1. *"Minimum clinically important differences for the primary outcome in the core randomised controlled trials (RCTs), i.e. Computed tomography (CT)-measured lung density, are not established in the literature…" [MSAC CA 1530, p1]*

Lung CT densitometry changes have proven to be the most sensitive marker of disease progression in patients with A1PI deficiency and COPD as compared to pulmonary function tests or quality of life assessments (Dirksen 2009, Chapman 2015). However, in absence of an established minimum clinically important difference (MCID) for lung density decline rates, the results seen in the RAPID and EXACTLE trials may be difficult to interpret. To help address this issue, a group of renowned A1PI researchers in Birmingham, UK are currently working to establish the MCID based on the CT density outcomes from the placebo-controlled trials (Dirksen 1999, Dirksen 2009, Chapman 2015). The researchers recently proposed an MCID of -2.89 g/L (95% CI: -2.59, -3.25) at the American Thoracic Society conference held in May 2018 (Crossley et al 2018).

Based on the annual preservation of lung tissue (0.74 g/L/year) demonstrated in the RAPID trial in favor of A1PI therapy, the proposed MCID would be achieved within 3.9 years as compared to an untreated patient. As the treatment effect was robust and largely consistent between the RAPID and RAPID OLE trials in the Early Start patients who received 4-years of weekly infusions, a patient continuously treated with A1PI 60 mg/kg each week can reasonably expect to maintain a reduced rate of lung density decline well beyond the point at which the proposed MCID has been reached, demonstrating a worthwhile clinical improvement in this rare and often fatal disease.

2. *"No significant differences were observed between A1PI and placebo for the remaining effectiveness outcomes." [MSAC CA 1530, p1]*

Demonstrating clinical efficacy in A1PI deficiency leading to COPD is challenging. It requires quantitative documentation of lung function changes in a chronic and slowly progressive process that may take decades to manifest clinically (Wewers and Crystal 2013). Despite showing a significant effect on lung density, the RAPID study did not show any statistical signal of efficacy in the secondary endpoints.

There are several possible reasons for this: First, and importantly, the study was powered to detect the treatment effect on lung density measures, not changes in pulmonary function tests, diffusion capacity of carbon monoxide (DLco), Incremental Shuttle Walking Test (ISWT), or St. George's Respiratory Questionnaire (SGRQ) scores. The sample size and trial duration reflect those necessary to demonstrate an effect to slow the annual lung density rates, whereas it has been shown that significantly more patients followed for periods longer than 2 years would be required to investigate benefits of A1PI therapy in the secondary endpoints. Furthermore, those estimates are based on the use of placebo which would be considered unethical for the treatment of A1PI deficiency. Secondly, the sensitivity of the clinical endpoints to detect change is much lower compared to CT lung density; EXACTLE, the second largest study in A1PI deficiency, established CT scans and DLco as the most sensitive measures.

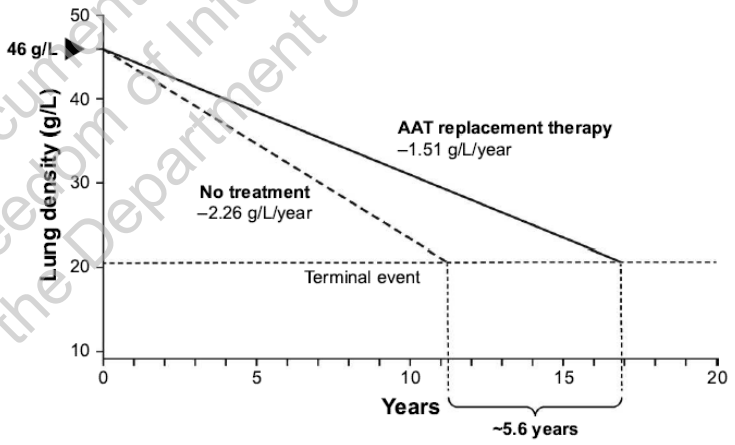
3. *"A1PI meets three of the four criteria warranting rule of rescue. It is unclear whether the proposed service provides worthwhile clinical improvement." [MSAC CA 1530, p146]*

s45

The recent work by Crossley et al to describe the MCID for CT density decline provides further clinical context for the results seen in the RAPID trial, and further demonstrates that A1PI offers worthwhile clinical improvement when evaluated across the appropriate time horizon, noting that A1PI deficiency is a chronic and slowly progressive disease.

Furthermore, evidence from a post hoc analysis of the RAPID programme suggests a mortality benefit following A1PI therapy. During the RAPID programme, the time required for progressive emphysema to develop into respiratory crisis was used to simulate the life-years gained as a result of A1PI therapy. Respiratory crisis was defined as death, lung transplant or a crippling respiratory condition. Seven patients withdrew with an average terminal lung density of 20 g/L. Using the average baseline lung density for all patients (46 g/L) and the rate of decline in lung density in A1PI versus placebo-treated patients, the projected time to terminal lung density was 16.9 years for those receiving A1PI therapy, compared with 11.3 years in the placebo group (Figure 1). This indicates a gain in life-years of 5.6 years with A1PI therapy (McElvaney et al 2017). Although conducted in a small sample size, these data are supported by results from the National Heart, Lung, and Blood Institute observational study showing that patients receiving A1PI therapy had a greater survival than those not receiving treatment (Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998).

Figure 1 Extrapolation of the effect of A1PI replacement therapy on the predicted time to reach terminal respiratory function in RAPID-RCT.



Source: Chapman et al 2018 *International Journal of COPD 18(13): 419-432*

No comments on the economic evaluation or financial implications are provided in this response as Section C, D, E were redacted from the report provided to s47G due to the commercial in confidence nature of the material.

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Proposal and Validation of a Minimal Clinically Important Difference (MCID) for Annual Pulmonary CT Density Decline

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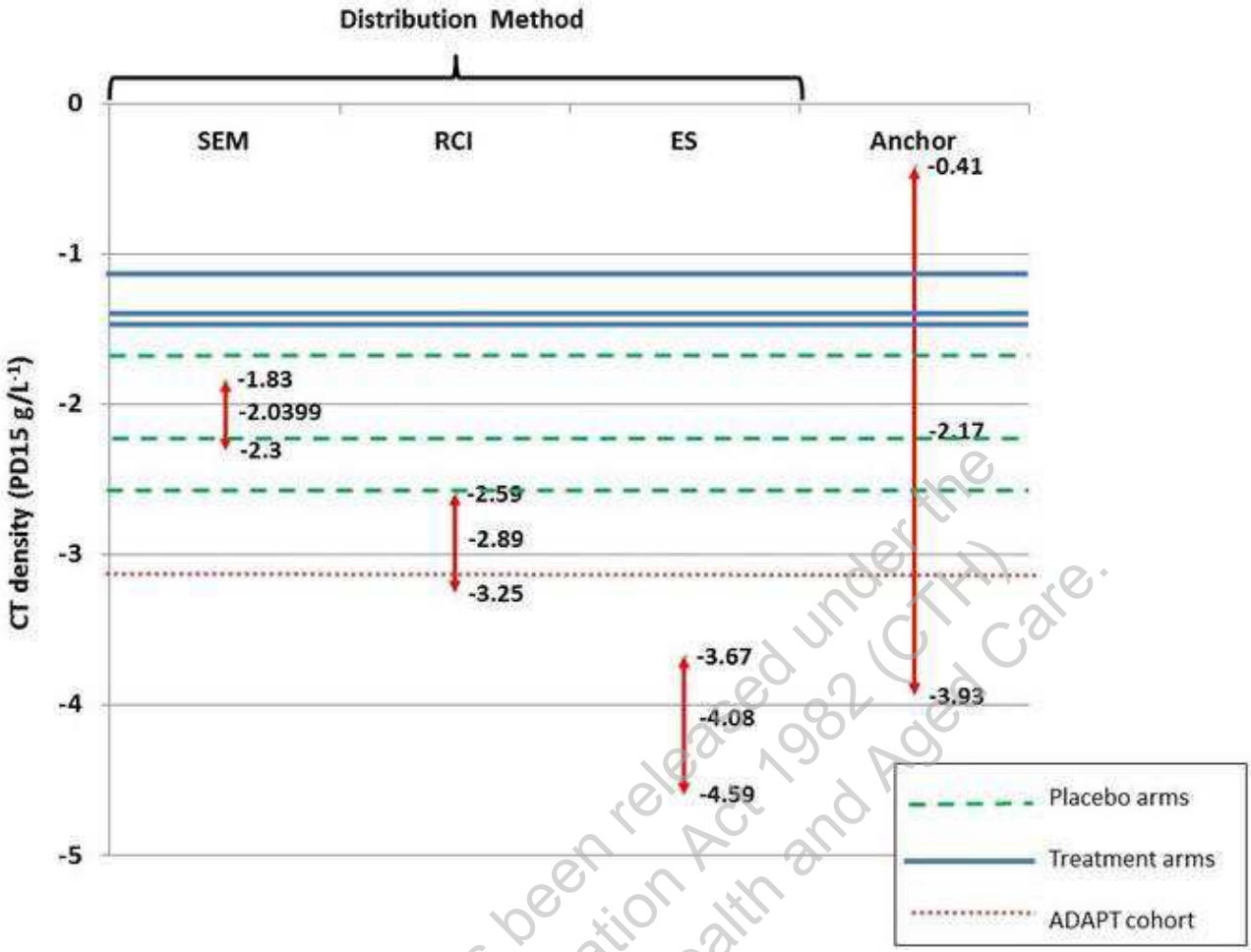
Rationale: Computed Tomography (CT) densitometry has been used as the primary outcome measure in several Randomised placebo Controlled Trials (RCTs) of Alpha one Augmentation Therapy (AAT) to assess amelioration of lung density decline. An MCID for CT density would provide more clarity of density changes that many perceive as having uncertain clinical impact. There are two recognised methods for proposing an MCID; namely the anchor and the distribution method. We aim to determine and validate an MCID for CT density decline in patients with AATD using both recognised methods. This would clarify the effect of AAT, and/or to identify those patients with significant decline who may need intervention. Methods: For the distribution method, studies were sought that reported the mean and standard deviation of CT density (as measured by the 15th Percentile Point; PD15 g/L) at baseline and with annual change. These were then used to calculate the MCID using the 3 variations of the distribution method: standard error of measurement (SEM), the reliable change index (RCI), and the effect size (ES). For the anchor method, any papers that reported annual CT density change with the relative change in FEV_1 as measured in mls without exposure to an intervention (the placebo arms) were reviewed. The MCID was then validated using the Birmingham AAT cohort. Patients who had received two or more CT scans plus at least three FEV_1 measurements over at least three years were identified. Annual slope FEV_1 (mls) was calculated and compared with the respective annual CT density change and compared by linear regression analysis. Results: Figure one illustrates each MCID and their confidence intervals. The confidence intervals from the anchor method encompassed those of the SEM and RCI. Given that a proposed MCID should originate from a variety of methods, it is reasonable to propose the MCID for CT density as -2.89g/L as this is the middle estimate from the three distribution methods, and still within the confidence intervals of the anchor method. Conclusion: The proposed MCID for CT density in patients with AATD is -2.89g/L. Values in excess of this in patients under surveillance would indicate rapid density decline, which may be one indication for AAT augmentation therapy.



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Am J Respir Crit are Med 2018;197:A3905
Internet address: www.atsjournals.org **Online Abstracts Issue**

14 September 2018

s47G response to MSAC Contracted Assessment 1530

Overall, the need for treatment of patients with alpha-1 antitrypsin deficiency (AATD), as well as the clinical evidence for augmentation therapy with alpha-1 proteinase inhibitor (A1PI), is well summarised in the Assessment Report.

With respect to the findings, s47G notes that the Assessment Report concluded that for the outcome of computed tomography (CT)-lung density, a statistically significant treatment effect was observed. Given that the aim of treatment with A1PI is to slow the rate of decline in lung function, improve quality of life and extend the patient's life-expectancy, this is a critically important finding. Indeed, the Assessment Report concurred with s47G submission that there is evidence supporting a correlation between CT-lung density decline, mortality and functional outcomes. While s47G acknowledges the uncertainty around the magnitude of the benefit, large randomised clinical trials are required to provide more accurate estimates. Due to the rarity of AATD, this is no longer ethically possible with the availability of A1PI therapies that are bioequivalent (i.e. Prolastin-C and Zemaira). Nonetheless, based on the totality of the clinical evidence, it is reasonable to expect that treatment with A1PI will slow rate of decline in lung function, improve quality of life and survival in Australian clinical practice.

With interest, s47G notes the Consumer Impact Statement from the foundation for patients with AATD which highlights its intention to establish an Australian register for patients to better understand the epidemiology of the disease if the A1PI therapies are funded through the NBA. In addition to the other consumer impact statements regarding the need for therapies with a demonstrated clinical benefit in AATD, s47G welcomes the thorough consideration of the Rule of Rescue in the Assessment Report including the acknowledgements that there is currently no treatment for patients with AATD, as well as the small number of patients that suffer from this severely debilitating disease that is associated with significant reduction in survival.

s47G

s47F

From: s47F
Sent: Thursday, 15 November 2018 11:03 AM
To: s47F
Cc:
Subject: RE: MSAC1530: Opportunity for comment on final ESC report [SEC=UNCLASSIFIED]
Attachments: 1530 REDACTED Ratified ESC Report October 2018.docx
Signed By: s47F

Dear s47F

On behalf of s47G we welcome the opportunity to provide comment on the Economic Subcommittee (ESC) report to the MSAC. Please see response below:

The ESC report noted the claim that A1-PI therapy meets three of the four criteria for the Rule of Rescue, but questioned whether CT-measured lung density *'is a sufficiently informative surrogate for the Rule of Rescue criterion of 'worthwhile clinical improvement.''* [ESC Advice p 5]. However, 12 studies reported a correlation between CT-measured lung density, other lung function measures and patient-relevant outcomes. Given this evidence, any reduction in the loss of lung density associated with A1-PI treatment is likely to translate into clinically meaningful and patient relevant benefits. The clinical evidence for A1-PI also demonstrates a trend towards slowing lung function decline as measured by FEV1, reduced incidence of lung infections, reduced severity of exacerbations, as well as a shorter duration of exacerbations. Overall therefore, the clinical evidence support the assertion that A1-PI treatment provides a worthwhile clinical improvement for patients with AATD; Criterion 4 of the Rule of Rescue.

To address uncertainty around the incremental cost-effectiveness of A1-PI treatment, the ESC report suggested that consideration be given to continuation rules. s47G is open to implementing such rules to ensure access to AI-P1 therapy for those patients who receive continued benefit thereby safeguarding the cost-effectiveness. s47G notes that the Assessment Group was instructed to undertake various continuation rule scenarios as a possible strategy to improve the ICER. It is however vitally important that any continuation rules should be determined by or in consultation with specialist clinicians experienced in the treatment and management of patients with AATD rather than based on cost-effectiveness alone. However, s47G agrees with the ESC report that treatment with A1-PI should be discontinued in patients who resume or initiate smoking. Indeed, smoking renders treatment entirely ineffective. Further, s47G supports the establishment of a registry for the purpose of addressing uncertainties with respect to the efficacy of AI-P1, for example confirming the correlation between lung density, FEV1 and mortality as well as informing any future alterations to continuation rules.

Please contact us directly if you have any questions.

Thanks s47F

Regards,

s47F
Business Unit Director | Bioscience | Australia & New Zealand
Global Bioscience Commercial Operations
Phone s47F · Mobile s47F
s47G

s47F

From: s47F
Sent: Thursday, 15 November 2018 5:01 PM
To: s47F
Cc:
Subject: RE: MSAC1530: Opportunity for comment on final ESC report [SEC=UNCLASSIFIED]
Attachments: s47G -pre MSAC response to 1530-Nov18.pdf; Benowitz et al 2002 Nicotine & Tobacco Research.pdf; s45 s45

Importance: High

Dear s47F

Please find attached s47G pre-MSAC response to item 1530 *"Purified human alpha1-proteinase inhibitor for the treatment of alpha1-proteinase inhibitor deficiency, leading to chronic obstructive pulmonary disease"*

Please do not hesitate to contact me if you require additional information from s47G on this matter.

Kind regards

s47F

s47G

See how we're driven by our promise

Please consider the environment before printing this e-mail

From: s47F
Sent: Monday, 12 November 2018 4:57 PM
To: s47F
s47F
Cc: s47F
Subject: [EXT] MSAC1530: Opportunity for comment on final ESC report [SEC=UNCLASSIFIED]
Importance: High

UNCLASSIFIED

Dear s47F

Please find attached a redacted version of the final Evaluation Sub-Committee (ESC) report for the above MSAC assessment for comment by s47G

Comments on the report should be not more than two pages long and should be forwarded to myself at the NBA by 5:00pm Thursday 15 November 2018. Any comments on the ESC report should only deal with new issues and should not reiterate input s47G has previously provided on this assessment.

I apologise for the unavoidably tight turnaround time at this stage of the process.

There is no necessity for s47G to make comments. Comments from s47G will be provided to MSAC for consideration.

Regards
s47F

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s47F
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National Blood Authority, Australia

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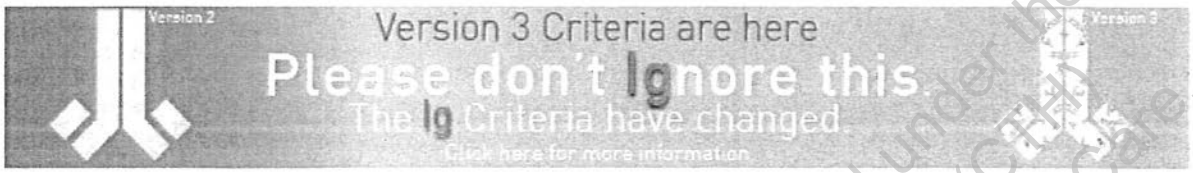

"ESC suggested...the assessment group explores...'continuation rule' scenarios... as a possible strategy for reducing the ICER..." [ESC Report, p2]

S47G welcomes the ESC's suggestion to explore different 'continuation rule' scenarios as a way to improve the cost-effectiveness of A1-PI therapy. The implementation of such criteria would be supported by S47G provided the criteria are evidenced-based, equitable, feasible and clinically acceptable.

The time point to measure and assess benefit is an important consideration when developing continuation criteria in the context of this disease. Measurable changes in lung function in both treated and untreated patients are subject to a high degree of variability and generally take place slowly so the suggestion of an assessment of benefit at 4 years by ESC may be an appropriate time point for implementation.

Expert clinical advice suggests no single clinical parameter is likely able to define clinical benefit in all patients since there is a wide variation in the clinical manifestations of progressive lung disease. In this context, it may be necessary to allow for one of several measures to be used in clinical practice as part of a composite approach to establish benefit and determine whether ongoing therapy remains appropriate. Physiological / biochemical lung function and/or radiological assessments are some measures which can be used, however clinical efficacy assessments may also be relevant and clinically meaningful such as change in exercise capacity as assessed by the incremental shuttle walking test, change in symptoms as assessed by the St. George's Respiratory Questionnaire and change in rate of pulmonary exacerbations.

Whilst prescriptive criteria may be able to be applied in practice, another option may be to rely on the judgement of the treating clinician to make an assessment, taking into account multiple factors, as to the degree of benefit experienced by the patient at a point in time. S47G notes precedents which may be relevant where access to initial PBS-subsidised therapy requires the patient to fulfil prescriptive eligibility criteria, however no specific criteria are required to be met to access continuing therapy (e.g., nintedanib for IPF).

Furthermore, and given A1-PI deficiency is a rare disease which requires expert management, it may also be appropriate that applications for continuing therapy be vetted by clinicians at designated specialist centres with expertise in the management of A1-PI deficiency (consistent with a draft model proposed by an expert group of Australian A1-PI clinicians to establish A1-PI centres of excellence), and potentially adjudicated by an expert committee against the agreed criteria prior to authorizing ongoing access to therapy. This model may provide additional reassurance to Governments that ongoing treatment is only prescribed in patients deriving benefit as determined by the expert treating physician and an expert committee located at a center of excellence. Given the complexities associated with specifying continuation criteria in this disease, S47G suggests consultation with the clinical expert is made to finalise the criteria to ensure it is clinically appropriate and feasible to implement in practice.

"Monitoring of smoking status should be a mandatory requirement... and consideration should be given to stopping...therapy in individuals who resume or initiate smoking..." [ESC Report, p2]

S47G is supportive of including a stopping rule for patients who resume smoking at any stage during therapy. The ESC refers to smoking status tests, without nomination of the proposed testing method. Whilst S47G S47G supports monitoring smoking status in treated patients, there are many issues with seeking to monitor tobacco use and cessation objectively[1], such as:

- Short biomarker half-life (e.g., cotinine 16 hours in saliva, carbon monoxide 2-4 hours in expired air). Smokers may abstain in the days preceding a test and consequently produce a result that does not reflect the use of tobacco over the timeframe of interest;
- Ability to distinguish smoking from environmental/dietary exposure (e.g. thiocyanate has poor specificity for detecting light smoking);
- Some biomarkers (e.g. thiocyanate) are metabolites of a combustion product, and therefore cannot detect smokeless tobacco use. Others (e.g. cotinine) cannot distinguish tobacco use from nicotine replacement therapy;
- A test of nicotine exposure is only needed to verify the truth of self-reported non-smoking status, whereas typically, eligibility criteria are linked to clinical indicators of response to treatment. S47G is not aware of a precedent for nicotine exposure testing as a requirement for government-subsidised therapy in other settings (e.g., completion of the second half of PBS-subsided varenicline treatment relies only on self-

[1] Benowitz NL, et al. 2002. Biochemical verification of tobacco use and cessation. Nicotine & Tobacco Research (4):149– 159

reporting; and in the lung transplantation setting, there is no requirement to verify smoking cessation in patients active on the waiting list, or following the procedure itself); and

- The risk of false positives must be carefully considered to avoid inappropriate cessation of therapy in true non-smokers.

Further, patients who accept the practical burden of undergoing once-weekly intravenous therapy are likely to be highly motivated to slow progression of emphysema, and therefore could be considered less likely to resume smoking whilst undergoing active therapy, which is counterproductive to the goal of therapy, compared to an untreated patient. In these circumstances, and noting the limitations outlined above, self-reported smoking status may be a reasonable approach to monitoring smoking status as a requirement for ongoing eligibility for therapy.

"ESC noted that no studies comparing A1-PI augmentation therapy to optimal pharmacological treatment and supportive care were identified" [ESC Report, p4]

The RAPID trial was conducted in a cohort of patients with emphysema due to A1-PI deficiency who were newly diagnosed, previously untreated or currently treated patients, as well as patients currently not on therapy but on therapy in the past. Whilst not studied in an entire population where optimal pharmacological treatment was explicitly used, more than three quarters of the patients enrolled into RAPID (77.2%) had previously received, or were concomitantly receiving, adrenergic and other drugs for the treatment of chronic obstructive airway disease (Table 14.1-2.6, pp270-305, RAPID CSR, attached).

"The potential role for a Risk Sharing Agreement between the NBA and the manufacturers could be explored to manage the real potential of under-estimation of diagnosis..." [ESC Report, p8]

s47G is amenable to discussing ways to manage risk with the NBA at the appropriate time to enable timely access to therapy for eligible patients. The target patient population, circumstances of use and pricing would need to be established prior to agreement of any additional contractual obligations.

"There is uncertainty surrounding both the primary outcome measure (CT-measured lung density), and also its correlation with survival, which suggests post-listing data collection would be warranted..." [ESC Report, p8]

s47G agrees post-listing data collection would be useful to help better understand this rare disease and is amenable to working with stakeholders to help meet this objective. The ESC Report notes the *"...proposed Australian Patient Registry could assist with* (the implementation of continuation rules)*"* [ESC Report, p8]. Whilst a registry could potentially assist in the implementation of the proposed continuation criteria, ongoing eligibility status could be confirmed and implemented via administrative arrangements as part of a governance framework or an endorsed management model.

"Public funding of A1-PI therapy may result in changes in management; for example, increased use of prior tests (i.e. capturing test-negative individuals as well as diagnosed individuals)..." [ESC Report, p8]

There are two pathology tests currently available on the MBS to detect alpha-1 deficiency. The number of tests carried out in Australia suggest a high level of awareness of the disease, and therefore may not be underdiagnosed to the extent of requiring an RSA as suggested in the ESC Report [p1][2]. Consequently, the use of tests may not substantially increase should A1-PI therapy be NBA-funded given current their current use. There are also broader ethical and economic issues associated with having a specific diagnostic test publically subsidised in absence of a publically-subsidised therapy registered for use by the health authority.

Grandfathering

s47G has been providing bridging access to ex-clinical trials patients in Australia since s45, s47G and currently financially supports s45, s47G to receive ongoing therapy at s45, s47G In addition, there s45, s47G s45, s47G It is unclear whether these patients would satisfy the initial eligibility criteria, given the criteria are not yet finalised, therefore so as to not disadvantage these patients in the future should A1-PI be recommended for public funding s47G requests these patients be grandfathered to NBA-funded product. Temporary administrative provisions for these patients may need to be established to facilitate this transition.

[2] 22,312 and 1,796 services processed for MBS item 66635 and MBS item 66638, respectively, in financial year 2017-2018

Nicotine & Tobacco Research (2002) **4**, 149–159

Taylor & Francis healthsciences

Biochemical verification of tobacco use and cessation

SRNT Subcommittee on Biochemical Verification*

[Received 25 October 2000; accepted 7 June 2001]

Objectives

The charge of our subcommittee was to assess the utility of biomarkers of tobacco use and cessation and make recommendations for their application in clinical trials. The committee addressed five specific questions:

1. Which biochemical markers are most useful for assessing tobacco use, with regards to smoking cessation, smoking cessation given other tobacco use, and concurrent use of nicotine medication to aid cessation?
2. What are optimal cut-off points for biomarker values to distinguish tobacco use vs. no tobacco use, with consideration given to data on specificity and sensitivity at various cut-points and influence of ethnicity?
3. What is an acceptable time window between self-reported last smoking and biochemical verification for different biomarkers?
4. What is the utility (and limitation) of using biochemical markers as indicators of severity of addiction?
5. When is biochemical validation necessary?

*Neal L. Benowitz (Chair), University of California, San Francisco; Peyton Jacob III, University of California, San Francisco; Karen Ahijevych, Ohio State University; Martin J. Jarvis, University College London; Sharon Hall, University of California, San Francisco; Jacques LeHouezec, Pharmacia Consumer Health Care; Anna Hansson, Pharmacia Consumer Health Care; Ed Lichtenstein, Oregon Research Institute; Jack Henningfield, Johns Hopkins University School of Medicine and Pinney Associates; Janice Tsoh, University of California, San Francisco; Richard D. Hurt, Mayo Medical School; Wayne Velicer, University of Rhode Island.

Correspondence: Neal L. Benowitz, MD, Chief, Division of Clinical Pharmacology and Experimental Therapeutics, University of California, San Francisco, Box 1220, San Francisco, CA 94143-1220, USA. Tel.: +1 (415)-206-8324; Fax: +1 (415)-206-4956; E-mail: nbeno@itsa.ucsf.edu

1. Which biochemical markers are most useful for assessing tobacco use, with regards to smoking cessation, smoking cessation given other tobacco use, and concurrent use of nicotine medication to aid cessation?

This section will consider the following issues:

a. Which biomarkers are useful for determining smoking status?
b. Which biomarkers are useful for estimating nicotine intake vs. tobacco smoke exposure?
b. Which biological specimens are useful for various applications?

The pros and cons of various measures will be discussed.

