited evidence base. Therefore, in light of the very limited available data, clinical effectiveness evidence relating to all augmentation therapies, not just Respreeza, will be considered.	Comment noted. The committee will consider all the available evidence in its evaluation of alpha 1-proteinase inhibitor in addition to established clinical management.
	Alpha-1 UK Support Group	Yes, we consider the description of the technology to be accurate. In addition, it should be noted that, due to the rarity of the disease and the complex nature of AATD, there are only a few specialists in England with sufficient clinical expertise in this condition to evaluate a patient's eligibility for AAT augmentation therapy as per the licensed indication. We would therefore expect that eligibility assessment and treatment initiation of human alpha1-proteinase inhibitor would be restricted to the specialist centres in England that will become nominated centres of the highly specialised NHS Service for	Comment noted. No action required.

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		AATD that NHSE will be commissioning from April 2019.	
	Association of Respiratory Nurse Specialists	*Is the description of the technology or technologies accurate?* Yes	Comment noted. No action required.
	Birmingham University	*Is the description of the technology or technologies accurate?* Yes	Comment noted. No action required.
	British Thoracic Society	*Is the description of the technology or technologies accurate?* Yes	Comment noted. No action required.
	Royal College of Physicians	*Is the description of the technology or technologies accurate?* Yes.	Comment noted. No action required.
Population	CSL Behring	*Is the population defined appropriately? Are there groups within this population that should be considered separately?* Yes.	Comment noted. No action required.
	Alpha-1 UK Support Group	The population is, in principle, defined appropriately. However, the definition of “progressive lung disease” is non-specific and may not be sufficient to accurately characterise patients with AATD in clinical practice who are most likely to benefit from the technology. Identification of AATD patients with “progressive lung disease” in clinical practice requires relevant experience of AATD management that not many clinicians in England have been able to acquire due to the rarity and complexity of the condition.	Comment noted. The technology will be evaluated within its marketing authorisation which includes a definition of progressive lung disease.

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		It might therefore be necessary to define more specifically how “lung disease” and “progression” are defined in this context, how it should be established clinically etc.	
	Association of Respiratory Nurse Specialists	May need to define severity of lung disease i.e. mild, moderate, severe, very severe	Comment noted. The technology will be evaluated within its marketing authorisation which includes a definition of progressive lung disease.
	Birmingham University	Generally yes but the scope should emphasise consideration of “patients with evidence of on-going deterioration despite best clinical practice” as once identified even those with established COPD may well stabilise and this can only be determined by prospective study and not retrospective Status.	Comment noted. The technology will be evaluated within its marketing authorisation which specifies that progressive lung disease should be evaluated by a healthcare professional.
	British Thoracic Society	Consider: “Adults with severe alpha1-proteinase inhibitor deficiency who have progressive lung disease <u>despite abstinence from smoking.”</u> Subgroups: published data focuses on a baseline FEV1 30% to 65% predicted. However: a) gas transfer and lung density are better indices of disease progression than FEV1, particularly when FEV1 <30%, and b) the phenotype of emphysema with relatively preserved spirometry is well recognised – some patients with FEV1 > 65% may show rapid progression of emphysema (gas transfer / lung density). Clinicians should have the freedom	Comment noted. The technology will be evaluated within its marketing authorisation, which is not restricted to non-smokers. The scope has been updated to specify that, if evidence allows,

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		to treat patients outside the FEV1 thresholds above when there is evidence of progression on gas transfer or lung density. The remit includes the PiSZ genotype. This is a borderline group among whom only a minority will have AAT <11 µM (those with severe deficiency and progression should still have access to Rx). Frequent exacerbators: there is conflicting data on the impact of augmentation therapy on exacerbations; this warrants further study.	consideration may be given to subgroups based on speed of decline, distribution of disease and frequency of exacerbations.
	Royal College of Physicians	The population is defined appropriately. However, it may have to be clarified how “progressive lung disease” in AATD is defined and how it is assessed in clinical practice. (This may require the use of serial full lung function testing and CT lung densitometry.)	Comment noted. The technology will be evaluated within its marketing authorisation which includes a definition of progressive lung disease. Comments received during consultation suggested that transplant and LVR are options for some people with AATD and that they may be delayed or displaced by the introduction of the technology.
Comparators	CSL Behring	Yes. Established clinical management without A1PI as listed in the scope is the same as best supportive care (BSC). Most patients with A1PI deficiency will receive a combination of corticosteroids, oxygen therapy and/or bronchodilators to treat the symptoms, which have short-term benefits but do	Comment noted. The comparators section of the scope has been updated.