Nicotine can be measured in various biological specimens including plasma, saliva, and urine (Davis & Curvall, 1999). Its specificity for tobacco use is excellent except for persons using nicotine-containing medications. There are dietary sources of nicotine, but they are insignificant compared to tobacco use (Benowitz, 1988; Davis, Stiles, deBethizy, & Reynolds, 1991). Nicotine concentrations are moderately expensive to measure, and a variety of methods are applicable, including gas chromatography (GC; Jacob & Byrd, 1999), high-performance liquid chromatography (HPLC; Crooks & Byrd, 1999), and immunoassays (Langone, Gjika, & Van Vunakis, 1999). Plasma levels, especially taken in the afternoon of a smoking day, correlate well with nicotine intake and may be used to estimate the extent of tobacco use (Benowitz & Jacob, 1984; Lawson *et al.* 1998a). Urine levels also correlate fairly well with nicotine intake (Jacob, Yu, Shulgin, & Benowitz, 1999; Lawson *et al.*, 1998b). Because of the short half-life of nicotine (about 2 h; Benowitz & Jacob, 1994; Benowitz, Jacob,

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DOI: 10.1080/14622200210123581

Denaro, & Jenkins, 1991), nicotine levels are not useful in assessing tobacco use that occurred more than 8–12 h previously.

Cotinine, the major proximate metabolite of nicotine, can be measured in various biological specimens including plasma, saliva, and urine (Davis & Curvall, 1999). Its specificity for tobacco use is excellent except for persons using nicotine-containing medications (Benowitz, 1988; Davis *et al.*, 1991). A variety of methods are available for measuring concentrations, including GC (Jacob & Byrd, 1999), HPLC (Crooks & Byrd, 1999; Harihan, Van-Noord, & Greden, 1988), and immunoassays (Langone *et al.*, 1999). Some immunoassays overestimate cotinine concentrations because of cross-reactivity with other nicotine metabolites (Anderson, Proctor, & Husager, 1991; Schepers & Walk, 1988; Zuccaro *et al.*, 1997). There is a good correlation between levels of cotinine in biological fluids with nicotine intake from tobacco (Benowitz, Kuyt, Jacob, Jones, & Osman, 1983; Rickert & Robinson, 1981). The relatively long half-life of cotinine allows detection for a few days after cessation of tobacco use (see section 3).

Colorimetric or 'dipstick' methods measure a combination of nicotine and metabolites in urine and may be useful for determining smoking status (Barlow, Stone, Wald, & Puhakainen, 1987; Peach, Ellard, Jenner, & Morris, 1985; Puhakainen, Barlow, & Salonen, 1987). These assays are simple and inexpensive, and are semi-quantitative, allowing a crude estimation of the extent of tobacco use. Certain drugs and dietary substances such as isoniazid, high doses of niacin, and other substances containing a pyridine ring may interfere with the assay and cause false positives (DynaGen, no date; Ubbink, Lagendijk, & Vennaak, 1993).

Carbon monoxide (CO) can be measured in expired air or in blood. The measurement of expired CO is simple and relatively inexpensive. Instrumentation for measurement of expired CO is commercially available (measures the rate of conversion of CO to CO_2 as it passes over a catalytically active electrode), and blood carboxyhemoglobin (COHb) can be measured spectrophotometrically (Sonnenworth & Jarrett, 1980). Expired CO and blood COHb are highly correlated (Jaffe, Kanzler, Friedman, Stunkard, & Vereby, 1981; Rickert & Robinson, 1981). CO is reasonably specific for detecting heavy cigarette smoking but is of marginal utility for detecting light smoking because CO levels from smoking are low, and there are environmental sources of CO of similar magnitude (Sonnenworth & Jarrett, 1980). One downside to using expired air CO is the initial cost ($800–2000) for the CO monitor. Measurement of CO is not applicable to detection of smokeless tobacco use because CO is a combustion product.

Thiocyanate (SCN) can be measured in plasma, saliva, and urine. Relatively simple and inexpensive spectrophotometric assays are available (Giraudi & Grillo, 1981). SCN is reasonably specific for heavy smoking, but specificity is not good for detecting light smoking, possibly because of dietary sources (Foss & Lund-Larsen, 1985; Galanti, 1997; Swan, Parker, Chesney, & Rosenman, 1985). It is not applicable to detection of smokeless tobacco use because it is a metabolite of a combustion product, hydrogen cyanide.

Anabasine and anatabine are two nicotine-related alkaloids present in tobacco. Concentrations in urine can be determined using combined gas chromatography–mass spectrometry (GC-MS; Jacob *et al.*, 1999), which is relatively expensive. Because they are not present in nicotine-containing medications, measuring concentrations of these alkaloids is useful for detecting tobacco use in persons undergoing nicotine replacement therapy (NRT). Because concentrations in urine correlate well with nicotine intake from tobacco, they can be used to estimate the extent of tobacco use (Jacob *et al.*, 1999). At present, only urine levels have been measured, but with more sensitive methodology under development it should be possible to measure concentrations in plasma and saliva. After cessation of smoking, half-lives are 16 h for anabasine and 10 h for anatabine (Jacob *et al.*, 1999).

In summary, nicotine measurement is highly specific for tobacco use (in the absence of NRT), but because of its short half-life and technical difficulty and expense in measurement, it is not recommended for general use. Cotinine is highly specific and sensitive for tobacco use (in the absence of NRT) and has the advantages of a fairly long half-life and moderate cost for analysis. When NRT is not employed, cotinine measurement appears to be the best biomarker for smoking cessation. CO measurement is useful for determining smoking status. Its sensitivity is limited by the rapid elimination of CO, such that after 1 day of not smoking, CO levels are no different than those of non-smokers (see section 3). Specificity is limited by endogenous and environmental sources of CO. For this reason, CO may not distinguish light smokers from non-smokers. SCN is not recommended as a biomarker for tobacco use because of inadequate sensitivity and specificity. Anabasine and anatabine are most useful for determining tobacco use in the presence of treatment with NRT. A potential limitation is the relatively high expense of the assay.

Which biological specimen should be used?

Generally, any specimen in which the biomarker can be measured is suitable for determining smoking status. Plasma levels of nicotine are likely to correlate best with the pharmacological effects of tobacco. Urine and saliva for cotinine are non-invasive and do not require venipuncture. The ratio of cotinine in saliva, compared to plasma, serum, or blood, averages about 1.3, with a range of 1.1–1.4 in various studies. Saliva cotinine concentration may also vary according to whether it is stimulated (such as with candy or wax). Saliva cotinine concentrations are lower in stimulated compared to unstimulated saliva. One study showed that cotinine concentrations were 26% lower with stimulation using a sugar cube and 6% lower with stimulation by chewing on paraffin wax,

Table 1. Time after smoking cessation to reach the cut-off concentration used to distinguish smokers from non-smokers (assuming average pre-cessation smoking rate)

	Cut-off	Half-life (h)	Time to cut-off (h)
Cotinine (saliva)			
General population	15ng/ml	16	80
African-American	15ng/ml	20	100
Pregnant women	10ng/ml	9	45
CO (expired air)			
Active	8–10ppm	2	6
Sedentary	8–10ppm	4	12
Sleep	8–10ppm	8	24
SCN (plasma)			
General population	78–89 μM/l	3–14 days	6–28 days

compared to unstimulated saliva levels (Schneider *et al.*, 1997). With some biomarkers, e.g. nicotine, cotinine, anabasine, and anatabine, urine levels are generally higher than levels in plasma or saliva, thus facilitating measurement and increasing the time period during which the biomarker can be measured. For SCN, better specificity/sensitivity has been observed using plasma compared to urine or saliva (Degiampietro, Peheim, Drew, Graf, & Colombo, 1987; Dourdoux, 1995). CO has the advantage of being measurable both in blood and in expired air. In addition, the results of expired CO measurement are available immediately.

2. What are optimal cut-off points for biomarker values to distinguish tobacco use vs. no tobacco use, with consideration given to data on specificity and sensitivity at various cut-points and influence of ethnicity?

A number of markers have been used as biochemical indicators of tobacco consumption, including nicotine, cotinine, SCN, and CO (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987; Ruth & Neaton, 1991; Saloojee, Vesey, & Russell, 1982). They vary in terms of cost and ease of administration, specificity to tobacco, and half-life. Measuring CO in expired air is the cheapest (once the instrument to measure it has been purchased) and most easily measured, providing feedback within seconds, and its sensitivity and specificity are both around 90%. Plasma or saliva cotinine perform best, with 96–97% sensitivity and 99–100% specificity, respectively. An advantage of cotinine is that optimal cut-points are little affected by the prevalence of smoking in the population sampled (Jarvis *et al.*, 1987). For markers whose concentrations are affected by factors other than tobacco use, such as SCN (diet) and CO (traffic, heating, and cooking emissions), optimal cut-points may vary according to prevalence of smoking, with higher cut-points being more appropriate where expected prevalence is lower (Cummings & Richard, 1988; Jarvis *et al.*, 1987; McNeill, Jarvis, West, Russell, & Bryant, 1987). Finally, the cut-points presented in this section are based on studies in general populations. For some populations, such as African-Americans or pregnant women, nicotine and cotinine metabolism differ from the general population, and optimal cut-points are likely to differ as well (Benowitz *et al.*, 1999; Klebanoff, Levine, Clements, DerSimonian, & Wilkins, 1998).

The following cut-points for the main biomarkers have been widely used and are likely to be appropriate for most circumstances:

- Plasma or saliva cotinine 15 ng/ml;
- Urinary cotinine 50 ng/ml;
- Expired air CO 8–10 ppm;
- Plasma SCN 78–84 μmol/l.

The sensitivity and specificity of cotinine does not vary much across a range of cut-points – from about 10 to 20 ng/ml – and is little influenced by variation in the prevalence of smoking in the underlying population. In many studies, urinary cotinine levels are adjusted for creatinine concentration. However, unadjusted levels may be entirely adequate for determining smoking status. Recommended cut-points for plasma and saliva nicotine are not given. This is because, in the case of salivary nicotine, concentrations are highly influenced by local exposure in the mouth because ambient tobacco smoke, for example, may not be a good indication of systemic levels. Plasma nicotine has not been widely used as a marker of smoking status, for reasons of short half-life and the need for invasive blood sampling. Salivary and urinary SCN lack sufficient sensitivity and specificity to make their use advisable.

3. What is a useful time window between self-reported last smoking and biochemical verification for different biomarkers?

The useful time window for the use of a biomarker to assess tobacco use depends on the specific biochemical marker, the level of exposure, and the selected cut-off point. The characteristic of the biomarker that is most useful in determining how long it will remain in the body

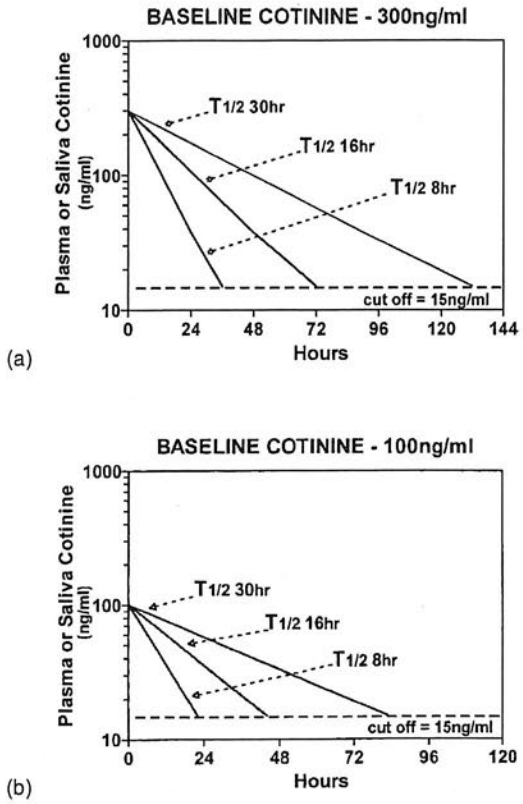

Figure 1. (a) Simulated blood or saliva cotinine concentrations over time, assuming an initial concentration of 300 ng/ml, and different half-lives. The dashed line represents a non-smoking cotinine level cut-off of 15 ng/ml. Cut-off would be reached at 130, 70, and 35 h if cotinine half-life was 30, 16, and 8 h, respectively. (b) Similar simulation to (a), but starting from a baseline cotinine level of 100 ng/ml. Cut-off would be reached at 83, 44, and 22 h if cotinine half-life was 30, 16, and 8 h, respectively.

is the half-life. The half-life of a drug is determined by the rate of clearance from the body and the extent of distribution of the drug in body tissues. Half-life for a particular biomarker can vary considerably from person to person. Therefore, estimates using half-life data need to consider not only the mean or median value but also the range of values.

The half-life of a chemical describes the time it takes for the level of the chemical to decline by 50%. At two half-lives, the level has declined to 25%, at three half-lives to 12.5%, and at four half-lives to 6.25% of the original value. Thus, knowing the initial level of a chemical in the body and the half-life, one can estimate how long it will take to reach a given cut-off point.

The three biomarkers that will be considered in this section are cotinine, CO, and SCN (Table 1). Cotinine levels peak in the body 1–2 h after the last dose of nicotine. African-Americans and Chinese-Americans metabolize cotinine more slowly than do Caucasians, and the half-life of cotinine is longer in these populations (Benowitz *et al.*, 1999). Pregnant women metabolize cotinine more quickly than when they are not pregnant, so their cotinine half-life is shorter (Dempsey, Jacob, & Benowitz, 2002).

For an initial cotinine level of 300 ng/ml, which is a typical level in a daily smoker, it would take five half-lives for this level to decline below the cut-off of 15 ng/ml (Figure 1). Assuming a half-life of 16 h, the duration of abstinence required to reach the non-smoker cut-off level would be 80 h. If a smoker has a lower level of cotinine, it would require four or even three half-lives, which would correspond to 64 or 48 h, respectively, to reach the cut-off concentration. Considering the range of half-lives in the population, for an 8-h half-life the interval from abstinence to reach cut-off would range from 24 to 40 h (three to five half-lives), whereas for a long half-life of 30 h it would take from 90 to 150 h. Considering the longest cotinine half-life (so as to minimize false positive results) and typical initial cotinine levels, 7 days is a reasonable interval to use to assess compliance with non-smoking in most studies. It should be recognized that false negatives may be seen in individuals who have stopped for 2 or more days prior to cotinine measurement, depending on the half-life.

The estimates for CO are more complicated because the half-life for CO depends on the level of physical activity. CO is eliminated in expired air, and the rate of elimination depends on the individual's pulmonary ventilation rate. With sedentary activity, the half-life of CO is 2–3 h, while during sleep the half-life is up to 4–8 h (Coburn, Forster, & Kane, 1965). During exercise, the half-life can be as brief as 1 h. The long half-life during sleep explains why smokers who have not smoked overnight can awaken in the morning with COHb levels as high as 5% (approximately 30 ppm in expired air).

A typical cut-off point for CO in expired air is 8 ppm. Assuming the level of CO during cigarette smoking begins at 40 ppm, it would require about three half-lives to decline to 8 ppm. Assuming a half-life of 2–3 h, this would correspond to 6–9 h to reach cut-off. In an individual who is physically active, the interval would be less. However, during sleep it would decline much more slowly. For an average smoker, considering the sleep/wake cycle, 24 h can be taken as a time point in which the CO level would almost certainly have declined to cut-off. However, it would be possible for someone to smoke a few cigarettes within 24 h and still be below cut-off, depending on the half-life. It should be noted that CO exposure from environmental sources can result in expired CO levels of 2–6 ppm, depending on the extent of exposure to traffic exhaust and other pollution.

SCN is eliminated from the body by excretion in the urine. Its excretion rate depends on kidney function. With normal kidney function, half-lives of 3–14 days have been reported in different studies (Schulz, Bonn, & Kindler, 1979). Even non-smokers have a considerable level of SCN in the body, derived from foods. On average, smokers have SCN levels two to four times higher than those of non-smokers (Vogt, Selvin, & Hulley, 1979). Assuming the level of SCN is four times

higher in smokers than in non-smokers, it would take an average of two half-lives, or 1–4 weeks, for the level to decline from a smoker's level to that typical of a non-smoker.

Studies of persons in the natural environment and the time to reach non-smoker levels or cut-off points were reviewed for empirical evidence to support the half-life data. Because more specific information was available for cotinine as a biomarker than for CO or SCN, cotinine is the focus of this discussion. Nine studies on the topic were identified and summarized. Study samples included subjects who quit smoking in the natural environment, those who were abstinent after completing a 5-day series of nicotine capsules, inpatient and outpatient subjects receiving placebo NRT, and those in 6- and 7-day inpatient studies where cotinine during abstinence was measured (Abrams, Follick, Biener, Carey, & Hitti, 1987; Ahijevych, Kihm, Dhatt, & Weed, 1999; Benowitz *et al.*, 1983; Carey & Abrams, 1988; Dale *et al.*, 1995; Hecht *et al.*, 1999; Jarvis, Russell, Benowitz, & Feyerabend, 1988; Trudgill, Smith, Kershaw, & Riley, 1998; Wewers *et al.*, 2000). Sample sizes were generally small, ranging from five to 31 subjects (mean, 13.7 subjects). Baseline cotinine levels and cigarettes per day (cpd) were not available in two of the nine studies. The mean plasma baseline cotinine levels across four studies ranged from 156 to 302 ng/ml. Saliva baseline cotinine ranged from 93 to 350 ng/ml (two studies). Urine cotinine averaged 1394 ng/ml in one study, and urine cotinine to creatinine ratio averaged 9.7 in another. Mean cpd by study ranged from 12 to 24. The cut-off points for cotinine were 10 or 14 ng/ml in plasma and saliva, 50 ng/ml in urine, 0.4 μg in 24-h urine sample, and a cotinine:creatinine ratio <2. Cut-points were not identified in two reports.

With heterogeneous study designs, small sample sizes, and some gaps in data, a definitive statement on time to reach non-smoker levels is problematic. However, a range of acceptable window estimates can be described. The shortest time to reach non-smoker levels was a mean of 2.8 days (SD, 1.3; range 1–5 days) for the sample with a low average baseline salivary cotinine level of 93 ng/ml and a baseline smoking rate of 12 cpd (Carey & Abrams, 1988). A similar time frame of 2.9 days to reach non-smoker levels was estimated for persons abstinent following administration of nicotine capsules (Jarvis *et al.*, 1988). A mean of 0% cotinine replacement was reported the evening of Day 4 of smoking abstinence in placebo NRT subjects, which would be comparable to non-smoker level (Dale *et al.*, 1995). An average of 4.7 days (range 3–6 days) was evident to reach <14 ng/ml in a small inpatient study (n=6) where smoking abstinence was monitored (Wewers *et al.*, 2000). Sixteen per cent of subjects (5/31) had plasma levels >14 ng/ml at 136 h of smoking abstinence on discharge (5.7 days) in a similar inpatient-monitored protocol (Ahijevych *et al.*, 1999). At 7 or more days of self-reported abstinence in the natural environment, cotinine was not detected in 96% (24/25) of subjects (Abrams *et al.*, 1987). Seven days to reach non-smoker levels was also reported for persons in a study using cotinine in 24-h urine samples as the biomarker (Hecht *et al.*, 1999). Approximately 80% (9/11) of quitters had cotinine to creatinine ratios in the non-smoker range at 7 days (Trudgill *et al.*, 1998).

Clearly, baseline cotinine levels are critical in determining a useful time window to biochemically verify non-smoking status. In field studies where baseline cotinine data are not readily available for every participant to estimate half-life and when non-smoker levels would be reached, a 7-day window of self-reported smoking abstinence would most likely capture and accurately classify almost all persons as non-smokers using cotinine as the biomarker.

4. What is the utility (and limitation) of using biochemical markers as indicators of severity of addiction?

Defining addiction

In the field of addictive disorders, the definition of addiction is made almost exclusively on behavioral or symptomatic indices and, for the most part, ignores drug (and by inference biomarkers of) intake. This has evolved over the years, as it became evident that intake was not a good assessment tool for whether a person was dependent upon that drug. For example, on a given day, an alcoholic might be at a very low level of intake and, because the half-life is short, have a low blood alcohol level. On the same day, an occasional non-problem drinker might be at a higher level of intake and have higher blood alcohol level. At one point, the National Council on Alcoholism used blood alcohol concentrations to define tolerance and, if the levels were high enough, to define dependence (Criteria Committee, NCoA, 1972). An individual with a blood alcohol concentration of 1500 μg/ml of alcohol without showing signs of intoxication was considered to be exhibiting tolerance. An individual who had a blood alcohol concentration of 3000 μg/ml at any time was considered to be alcoholic because in order to drink enough to reach this blood level would require tolerance. Blood alcohol concentrations have not been a part of the DSM classification of alcoholic dependence (APA, 1994).

Tobacco appears to be an exception, because levels of intake tend to be stable in most smokers, and biomarkers such as cotinine are related to the level of nicotine intake. There is considerable inter-individual variability in the relationship between levels of cotinine and the daily intake of nicotine from tobacco, but cotinine levels predict nicotine intake better than cpd (APA, 1994). The reasonably long half-life of cotinine means that a particular level reflects nicotine intake over the past 2–3 days.

Nicotine dependence and its severity may be defined both in behavioral terms and in terms of a biomarker(s). Most researchers would agree that higher levels of

consumption of tobacco products are related to the severity of dependence, i.e., the more consumed, the more likely a higher level of dependence. When smokers are categorized according to light, moderate, and heavy, then biomarkers such as nicotine and cotinine are correlated with the level of smoking. In some studies where there has not been a relationship between smoking rate and cotinine, the smokers may not have been stratified well enough to have a clear demarcation in the smoking rate (Lawson *et al.*, 1998b). The Fagerström test for nicotine dependence (FTND) includes, as one of its more important questions, quantity of smoking (Fagerström, 1978). A relationship between the FTND score and plasma cotinine levels has been observed (Pomerleau, Pomerleau, Majchrzak, Kloska, & Malakuti, 1990). In that study, shorter latency to the first cigarette in the morning was also related to the cotinine levels, as was the question, 'Do you smoke if you are so ill that you are in bed most of day?' While the FTND has not been consistent in predicting successful treatment outcome for nicotine dependence across all studies, it has been reported to be predictive in many studies (Fagerström & Schneider, 1989). Furthermore, using the 4-mg dose of nicotine gum in people with higher FTND scores has been shown to be more effective than the 2-mg dose (Sachs, 1995).

Biomarkers and behavioral predictors of outcome

Cotinine has also been shown in some (but not all) studies to be a predictor of treatment outcome, with those with higher levels of cotinine having a poorer outcome during nicotine dependence treatment, whether it be behavioral treatment or nicotine replacement (Hall, Herning, Jones, Benowitz, & Jacob, 1984). For NRT, these outcome data may simply be related to inadequacy of nicotine replacement, which might be improved were the doses to be increased. CO levels and the FTND scores have also been shown to be related, reflecting most likely the number of cigarettes smoked per day (Fagerström & Schneider, 1989).

Biomarkers and addiction

Because tobacco intake and severity of addiction appear to be related, we believe that biomarkers can be valid indices of dependence level, medication need, or both. As discussed previously, the biomarkers to be considered are nicotine, cotinine, SCN, and CO levels of expired air. Each has its own strengths and weaknesses. In brief review, SCN is not specific for tobacco use and may have too long a half-life to make it clinically useful in defining the severity of dependence. On the other end of the spectrum, CO and serum nicotine levels may have too short a half-life such that they are highly dependent on the recency of last smoking. Cotinine appears to be the best marker to gauge the severity of dependence, although CO, SCN, and cotinine in combination could be used in a complementary way to assess an individual's nicotine intake over time. Clinically, cotinine levels reflect nicotine intake over time in a way similar to the use of glycosylated hemoglobin in assessing the adequacy of control of an insulin-dependent diabetic. In this analogy, plasma glucose is used much in the same way as serum nicotine, for example, and a more immediate marker.

Thus, from an assessment and treatment standpoint, plasma cotinine levels could be used to assess severity of nicotine dependence and assess the level of medication needed, especially with regards to NRT.

5. When is biochemical verification necessary?

In considering statistical issues in smoking treatment research, we limited ourselves to randomized trials and focused our discussion on two variants of these trials frequently reported in the literature.

The first is the 'clinic-based randomized trial,' which has a sample size usually under 500, typically 150–250. Participants are volunteers. These volunteers participate in a good deal of face-to-face contact with researchers. There are multiple assessments – frequently at baseline, post-treatment, and 6–12 months. The primary outcome variables are point-prevalence abstinence and 12-month continuous abstinence, biochemically verified. By the end of 1 year, about 10–20% of the sample has dropped out. 'Missingness' does not differ between conditions, but it is related to gender and number of cigarettes smoked at baseline.

The second is the population-based trial that is characterized by a much larger sample size – usually 1000+ – often recruited through healthcare settings or worksites or by random-digit dialing from a defined geographic region. The goal of a population-based study is to produce a sample that is representative of a defined population. Biochemical validation could produce a selection bias unrelated to smoking status. The primary outcome variables are the same as in the clinic-based trial, but biochemical verification is not generally used. Follow-up periods tend to be longer, often stretching to 24 months. Missing data rates tend to be somewhat higher – perhaps more like 30% than 20% at the end of follow-up – and may well differ between groups, particularly if one group received more active and time-consuming interventions. The higher missing data rates may also reflect the somewhat longer follow-up rates. They may also be related to baseline variables such as number of cigarettes smoked, education or gender.

Clinic-based studies

Biochemical verification has been generally recommended for clinic-based randomized trials. However, empirical data have been lacking to support this recommendation (e.g., Glasgow *et al.*, 1993; Patrick *et al.*, 1994; Velicer, Prochaska, Rossi, & Snow, 1992).

A review was conducted to address the following questions:

a. Does biochemical verification affect outcome in clinic-based trials?
b. Which populations are more likely to have biochemical verification affect outcome?
c. What other study conditions/characteristics are related to such effect?

A literature search using the *MEDLINE* database was conducted for studies published between 1990 and 1999, with 'smoking cessation' as subject, and 'controlled clinical trials, or randomized clinical trials' as publication type. From a total of 471 studies that met the search criteria, we identified 163 non-duplicate studies that met the following criteria: (1) some participants received smoking cessation treatment; (2) there was more than one treatment condition; (3) abstinence rates were reported; and (4) the total sample size was less than 500. Out of the 163 studies, 101 (61.9%) of the studies indicated using biochemical verification for smoking abstinence reported. Eighteen (11.0%) studies provided sufficient data for treatment outcome to be re-analyzed based on self-report abstinence rates alone vs. rates verified by biochemical verification. Three additional studies from Hall and colleagues (Hall, Munoz, & Reus, 1994; Hall *et al.*, 1996, 1998), for which we had the raw data for both self-reported and biochemically verified rates, were included in the analyses with the 18 studies. Thus, 21 studies provided data for this review. Eighteen of these had sufficient data for analysis in the published reports; three, those from Hall's laboratory, were based on data not available in the published articles.

For the purpose of this review, outcome data containing abstinence rates that were self-reported or biochemically verified were abstracted from these 21 studies at two time points: end of treatment, and 12-month follow-up or the longest follow-up assessment available. When end-of-treatment assessment data were not available, data were abstracted from the first and the last assessments reported. For each study, data were re-analyzed using Pearson χ^2 tests based on self-reported abstinence rates alone and biochemically verified rates (self-report plus biochemical verification).

Treatment outcome was concluded to be affected by biochemical verification when the result from the analysis based on self-reported abstinence alone was different from that based on biochemical verification using $p<0.05$. The data were analyzed using two approaches: (1) complete-case analysis: excluding participants with missing data (self-reported smoking, biochemical verification, or both) and (2) intent-to-treat: including all participants who were randomized into treatment conditions and treating missing data as smoking or relapse. The complete-case analysis would yield the 'highest' abstinence rates; and the intent-to-treat approach would yield the 'lowest' abstinence rates. These two approaches were, therefore, chosen to evaluate the impact of biochemical validation on outcome analyses.

Data from a total of 34 comparisons derived from 21 studies were included in the analyses. Twelve studies provided data from only one assessment. Seven studies provided data from two assessment points: end-of-treatment, and 12-month follow-up or the longest assessment available. These seven studies thus accounted for 14 comparisons. Two studies (Hall *et al.*, 1996, 1998) used a 2×2 factorial design and provided data from two assessments; in these two studies, treatment outcome was compared separately for each factor, resulting in four comparisons from each of these two studies. Thus, these two studies account for eight comparisons.

Does biochemical verification affect outcome in clinic-based trials with sample size less than 500?

Using the complete-case approach, four out of 31 comparisons (12.9%) derived from four out of 19 studies (21.0%) showed that treatment outcome was affected by biochemical verification (three comparisons derived from two studies were excluded from the complete-case analysis because attrition information was not available). Under the intent-to-treat approach, five out of the 34 (14.7%) comparisons derived from five out of the 21 studies (23.8%) showed the impact of biochemical verification on treatment outcome. Most of the differences occurred where a significant treatment effect was found based on self-reported abstinence, but not when based on biochemical verification. Two comparisons derived from two studies, however, indicated that analyses based on biochemical verification yielded a significant treatment effect when self-report did not. Both of these were studies of pregnant women.

Which populations are more likely to have biochemical verification affect outcome?

The data included in the current review were abstracted from various study populations. Out of the 34 comparisons, 15 (44.1%) were from special populations, which were derived from 12 studies (57.1%). The special populations studied in the current review included pregnant women, primary care patients, VA patients, hospitalized patients, cancer patients, drug dependence patients, and individuals with a history of depression and alcohol dependence. Using complete-case analysis, among the four studies where outcome evaluation was affected by biochemical verification, three of them were from a special population. Similarly, using the intent-to-treat approach, three out of five studies that showed an impact of biochemical verification on treatment outcome used special populations. The special populations, on which the data suggested an impact of biochemical verification on treatment outcome, were pregnant women, patients with alcohol and depression history, and VA-hospitalized patients after surgery. Among the four studies of pregnant women, two indicated an impact on

outcome from biochemical verification. Both of these studies showed that the outcome analyses based on biochemical verification yielded a significant treatment effect under either or both of the analytic approaches.

What other study conditions/characteristics are related to the effects of biochemical verification on outcome?

Other study characteristics included: what portion of the sample was asked to provide biochemical verification: all subjects vs. subjects reporting abstinence only, percentage of participants providing biochemical verification, or assessment time points? The percentage of participants providing biochemical verification was the only characteristic that appeared to determine whether biochemical verification affected outcome. Using the complete-case approach, three out of four studies in which outcome was affected by biochemical verification had more than 10% of biochemical verification data missing. Similarly, under the intent-to-treat approach, four out of five studies that were affected by biochemical verification had more than 10% of these data missing.

This review did not yield definitive findings with respect to the necessity of biochemical verification in clinical trials. Indeed, the most striking finding was that only 18% of the studies identified reported enough self-report and biochemical data to make comparisons possible. Reporting of both outcomes in a format that allows ready comparisons would contribute to our understanding of when biochemical verification is useful.

Also, given the usual requirements around disclosure to human participants, it is a reasonable assumption that most participants in the studies reviewed knew that the veracity of their self-report would be evaluated by biochemical verification. Results may be different when this is not the case.

Even so, some findings warrant further study. First, it appears that special populations may indeed be more likely to provide self-report data that is discordant with biochemically verified data. Second, a high rate of missing biochemical data and discrepancies between biochemical data and self-report appear to be related.

Population-based studies

There is an extensive body of evidence relating to the utility of and necessity for biochemical validation in large population-based studies. Four major papers have either reviewed the literature or evaluated an extensive sample:

a. Velicer *et al.* (1992) provide an extensive literature review, including 21 studies involving cotinine and 29 studies involving CO. They conclude that misreporting rates are generally very low, typically near zero and seldom exceeding 5% except in high-risk medical settings, such as involving patients with heart disease or pregnant women, where the misreporting rate averaged 13%.
b. Glasgow *et al.* (1993) concluded that biochemical validation was sometimes not feasible and did not alter the conclusions of low-intensity intervention trials. These authors also dismissed the implications that participants refusing to provide biological fluids for analysis were cessation failures.
c. Patrick *et al.* (1994) performed a meta-analysis on 51 comparisons and concluded that self-reports are accurate in most studies. They also suggested that biochemical validation could improve accuracy in student samples and intervention studies.
d. The COMMIT Research Group performed an ancillary study to investigate the validity of self-report. The full report of that study is not available at this time, but a summary has been presented (COMMIT Research Group, 1995). Preliminary analysis found no difference in misrepresentation between the intervention groups and the comparison group in either the heavy smoker or the light-to-moderate smoker cohorts. The direction of the differences should be noted. Misreporting rates were lower in the intervention condition (5.1% and 6.8%) than in the comparison condition (7.7% and 8.8%).

The results of these four studies are consistent and suggest that biochemical validation is not always necessary in smoking cessation studies. The levels of misrepresentation are generally low. Alternative methods of validation such as employing multiple items to verify smoking status are likely to produce accurate estimates, and there is little reason to expect differential misrepresentation rates in most smoking cessation studies.

The decision to employ biochemical validation

Three broad issues that impact the decision about whether to employ biochemical validation in a specific study will be considered:

a. *Demand characteristics* – That is, aspects of the intervention that increase demand on smokers to quit. Different types of clinical trials present different levels of demand characteristics. Population-based intervention trials typically have very low demand characteristics, while clinic-based studies may involve very high demand characteristics. Special populations are to some extent defined by a contextual demand characteristic. The adolescent is smoking illegally, and parents and teachers often will express strong disapproval. Pregnant women and medical patients face strong demand characteristics from medical service providers and society in general. In large population-based trials with low-demand situations, biochemical validation appears not to be necessary. There are inadequate data for trials in high-demanding settings.
b. *Type of study.* Clinic-based trials are widely employed in the initial stages of evaluating the efficacy of an intervention. They often rely on reactively recruited

volunteer subjects, involve extensive experimental controls, and are of relatively brief duration. Population-based interventions are employed to demonstrate the generalizability of established interventions. Proactive recruitment is employed to recruit a representative sample, the degree of participation is at least partially under the control of the participants, and an extended follow-up is employed.

c. *Type of population.* That is, general population vs. special subgroup. Special subgroups include adolescents, pregnant smokers, intensive group interventions, and medical patients.

Three issues should be considered in making the decision to employ biochemical validation in a high-demand study. Underlying each of these three issues is a need to clearly establish the purpose of knowing a person's smoking status. Each of these issues is important not only with respect to the decision to use biochemical validation but also to such basic issues as accuracy of conclusions and statistical power.

a. What is the likely rate of refusal of biochemical testing, and how will those subjects who refuse be classified? Traditionally, subjects who refuse have been assumed to be smokers. Refusal rates for clinic studies are extremely low (i.e., under 15%). Refusal rates for population-based interventions have been as high as 70%. Refusal-rate problems can result in an overestimate of smoking rates if all refusers are classified as smokers. In some studies, patients receive intervention as part of routine clinical care and are 'informed' there is a study as part of follow-up assessment. Such participants may understandably refuse to provide biochemical data.
b. What alternative explanations exist for false positive testing results? The assumption that all inconsistencies between self-report and biochemical testing are because of inaccurate self-report may not be justified. SCN and CO are particularly vulnerable to environmental influences, especially in light smokers who have relatively low levels of these biomarkers from their tobacco use. Cotinine testing must carefully assess the presence of other forms of nicotine, including the use of nicotine replacement products and extensive exposure to secondhand smoke. The former problem can be addressed by measurement of minor tobacco alkaloids, although such measurements are not currently widely available.
c. What is the likely impact of inaccurate self-report on the evaluation of the intervention? A goal of an intervention study is typically to determine the relative difference in smoking rates between two groups. For biochemical validation to modify the estimates, it would be necessary to demonstrate that a differential misreporting rate exists between the intervention and the control groups and apply a correction to the estimate of the relative difference. Most studies do not have adequate power to detect such a difference because it would involve multiplying the proportion of participants who quit smoking by the proportion of self-reported quitters who fail biochemical validation. It would require considerably larger sample sizes to perform the correction than is feasible in most smoking cessation studies.

These three issues, in combination, suggest that in large-population, low-intensity intervention trials, biochemical verification is neither feasible nor necessary. While it is likely that self-report inflates quit rates, the magnitude of such inflation is small, and there rarely is differential across intervention conditions.

On the other hand, for small-population, high-demand clinical trials of new interventions, where accurate estimation of quit rates is necessary for regulatory approval and for determining benefits vs. risks of a treatment, biochemical verification is feasible and is strongly encouraged. Likewise, biochemical testing is recommended for special populations, where there is an incentive to deceive, such as in adolescents, pregnant women, and medical patients with smoking-related diseases. Finally, biochemical information is mandatory for studies evaluating novel nicotine-delivery products (such as devices that heat rather than burn tobacco, which are currently being test-marketed in the USA) or for harm reduction studies, where the level of exposure to nicotine and other tobacco smoke toxins is an essential end-point.

Recommendations

Considering all of the above, we recommend the following. In most settings, biochemical verification provides additional assurance that the participant's self-reports are accurate. Because currently available methods of verification are relatively inexpensive and not invasive, it is our recommendation that they be used in most new product and all harm-reduction studies. We also recommend that biochemical verification be used in most or all studies of smoking cessation in special populations, such as adolescents, pregnant women, and medical patients with smoking-related diseases. There are circumstances under which the added precision gained by biochemical verification is offset in such a way that its use is not required and may not be desirable. Examples include large-scale population-based studies with limited face-to-face contact and studies where the optimal data collection methods are through the mail, telephone, or Internet. We also recommend that researchers who collect both self-report and biochemical verification data report both separately in published articles, indicating discrepancies between the two in various intervention conditions, so that future research may better address the question of the utility of biochemical verification across a range of studies, treatment modalities, and populations.

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Purified human alpha1-proteinase inhibitor for the treatment of alpha1-proteinase inhibitor deficiency, leading to chronic obstructive pulmonary disease

August 2018

MSAC application no. 1530

Assessment report

Internet site http://www.msac.gov.au/

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at http://www.msac.gov.au/

Enquiries about the content of the report should be emailed to hta@health.gov.au.

The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee that has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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LIST OF TERMS

Acronym/Abbreviation	Definition
A1PI	Alpha-1 proteinase inhibitor
AATD	Alpha-1 anti-trypsin deficiency
AT	Augmentation therapy
ARTG	Australian Register of Therapeutic Goods
BOS	Bronchiolitis obliterans syndrome
BODE	BMI, obstruction, dyspnoea, exercise capacity
BSC	Best supportive care
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
D_{LCO}	Diffusing capacity for carbon monoxide
EQ-5D	Euroqol group 5 domain questionnaire
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FVC	Forced vital capacity
GOLD	Global initiative for chronic obstructive lung disease
ICER	Incremental cost-effectiveness ratio
IgA	Immunoglobulin A
IPD	Individual patient data
K_{CO}	Diffusing coefficient for carbon monoxide
MBS	Medicare benefits schedule
MCIDs	Minimal clinically important differences

MITT	Modified intention-to-treat
MSAC	Medical Services Advisory Committee
NBA	National Blood Authority
NPL	National Product List
PASC	PICO Advisory Sub-committee
PBAC	Pharmaceutical Benefits Advisory Committee
PD15	15th Percentile lung density
PI	Product information
PICO	Population, intervention, comparator, outcomes
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trials
SGRQ	St Georges Respiratory Questionnaire
SMD	Standardised mean difference
TGA	Therapeutic Goods Administration
TLC	Total lung capacity

EXECUTIVE SUMMARY

Main issues for MSAC consideration

- Minimum clinically important differences (MCIDs) for the primary outcome in the core randomised controlled trials (RCTs), i.e. Computed tomography (CT)-measured lung density, are not established in the literature. The best available evidence suggests a correlation between CT-lung density decline and mortality and functional outcomes, however, it is currently unclear whether, or to what extent, this translates to a clinically important impact of augmentation therapy (AT) with Alpha-1 proteinase inhibitor (A1PI). No significant differences were observed between A1PI and placebo for the remaining effectiveness outcomes.
- Only a limited number of economic studies relating to AT cost effectiveness were identified in the literature. Two American studies related resource use to expected life gain using USA registry data. High incremental expected survival of 7+ years in non-smokers resulted in AT appearing relatively cost effective. The RAPID trial was not powered to determine differences in forced expiratory volume in 1 second (FEV_1) or mortality, so uncertainty surrounds the magnitude of this clinical benefit given available trial data.
- The modelling in this assessment generated a lifetime incremental cost-effectiveness ratio (ICER) of s47(1)(b) per quality-adjusted life year (QALY) and a trial period ICER of s47(1)(b). It is evident that most benefits accrue after the RAPID trial period. The assumption about the price paid for the AT product is the key driver of model results. The base cost of AT assumes a price per 1,000 ml of s47(1)(b). This varies from s47(1)(b) to s47(1)(b) per 1,000ml vial. The estimated ICER varies considerably from s47(1)(b) to s47(1)(b) per QALY.
- The estimated NBA financial cost of AT listing is presented over a six-year costing proposal period and is based on a s47(1)(b) uptake rate for AT by 2023. Uptake begins at s47(1)(b) and increases by s47(1)(b) per year. The cost to the national blood authority (NBA) for the total AT market is estimated to be s47(1)(b) in 2019, increasing to s47(1)(b) in 2023.
- A key uncertainty is the price of AT. Given the large contribution of the AT product itself to overall resource in the economic model, variations in price have a large impact on both financial and economic attractiveness.

This contracted assessment examines the evidence supporting the listing of purified human A1PI on the National Product List (NPL) for blood products. The service would primarily be used in the outpatient hospital or clinic setting for the treatment of A1PI deficiency, also known as alpha-1 antitrypsin deficiency (AATD). Some patients may be able to self-administer the intervention at home. The target population is people with severe A1PI deficiency (defined as serum A1 ≤11 µM)

plus emphysema. The applicant claims that successful listing of the technology in the target population and setting will lead to slower disease progression compared to best supportive care.

ALIGNMENT WITH AGREED PICO CONFIRMATION

This contracted assessment largely conforms to the PICO elements that were pre-specified in the PICO Confirmation ratified by the PICO Advisory Sub-Committee (PASC). Only placebo-controlled trials were identified for the evaluation of effectiveness outcomes (i.e. not best supportive care), and eligible indications were broadened slightly for the evaluation of safety outcomes (i.e. not limited to phenotype PiZZ).

PROPOSED MEDICAL SERVICE

The proposed medical service is for lifelong intravenous blood augmentation via weekly infusions of purified human A1PI. The currently recommended dosing strategy is 60mg/kg per week, noting that ongoing trials are investigating optimal dosing regimens. Augmentation therapy with A1PI is not currently funded or reimbursed in private or public settings in Australia for this or any other clinical indication.

PROPOSAL FOR PUBLIC FUNDING

AT with A1PI is proposed for reimbursement on the National Products List (NPL), managed by the National Blood Authority (NBA). As such, no Medicare Benefits Schedule (MBS) item descriptor is required.

POPULATION

The intended population includes ex- or never-smoking patients with emphysema and severe A1PI deficiency (serum A1 ≤ 11 µM). The frequency of Australians with PiZZ allele, which indicates the most severely affected patients with greatly increased risk of emphysema, is estimated at 1 in 5,584. Null allele is very rare and its occurrence cannot be estimated. Based on educated estimates, the number of people meeting the criteria for treatment with A1PI in Australia in 2018 was s47(1)(b) Considering treatment is lifelong and not curative, the number of patients being treated is expected to have a moderate cumulative increase over time.

COMPARATOR DETAILS

The comparator intervention for patients with chronic obstructive pulmonary disease (COPD) is best supportive care (BSC). Strategies for the management of stable COPD include non-pharmaceutical strategies (pulmonary rehabilitation and physical activity), pharmacological strategies (inhaled

medications, corticosteroids and antibiotics), and prevention of deterioration and end-stage strategies.

CLINICAL MANAGEMENT ALGORITHM(S)

Patients with A1PI deficiency are currently managed with BSC, which aims to provide symptomatic relief. AT is an additive intervention to supplement BSC for patients with emphysema. The current (Figure 2) and proposed (Figure 3) clinical management algorithms are presented in the report.

CLINICAL CLAIM

The applicant claims that, relative to best supportive care, A1PI slows disease progression in patients with severe A1PI deficiency and emphysema.

APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

A systematic review of published and unpublished literature was undertaken. The medical literature was searched to identify relevant studies in Embase on 23 May 2018 and in PubMed and The Cochrane Library on 24 May 2018. RCTs were appraised for risk of bias using the Cochrane RoB 2.0 tool, non-randomised studies were appraised using the Cochrane ROBINS-I tool, and single-arm studies were appraised using the IHE checklist for observational studies.

CHARACTERISTICS OF THE EVIDENCE BASE

Three RCTs were identified that evaluated the effectiveness of A1PI compared to placebo in 313 patients. Included patients were relatively homogenous across the included studies, representing ex- or never-smokers with severe A1PI deficiency (serum A1 ≤11μM) and emphysema (FEV_1 25% to 80%). The included RCT outcomes were generally well conducted; however, method of allocation concealment was poorly reported across all trials. Seventeen single arm studies were identified that provided evidence on the safety of A1PI.

RESULTS

SAFETY

Seventeen single arm studies were included for the evaluation of safety outcomes. Key safety outcomes were: death due to adverse events, severe adverse events, and discontinuation or hospitalisation due to adverse events.

Six deaths occurred in the eligible studies, which included 899 patients. None of these deaths were reported to be treatment-related. Severe adverse events were also uncommon, with a median occurrence of 2% in the patient population (range 0%-38%). Discontinuation due to adverse events had a median occurrence of 0.5% in the patient population (range 0%-12%) across nine studies.

Hospitalisation had a median occurrence of 1.5% in the patient population (range 0%-14%) across four studies.

Three studies reported safety in patients treated with one of the two therapies under assessment, Zemaira and PROLASTIN-C. All of these studies found that rates of severe adverse events were unchanged across intervention groups.

Fifteen studies reported any adverse event, with a rate ranging from 0% to 100% and a median of 37%. Differences between the RCTs and observational studies in the rates of any adverse event may indicate under-reporting in the observational studies. Dyspnoea and treatment-related adverse events were also reported. Dyspnoea occurred after AT in 12.5% of the patient population (range 0%-35%). Events reported by the authors to be treatment-related had a median occurrence of 11% in the patient population (range 0%-38%).

Overall, it appears that the intervention is safe, with most events being related to the underlying disease.

EFFECTIVENESS

No direct trials comparing A1PI to BSC were identified. Three RCTs investigated the clinical efficacy of A1PI compared to placebo. CT-measured lung density was the primary outcome in two RCTs, and FEV_1 was the primary outcome in one RCT.

No significant differences between A1PI and placebo were identified in relation to mortality, exacerbation of COPD, hospitalisation due to COPD exacerbation, quality of life (SGRQ), respiratory function (FEV_1), exercise capacity (incremental shuttle walk test) or carbon monoxide diffusion capacity (D_{LCO}). No relevant data was identified for dyspnoea.

The only statistically significant difference was observed for CT-measured lung density, which favoured A1PI, however, the clinical significance of this difference is uncertain, as MCIDs for changes in CT-lung density have not been established in the literature.

The summary of findings (incorporating both benefits and harms) is shown in Table 1.

Table 1 **Balance of clinical benefits and harms of A1PI relative to placebo as measured by the critical patient-relevant outcomes in the key studies**

Outcomes (units) Follow-up	Risk with placebo	Risk with A1PI (95% CI)	Relative effect (95% CI)	Participants (studies)	Quality of evidence (GRADE)	Comments
Mortality F/U 24 months	34 per 1,000	12 per 1,000 (2 to 78)	RR 0.35 (0.05 to 2.27)	180 (1 RCT)	⊕⊕⊕⊙ MODERATE	Uncertain due to low event rate, RR subject to error
Quality of life (SGRQ) F/U 24 to 30 months	-	MD 0.83 points lower (3.49 points lower to 1.82 points higher)	-	248 (2 RCT)	⊕⊕⊙⊙ LOW	Direction favours placebo; not statistically significant
Annual exacerbation rate F/U 24 to 30 months	-	-	Higher reported RR (1.26, 95% CI 0.92 to 1.74), MD (0.36, 95% CI -0.44 to 1.16) in A1PI group	257 (2 RCT)	⊕⊕⊕⊙ MODERATE	Direction favours placebo; not statistically significant
CT-measured lung density F/U 24 to 30 months	-	SMD 0.87 g/L higher (0.31 higher to 1.42 higher)	-	304 (3 RCT)	⊕⊕⊕⊕ HIGH	Direction favours A1PI; statistically significant
Mortality due to treatment-related adverse events F/U 24 months	No treatment-related deaths reported			180 (1 RCT)	⊕⊕⊕⊙ MODERATE	No reported deaths due to treatment-related adverse events
Severe adverse events F/U 24 to 30 months	341 per 1,000	283 per 1,000 (195 to 406)	RR 0.83 (0.57 to 1.19)	257 (2 RCTs)	⊕⊕⊕⊕ HIGH	Direction favours A1PI; not statistically significant
Discontinuation due to adverse events F/U 24 to 30 months	48 per 1,000	10 per 1,000 (2 to 62)	RR 0.22 (0.04 to 1.30)	248 (2 RCTs)	⊕⊕⊕⊙ MODERATE	Direction favours A1PI; not statistically significant
Hospitalisation due to adverse events F/U 3 to 6 years	Median rate 1.4% (range 0.0% to 14.3%)			497 (4 observational studies)	⊕⊕⊙⊙ LOW	-

Abbreviations: **F/U** = follow-up, **MD** = mean difference, **RR** = relative risk, **SGRQ** = St George's Respiratory Questionnaire, **SMD** = standardised mean difference.
GRADE Working Group grades of evidence (Guyatt et al., 2013)
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

On the basis of the benefits and harms reported in the evidence base (summarised above), **it is suggested that, relative to BSC, A1PI has inferior safety and uncertain effectiveness.** This conclusion is predicated on the understanding that the intervention poses an additional risk of adverse events in addition to conservative management, noting that most adverse events associated

with the intervention were mild, and severe adverse events were not significantly different across treatment and placebo arms in the RCTs. Relative to placebo, there were no important differences in safety outcomes.

TRANSLATION ISSUES

Three key issues arise in translating the evidence provided in Section B to an economic model presented in Section D. The first, relates to the applicability of the populations in the pivotal RAPID trial to clinical practice in Australia; the second, concerns selection of utilities; and the third, involves extrapolation of trial evidence beyond the maximum follow-up of RAPID. The key uncertainty is that the RAPID trial only had a maximum follow-up of four years on the intervention arm, however, AATD is a chronic condition for which AT is likely to provide longer-term clinical impacts. A base four-year trial analysis and a stepped analysis, where the model timeframe is extrapolated over a lifetime, are included in the economic analysis. Patients are assumed to stay on no decline, slow and rapid decline tracks for the remaining 26 years of the projection after the trial period. Annual mortality during the RAPID trial is used for the trial period, after which extrapolation of survival is undertaken using parametric models fitted to the UK registry data using analysis undertaken by CSL Behring. Given that the majority of clinical benefits are estimated during the extrapolated period, for which there is no trial evidence, considerable uncertainty exists around economic results.

ECONOMIC EVALUATION

A cost-utility analysis was undertaken to determine the value of AT in addition to optimal pharmacological treatment and supportive care (best supportive care). A summary of the key characteristics of the economic evaluation are provided below (Table 2), for more detail see Table 62.

Table 2 Summary of the economic evaluation

Perspective	This economic evaluation was conducted from the perspective of the Australian health system. It includes resource use supported by government and patients, along with health outcomes applicable to the treatment of patients with emphysema due to A1PI deficiency.
Intervention	Augmentation therapy in addition to optimal pharmacological treatment and supportive care.
Comparator	Best Supportive Care. Optimal pharmacological treatment and supportive care
Type of economic evaluation	Cost-utility analysis
Sources of evidence	RAPID study, RAPID-OLE study, UK Registry data
Time horizon	30-year time horizon in the base case Sensitivity analyses include a time horizon of 20 years and 40 years
Outcomes	Quality-adjusted life years (QALY)/ life-years gained
Methods used to generate results	Cohort expected value analysis

Health states	1. $FEV_1 \geq 50\%$ predicted, no lung density decline 2. $FEV_1 \geq 50\%$ predicted, slow lung density decline 3. $FEV_1 \geq 50\%$ predicted, rapid lung density decline 4. $FEV_1 < 50\%$ predicted, no lung density decline 5. $FEV_1 < 50\%$ predicted, slow lung density decline 6. $FEV_1 < 50\%$ predicted, rapid lung density decline 7. Lung transplant 8. Dead
Cycle length	1 year
Discount rate	5% used for base and 3.5% and 7% sensitivity analyses
Software packages used	Microsoft Excel 2010

Abbreviations: **MBS** = Medicare Benefits Schedule; **QALY** = quality adjusted life year.

Only a limited number of economics studies relating to AT cost-effectiveness were identified in the literature. Two studies related resource use to expected life gain using USA registry data. High incremental expected survival of more than seven years in non-smokers resulted in AT appearing relatively cost-effective. Gildea et al. (2003) developed a model where health states were stratified by COPD severity using FEV_1 defined ranges. This approach is also adopted in COPD modelling more broadly. RAPID was powered to detect changes in CT-scanned lung density. Correspondingly, the patient level data and model developed by CSL Behring defined health states by FEV_1 predicted and CT lung density decline tracks. This approach is followed in this assessment.

The incremental cost and the incremental effectiveness of adding AT to BSC as an intervention relative to BSC as a comparator are presented in Table 79, and briefly in Table 3. The incremental cost-effectiveness ratio is presented as the incremental cost of achieving an additional QALY. It has been found that the lifetime ICER is s47(1)(b) per QALY and for the trial period is s47(1)(b). It is evident that most benefits accrue after the RAPID trial period, which is not based on clinical evidence.

Table 3 Incremental Cost Effectiveness Ratio (1,000-patient cohort)

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Trial period					
A1PI Augmentation Therapy	s47(1)(b)		3,018.2	170.3	s47(1)(b)
Best Supportive Care	18,531,803		2,847.9		
Lifetime					
A1PI Augmentation Therapy	s47(1)(b)		6,010.6	1,351.5	s47(1)(b)
Best Supportive Care	37,389,939		4,659.1		

Abbreviations: **A1PI** = alpha-1 proteinase inhibitor; **ICER** = incremental cost effectiveness ratio; **QALY** = quality-adjusted life year.

The assumption about the price paid for the AT product is the key driver of model results (Table 4). The base cost of AT assumes a price per 1,000 ml of s47(1)(b). This varies from s47(1)(b) to s47(1)(b) per 1,000ml vial. The estimated ICER varies considerably from s47(1)(b) to s47(1)(b) per QALY. The transitions assumed between no, slow and rapid decline patient states in the RAPID trial period also have a

large impact on the estimated ICER. CSL Behring provided confidential trial data at the patient level that tracks the proportion of patients on the AT and BSC arms over the first two years for BSC and four years for AT. Given that large proportions of patients are estimated to transition to the FEV_1<50 rapid-decline group, the choice of parametric model for the purpose of estimating annual mortality for this health state is important.