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		not address the underlying problem of the deficient protein. The placebo arm of the pivotal study is representative of patients receiving BSC. End-stage disease may be treated by lung transplantation and/or lung volume reduction surgery. Respreeza may act as a bridge to lung transplant by keeping patients alive long enough to be eligible to receive a transplant. Therefore, lung transplant and/or reduction surgery should be considered as downstream options within the treatment pathway.	**C**omments received during consultation suggested that transplant and LVR are options for some people with AATD and that they may be delayed or displaced by the introduction of the technology**.**
	Alpha-1 UK Support Group	The listed comparators are appropriate, with the exception of lung transplantation and lung volume reduction surgery. Although lung transplantation is a recognised treatment option for AATD patients with terminal respiratory failure due to severe emphysema, where the only alternative options are death or intolerable breathlessness, we would not consider it as a standard treatment available to patients for the following reasons: • The shortage of available donor organs results in inequitable access to this intervention and, in reality, transplantation is therefore only available to a small number of AATD patients. Patients may also not survive on the waiting list because of limited organ availability. • Many patients in our charity who had positive lung transplantation assessments, have decided not to be added to the transplant waiting list, as they feel unable to cope with the psychological impact of such a major decision and risky intervention. Similarly, for AATD patients with predominantly basal emphysema, lung	Comment noted. Comments received during consultation suggested that transplant and LVR are options for some people with AATD and that they may be delayed or displaced by the introduction of the technology.

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		volume reduction surgery (LVRS) is also a symptomatic treatment option that may reduce breathlessness. It should be noted, however, that the suitable patient population is very small, and the durability of the benefits derived from LVRS in patients with AATD seems inferior to that of patients with usual COPD and it is not generally recommended (Donahue and Cassividi. Thorac Surg Clin. 2009; 19(2):201-208). We had reports from patients who were declined for lung transplantation due to prior LVRS, which further limits the available treament options.	
	Association of Respiratory Nurse Specialists	The list should include smoking cessation advice & support as an intervention in established clinical management?	Comment noted. Smoking cessation advice and support is expected to continue, and so is not a comparator that may be displaced by the new technology. No action required.
	Birmingham University	At present there are several companies with similar products that have not been subjected to the same clinical evaluation. However there are no new approaches currently available and this technology remains the best available Internationally.	Comment noted. No action required.
	Royal College of Physicians	Most of the compartors listed in the draft scope are appropriate. However, lung transplantation should not be viewed as a standard comparator, as it is not readily available to most patients with AATD due to a shortage of donor organs and exclusion criteria for transplantation, such as age, general fitness/comorbidity. In addition, it it viewed by clinicians and patients as a last resort. Lung volume reduction surgery is also not a standard comparator, because it is only suitable in a restricted number of patients and efficacy in AATD is	Comment noted. Comments received during consultation suggested that transplant and LVR are options for some people with AATD and that they may be delayed or

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		considered short-lived.	displaced by the introduction of the technology.
Outcomes	CSL Behring	Yes. However, it is not possible to conduct a clinical trial powered for observing changes in mortality and quality of life in such a rare population as it would have to be an unfeasibly large study conducted over many years to detect significant treatment effects. Therefore, outcomes such as mortality and health-related quality of life will not be based on trial outcomes but derived indirectly using published data.	Comment noted. No action required.
	Alpha-1 UK Support Group	The outcome measures listed in the draft scope are appropriate to capture the most important health-related benefits of human alpha1-proteinase inhibitor.	Comment noted. No action required.
	Association of Respiratory Nurse Specialists	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?* Yes	Comment noted. No action required.
	Birmingham University	These all need to be considered but it is important to realise this is a disease modifying therapy and should not be expected to produce and immediate clinical or physiological impact although Patient perspective will have a positive effect.	Comment noted. No action required.
	British Thoracic Society	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?* Yes	Comment noted. No action required.
	Royal College of	In principle, the outcomes listed are appropriate to capture the most important health-related benefits of the technology.	Comments noted. No