Table 4 Drivers of the economic model

Description	Method/Value	Impact
Cost of the AT product	The average dosing for AT is taken from the RAPID trial and applied to an average weight of 75.9 kg. The number of vials (rounded to a whole number) is multiplied by average, high and low AT product prices.	The base cost of AT assumes a price per 1,000 ml (s47(1)(b)). This varies from s47(1)(b) to s47(1)(b) per 1,000ml vial. The estimated ICER varies considerably between s47(1)(b) and s47(1)(b) per QALY.
Transition between FEV_1 and CT density decline during RAPID drives clinical benefit	There were considerable differences in transition between health states for the AT and BSC arms in the RAPID trials. The economic model assumes movement to no, slow and rapid decline tracks during the trial period is sustained for a lifetime.	A higher number of patients move to the FEV_1<50 decline states on the BSC arm in RAPID. Movement during the trial period drives economic results. Allowing transition between no, slow and rapid tracks after 4 years has limited impact on the estimated ICER.
Selection of extrapolation model for the FEV_1<50 rapid-decline group survival	In most cases the Gompertz model is the best fit model to extrapolate survival and this model is used across all non-transplant states. The model is varied as part of sensitivity analyses that included use of the Log-logistic, Lognormal, Weibull, Exponential and Generalised Gamma specifications. Large numbers of patients transition to this state during the trial period, particularly on the BSC arm.	The specification of the FEV<50 rapid-decline model had the largest impact on the estimated ICER. The use of Lognormal, Generalised Gamma and Weibull models resulted in the ICER being 10% more cost effective, while use of the Exponential model resulted in a 10% decrease in cost effectiveness.
Disease management costs for COPD	Disease management costs in many reviewed COPD economic models were an aggregate of maintenance and acute care costs during flare ups. The frequency of flare ups was not explicitly modelled in this assessment. The Thomas et al. 2014 analysis included acute care proportions for each state. They are varied by 20% for each COPD state.	This variation has limited impact as economic results are governed by AT product costs. The proportion of severe COPD patients who are very severe, assumed to be 74% in the base cases, also varied. Similarly, this scenario had limited impact on the estimated ICER.

Abbreviations: **AT** = augmentation therapy, **BSC** = best supportive care, **COPD** = chronic obstructive pulmonary disease, **CT** = computed tomography, **FEV_1** = forced expiratory volume in 1 second, **ICER** = incremental cost effectiveness ratio.

ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

The financial impact of the potential listing of A1PI AT is calculated using an epidemiological approach over a six-year period, based on an estimate of the number of patients eligible for treatment. The financial impact of AT on the NBA is summarised in Table 5. The estimated cost is presented over the six-year costing proposal period and is based on a s47(1)(b) uptake rate for AT by 2023. Uptake begins at s47(1)(b) and increases by s47(1)(b) per year. The cost to the NBA for the total AT market is estimated to be s47(1)(b) in 2019, increasing to s47(1)(b) in 2023.

Table 5 Total costs to the NBA associated with AT

	2019	2020	2021	2022	2023
AT-eligible patients	s47(1)(b)				
% uptake of AT					
AT patients across Australia					
Average weight (kg)	76	76	76	76	76
Recommended dose (mg/kg body weight)	60	60	60	60	60
Grams of AT per patient per week	4554	4554	4554	4554	4554
Vials per patient per week	5	5	5	5	5
Adherence	94%	94%	94%	94%	94%
Number of vials across Australia	s47(1)(b)				
Cost per 1,000ml vial ($)					
Cost per patient per year ($)					
Total cost of AT $					

Abbreviations: **AT** = augmentation therapy.

A key uncertainty is the price of AT. Variations in price have a large impact on both financial and economic attractiveness because of the large contribution of the AT product itself to overall resource in the economic model. The proposed price of PROLASTIN-C is s47(1)(b) per 1,000ml vial and ZEMAIRA s47(1)(b). An average price of s47(1)(b) is included, with s47(1)(b) and s47(1)(b) used as high and low bounds in sensitivity analyses. Varying the prevalence proportions by 10% has a lesser financial impact. Uptake rate also has an impact. A decrease in year 2022 uptake from s47(1)(b) to s47(1)(b) results in a s47(1)(b) budget requirement in that year.

CONSUMER IMPACT SUMMARY

Six associations provided targeted feedback, and one individual provided non-targeted feedback on this consultation. All respondents using the feedback form 'strongly agreed' with the clinical claim made by the applicant.

OTHER RELEVANT CONSIDERATIONS

The accessibility of A1PI to rural and remote patients is potentially limited owing to distance from specialist centres, respiratory physicians and temperature-controlled transport. Training required to self-administer A1PI and the eligibility of lung transplant patients and current smokers for A1PI therapy needs to be addressed.

A1PI meets three of the four criteria warranting rule of rescue. It is unclear whether the proposed service provides worthwhile clinical improvement. Owing to the rarity of A1PI deficiency, clinical trials are often under-powered to detect statistical differences in outcomes such as quality of life (QoL) and mortality. Rather, studies use lung CT densitometry, an outcome correlative to markers of lung health and mortality, to infer clinical efficacy. When this is taken into consideration with the results from the trials listed in section B it is unclear whether A1PI provides worthwhile clinical improvement.

SECTION A CONTEXT

This contracted assessment of purified human A1PI for the treatment of Alpha-1 anti-trypsin deficiency (AATD) leading to chronic obstructive pulmonary disease (COPD) is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of safety, effectiveness and cost effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise. This application was received on behalf of the National Blood Authority, for listing of A1PI on the NPL for blood products.

Research and Evaluation, incorporating ASERNIP-S of the Royal Australasian College of Surgeons has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of purified human A1PI for the treatment of alpha1-proteinase inhibitor deficiency, leading to COPD. This assessment has been undertaken in order to inform MSAC's decision-making regarding whether the proposed medical service should be publicly funded. Appendix A provides a list of the people involved in the development of this assessment report.

The proposed use of A1PI in Australian clinical practice was outlined in an MSAC application that was released in a targeted consultation on 2 February 2018. The subsequent PICO Confirmation was presented to the PICO Advisory Sub-Committee (PASC) and ratified on 7 June 2018.

A.1. ITEMS IN THE AGREED PICO CONFIRMATION

This contracted assessment largely conforms to the PICO elements that were pre-specified in the PASC-ratified PICO Confirmation. There are two key deviations from the proposed PICO criteria:

1. The proposed population was focussed on the primary indication of severe A1PI deficiency (serum levels ≤11 µM) and emphysema with FEV_1 <80%. Evidence for effectiveness was limited to this population group. Safety data investigating adverse events of A1PI infusion were broadened slightly in order to capture adverse events associated with AT.

2. No studies comparing AT to optimal pharmacological treatment and supportive care were identified. In lieu of this, placebo-controlled trials were included.

A.2. PROPOSED MEDICAL SERVICE

The proposed medical service is for lifelong intravenous blood augmentation via weekly infusions of purified human A1PI. This is the first time that purified human A1PI has been assessed by MSAC.

AT is an additive intervention that will be given in addition to BSC for patients with emphysema (Ranes and Stoller 2005). Therapeutic concentrations of A1PI are prepared from the blood of plasma donors. The product is presented as a sterile lyophilised powder in a 1g vial. It needs to be reconstituted in 20 mL of water for intravenous administration. Treatment takes fifteen minutes and is conducted in an outpatient hospital or clinic setting in the first instance. Patients may administer the therapy at home after receiving adequate training and when deemed appropriate by the treating specialist.

There are currently no established doses or regimens for A1PI augmentation therapy. Product information for PROLASTIN-C recommends administering 60mg/kg of the drug intravenously once a week (Therapeutic Goods Administration 2016). This dose and frequency was used in the RAPID and EXACTLE RCTs (Chapman et al. 2015; Dirksen et al. 2009), however, the precise dose that confers the greatest clinical efficacy is yet to be determined. Higher weekly doses of up to 120 mg/kg have been evaluated for safety outcomes. The SPARK study was a multicentre RCT with four months follow-up. Participants were treated with a weekly infusion of either 60mg/kg or 120mg/kg of PROLASTIN-C for eight weeks, followed by a cross-over period. This study reported that the higher dose can be given for at least eight weeks, being safe and well tolerated. It should, however, be studied for a longer period to ascertain effectiveness (Campos et al. 2013). In contrast, a pharmacokinetic case series study of A1PI treatment found that, while safe, 120mg/kg every two weeks did not maintain appropriate serum levels above 80mg/dL for the whole two weeks (Barker et al. 1997). An ongoing trial, the SPARTA trial, aims to investigate the efficacy and safety of weekly 60mg/kg or 120mg/kg doses of PROLASTIN-C versus placebo in a multicentre RCT with three years follow-up. The findings of this study are not yet published (Sorrels et al. 2015).

Access issues could exist in rural and remote areas of Australia where specialist care is not always available to provide AT. Patients may opt to move nearer to specialist centres to receive weekly AT, however, this is not always an option.

PROLASTIN-C and Zemaira (marketed as Respreeza in Europe), are two AT products registered on the Australian Register of Therapeutic Goods (ARTG) in Australia. The two therapies consist of the same components with slightly different eligibility criteria (see Table 6). Both products are provided in a pack containing:

- 1 vial 1g lyophilised powder
- 1 vial 20 mL sterile water for injection
- 1 sterile filter needle
- 1 vented transfer device

Table 6 Approved augmentation therapies and their indications

Product	ARTG ID and details
PROLASTIN-C	ARTG ID 234553: indicated to increase serum A1PI levels in adults with congenital deficiency of alpha-1 anti-trypsin and with clinically significant emphysema (FEV_1 less than 80%). The data for clinical efficacy of PROLASTIN-C is derived from changes in the biomarkers alpha-1 anti-protease level and CT lung density. Efficacy on FEV_1 or patient relevant endpoints such as quality of life or pulmonary exacerbations has not been established in randomised clinical trials. Clinical trials have only included patients who were not smoking.
Zemaira	ARTG ID 273182: indicated for maintenance treatment, to slow the progression of emphysema in adults with documented severe A1PI deficiency (A1PI less than 11 μM) and progressive lung disease. Patients are to be under optimal pharmacologic and non-pharmacologic treatment.

Abbreviations: **ARTG** = Australian Register of Therapeutic Goods, **FEV_1** = forced expiratory volume in 1 second, **μM** = micromolar.

EQUIVALENCE OF PROLASTIN-C AND ZEMAIRA

Two studies have investigated the bioequivalence of PROLASTIN-C and Zemaira to Prolastin (Table 7). PROLASTIN-C has been proven by a 24-week crossover study to have pharmacokinetic equivalence and a comparable safety profile to Prolastin (Stocks et al. 2010b). Prolastin has been approved for use in the United States for over 35 years. Another study by the same group demonstrated that the newer product, Zemaira, is bioequivalent to Prolastin by a 24-week double blind study with an open label extension (Stocks et al. 2006). Since both products are equivalent to Prolastin, they are considered in this assessment to be equivalent to each other.

Table 7 Studies evaluating the biocompatability of A1PI therapies

Authors Publication Year Study ID	Study design Evidence level	Location Length of follow-up	Description of Intervention	Description of Comparator	Relevant outcomes assessed	Measurement of outcomes and analysis	Outcomes
Stocks et al. 2006	RCT Cross over Level II	United States 24 weeks	Weeks 1 – 24 Zemaira 60mg/kg per week N = 30 *analysis performed on 29 patients	Weeks 1 – 10 Prolastin 60mg/kg per week Weeks 11 – 24 Zemaira 60mg/kg per week N = 14	**Primary outcome** • Trough serum antigenic A1PI levels **Secondary outcome** • Adverse events	T-test	Mean difference from baseline (Zemaira – Prolastin) 447.5nM p = 0.40 Zemaira vs Prolastin 121 vs 73 AE 2 vs 3 TAE 3 vs 10 SAE 0 vs 0 TSAE

Stocks et al. 2010	RCT Cross over Level II	United States 24 weeks	Weeks 1 - 8 PROLASTIN-C 60mg/kg per week Weeks 9 - 16 Prolastin 60mg/kg per week Weeks 17 - 24 PROLASTIN-C 60mg/kg per week N = 12	Weeks 1 - 8 Prolastin 60mg/kg per week Weeks 9 - 16 PROLASTIN-C 60mg/kg per week Weeks 17 - 24 PROLASTIN-C 60mg/kg per week N=12	**Primary outcome** • Pharmacokinetic comparability: $AUC_{0\text{-}7\ days}$ **Secondary outcome** • Adverse events	ANOVA Wilcoxon Rank test	Ratio of point estimates and 90% CIs for $AUC_{0\text{-}7\ days}$ PROLASTIN-C vs Prolastin 1.03 (0.97, 1.09) vs 0.98 (0.95, 1.02) PROLASTIN-C vs Prolastin 11 vs 9 AE 0 vs 2 SAE 0 vs 0 TAE PROLASTIN-C weeks 17 - 24 11 AE and 0 SAE in

Abbreviations: **A1PI** = alpha-1 proteinase inhibitor, **AE** = adverse event, **ANOVA** = analysis of variance, **AUC** = area under the curve, **CI** = confidence interval, **RCT** = randomised controlled trial, **SAE** = serious adverse event, **TAE** = treatment-related adverse event, **TSAE** = treatment-related serious adverse event.

CURRENT FUNDING ARRANGEMENTS

The proposed intervention is not currently reimbursed in Australia. AT is currently provided via out-of-pocket payments, however, for many patients, the majority of whom are not working, the cost is prohibitive for lifelong treatment.

A.3. PROPOSAL FOR PUBLIC FUNDING

No MBS item descriptor is required for this application. AT is proposed for reimbursement on the NPL managed by the National Blood Authority. New blood and blood-related products reviewed by the Jurisdictional Blood Committee may be referred to MSAC for evidence-based evaluation of the safety, clinical effectiveness or cost-effectiveness. This is the case with A1PI augmentation.

A.4. PROPOSED POPULATION

The population to be considered in this assessment is ex- or never-smoking patients with emphysema and severe A1PI deficiency. Severe A1PI deficiency is defined as serum levels below 11 µM (approximately 59 mg/dL) (Hatipoglu and Stoller 2016). Clinically, this deficiency manifests as panacinar emphysema or hepatitis, cirrhosis, and/or hepatoma (Pharmacy and Therapeutics 2010). Less commonly, vasculitis and panniculitis are observed (Pharmacy and Therapeutics 2010).

The chance of emphysema developing with A1PI deficiency increases across the PiMZ, PiSZ and PiZZ phenotypes, with the most significant contributor being the PiZZ phenotype (de Serres and Blanco

2014). The assessed treatment is to be limited to patients with the PiZZ or null phenotypes (see Table 8 for detail on these phenotypes).

PATHOPHYSIOLOGY OF CONDITION

AATD is an inherited genetic condition that results in decreased circulating, and/or abnormally functioning, A1PI protein. A1PI is predominantly synthesized by hepatocytes and released into the bloodstream where it acts as a serine protease inhibitor, with neutrophil elastase being its primary substrate (de Serres et al. 2003). A1PI deficiency, defined as ≤30% of normal serum levels, is known to have a role in the development of liver disease and emphysema, and has been hypothesised to be part of pathological processes underlying a range of health conditions.

The consequences of A1PI deficiency for lung and liver function occur via different pathways. In the lungs, neutrophil elastase, which has an important role in fighting infection, is normally bound and inactivated by A1PI. Low levels of A1PI mean that the enzymatic activity of neutrophil elastase goes unchecked and ultimately its detrimental impact on elastin compromises the bronchia and alveoli. Conversely, liver damage occurs when the A1PI protein forms polymers that accumulate within hepatocytes, leading to scarring, inflammation or malignancy. Figure 1 shows a simplified schematic of the mechanisms underlying disease associated with the most prevalent allele causing A1PI deficiency (Fregonese and Stolk 2008).

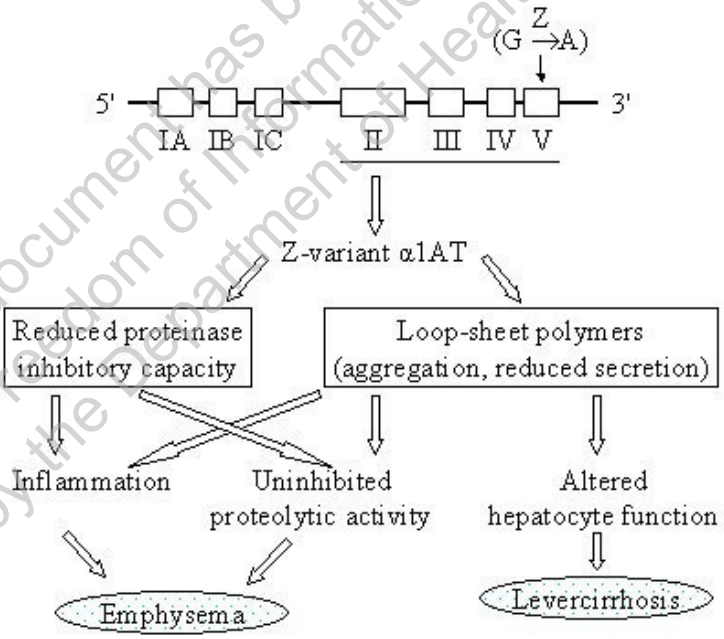


Figure 1 **Simplified schematic of the pathway to lung and liver disease associated with A1P1 deficiency (Fregonese and Stolk 2008)**

A1PI production is specified by a pair of co-dominant alleles on the SERAPINA1 gene, of which the PiMM (protease inhibitor, homozygote M) is the most common and normal functioning state. Individuals with only one abnormal gene (e.g. PiMZ or PiMS) may have reduced production of A1PI

but are often asymptomatic and are considered carriers. Genetic variants with at least 100 alleles have been described. The most prevalent deficiency-causing allele is the Z allele, of which the PiZZ state is amongst the most severe manifestations of deficiency (Brode et al. 2012). PiSZ and other rare variants also contribute to the burden of disease attributable to A1PI deficiency (Häggblom et al. 2015). In rare cases, patients with a PiNull/Null phenotype do not produce any A1PI.

INCIDENCE IN AUSTRALIA

Serum A1PI levels associated with selected variants, including those contributing to early onset emphysema, are shown in Table 8 (adapted from Hatipoglu and Stoller 2016). Prevalence data from Australia is limited, however, de Serres et al. (2003) reported gene frequencies per 1,000 people from a range of cohort studies conducted in various populations in Australia. De Serres et al. (2003) reported that the estimated prevalence of carriers of deficiency alleles in the Australian population is 1 in 8.9 individuals; the majority of whom are carriers. For PiSZ the prevalence was estimated to be 1 in 841 and for PiZZ it is estimated at 1 in 5,584. It is the PiZZ allele that contributes to the greatest burden of lung disease in the A1PI deficient population.

Lung manifestations of disease present in adulthood and early symptoms are common to a range of conditions, thus the number of patients with a diagnosis is likely to be an under-estimate of the true prevalence of the condition. Changes in the reported prevalence estimates are only likely to affect uptake. However, if genetic or phenotype testing for A1PI deficiency becomes more common for COPD patients or family members of known A1PI deficient patients.

Further, it was noted by PASC that not all people with PiZZ A1PI deficiency will go on to develop severe emphysema. Based on estimations made by the commercial sponsors, the incidence of people meeting the criteria for treatment with A1PI in Australia was s47(1)(b) in 2018. More precise estimates of the prevalence of the condition and potential uptake are reported in Section E.1. Considering treatment is expected to be lifelong and is not curative, the number of patients being treated will have a cumulative increase over time.

Table 8 Serum A1PI levels associated with normal and SZ or ZZ allele variations known to increase the risk of emphysema (Hatipoglu and Stoller 2016)

Alleles	Impact	Serum A1PI levels Mg/dL (Mean [5th–95th Percentile])	Genetic prevalence in the Australian population (de Serres et al. 2003)**
MM	Normal	147 (102–254)	Not applicable
MS or MZ	Carriers, usually asymptomatic	125 (86–218) 90 (62–151)	1 in 12 1 in 40
SS	Slightly increased emphysema risk, mildly symptomatic or asymptomatic	95 (43–154)	1 in 507
SZ	Individuals produce less A1PI than normal and have an increased risk of emphysema	62 (33–108)	1 in 841

Alleles	Impact	Serum A1PI levels Mg/dL (Mean [5th–95th Percentile])	Genetic prevalence in the Australian population (de Serres et al. 2003)**
ZZ*	Most severely affected , individuals have a greatly increased risk of emphysema and liver disease	≤29 (≤29–52)	1 in 5,584
Null	Very rare, no A1PI produced	0	Very rare, cannot be estimated

Abbreviation: **A1PI** = alpha-1 proteinase inhibitor.
*It has been estimated that the number of individuals with the ZZ form in Australia is 4,126 (between 2,894–5,695)(Blanco et al. 2017).
**Genetic prevalence (95% confidence interval) per 1,000 for the PiS allele is 44.4 (40.7–48.5); for the PiZ allele it is 13.4 (11.4–15.7).

A.5. COMPARATOR DETAILS

There are currently no active comparators for AT that modify the progression of emphysema or COPD in patients with AATD. The comparator for this intervention is best supportive care, which is aimed primarily at symptom management and control of COPD exacerbations and respiratory infections. Strategies for the management of stable COPD are provided in the Australian and New Zealand guidelines for the diagnosis and treatment of COPD (Yang et al. 2017) as follows:

NON-PHARMACEUTICAL STRATEGIES

Pulmonary rehabilitation and physical activity are strongly evidenced to be effective in optimising function (Yang et al. 2017). Pulmonary rehabilitation includes supervised exercise training and can be given in conjunction with any number of the following: behaviour change, nutritional advice or psychosocial support.

PHARMACOLOGICAL STRATEGIES

Inhaled medications are the primary pharmacological strategy for managing COPD (Yang et al. 2017). A stepwise approach is recommended for taking inhaled medicines, irrespective of severity, until adequate control is reached (Lung Foundation Australia). The aim of pharmacological strategies is to reduce symptoms, prevent exacerbations, and improve health status by targeting the pathophysiology of the disease.

Apart from inhaled medications, corticosteroids and antibiotics can be recommended. Oral corticosteroids hasten resolution of exacerbations and reduce the likelihood of relapse. For purulent sputum, antibiotics may also be recommended to address typical and atypical organisms.

Furthermore, comorbidities that often accompany COPD, the main ones being anxiety and depression, increase hospitalisation and need to be managed. Osteoporotic fractures are also a common problem in patients with COPD, hence bone mineral density testing is important for prevention and monitoring. COPD and its resulting hypoxaemia are known to lead to pulmonary hypertension and right heart failure, especially when occurring with sleep apnoea. When this is

suspected clinically, arterial blood gas or a sleep study should be conducted, leading to oxygen therapy or continuous positive airway pressure.

PREVENTION OF DETERIORATION

Behavioural change is also recommended (Yang et al. 2017). In the hope of preventing deterioration, patients are recommended to cease cigarette smoking (of utmost importance), reduce alcohol consumption, increase physical activity, and avoid environmental irritants.

Another helpful approach is vaccination against influenza and pneumococcal, as it reduces exacerbations due to influenza and pneumococcal in high-risk seasons. When used together there is an additional benefit.

Long-term use of supplemental oxygen assists correction of severe hypoxaemia and might also improve survival. Use of supplemental oxygen for longer periods has been reported to have greater benefits. For all COPD patients, ambulatory oxygen may be of benefit when blood is desaturated due to exertion.

END STAGE STRATEGIES

Lung transplantation or lung volume reduction, either by surgery or bronchoscopically, might be required for patients with very severe disease (Yang et al. 2017). Only certain patients may be considered appropriate for lung volume reduction, such as those with severe emphysema, hyperinflation and ongoing symptoms despite best management and pulmonary rehabilitation. Likewise, patients considered for lung transplantation would be those suffering severe functional impairment and airflow obstruction not appropriately managed by other strategies. PASC noted that lung transplantation is not curative and transplant recipients would still be in need of A1PI supplementation to prevent gradual deterioration of the lungs.

A.6. CLINICAL MANAGEMENT ALGORITHM

The current and proposed clinical management algorithms are presented in Figure 2 and Figure 3, respectively. Patients are currently managed with BSC, including pharmacological symptom management and non-pharmacological strategies mentioned in Section A.5. Current treatment strategies are primarily aimed at alleviating COPD symptoms, and are not disease modifying.

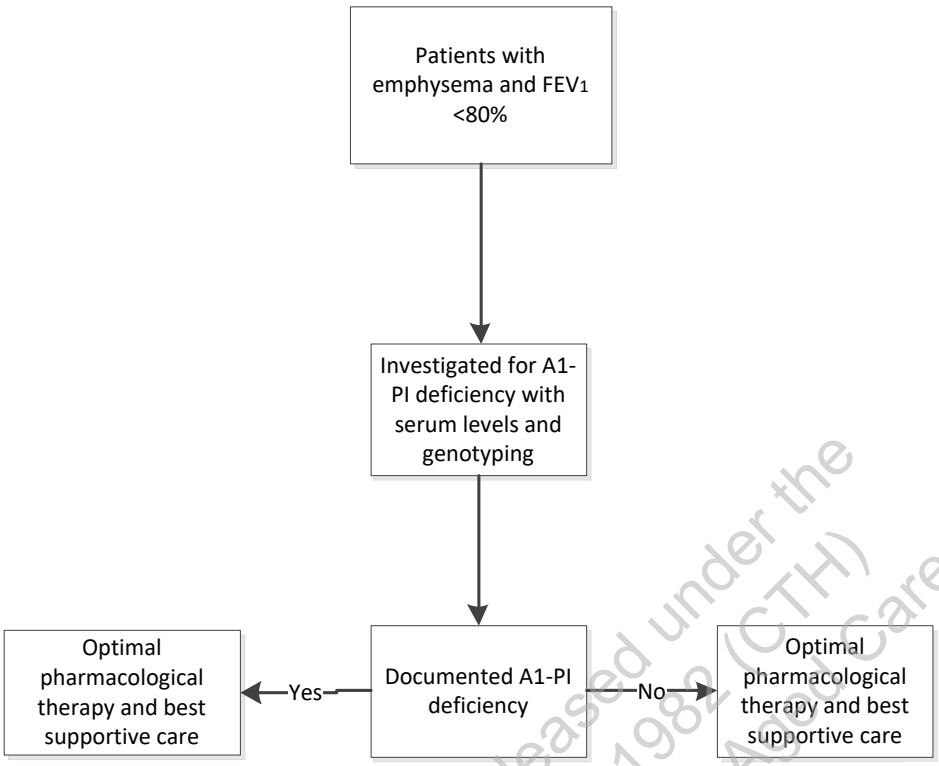


Figure 2 **Current clinical management algorithm for patients with emphysema and FEV1 <80%**

AT is an additive intervention, which will be given in addition to BSC for patients with emphysema (Ranes and Stoller 2005). The main difference in the current and proposed treatment pathways is the necessity for patients to stop smoking in order for AT to be effective.