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	Physicians	Augmentation therapy has been shown to reduce the severity of exacerbations (Dirksen et al Eur Resp J 2009; 33: 1345-53) and may, therefore, have a beneficial and important effect on the need for hospitalisation. CT lung densitometry is the optimum outcome measure for use in trials of emphysema modifying therapy (as defined by the ATS and FDA) because it is the most specific and sensitive measure. It has been validated as a surrogate measure of emphysema severity and as an outcome measure for use in interventional studies of emphysema modifying therapy. However, CT lung densitometry requires expert knowledge and a high level of quality control because it is technically demanding. Lung function outcomes are non-specific and insensitive surrogate measures of emphysema in AATD and requi excellent quality control for use as a tool for monitoring emphysema progression. FEV1 and gas diffusion have poor reproducibility for use as outcome measures, hence the development of CT densitometry for use in interventional studies (Schluchter et al. Am J Respir Crit Care Med. 2000; 161:796-801). Nevertheless, these measures are widely available in the majority of Respiratory Physiology Departments. The use of a single lung function index, such as FEV1 or KCO, is not advisable because patient heterogeneity leads to variable patterns of functional impairment and decline (Parr et al AJRCCM 2004; 170:1172-1178, Parr et al. Thorax 2006; 61; 485-490). Full lung function testing is therefore necessary to capture progressive physiological impairment in all patients. Exercise capacity relates to disease severity and will reflect disease progression. Reduction in exacerbation severity, hospitalization and the rate of disease progression are all expected to lead to a reduction in mortality. Health-related quality of life metrics have not been developed in AATD. There is a need to identify suitable disease-specific PROs.	action required.

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Equality and Diversity	CSL Behring	A positive review of Respreeza will enable equity of access to treatment for a minority group with a rare genetic disease.	Comment noted. No action required.
	Alpha-1 UK Support Group	It is widely accepted that AATD is a disease with a genetic line of Northern European extraction. It is therefore almost solely limited to Caucasians of this demographic group and its descendants.	Comment noted. The prevalence of this condition in populations with specific family origins is not expected to be an equality issue. No action required.
	Association of Respiratory Nurse Specialists	No issues in equality	Comment noted. No action required.
	Birmingham University	This should not be relevant as the technology can be administered in any setting although ability to undertake accurate physiological monitoring can be a problem for compliance in some(though few) subjects	Comment noted. No action required.
	British Thoracic Society	No concerns	Comment noted. No action required.
	Royal College of Physicians	There are no equity considerations that need to be taken into consideration, other than the fact that AATD occurs almost exclusively in Caucasian populations, believed to have descended from Northern Europeans.	Comment noted. The prevalence of this condition in populations with specific family origins is not expected to be an equality issue. No action required.

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Other considerations	Alpha-1 UK Support Group	None.	Comment noted. No action required.
	Association of Respiratory Nurse Specialists	Patients often have severe lung disease before diagnosis of Alpha 1 antitrypsin deficiency, but would benefits from such a treatment come from early diagnosis and commencement of replacement therapy – therefore how does the proposal suggest identification of patients in a timely fashion, treatment of those with early decline in FEV1, how many patients could benefit if identified at this earlier stage. What are the benefits of earlier replacement therapy versus replacement therapy at a later decline of lung function?	Comment noted. The technology will be evaluated within its marketing authorisation. Diagnosis of alpha-1 antitrypsin deficiency is outside the scope of this evaluation.
	Birmingham University	A clear assessment and management strategy has to be part of the remit with guidance for both treatment and documentation of individual ineffectiveness. The establishment and maintenance of a national registry is essential.	Comment noted. No action required.
	Royal College of Physicians	The rarity of the condition, the small number of eligible patients for this treatment, the high burden of disease, the absence of any disease-modifying treatment alternatives and the high manufacturing costs of this plasma-derived therapy should be fairly taken into account. Many carers of patients with AATD report a reduced quality of life due to the high burden of care, which should be taken into consideration.	Comment noted. This topic will be evaluated through the Highly Specialised Technologies programme, and will take into account the full range of factors that may affect the recommendation. See the interim highly specialised technologies methods and process guide for more information.