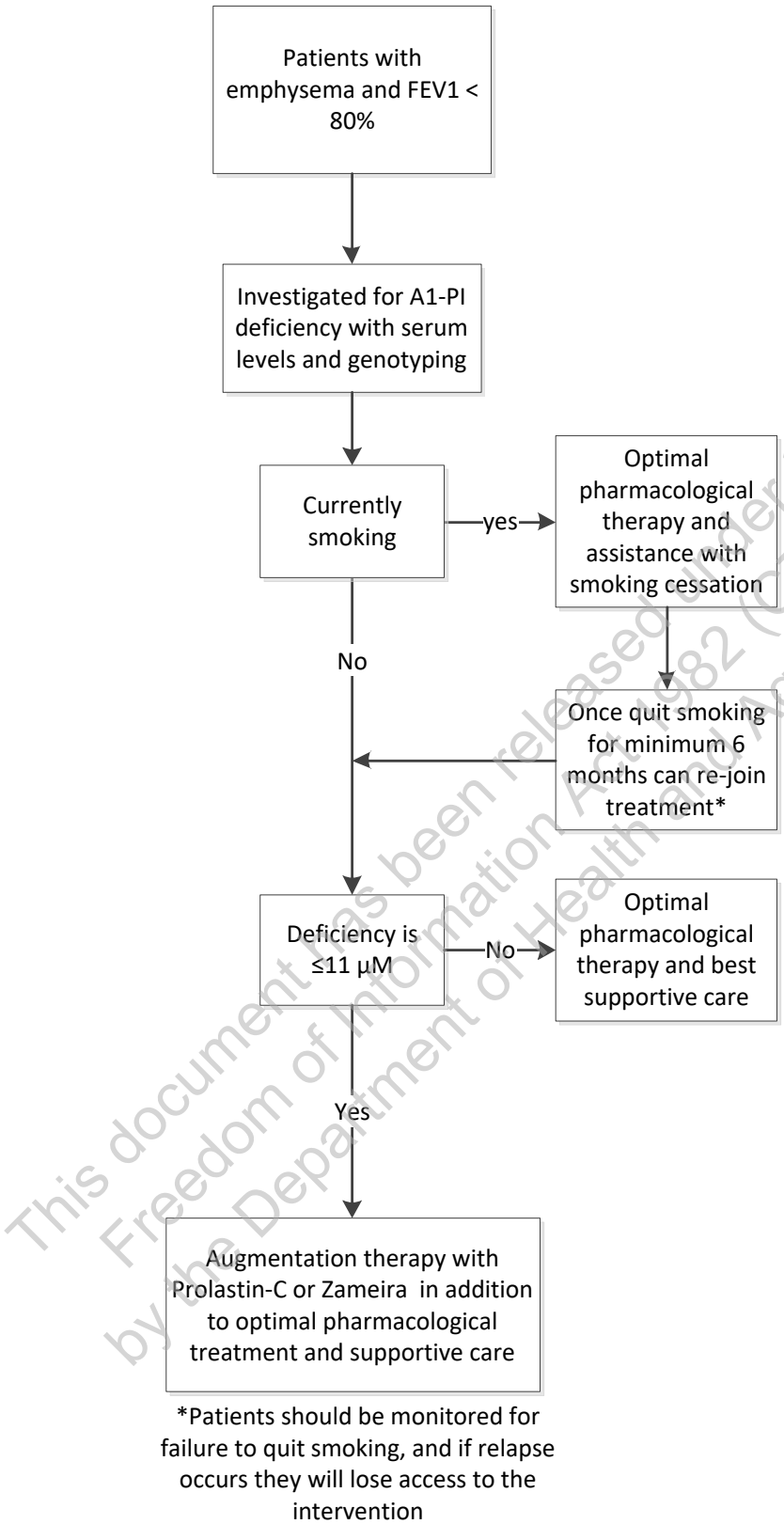


Figure 3 **Proposed clinical management algorithm for patients with emphysema and FEV1 <80%**

A.7. KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

The key difference is the outcome that the intervention and comparator attempt to achieve. The comparator of BSC includes a number of approaches aiming to address the symptoms of the condition, optimise function, and prevent deterioration. The proposed service is intended to be used in combination with BSC, and is proposed to slow progression of the disease.

A.8. CLINICAL CLAIM

The applicant claims that A1PI augmentation will slow the progression of A1PI deficiency and its accompanying symptoms, and is superior to currently available treatments forming the comparator intervention.

A.9. SUMMARY OF THE PICO

The guiding framework of a PICO Confirmation is recommended by MSAC for each assessment. The PICO Confirmation describes current clinical practice and reflects the likely future practice with the proposed medical service.

The Population, Intervention, Comparator and Outcomes (PICO) that were pre-specified to guide the systematic literature review are presented in Box 1 and Box 2.

Box 1 **Criteria for identifying and selecting studies to determine the safety of purified human A1PI for the treatment of A1PI deficiency, leading to COPD**

Selection criteria	Description
Population	A1PI deficiency
Intervention	AT with any A1PI product (PROLASTIN-C, Zemaira, or other)
Comparator	Best supportive care for COPD
Outcomes	Critical for decision making: • Mortality due to adverse events • Severe adverse events • Discontinuation due to adverse events • Hospitalisation due to adverse events Important, but not critical for decision making: • Treatment-related adverse event • Any adverse event • Infection from treatment • Dyspnoea
Systematic review question	What is the safety of purified human A1PI for the treatment of alpha1-proteinase inhibitor deficiency, leading to COPD?

Abbreviations: **A1PI** = alpha-1 proteinase inhibitor, **AT** = augmentation therapy; **COPD** = chronic obstructive pulmonary disorder.

Box 2 **Criteria for identifying and selecting studies to determine the effectiveness of purified human A1PI for the treatment of A1PI deficiency, leading to COPD**

Selection criteria	Description
Population	A1PI deficiency
Intervention	AT with either Prolastin or Zemaira
Comparator	Best supportive care for COPD
Outcomes	Critical for decision making: • Mortality, including deaths from respiratory failure • Patient quality of life (measured by validated tool for COPD or respiratory impairment) • Number of exacerbations and hospitalisations associated with emphysema • Surrogate measures: CT-measured lung density, carbon monoxide transfer or diffusion capacity (DLCO) Important, but not critical for decision making: • The BODE index- body mass index, airflow obstruction, dyspnoea and exercise index • Changes in exercise capacity (per 6-minute walking test) • Dyspnoea (measured with a validated tool e.g. baseline dyspnoea index, transition dyspnoea index) • Respiratory function measured by spirometry (FEV_1) and FEV_1/Forced vital capacity (FVC) ratio
Systematic review question	What is the efficacy of purified human A1PI for the treatment of alpha1-proteinase inhibitor deficiency, leading to COPD?

Abbreviations: **A1PI** = alpha-1 proteinase inhibitor, **AT** = augmentation therapy; **BODE** = BMI, obstruction, dyspnea, exercise capacity; **COPD** = chronic obstructive pulmonary disorder, **CT** =computed tomography, **DLCO** = diffusing capacity for carbon monoxide, **FEV_1** = forced expiratory volume in 1 second, **FVC** =forced vital capacity.

A.10. CONSUMER IMPACT STATEMENT

Six associations provided targeted feedback and one individual provided non-targeted feedback on this consultation. All respondents using the feedback form 'strongly agreed' with the clinical claim made by the applicant. Respondents have been de-identified for the purpose of this report.

Australia's foundation for the affected organ supports the assessment of this intervention. In parallel to this assessment it is forming a working group and a position statement or guideline on AT. This statement will be updated in response to the results of the assessment. The quote below perhaps best outlines the reasons for this assessment and confirms the current state of AT, including uncertainties around the dosing strategy and cost effectiveness:

"It is noted that the optimal dosing regimen has not yet been determined, and the cost-effectiveness of AT is not known. On the balance of the evidence to date and methodological considerations, AT with this current treatment approach is not yet recommended, and results from additional randomised controlled trials (RCTs) underway and other analyses are awaited."

A binational health promotion charity noted the low availability of data due to the rare nature of this condition. It noted that the efficacy of AT is only supported by clinical consensus at this stage.

This group strongly suggests that strict access to augmentation should be provided, with criteria such as: “prescription through a respiratory specialist, with further assessment of patient lung function within an accredited respiratory function laboratory.”

The Australian foundation supporting patients with Alpha-1 provided evidence that it believes shows a significant increase in life expectancy for patients treated with AT. Subject to funding, it wishes to establish an Australian register for Alpha-1 patients to better understand the epidemiology of the condition.

The foundation provided two letters to the National Blood authority (the applicant) regarding the need for AT for AATD patients and supporting efforts to secure public reimbursement. It also provided an article from the foundation’s newsletter introducing the AlphaNet study and reporting the unpublished results, and a conference poster on the AlphaNet study reporting survival analysis on the three cohorts of A1PI patients receiving AT.

In addition, the foundation provided seven written communications from patients, all expressing the sentiment that the public funding of AT is critical to their ongoing disease management. The foundation claims that these are merely examples put into writing of the kinds of contact it has been receiving from those affected by A1PI for the past 12 years.

Another personal account has been received directly from a patient/private individual to the effect that his/her life situation could have been greatly improved if AT were available.

The manufacturers of the two products provided feedback as well as information for the application. Overall, much consideration was put into the responses, with most respondents providing additional sources with the response form.

SECTION B CLINICAL EVALUATION

B.1. LITERATURE SOURCES AND SEARCH STRATEGIES

To identify relevant studies, the medical literature was searched in Embase on 23 May 2018, and in PubMed and The Cochrane Library on 24 May 2018. No date limit was used in these searches. Search terms were aimed at retrieving information on all A1PI augmentation therapies.

Attempts were also made to source unpublished or grey literature from New York Academy of Medicine Grey Literature Report, CEA Registry, National Information Centre of Health Services Research and Health Care Technology (NICHSR), National Library of Medicine Health Services/Technology Assessment Texts (HSTAT), EuroScan International Network, National Institute for Health and Care Excellence (NICE), NHS National Institute for Health Research (NIHR) — including HTA programme and Online Mendelian Inheritance in Man, as well as the manufacturers and specialty societies: Grifols, CSL Behring and SHIRE, National Blood Authority, Lung Foundation Australia, the Thoracic Society of Australia and New Zealand, and Alpha-1 Foundation.

Databases, sources, search terms and outcomes for each database are described in Appendix B.

B.2. RESULTS OF LITERATURE SEARCH

A PRISMA flowchart (Figure 4) provides a graphic depiction of the results of the literature search and the application of the study selection criteria (listed in Box 1 and Box 2) (Liberati et al. 2009).

Studies were selected independently by two reviewers (TV, AS). Disagreements regarding study selection were resolved by discussion between the two reviewers.

Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed as Excluded Studies in Appendix D. All other studies that met the inclusion criteria are listed in Appendix C. A list of trials that appeared to be relevant but were excluded on full-text review is provided in Appendix E.

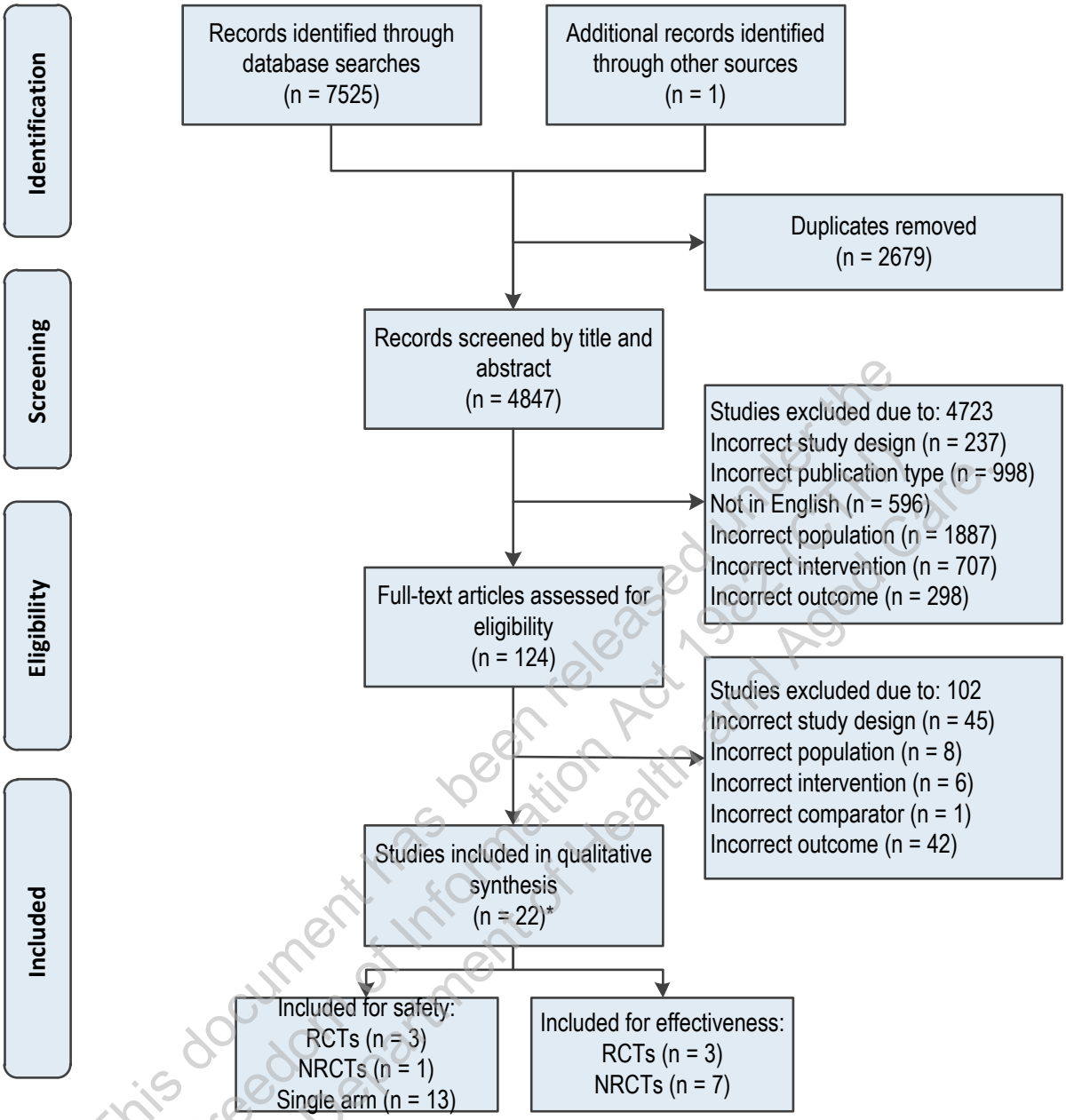


Figure 4 Summary of the process used to identify and select studies for the assessment

*Three RCTs and two single arm (NRCT) studies were included for both safety and effectiveness analysis.

Table 9 lists the included randomised controlled trials (RCTs) and published reports based on each trial. A profile of each included study is given in Appendix C. Appendix C This study profile describes the authors, study ID, publication year, study design and quality (level of evidence and risk of bias), length of patient follow-up, study population characteristics, description of the intervention, description of the comparator, relevant outcomes assessed, and measurement of outcomes and analysis. Study characteristics are also summarised in a shorter format in Section B.4.

In addition to the RCTs, 14 observational studies were included to evaluate the safety of A1PI. Characteristics of these studies are outlined in Section B.4, and Appendix B.

Table 9 Trials (and associated data) presented in the assessment report

Trial	Reports
Effectiveness	
RCTs	
RAPID	Chapman K, Burdon J, Piitulainen E, et al. 2015. Intravenous augmentation treatment and lung density in severe A1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial, *Lancet*; 386(9991); 360-368. McElvaney N, Burdon J, Holmes M, et al. 2017. Long-term efficacy and safety of A1 proteinase inhibitor treatment for emphysema caused by severe A1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE), *Lancet Respir Med*, 2017, 5(1): 51-60. NCT00261833, Zemaira in subjects with emphysema due to alpha1-proteinase inhibitor deficiency. clinicaltrials.gov/ct2/show/NCT00261833, last update posted 19-09-2015, accessed 25-06-2018
EXACTLE	Dirksen A, Piitulainen E, Parr D, et al. 2009. Exploring the role of CT densitometry: a randomised study of augmentation therapy in alpha1-antitrypsin deficiency, *Eur Respir J*, 33(6): 1345-53. Parr DG, Dirksen A, Piitulainen R, et al. 2009. Exploring the optimum approach to the use of CT densitometry in a randomised placebo-controlled study of augmentation therapy in alpha 1-antritypsin deficiency, *Respir Res*, 10: 75. NCT00263887, Alpha-1-Antitrypsin (AAT) To Treat Emphysema In AAT-Deficient Patients (EXACTLE). clinicaltrials.gov/ct2/show/NCT00263887, last updated 21-08-2014, accessed 25-06-2018
DIRKSEN99	Dirksen A, Dijkman J, Madsen F, et al. 1999. A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy, *Am J Respir Crit Care Med*, 160(5): 1468-72.
Non-RCTs	
(Karl et al. 2017)	Karl F, Holle R, Bals R, et al. 2017 Costs and health-related quality of life in Alpha-1-Antitrypsin Deficient COPD patients. *Respir Res*, 18(1): 60.
(Barros-Tizon et al. 2012)	Barros-Tizon, J C, Torres, M L, Blanco I, et al. 2012. Reduction of severe exacerbations and hospitalization-derived costs in alpha-1-antitrypsin-deficient patients treated with alpha-1-antitrypsin augmentation therapy, *Ther Adv Respir Dis*, 6(2): 67-78.
(Tonelli et al. 2009)	Tonelli, A R, Rouhani F, Li N, et al. 2009. Alpha-1-antitrypsin augmentation therapy in deficient individuals enrolled in the Alpha-1 Foundation DNA and Tissue Bank, *Int J Chron Obstruct Pulmon Dis,* 4: 443-452.
(Wencker et al. 1998)	Wencker, M, Fuhrmann, B, Banik, N, et al. 2001. Longitudinal follow-up of patients with alpha(1)-protease inhibitor deficiency before and during therapy with IV alpha(1)-protease inhibitor, *Chest*, 119(3): 737-744.
(Lieberman 2000)	Lieberman, J. 2000. Augmentation therapy reduces frequency of lung infections in antitrypsin deficiency: a new hypothesis with supporting data, *Chest*, 118(5): 1480-1485.
(The Alpha-1-Antitrypsin Deficiency Registry Study Group 1998)	The Alpha-1-Antitrypsin Deficiency Registry Study Group. 1998. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. The Alpha-1-Antitrypsin Deficiency Registry Study Group, Am J *Respir Crit Care Med*, 158(1): 49-59.
(Seersholm et al. 1997)	Seersholm N, Wencker M, Banik N, et al.1997. Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group, *Eur Respir J*, 10(10): 2260-2263.
Safety	
The Alpha-1-	The Alpha-1-Antitrypsin Deficiency Registry Study Group. 1998. Survival and FEV_1 decline in individuals

Trial	Reports
Antitrypsin Deficiency Registry Study Group 1998	with severe deficiency of alpha1-antitrypsin. The Alpha-1-Antitrypsin Deficiency Registry Study Group, *Am J Respir Crit Care Med*, 158(1), pp. 49-59.
Barker et al. 1994	Barker, AF, Siemsen, F, Pasley, D et al. 1994. Replacement therapy for hereditary alpha1-antitrypsin deficiency. A program for long-term administration, *Chest*, 105(5), pp. 1406-1410.
Barker et al. 1997	Barker, AF, Iwata-Morgan, I, Oveson et al. 1997. Pharmacokinetic study of alpha 1-antitrypsin infusion in alpha 1-antitrypsin deficiency, *Chest*, 112(3), pp. 607-613.
Barros-Tizón et al. 2012	Barros-Tizon, JC, Torres, ML, Blanco, I et al. 2012. Reduction of severe exacerbations and hospitalization-derived costs in alpha-1-antitrypsin-deficient patients treated with alpha-1-antitrypsin augmentation therapy, *Ther Adv Respir Dis*, 6(2), pp. 67-78.
Campos et al. 2013	Campos, MA, Kueppers, F, Stocks et al. 2013. Safety and pharmacokinetics of 120 mg/kg versus 60 mg/kg weekly intravenous infusions of alpha-1 proteinase inhibitor in alpha-1 antitrypsin deficiency: a multicenter, randomized, double-blind, crossover study (SPARK), *COPD*, 10(6), pp. 687-695.
Hubbard & Crystal1988	Hubbard, RC & Crystal, RG, 1988. Alpha-1-antitrypsin augmentation therapy for alpha-1-antitrypsin deficiency, *Am J Med*, 84(6), pp. 52-62.
McElvaney et al. 2017	McElvaney, NG, Burdon, J, Holmes, M et al. 2017. Long-term efficacy and safety of alpha1 proteinase inhibitor treatment for emphysema caused by severe alpha1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE), *Lancet Respir Med*, 5(1), pp. 51-60.
Sandhaus et al. 2014	Sandhaus, RA, Stocks, J, Rouhani et al. 2014, Biochemical efficacy and safety of a new, ready-to-use, liquid alpha-1-proteinase inhibitor, GLASSIA (alpha1-proteinase inhibitor (human), intravenous), COPD, 11(1), pp. 17-25.
Schmidt et al. 1988	Schmidt, EW, Rasche, B, Ulmer et al. 1988. Replacement therapy for alpha-1-protease inhibitor deficiency in PiZ subjects with chronic obstructive lung disease, *Am J Med*, 84(6), pp. 63-69.
Schwaiblmair et al. 1997	Schwaiblmair, M, Vogelmeier, C & Fruhmann, G, 1997. Long-term augmentation therapy in twenty patients with severe alpha-1-antitrypsin deficiency--three-year follow-up, *Respiration*, 64(1), pp. 10-15.
Stocks et al. 2010	Stocks, J, Brantly, M, Wang-Smith, L et al. 2010. Pharmacokinetic comparability of Prolastin®-C to Prolastin® in alpha1-antitrypsin deficiency: a randomized study, *BMC Clin Pharmacol*, 10pp. 13.
Stoller et al. 2003	Stoller, JK, Fallat, R, Schluchter, MD et al. 2003. Augmentation therapy with alpha1-antitrypsin: patterns of use and adverse events, *Chest*, 123(5), pp. 1425-1434.
Wencker et al. 1998	Wencker, M, Banik, N, Buhl, R et al. 1998. Long-term treatment of alpha1-antitrypsin deficiency-related pulmonary emphysema with human alpha1-antitrypsin. Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL)-alpha1-AT-study group, *European Respiratory Journal*, 11(2), pp. 428-433.
Wewers et al. 1987	Wewers, MD, Casolaro, MA, Sellers, SE et al. 1987. Replacement therapy for alpha 1-antitrypsin deficiency associated with emphysema, *N Engl J Med*, 316(17), pp. 1055-1062.

Information on current clinical trials was searched from Clinicaltrials.gov, Cochrane Central Register of Controlled Trials, EU Clinical Trials Registry, WHO International Clinical Trials Registry Platform, Current Controlled Trials MetaRegister, and the Australian New Zealand Clinical Trials Registry. Search strategies for the clinical trial search are reported in Appendix B, and details of identified trials are presented in Tables 10, 11 & 12.

Overall, 11 clinical trials were identified as recruiting or active studies on A1PI augmentation therapy (Tables 10, 11 & 12). Six of these were multinational trials. The largest estimated enrolment was 400 patients.

One A1PI clinical trial on the lung was marked as terminated because the intervention drug, Aralast, was phased out of the market (NCT00313144). Otherwise, there seems to be no indication of potential publication bias.

Table 10 Details of clinical trials identified on Clinicaltrials.gov

Trial ID; location	Status Estimated completion	Design Target N	Patient indication	Intervention	Comparator	Outcome measure(s)
NCT02525861 Canada, United States	Recruiting May 2020	RCT 36	Alpha1-Proteinase Inhibitor deficiency	GLASSIA: 60mg/kg BW administered at a rate of 0.2 mL/kg/min; At lower particulate level	GLASSIA: 60mg/kg BW administered at a rate of 0.2 mL/kg/min; At higher particulate level	Proportion AEs, incidence treatment-emergent ARs, proportion discontinued treatments, proportion experiencing binding or neutralising A1PI, antigenic A1PIA levels, functional A1PI
NCT02722304 Australia, Canada, United States	Recruiting July 2021	RCT 138	Alpha-1 Proteinase Inhibitor < 8 µM	ARALAST: 60 or 120 mg/kg body weight/week GLASSIA: 60 or 120 mg/kg weight/week	Placebo	Rate of change in lung density
NCT02614872 Israel	Active December 2020	RCT 30	Planning to undergo lung transplant	GLASSIA treatment in addition to SOC	SOC	Incidence of AEs, incidence /rate of acute rejection
NCT01983241 (SPARTA) 13 countries	Recruiting August 2021	RCT 339	Alpha-1 Proteinase Inhibitor < 11 µM	PROLASTIN-C: 60 or 120 mg/kg body weight/week	Placebo	Change in baseline in whole lung PD15 measured by CT scan
NCT02796937 (SPARTA-OLE) 7 countries	Recruiting by invitation July 2018	Open-label extension of SPARTA RCT 250	Completed the SPARTA trial	PROLASTIN-C: 60mg/kg body weight/week	NA	Number AEs, number SAEs, discontinuation of study due to AEs

Trial ID; location	Status Estimated completion	Design Target N	Patient indication	Intervention	Comparator	Outcome measure(s)
NCT01974830 (AL1TER) United States	Recruiting October 2020	Prospective cohort study 400	Requiring A1PI therapy and agree to use Coram's home infusion services	NR	NA	Change in pulmonary function, including FEV1, at 1 year

Abbreviations: **A1PI** = alpha-1 proteinase inhibitor, **AE** = adverse events, **AR** = adverse reactions, **NA** = not applicable, **NR** = not reported, **PD15** = 15th percentile point, **RCT** = randomised controlled trial, **SAE** = serious adverse events, **SOC** = standard of care.

Table 11 Details of clinical trials identified on EU Clinical Trials Registry

EudraCT Number Location	Design Estimated enrolment	Status	Start date	Patient indication	Intervention	Comparator
2005-002402-36 Spain	Multi-centre, open-label trial 35	Ongoing	April 2006	Alpha-1 Antitrypsin deficiency	A1PI	NA
2007-004869-18 Israel	Case series 26	Ongoing	July 2008	Alpha-1 proteinase inhibitor deficiency	Prolastin	NA

Table 12 Details of clinical trials identified on WHO International Clinical Trials Registry Platform

Study ID Location	Design Estimated enrolment	Status	Start date	Patient indication	Intervention	Comparator
EUCTR2015-004110-23-DK 16 countries	Multi-centre, open-label trial 250	Authorised	January 2016	Patients who have completed participation in SPARTA Study	PROLASTIN-C	NA
EUCTR2008-005326-36-GB 7 countries	RCT 200	Authorised	August 2009	Alpha-1 antitrypsin deficiency	A1PI	Placebo

Abbreviations: **A1PI** = alpha-1 proteinase inhibitor, **EUCTR** = EU Clinical Trials Registry, **NA** = not applicable.

APPRAISAL OF THE EVIDENCE

Appraisal of the evidence was conducted in four stages:

Stage 1: Appraisal of the risk of bias within individual studies (or systematic reviews) included in the review. Some risk-of-bias items were assessed for the study as a whole, while others were assessed at the outcome level (Section B.3).

Stage 2: Extraction of the pre-specified outcomes for this assessment, synthesising (meta-analysing or a narrative synthesis) to determine an estimate of effect per outcome.

Stage 3: Rating the overall quality of the evidence per outcome, across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias. This was done to provide an indication of the confidence in the estimate of effect in the context of Australian clinical practice (Evidence profile tables, Table 102 and Table 104 are presented in Appendix C).

Stage 4: Integration of this evidence to draw conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice (Sections B.6-8).

B.3. RISK OF BIAS ASSESSMENT

RANDOMISED CONTROLLED TRIALS

The overall risk of bias in the core RCTs was low to moderate. Summary scores for the individual domains of bias are presented in Figure 5 and Figure 6. The oldest trial was difficult to score due to inadequate reporting of the study design (Dirksen et al. 1999).