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Innovation	CSL Behring	Respreeza is a highly innovative medicine that addresses an important unmet public health need, providing the only licensed and clinically proven disease modifying agent that slows the progression of emphysema due to A1PI deficiency, which is associated with significant morbidity and mortality, for a subset of patients with severe A1PI deficiency and evidence of progressive lung disease.	Comment noted. The committee will consider the innovative nature of the technology in the evaluation.
	Alpha-1 UK Support Group	We do consider human alpha1-proteinase inhibitor to be a step-change in the management of severe AATD-associated lung disease because it would be the first time a treatment would be available that modifies the natural history of the disease. At present, only symptomatic treatments are used for disease management and these do not slow disease progression. We work closely with AATD patient charities in countries where human alpha1-proteinase inhibitor from two different manufacturers has been available for many years for specific sub-groups of individuals with AATD. We frequently receive reports of significant health-related benefits that patients experience with this therapy. We would therefore expect that similar benefits would be enjoyed by patients in England if human alpha1-proteinase inhibitor was made available.	Comment noted. The committee will consider the innovative nature of the technology in the evaluation.
	Association of Respiratory Nurse Specialists	I think the impact would be limited due to the low number of patients affected. However, within this small group it has the potential of making a substantial difference as long as a system of early identification is sought.	Comment noted. No action required. Diagnosis of alpha-1 antitrypsin deficiency is outside the scope of this evaluation.
	Birmingham University	The condition is a genetic deficiency and replacement/augmentation is an innovative approach. The delay over the past 25 years has been failure to deliver a classical clinical trial of efficacy with historical outcomes in this rare	Comment noted. The committee will consider the innovative nature of

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		disease population. This has been recognised by many other countries and hence treatment is available elsewhere. Recent sensitive clinical outcomes has provided evidence of efficacy.	the technology in the evaluation.
	British Thoracic Society	Yes	Comment noted. No action required.
	Royal College of Physicians	Current management strategy is restricted to symptom alleviation through the application of management therapies for 'usual COPD'. Access to augmentation therapy would be a step-change in the management of AATD-related emphysema, because this would be the first time that patients in England would be able to receive a treatment that would modify their disease and reduce the rate of emphysema progression. Treatment with human alpha1-protease inhibitor is known to be associated with other health-related benefits that are not adequately captured in the QALY calculation, as many of them either occur with a long delay or accumulate over many years due to the relatively slow progressive nature of the disease (reduced mortality, delayed disability, reduced healthcare utilisation due to reduced exacerbation severity, prevention of transplantation etc).	Comment noted. The committee will consider the innovative nature of the technology in the evaluation.
Questions for consultation	CSL Behring	***Are other alpha 1-proteinase inhibitors available in the England? Are they used in clinical practice?*** Respreeza is the only licensed A1PI in England. No A1PIs are currently used to treat emphysema due to A1PI deficiency in clinical practice. ***Which treatments are considered to be established clinical practice in the NHS for emphysema?*** The treatments listed as being part of established clinical management are appropriate. It may be more appropriate to simply state the comparator as	Comment noted. No action required. Comment noted. No action required.

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		being 'Best supportive care'. ***Is alpha 1-proteinase inhibitor an emphysema-modifying treatment or is symptomatic relief the aim of treatment?*** The licensed indication for Respreeza is to slow the progression of emphysema. It is therefore an emphysema-modifying treatment. ***Is the aim of treatment to get people fit enough to undergo lung transplantation?*** The aim of treatment is to slow down the progression of the disease. Lung transplant provide patients with a significant increase in their quality of life. Respreeza may act as a bridge to lung transplant by keeping patients alive long enough to be eligible to receive a transplant. ***Are the outcomes listed appropriate? Is impact on liver disease (e.g. cirrhosis and jaundice) or skin conditions (e.g. panniculitis) appropriate outcomes?*** The population under consideration is patients with emphysema as a result of A1PI deficiency, as per the licensed indication for Respreeza. The impact on liver disease or skin conditions is not an appropriate outcome as it is effectively outside of the licensed indication for Respreeza. ***How is this population defined in clinical practice?*** Severe alpha1-proteinase inhibitor deficiency is defined as patients with a serum A1PI level < 11 µmol/L. This is typically patients with genotypes PiZZ, PiZ(null) and Pi(null,null). Some patients with genotype PiSZ have severe disease. Evidence of progressive lung disease can be a lower forced expiratory	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		volume per second (FEV1) predicted, impaired walking capacity or increased number of exacerbations as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency. ***How many patients would be eligible for treatment with alpha 1-proteinase inhibitor?*** It is estimated that 670 people in England have emphysema caused by A1PI deficiency. About 540 of these people (80%) will have clinically significant emphysema that requires treatment. A proportion of this group of patients is anticipated to be treated with A1PI based on clinical expert opinion, where evidence of progressive lung disease is demonstrated, as per the licensed indication for Respreeza. ***Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?*** No. Subgroup analysis of patients in the pivotal study has not suggested that there is a group of patients in which the treatment provides greater clinical benefits. ***Would you expect a difference in clinical benefit in people experiencing a fast decliner (in lung density and/or lung function) vs. slow decline?*** It is likely that, as a treatment which slows progression, it will appear that there could be a greater treatment effect in patients that are more rapidly declining. However, since A1PI is a highly heterogeneous condition, in which patients may have sudden rapid declines, it would be challenging to define patients as fast/slow decliners since they may switch between rates of decline with time. Defining a patient's rate of decline would require CT scans one year apart, so it is not a practical starting rule for treatment as a patient might	Comment noted. No action required. Comment noted. The scope has been updated to specify that, if evidence allows, consideration may be given to subgroups based on speed of decline, distribution of disease and frequency of exacerbations.