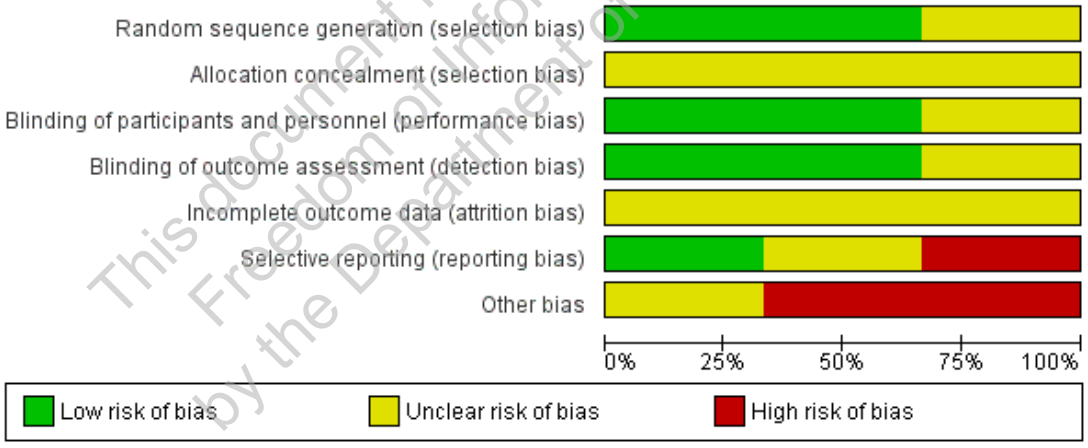


Figure 5 Summary of the overall risk of bias across the included studies

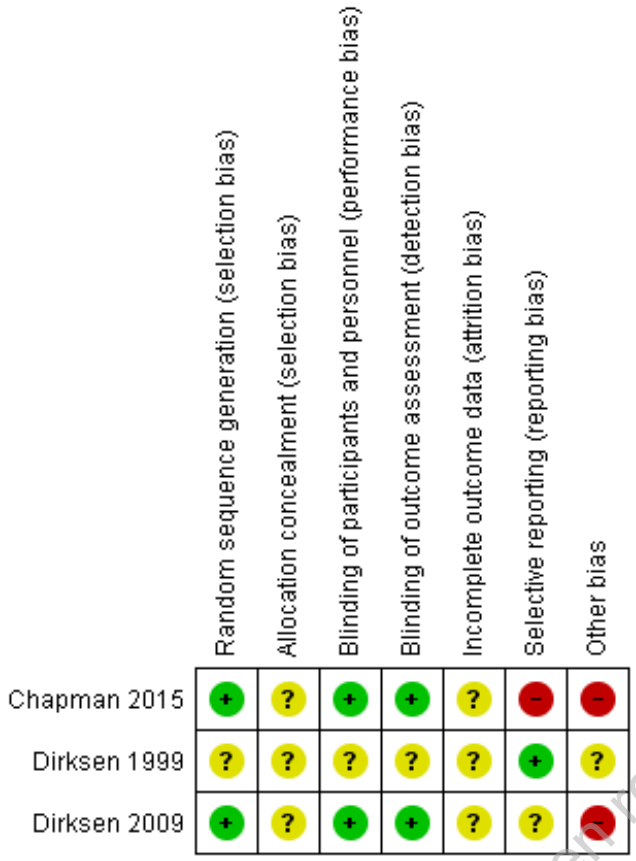


Figure 6 **Risk of bias in the included randomised controlled trials**

Randomisation and allocation concealment

Both the RAPID and EXACTLE trials used an adequate method of randomising patients, conducted by an independent third party, and there was no evidence of important baseline imbalances (Chapman et al. 2015; Dirksen et al. 2009). The final trial stratified patients by age, level of FEV_1 and nationality, and randomised by the minimisation method (Dirksen et al. 1999). This was appropriate given the relatively small sample size for the trial (n=58). There were no obvious imbalances in the baseline lung function or CT density, however, demographic characteristics (e.g. age, nationality, etc.) were not reported across treatment groups (Dirksen et al. 1999).

The RAPID trial provided masked, sequential enrolment numbers to each site (Chapman et al. 2015). Patients were assigned a consecutive number after meeting the requirements for study entry, however, it is unclear how the treatments were masked to the study investigator responsible for patient enrolment. In the EXACTLE trial, it was not reported who enrolled patients into the study (Dirksen et al. 2009). The pharmacists responsible for preparing medication were not blinded to the treatment allocation. The final study did not report the method of allocation concealment (Dirksen et al. 1999).

Blinding

Patients and investigators, including outcome assessors, were effectively blinded to the treatment allocation in the RAPID and EXACTLE trials (Chapman et al. 2015; Dirksen et al. 2009). In both studies, medication was prepared in opaque sleeves to the same volume per kg body weight in the placebo and A1PI groups. Only the pharmacists preparing the medication were aware, or could potentially have been aware, of the treatment allocation. The pharmacists had no interaction with the patients or investigators. DIRKSEN99 was reportedly double-blinded, however, the method for ensuring blinding was established and maintained was not reported (Dirksen et al. 1999).

Incomplete outcome data

Patient flow through the clinical trials is presented in Table 13.

The RAPID trial reported missing data in 10 A1PI patients (9.7%) compared to 20 placebo patients (23.0%) (Chapman et al. 2015). The reasons for withdrawals were similar, but the total numbers were large enough to potentially have impacted the results. A modified intention-to-treat (mITT) was reported, but it was unclear how missing data was accounted for in the analysis. The outcome tables included the total number of patients randomised to each treatment arm, but not the number of patients included in the analysis.

There were 8% (3/38) versus 18% (7/39) losses to follow-up between A1PI and placebo groups in the EXACTLE trial (Dirksen et al. 2009), although overall numbers were small.

DIRKSEN99 reported two study drop-outs, for patients who resumed smoking (Dirksen et al. 2009). It was unclear to which treatment arm these patients were assigned.

Table 13 Patient flow in randomised controlled trials

Study ID Intervention Comparator	Length of study (main paper)	Randomised, n	Death, n (%)	Undergoing lung transplantation, n (%)	Discontinued due to various reasons, n (%)	Loss of follow-up reasons unspecified, n (%)	Analysed, n (%) *
RAPID							
α1-antitrypsin	24 months	93	1 (1%)	1 (1%)	6 (6%)	1 (1%)	84 (90%)
Placebo	24 months	87	3 (3%)	1 (1%)	14 (16%)	0 (0%)	69 (79%)
RAPID-OLE (non-randomised)							
α1-antitrypsin	48 months	84	0 (0%)	0 (0%)	11 (13%)	23 (27%)	50 (60%)
Placebo	48 months	69	0 (0%)	0 (0%)	8 (12%)	14 (20%)	47 (68%)
EXACTLE							
α1-antitrypsin	24 months	38	0 (0%)	1 (3%)	1 (3%)	0 (0%)	36 (95%)
Placebo	24 months	39	0 (0%)	1 (3%)	5 (13%)	0 (0%)	33 (85%)
α1-antitrypsin	30 months	36	0 (0%)	1 (3%)	17 (47%)	0 (0%)	19 (53%)
Placebo	30 months	35	0 (0%)	2 (6%)	16 (46%)	0 (0%)	17 (49%)
DIRKSEN99							
α1-antitrypsin	36 months	28±2	0 (0%)	0 (0%)	±2 (7%)	0 (0%)	28 (100%)
Placebo	36 months	28±2	0 (0%)	0 (0%)	±2 (7%)	0 (0%)	28 (100%)

*The RAPID trial reportedly conducted an ITT analysis for all of the included outcomes, however, it was unclear how these losses to follow-up were accounted for in the analysis.

Selective reporting

Several secondary outcome measures reportedly collected in the RAPID trial, based on the clinicaltrials.gov entry, were not reported in the trial publication (Chapman et al. 2015). These included per cent change in FEV_1, per cent change in FEV_1 as a ratio of FVC, change in lung density, and severity of exacerbations (Chapman et al. 2015). The EXACTLE trial reported FEV_1, D_{LCO} and diffusing coefficient for carbon monoxide (K_{CO}) online only, noting that no significant differences were observed. Mortality was measured but not reported (Dirksen et al. 2009). There were no reporting issues with the final trial (Dirksen et al. 1999).

Other bias

Two of the trials had important conflicts of interest. The RAPID trial was deemed to have a high risk of bias due to conflicts of interest (Chapman et al. 2015). The trial was funded by CSL Behring, the manufacturer of Zemaira, and employees of the funding body were involved in the data analysis, data interpretation and writing of the trial publication. In addition, four of the study authors had received consulting, research and/or personal funding from CSL Behring and other manufacturers of A1PI products (i.e. Grifols). Funding for the EXACTLE trial was provided by the manufacturer of the study medication, Prolastin® (Talecris Biotherapeutics, Inc., Research Triangle Park, NC, USA)(Dirksen et al. 2009). Two authors were employees of Talecris Biotherapeutics, Inc., however, their involvement in the study is unclear. Editorial assistance was provided by an international biopharmaceutical consulting organisation (PAREXEL, Worthing, UK), whose involvement was also funded by Talecris Biotherapeutics, Inc. No information was provided about funding or conflicts of interest in the final trial (Dirksen et al. 1999).

NON-RANDOMISED COMPARATIVE STUDIES

Seven non-randomised comparative studies were used in the assessment of safety and efficacy. Three studies were interrupted time-series which compared lung function or infection pre and post A1PI in a single population. Three studies used registry data or hospital medical records to retrospectively compare patients treated with or without A1PI. One study evaluated the healthcare costs and health-related quality of life in COPD patients with and without AATD; a subgroup analysis further classified COPD patients with AATD into those treated with or without A1PI.

The quality of the non-randomised comparative studies was appraised using the Risk of bias in non-randomised studies of interventions (ROBINS-I) (Sterne et al. 2016b). According to this appraisal, all seven studies were considered of serious risk of bias. All studies were graded serious in the “bias due to confounding” section as they failed to report pertinent patient demographic details. Further, most studies failed to accurately report the intervention and the follow-up time often differed between groups. Most studies were of moderate bias in terms of the outcomes reported owing to their retrospective design (the assessors where aware of the intervention each patient received).

Full results of the risk of bias appraisal are presented in Appendix D. A summary of the overall risk of bias per item is presented in Figure 7.

Most studies retrospectively analysed patient data from either registries or patient records from multiple sites. Reported characteristics of patients included in the studies were age, gender and smoking status. The most common issue that may lead to bias was the limited patient demographic information provided in the studies, with most omitting details regarding health status, environmental exposure (toxin exposure or packet years), socioeconomic status and lung function. Further, owing to the retrospective nature of trial data, there may be differences in the duration of exposure between participants or change in practice to manage AATD. Studies attempted to limit the influence of confounding variables on outcome measures by using multivariate random or fixed effects modelling. However, this was not performed for all outcomes of interest nor did it include all variables and consequently, some of the results were still prone to bias. The number and severity of adverse events were reported in one study (Barros-Tizon et al. 2012). The remaining studies neglected this variable.

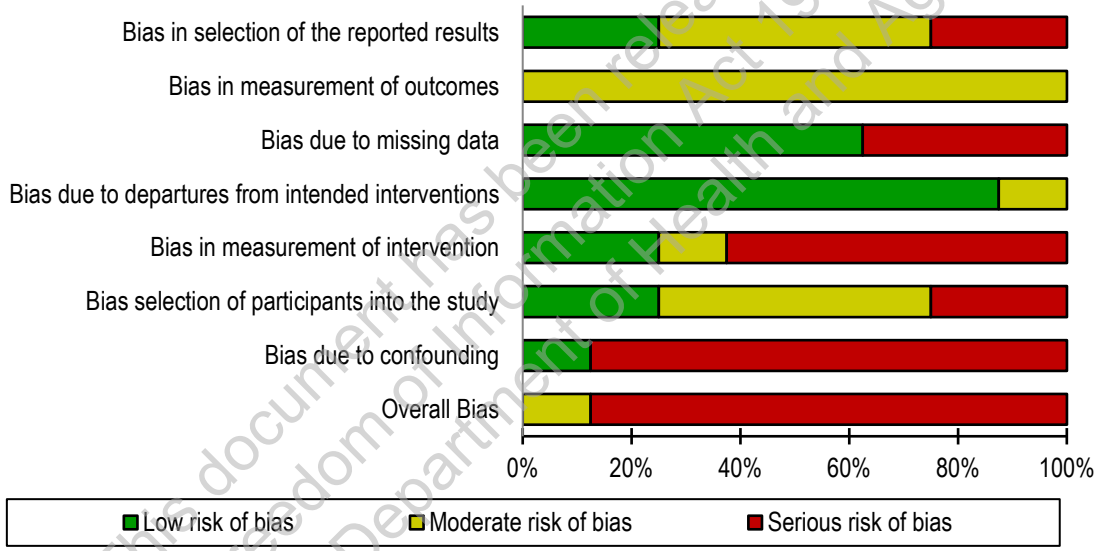


Figure 7 **Summary of risk of bias across the included non-randomised studies**

OBSERVATIONAL TRIALS (SAFETY OUTCOMES)

Thirteen single-arm studies were used in the assessment of safety. Four of the single-arm studies had a comparator group also receiving A1PI, the difference being dose or duration of AT. As the intervention was not significantly different, they were treated as single-arm studies.

The quality of the single-arm studies was appraised using the IHE Quality Appraisal of Case Series Studies (Guo et al. 2016). The open-label extension is referred to as a non-randomised study and its quality was appraised using ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions (Sterne et al. 2016a)).

The 13 single-arm studies were appraised under the IHE Quality Appraisal tool. According to this appraisal, eight studies were considered to have a high risk of bias, and five were considered to have a moderate risk of bias. No studies were considered to have low risk of bias. Full results of the risk of bias appraisal are presented in Appendix C. A summary of the overall risk of bias per item is presented in Figure 8.

The studies were mostly prospective, multi-centre studies. Common issues that may lead to bias include patients not being included consecutively, and wide variations in FEV standard deviation, indicating that patients were not included at a similar point in the disease. Reported characteristics of patients in the studies included age, gender, A1P1 serum concentration and smoking status. Most studies did not report patient height weight and ethnicity data. Outcomes mostly were not assessed using appropriate methods. It was expected that a method for reporting and grading the severity of adverse events would be described, but only two studies used such a method and two further studies partially did so. Many studies (all but two) neglected to report estimates of random variability in the data, although this is uncommon in adverse event reporting. The conclusions were supported by the results in all studies. Reporting of competing interests and sources of support were evident in three studies only. The IHE Quality Appraisal of Case Series Studies is reported in Table 107.

Studies were considered to be at low risk of bias if 12-17 yes responses were given during the appraisal, moderate risk of bias if 6-11 yes responses were recorded, and high risk of bias if 0-5 yes responses were recorded. Inadequate length of follow-up (<12 months) was also used as an automatic trigger for high risk of bias for the safety outcomes.

The quality of the RAPID-OLE trial was appraised using the ROBINS-I appraisal tool. Low risk of bias was identified in relation to confounding, selection of participants into the study, adherence to intended interventions, and missing data. Risk of bias in measurement of outcomes was considered to be moderate, as the assessors were not blinded to the intervention and the outcome of all-cause mortality could be subject to negligible assessor judgement. There was considered to be moderate bias in selection of reporting results, as while was there is no published protocol the outcomes are consistent with an a priori plan, there is no indication of selection of reported patients of analyses. The ROBINS-I appraisal is reported in Table 108.

Another potential for bias was identified in a systematic review retrieved in the scoping stage (Sandhaus et al. 2016). The systematic review enquired if medical management of COPD should be altered in patients with COPD due to AATD. The review found no reliable data suggesting a different treatment response to BSC in COPD patients with or without AATD.

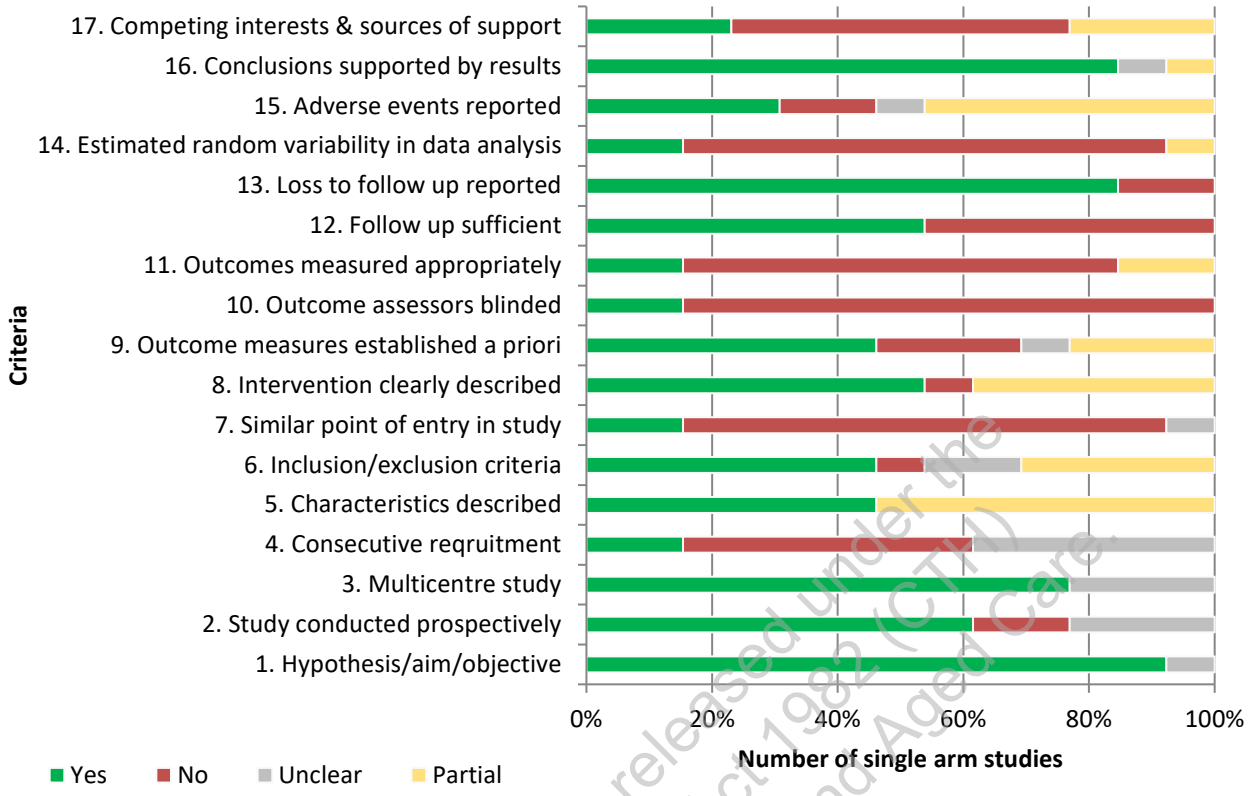


Figure 8 **Summary of risk of bias across the included single-arm studies**

B.4. CHARACTERISTICS OF THE EVIDENCE BASE

Full details on the individual studies included in the evidence base appear in Appendix C, Table 102. Summaries are provided in Table 14 and

Table 15. Overall, the included RCTs had good applicability to the proposed population, except for ethnicity. All patients in the RAPID and EXACTLE trials were Caucasian. DIRKSEN99 did not report the ethnicity of trial participants, but patients were recruited from similar centres to the EXACTLE trial (i.e. Danish A1 registry). Patient characteristics across the included RCTs were largely homogenous. The included patients were ex- or never-smokers, with severe A1 deficiency (serum A1 ≤ 11 µM), and emphysema. Mean baseline FEV_1% predicted values ranged from 46% ± 20% to 50% ± 3%. Dosing regimens differed across the included trials, from 60mg/kg per week (Chapman et al. 2015; Dirksen et al. 2009) to 250mg/kg per month (Dirksen et al. 1999).

Table 14 **Key features of the included RCTs comparing A1PI augmentation therapy with placebo**

Trial/Study	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
RAPID	180	MC, R, DB 24 mths	Low	• Serum A1 ≤11µM • FEV_1 35% to 70% predicted (mean 74% ± 12%) • Ex- or never-	• Mortality • QoL • FEV_1 % predicted • CT lung density	Yes

				smokers	• Severe adverse events • Death due to adverse event • Discontinuation due to adverse events	
EXACTLE	77	MC, R, DB 24/30 mths	Low	• Serum A1 <11µM • FEV_1 ≥25% to ≤80% predicted (mean 47% ± 20%) • Ex- or never-smokers	• QoL • FEV_1 % predicted • CT lung density • Severe adverse events • Discontinuation due to adverse event	Not used
DIRKSEN99	58	MC, R, DB 36 mths	High	• PiZZ phenotype • FEV_1 30% to 80% predicted (mean 49% ± 20%) • Ex-smokers	• QoL • FEV_1 % predicted • CT lung density	Not used
Meta-analysis	315 k=3			Random effect model; overall pooled presented; heterogeneity analysis; FEV_1 % predicted, CT lung density, D_{CO} analysed		Not used

Abbreviations: **CT** = computed tomography, **DB** = double blind; **FEV_1** = forced expiratory volume in 1 second, **k** = studies; **MC** = multi-centre, **QoL**= quality of life; **R** = randomised.

The population demographics of the non-RCTs were fairly homogenous and generally represent the proposed population for the intervention. Patients were mostly male (range, 50%–75%), ex-smokers (range, 78%–96%) with a PiZZ phenotype (range, 89%–100%). Patients predicted FEV_1 % typically ranged between 35%–40% however, the comparator group in Barros-Tizon et al. (2012) reported an average predicted FEV_1 of 77%. Two and three studies included patients with other Pi* phenotypes (0.8%–8%) and current smokers (5%–14%) respectively. Most studies did not list ethnicity, BMI or serum A1 levels (however, eligibility criteria of serum A1 levels <11 or 12 µM was listed in two studies). The most commonly reported augmentation therapy was Prolastin administered intravenously at 60mg/kg (body weight) once per week. The comparator was no augmentation therapy, no further details were provided regarding what the comparator constituted.

Table 15 Key features of the included studies assessing alpha-1 antitrypsin augmentation for safety outcomes

Trial/Study	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Alpha-1-Antitrypsin Deficiency Registry Study Group 1998	927	NR, OL, Coh 52 months	Serious	• Serum A1 <11µM or PiZZ phenotype • Ex- or never-smokers	• ΔFEV1 • Survival	Not used
Barros-Tizon et al. 2012	127	MC, NR, Coh 36 months	Serious	• Serum A1 <11µM • PiZZ, PiSZ, other phenotype • Ex- or never-	• Number of exacerbations • Lung function • Adverse events	Not used

				smokers, smokers	• Costs associated with hospitalisation	
Karl et al. 2017	2,186	MC, NR 1 year	Serious	• Current, ex- and never-smokers	• Direct and indirect health care costs • Health-related QoL	Not used
Lieberman 2000	143	NR NA	Serious	• PiZZ or PiSZ phenotypes • Ex- or never-smokers, smokers	• Number of infections • Perceived benefit	Not used
Seersholm et al. 1997	295	MC, NR, OL 3-5 years	Serious	• PiZZ phenotype • Serum A1 ≤12μM • FEV_1 37 to 42% predicted (mean) • Ex- or never smokers	• ΔFEV1(mL/year)	Not used
Tonelli et al. 2009	164	R, NR, OL 42 months	Serious	• PiZZ phenotype • FEV_1 43 to 77% predicted (mean) • Current or ex-smoker	• ΔFEV1(mL/year) • Mortality	Not used
Wenker et al. 2001	96	MC NR, Coh 98 months	Serious	• PiZZ, PiSZ, other phenotypes • Current, ex- and never-smokers • FEV_1 41% predicted (mean)	• ΔFEV1(mL/year)	Not used

Abbreviations: **AAT** = alpha-1-antitrypsin, **Coh** = cohort, **CS** = case series, **DB** = double-blind, **FEV_1** = forced expiratory volume in 1 second, **k** = studies; **MC** = multi-centre, **NR** = non-randomised, **OL** = open label (unblinded), **R** = randomised, **SB** = single blind, **μM** = micromolar.

*Including RCTs

B.5. OUTCOME MEASURES AND ANALYSIS

Additional details on the outcomes measured in the included studies appear in Appendix C. The claimed benefit of A1PI is that it slows the progression of emphysema in patients that are A1PI deficient. Thus the primary outcomes of interest relate to monitoring the relative speed of disease progression in patients treated with A1PI compared to those treated with BSC or placebo. The most relevant clinical outcome for monitoring disease progression is the relative mortality rate over time, however, mortality was investigated as a secondary outcome in the included studies, and they were underpowered to detect significant differences in relative survival. In lieu of patient-important outcomes, the RCTs were designed to detect changes in surrogate markers for disease progression.

PRIMARY EFFECTIVENESS OUTCOMES

The primary effectiveness outcomes defined in the included RCTs are outlined in Table 16. The primary outcomes were independent, that is they were unaffected by clustering. The RAPID and EXACTLE trials primarily aimed to measure disease progression using annual rates of CT-measured

lung density decline (Chapman et al. 2015; Dirksen et al. 2009), whereas the Dirksen et al. (1999) trial investigated changes in FEV_1 as the primary outcome. The primary effectiveness outcomes in the non-RCTs are outlined in Table 16. The outcomes differed substantially between the included trials. ΔFEV1 and mortality/survival were the most frequently reported outcomes (four and two studies respectively). One study each addressed healthcare costs, exacerbations and the number of infections.

Table 16 Primary outcomes and statistical analyses of the randomised and non-randomised controlled trials

Trial ID	Definition of primary outcome	Method of primary statistical analysis
RCTs		
RAPID Chapman et al. (2015) [A]	Annual rate of decrease in lung density, calculated from the shift in the 15th percentile of CT lung density (PD15), measured as a combination of TLC and FRC.	Mixed-effects regression model, adjusted PD15 at baseline, 3, 12, 21 and 24 months.
EXACTLE Dirksen et al. (2009) [B]	Progression rate of emphysema determined by change in PD15, measured by annual CT scan of TLC.	Linear regression on time of PD15 measurement in a random coefficient regression model.
DIRKSEN99 Dirksen et al. (1999) [C]	Annual mean changes in FEV_1	Random-effects regression model with FEV_1 and CT densitometry parameters as effect variables, and time, nationality and treatment group as explanatory variables.
Non-RCTs		
Alpha-1-Antitrypsin Deficiency Registry Study Group 1998	Annual mean changes in FEV_1 Survival	FEV1: linear mixed effects modelling (covariates: mean FEV1 % predicted) Survival: kaplan-meier, log-rank test, cox proportional hazards regression (covariates: baseline FEV1 % and time)
Barros-Tizon et al. 2012	Number of exacerbation (worsening of the patients basal condition which requires a change of the patient's COPD medical regimen).	Multivariate logistic regression
Karl et al. 2017	Direct and indirect health care costs	Generalised linear model (covariates: GOLD grade, age, sex, education, smoking status, BMI, comorbidities)
Lieberman 2000	Number of infections per year	Chi squared test
Seersholm et al. 1997	Annual mean changes in FEV_1	Random effects modelling (covariates: age at baseline, follow-up time, treatment, gender, initial FEV_1, individual patients)
Tonelli et al. 2009	Annual mean changes in FEV_1 Mortality	FEV_1: random effects modelling (covariates: gender, age at baseline, smoking status, individual patient, follow-up duration) Mortality: logistic regression (covariates: age, gender, baseline FEV1, COPD, smoking status)
Wenker et al. 2001	Annual mean changes in FEV_1	Mixed effects modelling (covariates: treatment, individual patient)

Abbreviations: **COPD** = chronic obstructive pulmonary disease; **CT** = computed tomography; **FEV_1** = forced expiratory volume in one second; **FRC** = functional residual capacity, **PD15** = 15th percentile density, **TLC** = total lung capacity.
[A] The RAPID trial was powered to detect a difference in PD15 of 1.07 g/L per year across treatment groups, however, the clinical importance of this difference has not been established in the literature.
[B] The EXACTLE trial was not powered to detect a difference in PD15 across treatment groups.
[C] The Dirksen et al. (1999) trial was powered to detect a mean change in FEV_1 of at least 50% between groups at three years.