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		have been declining for one year before they are detected as so. As per the licensed indication, evidence of progressive lung disease is required to start treatment, so expert clinical judgment based on extensive experience of A1PI deficiency will be critically important to ensure appropriate treatment in eligible patients. ***Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?*** Respreeza is a highly innovative medicine that addresses an important unmet public health need, providing the only licensed and clinically proven disease modifying agent that slows the progression of emphysema due to A1PI deficiency, which is associated with significant morbidity and mortality, for a subset of patients with severe A1PI deficiency and evidence of progressive lung disease. ***Do you consider that the use of for human alpha 1-proteinase inhibitor can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?*** Yes; • The potential for long-term benefits to the NHS of research and innovation • The benefits gained outside of the NHS (increased societal productivity and reduced disutility for carers)	Comment noted. No action required. Comment noted. The committee will consider the innovative nature of the technology in the evaluation. Comment noted. The committee will consider

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			all benefits of the technology in its evaluation.
	Alpha-1 UK Support Group	No other alpha1-proteinase inhibitors are available in England for the stated indication. Unlike all other available treatments available for emphysema that provide symptomatic relief only, alpha 1-proteinase inhibitor is an emphysema-modifying treatment. It is the only treatment licensed specifically for AATD-associated emphysema. The aim of treatment with alpha 1-proteinase inhibitor is not to bridge the time to a lung transplantation but to use it as a long-term treatment to slow, or ideally halt, emphysema progression and to avoid the need for transplantation altogether. As detailed above in the Comparator section, transplantation is not considered a viable, long-term treatment option by many patients. Human alpha 1-proteinase inhibitor is not believed to have an impact on AATD-associated liver disease. Strong anecdotal evidence shows good efficacy of the treatment in AATD-associated panniculitis. Our patient charity has assisted several AATD patients with severe panniculitis to get access to short-term treatment (off-label) with alpha 1-proteinase inhibitor, and all patients experienced significant improvements or resolution of their panniculitis bouts under treatment. However, little or no systematically generated efficacy data exists on the use of alpha 1-proteinase inhibitor for the treatment of AATD-associated panniculitis. Based on data from the AATD registry in Birmingham, we would expect 500-550 patients in England to be eligible for treatment with alpha 1-proteinase inhibitor. The effectiveness of human alpha 1-proteinase inhibitor has not been assessed prospectively in sub-groups but there is evidence that the effect of treatment is most pronounced in the lower parts of the lung, which is where	Comment noted. The committee will consider the innovative nature of the technology in the evaluation. Comment noted. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		emphysema is usually seen in patients with AATD (Parr et al. Resp Res. 2009:10:75) and in patients who are classified as 'rapid decliners' (Wencker et al. Chest. 2001;119:737-744). We do consider that the use of human alpha 1-proteinase inhibitor can result in potentially significant and substantial health-related benefits that are unlikely to be included in the QALY calculation.	Comment noted. The committee will consider all benefits of the technology in its evaluation.
	Association of Respiratory Nurse Specialists	It would be assumed that treatment may slow decline so to enable more patients to be considered for lung transplant As the population across the country is so small it may be useful to identify numbers in areas of the country to better define the population being considered.	Comment noted. No action required. Comment noted. No action required.
	Birmingham University	Nil	Comment noted. No action required.
	British Thoracic Society	For clarity, I have answered all specific questions below in order: 1. Comparator – established treatment for emphysema, randomised to add on augmentation therapy 2. Established therapy includes insertion of endobronchial valves and coils to achieve lung volume reduction, immunisation, smoking cessation/avoidance and avoidance of other environmental risk factors. 3. Augmentation therapy is disease modifying, slowing the rate of progression of emphysema. The aim of augmentation is to delay or prevent the need for lung transplantation. It is not to get people fit	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		enough to undergo lung transplantation. 4. Augmentation does not substantially improve liver disease and is not licenced for this purpose (other drugs are in development). Augmentation can improve skin disease (case series data) and is available on a named patient basis for this indication (not controlled with Dapsone). 5. The population will predominantly be Pi zz/znull/nullnull with AAT level < 11 µM, who show progression despite not smoking. The SZ genotype are a borderline group, and whilst they can develop emphysema only a minority will have AAT levels < 11 µM. 6. n~ 200 -250, if restricted to the group described above. 7. Subgroups: published data focuses on FEV1 30 -65%. However: a) below FEV1 = 30%, gas transfer is a better index of disease progression, and b) the phenotype of emphysema with relatively preserved spirometry is well recognised – some patients with FEV1 > 65% may show rapid progression with a substantial impairment in gas transfer and symptoms. Clinicians should have the freedom to treat patients outside the FEV1 thresholds above when there is evidence of progression on gas transfer or lung density. 8. Rate of decline (lung function and/or lung density) would be expected to influence response to treatment. 9. There is conflicting data on the impact of augmentation therapy on	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. The scope has been updated to specify that, if evidence allows, consideration may be given to subgroups based on speed of decline, distribution of disease and frequency of exacerbations. Comment noted. No action required. Comment noted. No action required.