The RAPID and EXACTLE trials measured lung density according to the change in the 15th percentile lung density (PD15) value, adjusted using physiological volume correction. PD15 is a measurement of lung density (measured in Hounsfield units or grams per litre), at which 15% of voxels, or pixels, on a CT scan have lower densities (Parr et al. 2006). Volume correction was applied by calculating total lung volume (measured on CT), divided by the individual patient's predicted total lung capacity (TLC), or maximal inhalation (Chapman et al. 2015; Dirksen et al. 2009). The RAPID trial also measured density at functional residual capacity (FRC) or full expiration, as well as a combination measure averaging TLC and FRC. DIRKSEN99 also recorded CT-measured lung density as a secondary outcome (Dirksen et al. 1999).

PD15 has been validated as a consistent measure of lung density and marker of emphysema progression (Parr et al. 2006). Research into CT-measured lung density decline has been conducted specifically on A1PI deficient patients in order to overcome the challenges of adequately powering a study to detect significant differences in functional outcomes such as FEV_1 (Parr et al. 2006; Schluchter et al. 2000); however, minimum clinically important differences (MCID) in CT densitometry for monitoring disease progression are not yet defined in the literature.

CORRELATION BETWEEN CT DENSITOMETRY, FUNCTIONAL AND PATIENT RELEVANT OUTCOMES

The published literature was searched to ascertain whether CT densitometry correlates with functional outcomes, thereby providing indirect evidence of clinical improvement. PubMed was searched on 23 July 2018 with the terms "Alpha 1 anti-trypsin deficiency AND CT". The search identified 110 results, of which 12 studies reported on correlations between CT density and FEV_1, K_{CO} (lung function measures), mortality and quality of life (Table 17).

There are, however, confounding variables that limit the generalisability of the results, for example the different method of assessing lung density and the lung zones examined. A recent meta-analysis assessing the relationship between CT densitometry and clinical outcomes in patients with COPD or AATD, supports these findings (Crossley et al. 2018). It is worth noting that many of the studies listed above form part of the evidence based used in this meta-analysis.

The meta-analysis determined that FEV_1 and K_{CO} gas transfer correlated with CT density (Crossley et al. 2018), although there was a high degree of heterogeneity among studies, attributable to the different acquisition parameters.

Six studies reported on mortality (Crossley et al. 2018). The study concluded that it was inappropriate to conduct a meta-analysis on this variable, even though each of the reported studies found a correlation/association between densitometry and mortality when assessed individually.

Five studies addressed quality of life as scored by the St George Respiratory Questionnaire (Crossley et al. 2018). The study authors concluded that it was inappropriate to conduct a meta-analysis on

this variable. Two studies found no relationship between CT density and quality of life, while three studies demonstrated an association between the two variables.

Overall, the results suggest that CT density (either PD15 or -950 hounsfield units) generally correlates with lung function measures (FEV_1 and K_{CO}) and mortality. However, the studies were inconsistent regarding correlations between CT lung density and quality of life (Table 18). Stolk et al. (2003) and Dowson et al. (2001) found a correlation between CT lung density and St George's Respiratory Questionnaire (SGRQ) whereas Dirksen et al. (2009) did not.

Table 17 Studies assessing correlation between CT lung density and function markers in AATD patients

Reference	Patient details	%LAA parameter	Statistical technique	Variable adjusted for	Results	p-value
FEV_1 and K_{CO}						
Bernspang et al. (2011)	Swedish infants born between 1972 – 1974 (n=53)	PD_{15}	Univariate and multivariate regression analysis	Diffusing capacity, FEV_1 and PD_{15}	PD_{15} correlated with FEV_1	FEV_1 $p < 0.05$
Stolk et al. (2003)	10 AATD registries in The Netherlands, UK, Sweden, Canada, Australia, New Zealand, Switzerland, Spain, Belgium and Germany (n=226)	PD_{15}	Spearman correlation	CT-derived lung volume	PD_{15} correlated with FEV_1 and K_{CO} when adjusted by lung volume. PD_{15} correlated with FEV_1 (r = 0.34) and K_{CO} (r = 0.29) not adjusted to TLC	Adjusted FEV_1 $p <$ 0.0001 K_{CO} $p <$ 0.0001 Not adjusted FEV_1 $p <$ 0.0001 K_{CO} $p <$ 0.0001
Dirksen et al. (2009)	AATD registries in Denmark, Sweden and UK (n=77)	PD_{15}	Random coefficient model		PD_{15} correlated with FEV_1 PD_{15} not correlated with K_{CO}	FEV_1 $p =$ 0.007 K_{CO} p = NR
Parr et al. (2006)	UK centre (n=74)	PD_{15} -950	Spearman correlation and the Jonckheere-Terpstra test		Upper zone PD_{15} and -950 index correlated FEV_1 Lower zone PD_{15} and -950 index did not correlate with FEV_1	Upper zone PD_{15} $p =$ 0.001 -950 $p =$ 0.012 Lower zone PD_{15} p = 0.35 -950 p = 0.09

Reference	Patient details	%LAA parameter	Statistical technique	Variable adjusted for	Results	p-value
Stolk et al. (2003)	Dutch centre (n=22)	PD_{15} -950	Spearman correlation		PD_{15} and -950 correlated with FEV_1 and K_{CO}	PD_{15} FEV_1 p = 0.001 K_{CO} p = 0.007 -950 FEV_1 p = 0.001 K_{CO} p = 0.004
Dowson et al. (2001)	UK centre (n=111)	-910	Spearman's rho test		Upper and lower zone inspiratory and expiratory CT density correlated with FEV_1 and K_{CO}	For all variables p < 0.001
Dirksen et al. (1999)	AATD registries in The Netherlands and Denmark (n=56)	PD_{15}	Pearson's correlation		PD_{15} correlated with K_{CO} but not FEV_1	K_{CO} p = 0.02 FEV_1 p = 0.39
Survival						
Green et al. (2016)	UK A1ADT registry (n=110)	PD_{15} -910	Univariate and multivariate regression analysis	FEV_1, lower zone density decline, whole lung density decline	Lower but not upper zone CT density associated with mortality	Lower zone p = 0.042 Upper zone p = 0.072
Dawkins et al. (2009)	ADAPT (n=488)	-910	Cox regression analysis	Age	Upper zone CT density associated with all-cause mortality	Age corrected analysis p = 0.008

Reference	Patient details	%LAA parameter	Statistical technique	Variable adjusted for	Results	p-value
Dawkins et al. (2003)	UK centre (n=256)	-910	Univariate and multivariate regression analysis Odds ratio	Age, lower and upper expiratory scan	*Univariate* Upper and lower zone CT density associated with all-cause mortality. *Multivariate* Upper expiratory associated with all cause and respiratory mortality	Univariate Upper ins p = 0.005 Upper ex p = 0.001 Lower ins p = 0.007 Lower ex p = 0.002 Multivariate Upper all-cause p = 0.001 Upper respiratory p = 0.001
Quality of life						
Vijayasaratha and Stockley (2012)	ADAPT (n=23)	PD_{15}	Spearman correlation		PD_{15} correlated with exacerbation length in days; delay of antibiotics in days; day 1 symptom scores but not resolution length	Length in days p = 0.003 Delay of antibiotics in days p < 0.001 Day 1 symptom scores p = 0.035 Resolution length p = NR
Dirksen et al. (2009)	AATD registries in Denmark, Sweden and UK	PD_{15}	Random coefficient model		PD_{15} not correlated with SGRQ	SGRQ p = NR
Stolk et al. (2003)	Dutch centre (n=77)	PD_{15} -950	Spearman correlation		PD_{15} and -950 correlated with SGRQ	PD_{15} SGRQ p = 0.028 -950 SGRQ p = 0.018
Dowson et al. (2001)	UK centre (n=111)	-910	Spearman's rho test		CT density correlated with all domains of SGRQ and SF-36	SGRQ p < 0.001 SF-36 p < 0.05

Abbreviations: **AATD** = alpha-1-antitrypsin deficiency, **CT** = computed tomography, **EX** = expiratory, **FEV_1** = forced expiratory volume in 1 second, **Ins** = inspiratory, **K_{CO}** = carbon monoxide transfer coefficient, **LAA%** = low attenuation area %, **NR** = not reported, **PD15** = volume-adjusted 15th percentile density, **R** = Pearson's correlation coefficient, **SF-36** = 36 item short form survey, **SGRQ** = St George Respiratory Questionnaire, **TLC** = total lung capacity.

SECONDARY EFFECTIVENESS OUTCOMES

The secondary effectiveness outcomes measured in the direct randomised trials are outlined in Table 18. Key outcomes are described below, noting that additional outcomes will be defined for the final report.

Table 18 Secondary outcomes and statistical analyses of the direct randomised trials

Trial ID	Definition of secondary outcomes
RAPID Chapman et al. (2015)	1. FEV_1
	2. A1PI concentrations (functional and antigenic assays)
	3. Single-breath diffusion capacity (D_{LCO})
	4. Incremental shuttle walk
	5. Quality of life (SGRQ)
	6. Mortality
	7. Adverse events: Any untoward medical event occurring during the trial, defined as not related, possibly related, probably related, or related to A1PI augmentation.
EXACTLE Dirksen et al. (2009)	1. FEV_1
	2. Diffusing capacity of the lung for carbon monoxide ($\mathbf{D_{LCO}}$)
	3. Transfer coefficient of the lung for carbon monoxide ($\mathbf{K_{CO}}$)
	4. Frequency of exacerbations collected in diary
	5. Mortality
	6. Quality of life (SGRQ)
DIRKSEN99 Dirksen et al. (1999)	7. Diffusion capacity ($\mathbf{D_{LCO}}$) at 3-month intervals
	8. Carbon monoxide diffusion constant ($\mathbf{K_{CO}}$)
	9. ***Patient-administered*** serial spirometry daily
	10. CT lung density

Abbreviations: **A1PI** = alpha-1 proteinase inhibitor, **CT** = computed tomography, $\mathbf{D_{LCO}}$ = diffusing capacity for carbon monoxide, $\mathbf{FEV_1}$ = forced expiratory volume in one second, $\mathbf{K_{CO}}$ = carbon monoxide transfer coefficient, **SGRQ** = St George's Respiratory Questionnaire.

Details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results, appear in Appendix D, Table 97 and Table 98.

QUALITY OF LIFE

Quality of life using the St. George's Respiratory Questionnaire (SGRQ) was reported in two of the direct randomised trials. The SGRQ is a disease-specific questionnaire that measures QoL in patients with obstructive airways disease. The questionnaire ranges from 0 to 100, with higher scores indicating greater limitations and worsening quality of life. A mean change score of 4-8 units is associated with a slightly efficacious treatment, 8-13 units for moderately efficacious treatment, and 13-16 units for very efficacious treatment (Jones 1994).

MORTALITY

The assessment of mortality separates patients into two groups; those which are dead and those which are alive. The effects of an intervention on death can be calculated by examining the per cent of patients alive or dead during follow-up, or modelling the rate of death using survival curves. Two non-RCTs and one RCT reported the overall mortality rate following augmentation therapy (Chapman et al. 2015; Tonelli et al. 2009; Alpha-1 registry study group 1998). One non-RCT used survival curves (Kaplan-Meier) to determine in which patient's augmentation therapy was most effective (Alpha-1 registry study group 1998).

EXACERBATIONS/HOSPITALISATION DUE TO EXACERBATIONS

There are multiple definitions of exacerbations. For example, (Calverley 2005) defines exacerbations as "an episode where a patient seeks medical help rather than a predefined change in one or more symptoms". However, exacerbations can be further stratified by frequency and severity and often need to take into account baseline disease severity (Chapman et al. 2013). Given this, the MCIDs for exacerbations in COPD patients vary substantially with studies demonstrating a reduction in exacerbations of 4 – 20% to be clinically meaningful (Chapman et al. 2013).

Exacerbations were reported in three trials (two RCTs and one non-RCT). One RCT and one non-RCT used a similar definition of exacerbation: the worsening of a patient's condition beyond normal day-to-day variation which requires a change to their medical regimen (Dirksen et al. 2009, Barros-Tizon et al. 2012). The RCT by Chapman et al. (2015) determined exacerbations in accordance with (Anthonisen et al. 1987) who categorised exacerbations based on the type and number of symptoms.

EXERCISE CAPACITY

Incremental Shuttle Walk

The incremental shuttle walk is an assessment of exercise capacity. The test requires the patients to walk up and down at 10m course. The speed at which a patient walks is dictated by an audio signal. The lapse between each audio signal decreases every minute requiring the patient to walk incrementally faster. The end of the tests occurs when the patient is too breathless to continue; they fail to reach complete the course in the allocate time or they reach of 85% of their predicted heart rate (Singh et al. 1992). The MCID for the incremental shuttle test in COPD patients is 48m (Singh et al. 2008). One RCT used the incremental shuttle walk test to infer exercise capacity, however the precise methodology was not reported (Chapman et al. 2015). The results of the study exhibited considerably variability among the included population as indicated by the standard deviations.

DYSPNOEA

Dyspnoea as defined by the American Thoracic Society (1999) is the "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity".

Dyspnoea is typically a patient reported event, however, measurements of gas transfer, spirometry, exercise ability and Borg or VAS scale can help diagnose dyspnoea. Dyspnoea was reported in one RCT (Chapman et al.2015). However, the methodology used to assess dyspnoea was not reported.

LUNG FUNCTION

D_{LCO}/K_{CO}

The diffusing capacity of the lungs for carbon monoxide (D_{LCO} or T_{LCO}) and the carbon monoxide transfer coefficient (K_{CO}) are measures of lung function. They assess the transfer of inspired carbon monoxide from the alveoli to the red blood cells in circulation. K_{CO} additionally takes into account the alveolar volume (the number of contributing alveolar units) and is calculated as D_{LCO}/VA. The MCID for D_{LCO} as reported by (Horita et al. 2015) was 1.1 ml/min/mmHg (11% of baseline D_{LCO}) when anchored to FEV_1 and six minute walk test. MCIDs for K_{CO} were not found in our literature search. All three RCTs reported D_{LCO} and two reported K_{CO}. Dirksen et al. (1999 and 2009) assessed D_{LCO} and K_{CO} in accordance with European guidelines (Quanjer et al. 1993). Chapman et al. (2015) did not report K_{CO} or the method used to measure D_{LCO}. One non-RCT reported D_{LCO} (Barros-Tizon et al. 2012), again however, the methodology was not specified.

FEV_1

FEV_1 is a functional outcome representing the amount of air forcibly expired within one second. It was measured accurately in the included trials, using standard spirometry protocols. FEV_1 has noted limitations in disease-modification trials, however, because it changes slowly over time (therefore requiring long follow-up, generally > 2 years), it exhibits individual variability and until certain thresholds are reached has limited correlation with endpoints such as mortality or exacerbations (Chorostowska-Wynimko 2016), and it requires large sample sizes to sufficiently power trials to detect this effect (Schluchter et al. 2000). Literature defines 100 mL as the minimum clinically important difference (Donohue 2005).

FEV1 was measured in four non-RCTs. Two studies did not report the methodology use to assess spirometry (Barros-Tizon et al. 2012, Wencker et al. 1998). The Alpha-1 registry study group (1998) measured FEV_1 before and after broncholdilator treatment and allowed subjects to perform up to eight expirations to generate three reproducible scores. In Seersholm et al. (1997) FEV_1 was calculated in accordance with European respiratory society recommendations. However, the intervention cohort measured FEV_1 after two puffs of salbutamol and repeated FEV_1 measurements at least three times. It is unclear whether the control cohort underwent a similar methodology.

ADVERSE EVENTS

Adverse events (any, severe, and treatment-related), dyspnoea in particular, hospitalisation, discontinuation, and death, were recorded as descriptive statistics. Most studies reported both the number of events and the proportion of the patient population experiencing the event. Nine studies,

including the RCTs, recorded the events prospectively with outcome measures established a priori. The remaining eight studies either recorded the events retrospectively (five studies) or only partially established outcome measures before study commencement (three studies). It is unclear whether important adverse events were captured in the retrospective trials; there was significant variation between reported adverse event rates between prospective and retrospective studies. These are highlighted in Section B.6.

META-ANALYSIS

Continuous outcomes were evaluated as mean differences or standardised mean differences. Standardised mean differences were calculated in order to account for differences in measurement scales across included studies. Dichotomous outcomes were evaluated using relative risks and associated 95% confidence intervals.

Missing standard deviations were evaluated from available standard errors using the following formula:

$$SD = SE \times \sqrt{N}$$

Missing standard deviations were evaluated from available 95% confidence intervals using the following formula:

$$SD = \sqrt{N} \times (\text{upper limit} - \text{lower limit}) / 3.92$$

Heterogeneity across studies was evaluated using I^2 statistics. Fixed-effects models were used for meta-analyses. Meta-analyses were conducted using RevMan version 5.3.

B.6. RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT SAFE?

Summary – What is the safety status of A1PI augmentation therapy relative to best standard care?

Safety outcomes reported in the included studies were death due to adverse events, severe adverse events, treatment-related adverse events, any adverse events, dyspnoea, infection from treatment, and hospitalisation/discontinuation due to adverse events. There were no significant differences in the rates of these outcomes identified in the direct RCTs.

Death was uncommon. Six deaths occurred in the eligible studies (899 patients), none of which were reported to be treatment related.

Severe adverse events were uncommon, with a median occurrence of 2.1% in the patient population (range 0.0-30.0%) across eleven studies. Discontinuation due to adverse events had a median occurrence of 0.6% in the patient population (range 0.0-7.1%) across nine studies; and hospitalisation due to adverse events had a median occurrence of 1.4% in the patient population (range 0.0-14.3%) across four studies.

All studies found the same rates of severe adverse events across intervention groups. Overall, it appears that the intervention is safe, with most events being related to the underlying disease.

Seventeen studies were included for the evaluation of safety outcomes: the three RCTs also included for effectiveness (Chapman et al. 2015; Dirksen et al. 1999; Dirksen et al. 2009), two open-label extensions of RCTs (Campos et al. 2013; McElvaney et al. 2017), two further nRCTs with comparator groups still taking a form of A1PI (varied by dose, product or time frame) (Sandhaus et al. 2014; Stocks et al. 2010a), and ten single-arms studies (Barker et al. 1997; Barker et al. 1994; Barros-Tizon et al. 2012; Hubbard and Crystal 1988; Schmidt et al. 1988; Schwaiblmair et al. 1997; Stoller et al. 2003; The Alpha-1-Antitrypsin Deficiency Registry Study Group 1998; Wencker et al. 1998; Wewers et al. 1987).

Key safety outcomes reported in the included studies were death due to adverse events, severe adverse events, treatment-related adverse events, any adverse events, dyspnoea, and hospitalisation or discontinuation due to adverse events. Summaries of these outcomes across studies are presented in Tables 17 to 23. Detailed safety outcomes in each study are presented in Appendix D, Table 109 and Table 110. In addition, Table 26 shows severe adverse events across studies on the particular intervention products, Zemaira and PROLASTIN-C. Because this evidence was limited, studies eligible for the safety assessment included patients receiving AT with any A1PI product. All considerations of safety and adverse effects should take this into account.

Meta-analysis was not conducted for the single arm studies due to differences in the duration of follow-up and the populations included across studies. A narrative summary of the primary safety outcomes is presented below.

CONTRAINDICATIONS

AT with Prolastin or Zemaira is contraindicated in patients with a history of severe or anaphylactic response to A1PI products, as well as any individuals with a known hypersensitivity to any of its components (Aventis Bering 2003). All inclusion criteria reflected this. Patients with both AATD and severe IgA deficiency are at risk of anaphylactic reaction and should not be treated (Alpha 1 Foundation 2015).

DEATH DUE TO ADVERSE EVENTS

Eight studies provided evidence on death due to adverse events. Six deaths occurred in the eligible studies, which included 899 patients in total. In the single arm studies, death had a mean occurrence of 2.3%, and a median occurrence of 0.0% in the patient population (range 0.0-7.1%). The total rates of death due to adverse events are presented in Table 19. For more detail on adverse events reported in the studies see Appendix D, Tables 101 & 102.

Table 19 Results of death due to adverse events across the included randomised controlled trials and single-arm studies

RCT ID	Risk of bias	Follow-up	Treatment dose/frequency	Intervention rate (proportion)	Comparator rate (proportion)	Relative difference RR (95% CI)
RAPID (Chapman et al. 2015)	Low	24 months	60mg/kg per week	1/93 (1.0%)	3/87 (3.4%)	0.31 (0.03 to 2.94)
Single-arm study ID	**Risk of bias**	**Follow-up**	**Treatment dose/frequency**	**Intervention rate (proportion)**	**NA**	**NA**
Barker et al. 1994	High	48 months	60mg/kg every 1-2 weeks	1/14 (7.1%)	NA	NA
Barker et al. 1997	High	4 months	120mg/kg every 2 weeks	1/23 (4.3%)	NA	NA
Barros-Tizón et al. 2012	Moderate	18 months	60mg/kg every 1-3 weeks	0/127 (0.0%)	NA	NA
Campos et al. 2013	High	4 months	60mg/kg per week	0/30 (0.0%)	NA	NA
Schwaiblmair et al. 1997	High	36 months	60mg/kg per week	1/20 (5.0%)	NA	NA
Stocks et al. 2010	High	6 months	60mg/kg per week	0/24 (0.0%)	NA	NA
Wencker et al. 1998	Moderate	6 years	60mg/kg per week	0/443 (0.0%)	NA	NA

Abbreviations: **CI** = confidence interval, **NA** = not applicable, **RCT** = randomised controlled trial, **RR** = relative risk.

The single RCT reported that death due to adverse events occurred in 2% of patients in the intervention group and 3% in the placebo group. The four deaths were due to respiratory failure, sepsis, pneumonia and breast cancer. Four single-arm studies reported that no patients died due to adverse events (Barros-Tizon et al. 2012; Campos et al. 2013; Schwaiblmair et al. 1997; Stocks et al. 2010a). Two studies reported death of a patient due to adverse events after receiving Zemaira

(Barker et al. 1997; Barker et al. 1994). One of these resulted from progression of the disease (Barker et al. 1994), and the other was noted to be unrelated to the intervention (Barker et al. 1997). Overall, none of the deaths were reported to be treatment-related.

SEVERE ADVERSE EVENTS

Thirteen studies provided evidence on severe adverse events occurring after treatment with the intervention (Barker et al. 1997; Barros-Tizon et al. 2012; Campos et al. 2013; Chapman et al. 2015; Dirksen et al. 2009; McElvaney et al. 2017; Sandhaus et al. 2014; Schmidt et al. 1988; Schwaiblmair et al. 1997; Stocks et al. 2010a; Stoller et al. 2003; Wencker et al. 1998; Wewers et al. 1987). In the RCTs, severe adverse events occurred less frequently in the A1PI arm than placebo overall (RR=0.83, 95% CI 0.57 to 1.19), noting that this difference was not statistically significant. In the single arm studies, severe adverse events had a median occurrence of 2.1% in the patient population (range 0.0-30.0%). The total rates of severe adverse events are presented in Table 20. For more detail on adverse events reported in the studies see Appendix D, Tables 101 & 102. The forest plot indicating pooled rate of severe adverse events is presented in Figure 9.

Table 20 Results of severe adverse events across the included randomised controlled trials and single-arm studies

RCT ID	Risk of bias	Follow-up	Treatment dose/frequency	Intervention rate (proportion)	Comparator rate (proportion)	Relative difference RR (95% CI)
RAPID (Chapman et al. 2015)	Low	24 months	60mg/kg per week	28/93 (30.1%)*	28/87 (32.0%)*	0.94 (0.61 to 1.44)
EXACTLE (Dirksen et al. 2009)	Low	30 months	60mg/kg per week	10/38 (26.3%)*	18/39 (46.1%)*	0.62 (0.31 to 1.23)
Non-RCT ID	**Risk of bias**	**Follow-up**	**Treatment dose/frequency**	**Intervention rate (proportion)**	**NA**	**NA**
Barker et al. 1997	High	4 months	120mg/kg every 2 weeks	2/23 (8.7%)	NA	NA
Barros-Tizon et al. 2012	Moderate	18 months	60mg/kg every 1-3 weeks	4/127 (3.1%)†	NA	NA
Campos et al. 2013	High	4 months	60mg/kg per week	0/30 (0.0%)	NA	NA
RAPID-OLE (McElvaney et al. 2017)	Moderate	48 months	60mg/kg per week	42/140 (30.0%)	NA	NA
Sandhaus et al. 2014	High	3 months	60mg/kg (frequency NR)	4/50 (8.0%)†	NA	NA
Schmidt et al. 1988	High	6 months	60mg/kg per week	0/20 (0.0%)	NA	NA
Schwaiblmair et al. 1997	High	36 months	60mg/kg per week	0/20 (0.0%)	NA	NA

Stocks et al. 2010	High	6 months	60mg/kg per week	2/24 (8.3%)	NA	NA
Stoller et al. 2003	Moderate	7 years	Unclear	63/720 (events)	NA	NA
Wencker et al. 1998	Moderate	6 years	60mg/kg per week	5/443 (1.1%)	NA	NA
Wewers et al. 1987	High	6 months	60mg/kg per week	0/21 (0.0%)	NA	NA

Abbreviations: **CI** = confidence interval, **NA** = not applicable, **NR** = not reported, **RCT** = randomised controlled trial, **RR** = relative risk.
*Data obtained from results tab on the NIH's clinical trials website. †Events reported to be "not related" to the intervention.

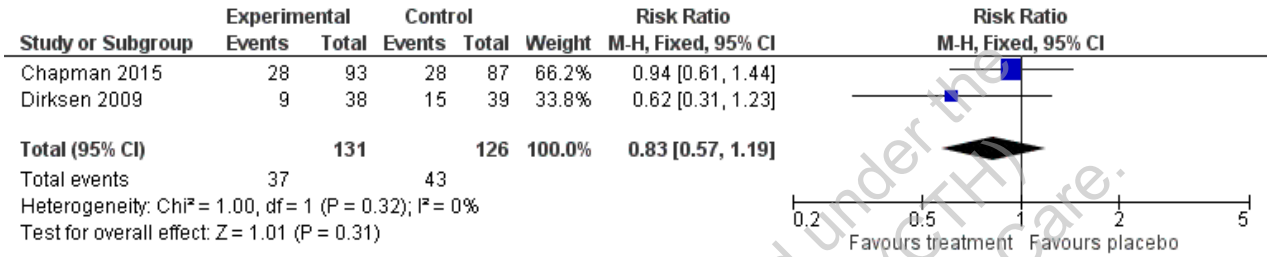


Figure 9 **Forest plot indicating the pooled rate of severe adverse events for A1PI compared to placebo**

Two RCTs, comprising a total of 257 patients, reported 84 severe adverse events in total. In the RAPID trial, the placebo group (32.0%) experienced a slightly higher proportion of severe adverse events than the intervention group (30.1%). Severe adverse events that occurred in more than 5% of patients in this study population were chronic obstructive pulmonary disorders, pneumonia and lower respiratory infection.

In the EXACTLE trial, the placebo group also experienced a higher proportion of severe adverse events (46.1%) than the intervention group (26.3%). The trial reported that pneumonia, atrial fibrillation, pulmonary embolism, and pneumothorax were severe adverse events that occurred in more than 5% of patients in this study population.

The patients in McElvaney et al. (2017) who had received A1PI intervention for 24 or 48 months, reported here as a single arm, experienced the same proportion of severe adverse events (30%). Five studies, with a total of 144 patients, reported that no severe adverse events had occurred. The remaining single arm studies reported low rates of seriousseverе adverse events (ranging from 1.1% to 8.7%)

Notably, the EXACTLE, RAPID and RAPID/OLE trials reported higher rates of serious severe adverse events than the single arm studies which were all had rates below ten percent. This may have been due to the RCTs and NRCT being conducted prospectively, defining adverse events intentionally by severity, and following patients more rigorously. Lengths of follow-up also might have played a part as their follow-up points are longer than all but three of the eleven single arm studies.