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		exacerbations; this warrants further study. 10. No concern about impact on people with particular disabilities or those protected by equality legislation.	Comment noted. No action required.
	Royal College of Physicians	There are no alpha 1-proteinase inhibitors currently in use in England. All relevant comparators for human alpha 1-proteinase inhibitor have been included in the scope. The listed comparators are considered established clinical practice in the NHS for emphysema. Human alpha 1-proteinase inhibitor is an emphysema-modifying treatment that is considered to have additional potential benefits on symptom relief, although evidence for these latter effects is sparse, at present. Human alpha 1-proteinase inhibitor is not a treatment aimed at getting people fit enough to undergo lung transplantation, which is seen by many patients as a worse alternative to death. Instead, the aim of treatment is to retard the rate of emphysema progression in order to prolong life, reduce the impact of symptoms, reduce healthcare utilisation, delay the onset of disability, and prevent the need for transplantation for the management of end-stage disease, respiratory failure and prevention of death. The listed outcomes are appropriate. However, it is not expected that augmentation therapy will have any impact on liver disease. Patients with panniculitis will likely benefit from augmentation therapy, but this condition is rare amongst patients with severe AATD. The population of patients eligible for augmentation therapy is appropriate. In clinical practice, patients are accurately assessed and appropriately characterised in specialist expert centres because the heterogeneity, complexity and rarity of the disease requires relevant and multi-disciplinary	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		expertise. Severe AATD is usually defined on the basis of the serum AAT concentration (which is traditionally considered to be below a putative protective threshold of 11micromol) (ATS/ERS, Am J Respir Crit Care Med. 2003; 168). Estimates of the number of patients in England who would potentially be eligible for treatment have been made on the basis of data obtained from the ADAPT programme (which holds the national patient registry) and is considered to be approximately 500-600 patients. There is no published data that indicates differential efficacy in subgroups of people with AATD but there is evidence of a more pronounced regional treatment effect in the basal lung regions, which is where emphysema is usually seen in patients with AATD (Parr et al. Resp Res. 2009:10:75). However, not all patients with severe AATD have this classical distribution of emphysema (Parr et al AJRCCM 2004: 170; 1172-1178) and there may, therefore, be a differential treatment effect based on the distribution of emphysema. Patients who are classified as 'rapid decliners' appear to experience a differential treatment benefit (Wencker et al. Chest. 2001;119:737-744) but patient numbers in this study were small. There is sufficient published evidence to justify further sub-group analyses to identify whether treatment benefits differ according to emphysema distribution and pathological sub-type, and rapid versus slow decliners.	Comment noted. No action required. Comment noted. The scope has been updated to specify that, if evidence allows, consideration may be given to subgroups based on speed of decline, distribution of disease and frequency of exacerbations.
Additional comments on the draft scope	Association of Respiratory Nurse Specialists	none	Comment noted. No action required.

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

Department of Health and Social Care

GlaxoSmithKline