TREATMENT-RELATED ADVERSE EVENTS

Nine studies provided evidence on treatment-related adverse events (Barker et al. 1997; Barros-Tizon et al. 2012; Campos et al. 2013; Chapman et al. 2015; Dirksen et al. 2009; McElvaney et al. 2017; Sandhaus et al. 2014; Schwaiblmair et al. 1997; Stocks et al. 2010a). The total rates of treatment-related adverse events are presented in Table 21. For more detail on adverse events reported in the studies see Appendix D, Tables 101 & 102.

In the RCTs, treatment-related adverse events occurred less frequently in the A1PI arm than placebo overall (RR=0.86, 95% CI 0.57 to 1.29), noting that this difference was not statistically significant. Treatment-related adverse events had a median occurrence of in the single arm studies of 10.0% in the patient population (range 0.0-28.6%). Though, this relationship was drawn at the discretion of the study authors and may not indicate true cause.

Table 21 Results of treatment-related adverse events across the included randomised controlled trials and single-arm studies

RCT ID	Risk of bias	Follow-up	Treatment dose/frequency	Intervention rate (proportion)	Comparator rate (proportion)	Relative difference RR (95% CI)
RAPID (Chapman et al. 2015)	Low	24 months	60mg/kg per week	21/93 (22.6%)	21/87 (24.1%)	0.94 (0.55 to 1.59)
EXACTLE (Dirksen et al. 2009)	Low	30 months	60mg/kg per week	11/38 (28.9%)	15/39 (38.5%)	0.75 (0.40 to 1.42)
Single arm study ID	**Risk of bias**	**Follow-up**	**Treatment dose/frequency**	**Intervention 1 rate (proportion)**	**Intervention 2 rate (proportion)**	**NA**
Barker et al. 1997	High	4 months	120mg/kg every 2 weeks	4/23 (17.4%)†	NA	NA
Barros-Tizón et al. 2012	Moderate	18 months	60mg/kg every 1-3 weeks	7/127 (5.5%)†	NA	NA
Campos et al. 2013	High	4 months	60mg/kg per week	4/60 (6.7%)	NA	NA
RAPID-OLE (McElvaney et al. 2017)	Moderate	48 months	60mg/kg per week	18/180 (10.0%)	NA	NA
Sandhaus et al. 2014	High	6 months	60mg/kg (frequency NR)	6/21 (28.6%)†	NA	NA
Schwaiblmair et al. 1997	High	36 months	60mg/kg per week	1/20 (5.0%)	NA	NA
Stocks et al. 2010	High	6 months	60mg/kg per week	2/24 (8.3%)	NA	NA

Abbreviations: **CI** = confidence interval, **NA** = not applicable, **NR** = not reported, **RCT** = randomised controlled trial, **RR** = relative risk.
†unknown if patients were included for multiple events

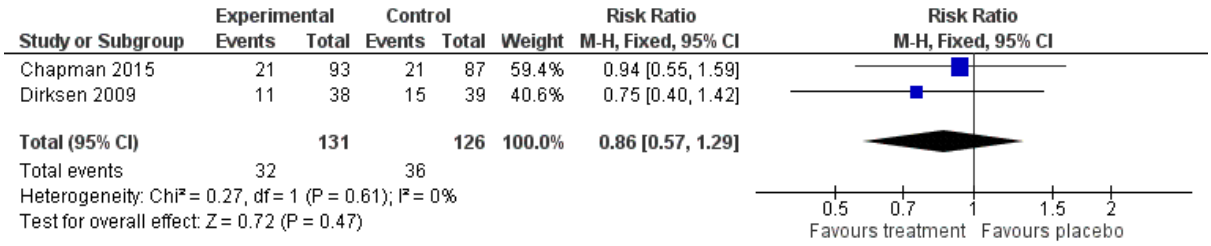


Figure 10 **Forest plot indicating rate of death due to adverse events in A1PI patients compared to placebo**

The RAPID and EXACTLE trials reported rates of treatment-related adverse events that were similar between intervention and placebo groups, and both slightly higher in the placebo group. The RAPID-OLE trial (McElvaney et al. 2017), reported a rate of 10% for patients receiving Zemaira.

Treatment-related adverse events that occurred more than once in four studies (totalling 224 patients) included headache, dyspnoea and pruritus (Barker et al. 1997; Barros-Tizon et al. 2012; Sandhaus et al. 2014; Stocks et al. 2010a). Schwaiblmair (1997) reported one treatment-related adverse event that was self-limiting.

DYSPNOEA

Six studies reported results on dyspnoea (Table 20). Two RCTs reported relative dyspnoea rates for patients treated with A1PI and placebo (Chapman et al. 2015; Dirksen et al. 2009). Dyspnoea was not reported in the EXACTLE trial publication, and was instead identified on clinicaltrials.gov. The pooled rate across RCTs was higher in patients treated with A1PI (RR=1.23, 95% CI 0.63 to 2.4), noting that the pooled estimate was not statistically significant, and was subject to moderate heterogeneity (I^2=60%, P=0.11). Two patients in the EXACTLE trial experienced dyspnoea, and one experienced severe dyspnoea, in the placebo arm; however, it is unclear if these were mutually exclusive.

Three single arm studies reported rates of dyspnoea per patient, and a fourth reported the number of dyspnoea events as a proportion of all adverse events (Barker et al. 1997; McElvaney et al. 2017; Stoller et al. 2003; Wencker et al. 1998). Single arm studies which reported a rate of patients experiencing dyspnoea after AT showed dyspnoea had a median occurrence of 18.3% in the patient population (range 3.8-34.8%). The total rates of dyspnoea are presented in Table 22. For more detail on adverse events reported in the studies see Appendix D, Tables 101 & 102.

Table 22 **Results of dyspnoea across the randomised controlled trials and single-arm studies**

RCT ID	Risk of bias	Follow-up	Treatment dose / frequency	Intervention rate (proportion)	Comparator rate (proportion)	Relative difference RR (95% CI)
RAPID (Chapman et al. 2015)	Low	24 months	60mg/kg per week	17/93 (18.3%)	10/87 (11.5%)	1.59 (0.77 to 3.28)
EXACTLE* (Dirksen et al.	Low	30 months	60mg/kg per week	0/38 (0.0%)	3/39 (7.7%)	0.15 (0.01 to 2.74)

2009)						
Single arm study ID	**Risk of bias**	**Follow-up**	**Treatment dose/frequency**	**Intervention rate (proportion)**	**NA**	**NA**
Barker et al. 1997	High	4 months	120mg/kg every 2 weeks	8/23 (34.8%)	NA	NA
RAPID-OLE (McElvaney et al. 2017)	Moderate	48 months	60mg/kg per week	28/140 (20.0%)	NA	NA
Stoller et al. 2003	Moderate	7 years	Unclear	61 events (8.5% of all events)	NA	NA
Wencker et al. 1998	Moderate	6 years	60mg/kg per week	17/443 (3.8%)	NA	NA

*Data obtained from results tab on www.clinicaltrials.gov.
Abbreviations: **CI** = confidence interval, **NA** = not applicable, **RCT** = randomised controlled trial, **RR** = relative risk.

Figure 10 Forest plot indicating rate of acute episodes of dyspnoea for A1PI compared to placebo

DISCONTINUATION DUE TO ADVERSE EVENTS

Ten studies, including two RCTs and eight single-arm studies, provided evidence on discontinuation due to adverse events (Barker et al. 1994; Barros-Tizon et al. 2012; Campos et al. 2013; Chapman et al. 2015; Dirksen et al. 2009; Sandhaus et al. 2014; Stocks et al. 2010a; Stoller et al. 2003; The Alpha-1-Antitrypsin Deficiency Registry Study Group 1998; Wencker et al. 1998). Discontinuation due to adverse events was rare in the included studies (Table 23).

Both RCTs demonstrated fewer patients discontinuing therapy in the A1PI arm, which is reflected in the pooled estimate (RR=0.22, 95% CI 0.04 to 1.30) without any evidence of heterogeneity (I^2, P=0.94); however, this estimate includes the possibility of no difference.

In the single arm studies, discontinuation had a median occurrence of 0.6% in the patient population (range 0.0-7.1%). It is worth noting that discontinuation rates reported in the A1PI registry study (1998) were higher due to lung transplantation (n=80/747, 10.7%), financial strain (n=16/747, 2.1%), and unknown reasons (n=37/747, 5.0%). The forest plot for the meta-analysis of discontinuation due to adverse events across the studies is presented in Figure 11.

Table 23 **Results of discontinuation due to adverse events across the included randomised controlled trials and single-arm studies**

RCT ID	Risk of bias	Follow-up	Treatment dose/frequency	Intervention rate (proportion)	Comparator rate (proportion)	Relative difference RR (95% CI)
RAPID (Chapman et al. 2015)	Low	24 months	60mg/kg per week	1/93 (1.1%)	4/87 (4.6%)	0.23 (0.03 to 2.05)
EXACTLE (Dirksen et al. 2009)	Low	30 months	60mg/kg per week	0/38 (0.0%)	2/39 (5.1%)	0.21 (0.01 to 4.14)
Single arm study ID	**Risk of bias**	**Follow-up**	**Treatment dose/frequency**	**Intervention rate (proportion)**	**NA**	**NA**
The A1PI Deficiency Registry Study Group 1998	Moderate	5 years	Unclear	4/747 (0.5%)	NA	NA
Barker et al. 1994	High	48 months	60mg/kg every 1-2 weeks	1/14 (7.1%)	NA	NA
Barros-Tizón et al. 2012	Moderate	18 months	60mg/kg every 1-3 weeks	0/127 (0.0%)	NA	NA
Campos et al. 2013	High	4 months	60mg/kg per week	0/30 (0.0%)	NA	NA
Sandhaus et al. 2014	High	3 months	60mg/kg (frequency NR)	2/50 (4.0%)	NA	NA
Stocks et al. 2010	High	6 months	60mg/kg per week	0/24 (0.0%)	NA	NA
Stoller et al. 2003	Moderate	7 years	Unclear	3/174 (1.7%)	NA	NA
Wencker et al. 1998	Moderate	6 years	60mg/kg per week	3/443 (0.7%)	NA	NA

Abbreviations: **A1PI** = alpha-1 proteinase inhibitor, **CI** = confidence interval, **NA** = not applicable, **NR** = not reported, **RCT** = randomised controlled trial, **RR** = relative risk.

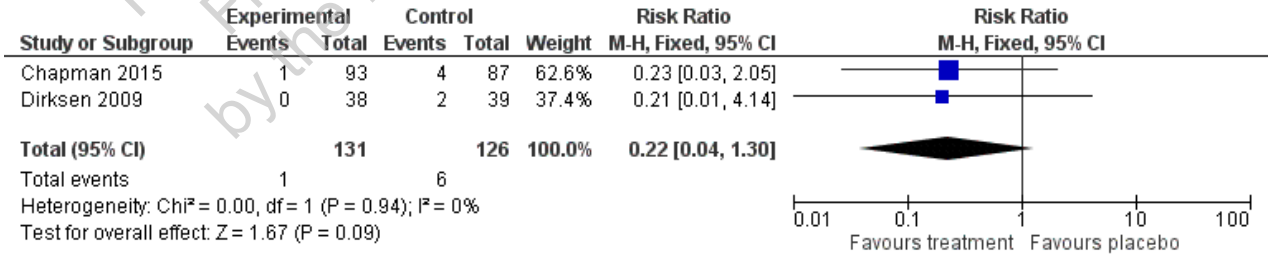


Figure 11 **Forest plot indicating discontinuation due to adverse events for A1PI compared to placebo**

RAPID reported 1% discontinuation in the intervention group and 5% in the placebo group. EXACTLE reported no discontinuations in the intervention group and 5% in the placebo group. Three single-arm studies reported that no discontinuations occurred, while low levels were reported in the remaining single-arm studies.

HOSPITALISATION DUE TO ADVERSE EVENTS

Hospitalisation due to adverse events was reported, in four single-arm studies (Barker et al. 1994; Schwaiblmair et al. 1997; Stoller et al. 2003; Wencker et al. 1998). No RCTs reported on this outcome. The total rates of hospitalisation due to adverse events are presented in Table 24.

Reported rates were relatively low in three studies; and Schwaiblmair et al. (1997) reported no patients were hospitalised due to adverse events. In addition to hospitalisation Stoller et al. (2003) reported patients that experienced a physician visit or new medication due to adverse events (21.1%). Hospitalisation had a median occurrence of 1.4% in the patient population (range 0.0-14.3%).

Table 24 Hospitalisation due to adverse events across the included studies

Single-arm study ID	Risk of bias	Follow-up	Treatment dose/frequency	Event rate (proportion)
Barker et al. 1994	High	48 months	60mg/kg every 1-2 weeks	2/14 (14.3%)
Schwaiblmair et al. 1997	High	36 months	60mg/kg per week	0/20 (0.0%)
Stoller et al. 2003	Moderate	7 years	Unclear	12/720 (1.7%)
Wencker et al. 1998	Moderate	6 years	60mg/kg per week	5/443 (1.1%)

In Barker et al. (1994), one hospitalised patient had been hospitalised three times prior to treatment, leading to the conclusion that this incident was due to continuation of pre-existing disease. The other hospitalised patient experienced hypotension and respiratory distress. Stoller et al. (2003) did not report reasons for hospitalisation for the 12 affected patients. In Wencker et al. (1998), four hospitalised patients experienced anaphylactic reactions to the treatment; one experienced worsened congestive heart failure and related respiratory failure.

ANY ADVERSE EVENTS

Sixteen studies, including all of the RCTs, provided evidence on any adverse events occurring after treatment with the intervention (Barker et al. 1997; Barker et al. 1994; Barros-Tizon et al. 2012; Campos et al. 2013; Chapman et al. 2015; Dirksen et al. 1999; Dirksen et al. 2009; Hubbard and Crystal 1988; McElvaney et al. 2017; Sandhaus et al. 2014; Schmidt et al. 1988; Schwaiblmair et al. 1997; Stocks et al. 2010a; Stoller et al. 2003; Wencker et al. 1998; Wewers et al. 1987). Total rates of adverse events are presented in Table 25. The rate of any patients experiencing any adverse event ranged from 0%-100%, with a median of 37%. For more detail on adverse events reported in the studies see Appendix D, Tables 101 & 102.

Table 25 Results of any adverse events across the included randomised controlled trials and single-arm studies

RCT ID	Risk of bias	Follow-up	Treatment dose/frequency	Intervention Total (proportion)	Comparator Total (proportion)	Relative difference RR (95% CI)
RAPID (Chapman et al. 2015)	Low	24 months	60mg/kg per week	92/93 (98.9%)	86/87 (98.9%)	1.0 (0.97 to 1.03)
EXACTLE (Dirksen et al. 2009)	Low	30 months	60mg/kg per week	37/38 (97.4%)	38/39 (97.4%)	1.0 (0.93 to 1.07)
DIRKSEN99 (Dirksen et al. 1999)	Low	36 months	250mg/kg per month	0/28 (0.0%)	0/28 (0.0%)	NA
Single arm study ID	**Risk of bias**	**Follow-up**	**Treatment dose/frequency**	**Intervention rate (proportion)**	**NA**	**NA**
Barker et al. 1994	High	48 months	60mg/kg every 1-2 weeks	4/14 (28.6%)	NA	NA
Barker et al. 1997	High	4 months	120mg/kg every 2 weeks	21/23 (91.3%)	NA	NA
Barros-Tizón et al. 2012	Moderate	18 months	60mg/kg every 1-3 weeks	11/127 (8.7%)	NA	NA
Campos et al. 2013*	High	4 months	60mg/kg per week	41/60 (68.3%)	NA	NA
Hubbard & Crystal 1988	Moderate	12 months	250 mg/kg every 28 days	0/9 (0.0%)	NA	NA
RAPID-OLE (McElvaney et al. 2017)	Moderate	48 months	60mg/kg per week	138/140 (98.6%)	NA	NA
Sandhaus et al. 2014	High	3 months	60mg/kg (frequency NR)	49/50 (98.0%)	NA	NA
Schmidt et al. 1988	High	6 months	60mg/kg per week	3/20 (15.0%)	NA	NA
Schwaiblmair et al. 1997	High	36 months	60mg/kg per week	1/20 (5.0%)	NA	NA
Stocks et al. 2010*	High	6 months	60mg/kg per week	11/24 (45.8%)	NA	NA
Stoller et al. 2003	Moderate	7 years	Unclear	174/720 (24.2%)	NA	NA
Wencker et al. 1998	Moderate	6 years	60mg/kg per week	65/443 (14.7%)	NA	NA
Wewers et al. 1987	High	6 months	60mg/kg per week	4/21 (19.0%)	NA	NA

Abbreviations: **CI** = confidence interval, **NA** = not applicable, **NR** = not reported, **RCT** = randomised controlled trial, **RR** = relative risk.
*The same patients at different time points/intervention products.

The RAPID trial reported the same proportion of adverse events in the intervention and placebo groups (98.9%). Events occurring in more than 10% of patients in the intervention group were: infections/infestations, respiratory disorders, administration site issues, gastrointestinal disorders, nervous system disorders, musculoskeletal disorders, nasopharyngitis, COPD, oropharyngeal pain,

cough, aggravation, lower respiratory disorders, dyspnoea, nausea, influenza, upper respiratory disorders, pyrexia, bronchitis, sinusitis, back pain, and pneumonia (Chapman et al. 2015).

The EXACTLE trial also reported the same proportion of adverse events in the intervention and placebo groups (97.4%). Events occurring in more than 5% of patients in the intervention group were severe exacerbations, pneumonia, pneumothorax, and atrial fibrillation (Dirksen et al. 2009). Patients in the DIRKSEN99 trial did not experience any adverse effects (Dirksen et al. 1999).

The RAPID-OLE trial stated that there were no safety concerns with the intervention. Adverse events reported in an appendix to the paper were similar between intervention groups, both of which were treated with open-label Zemaira at this stage of the RAPID trial.

A large disparity is noted between the RCTs and the observational studies in terms of number of adverse events reported. In the single arm studies, the rate of any patients experiencing any adverse event ranged from 0.0 to 100.0% with a median of 24.2%. This may indicate that adverse events have been under-reported in the observational studies. Adverse events reported most frequently in the observational studies (in descending order of occurrence) were headache, fever, dyspnoea, cough, nausea, and COPD exacerbation. These were mainly self-limiting with minimal medical attention required.

INFECTION

Products derived from human plasma may contain infectious viruses that cause disease. The risk of infectious agents is reduced by screening blood donors for exposure to certain viruses, and by inactivating or removing viruses during manufacture (Aventis Bering 2003). Seven studies took blood tests pre- and post-intervention to test if infection with human immunodeficiency virus (HIV), Hepatitis B virus, Hepatitis C virus, and parvovirus B19 had occurred during the treatment (Hubbard and Crystal 1988; Schmidt et al. 1988; Schwaiblmair et al. 1997; Stocks et al. 2010a; Stoller et al. 2003; Wencker et al. 1998; Wewers et al. 1987). No case of infection was reported in any of the studies.

PROLASTIN-C AND ZEMAIRA SAFETY OUTCOMES

The specific products under assessment featured in four studies. Zemaira was the treatment given to intervention patients (n=93) in the RAPID and RAPID-OLE trials (Chapman et al. 2015; McElvaney et al. 2017). PROLASTIN-C was the treatment given to patients (n=54) in two single-arm studies (Chapman et al. 2015; Stocks et al. 2010a). Rates of severe adverse events in these studies are reported in Table 26.

Table 26 **Results of severe adverse events across the RCTs and non-controlled trials treating with Zemaira and PROLASTIN-C**

RCT ID	Risk of bias	Follow-up	Treatment product	Intervention Total (proportion)	Comparator Total (proportion)	Relative difference RR (95% CI)
RAPID (Chapman et al. 2015)	Low	24 months	Zemaira	28/93 (30.1%)*	28/87 (32.0%)*	0.94 (0.61 to 1.44)
Single arm study ID	**Risk of bias**	**Follow-up**	**Treatment product**	**Intervention rate (proportion)**	**NA**	**NA**
Campos et al. 2013	High	4 months	PROLASTIN-C	0/30 (0.0%)	NA	NA
RAPID-OLE (McElvaney et al. 2017)	Moderate	48 months	Zemaira	42/140 (30.0%)	NA	NA
Stocks et al. 2010	High	6 months	Prolastin PROLASTIN-C	2/24 (8.3%)	NA	NA

Abbreviations: **CI** = confidence interval, **RCT** = randomised controlled trial, **RR** = relative risk.
* Data obtained from results tab on the NIH's clinical trials website.

In the RAPID trial, severe adverse events in both intervention (Zemaira) and control (placebo) groups was approximately 30% for both groups. Events occurring in more than 5% of patients were COPD in the Zemaira group, and pneumonia and upper respiratory infection in the placebo group (Chapman et al. 2015).

In the RAPID-OLE trial, McElvaney (2017) reported that 30% of patients experienced serious adverse events for both groups.

Campos et al. (2013) is a cross-over RCT comparing doses, which for the purposes of the safety evaluation of A1PI versus Best Supportive Care only provides single-arm data to inform the research question. As such, this has been treated as a single-arm study. The patient population (n=30) was treated with PROLASTIN-C, and the study compared the standard dose (60mg/kg) to a double dose (120 mg/kg). Safety outcomes were similar to those in the other included studies. No patients experienced severe adverse events.

The study by Stocks et al. (2010), is also treated as a single-arm study. Half of the patients (n=24) were treated with PROLASTIN-C and the other half with Prolastin. Patients in this study experienced two serious adverse events thought to be related to the treatment (two cases of pruritus in one patient after administration with PROLASTIN-C).

IS IT EFFECTIVE (RCT EVIDENCE)?

Summary – Is A1PI more effective than BSC or placebo?

Three RCTs investigated the clinical efficacy of A1PI AT compared to placebo. CT-measured lung density was the primary outcome in two RCTs, and FEV_1 was the primary outcome in one RCT.

At 24-30 months there were no significant differences between A1PI AT and placebo in relation to mortality, exacerbation of COPD, hospitalisation due to COPD exacerbation, quality of life, respiratory function (FEV_1), exercise capacity (incremental shuttle walk test) or carbon monoxide diffusion (D_{LCO}). No relevant data was identified for dyspnoea as a measure of respiratory function, or the BODE index (BMI, obstruction, dyspnoea, exercise capacity).

The only statistically significant difference that was observed was for CT-measured lung density, which favoured AT. The clinical significance of this difference is uncertain, however, as MCIDs for changes in CT-lung density have not been established in the literature.

MORTALITY

Randomised controlled trials

One RCT, with 180 patients followed for 24 months, investigated relative mortality rates of A1PI and placebo or no treatment (Chapman et al. 2015). One patient died of respiratory failure in the A1PI group, and three patients died in the placebo group due to sepsis, pneumonia, and metastatic breast cancer. Due to the small number of events in each group, the calculated relative difference reported in Table 27 is subject to error and should be interpreted with caution. Based on the identified data, the estimated relative survival gain within 24 months is highly uncertain. The DIRKSEN99 study reportedly collected data on mortality but this was not reported.

Table 27 Results of mortality across the randomised controlled trials at 24 months

Study ID	Risk of bias	Follow-up	Intervention n with event/N (%)	Comparator n with event/N (%)	Relative difference RR (95% CI)
RAPID (Chapman et al. 2015)	Low	24 months	1/93 (1.1%)	3/87 (3.4%)	0.31 (0.03 to 2.94)

Abbreviations: **CI** = confidence interval, **RR** = risk ratio.

The RAPID trial also reported a "terminal event" as a composite endpoint of progressive emphysema (Chapman et al. 2015). A terminal event was defined as lung transplantation or mortality. Five patients experienced a terminal event. For these patients, the average lung density at terminal event was 19.0 g/L (95% CI 3.5 to 29.5). The study authors then calculated expected life years gained, by working out the difference between lung density of the whole sample at the baseline (47.1 g/L, 95% CI 23.0 to 76.1) and the averaged lung density at terminal events, and then this difference was divided by the annualised rate of lung density decline. Based on this estimate, the authors calculated

an interpolated survival gain of 18.1 years (12.2 to 30.1) for A1PI patients, compared to 12.3 years (95% CI 8.1 to 19.9) in the placebo group. The internal validity of this estimate is questionable, due to the low number of terminal events. Further, this calculation assumes a linear progression of lung density decline, which is uncertain based on the available trial data.

Non-randomised controlled trials

Two studies investigated the relative mortality rate in A1PI deficient patients undergoing augmentation therapy or not (Table 28). The studies comprised a total of 1091 patients, who were followed for an average of 42–52 months (Tonelli et al. 2009; Alpha-1-Antitrypsin Deficiency Registry Study Group 1998).

The Alpha-1-Antitrypsin Deficiency Registry Study Group performed a retrospective analysis of registry data from March 1989 to October 1992. There were 147 deaths, the cause of which could be identified in 118 deaths. Emphysema (n = 85) and cirrhosis (n = 12) were the predominant causes of death. There were 16 other causes of death which comprised one to three patients. Morality risk was significantly lower for patients receiving AT compared to those not receiving AT when adjusted for age, education and initial FEV_1 % predicted (RR 0.64, 95% CI 0.43 to 0.94, p = 0.02). It was further observed that the effect of augmentation therapy on mortality varied according to FEV_1 % predicted. For patients with FEV_1 < 35% or ≥ 50% there was no effect of augmentation therapy (p = 0.44 and 0.64 respectively). However, for patients with a FEV_1 between 35% and 49%, augmentation was associated with a reduced risk of mortality (p < 0.001). The results of this study were not adjusted for differences in baseline socioeconomic status, smoking status or co-morbidities.

Tonelli et al. (2009) conducted a retrospective analysis of the Alpha-1 Foundation DNA and Tissue bank. Reported 5-year mortality rates were 4.0% for A1PI augmentation and 2.5% (P = 0.58) in non-augmented patients respectively; however, it was unclear how many patients were included in each arm of the analysis (i.e. how many had 5-year follow-up data). These were adjusted for in the analysis. Socioeconomic status was not reported, but is a recognised confounding domain.

Table 28 Results of mortality across the non-randomised controlled trials

Study ID	Follow-up Median (range)	Risk of bias	Patient population	Intervention n with event/N (%)	Comparator n with event/N (%)	Relative difference RR (95% CI)
Alpha-1-Antitrypsin Deficiency Registry Study Group 1998	52 (12 – 86) months	High	Partly receiving Always receiving	33/261 (12.6%) 46/389 (11.8%)	24/277 (8.7%)	NR
Tonelli et al. 2009	41.7 (2.6) months	High		NR (4.0%)	NR (2.5%)	NR

Abbreviations: **CI** = confidence interval, **NR** = not reported, **RR** = risk ratio, **SD** = standard deviation.

EXACERBATION OF COPD

Randomised controlled trials

Two RCTs reported exacerbations of COPD at 24 months, with a total of 257 patients (Table 29) (Chapman et al. 2015;Dirksen et al. 2009). Data were not meta-analysed, as the distributions were not normally distributed in the EXACTLE trial. The RAPID trial presented as an adjusted risk ratio (RR = 1.26, 95% CI 0.92 to 1.74) from a negative binomial regression model, in which country and treatment were fixed effects, and adjustment was made for treatment duration. The EXACTLE trial reported an annualised mean difference of 0.36 (95% CI -0.44 to 1.16). In both studies, patients treated with A1PI experienced a greater number of exacerbations; however, this difference was not statistically significant.

Table 29 Results of exacerbations across the direct randomised controlled trials

Study ID	Follow-up	Risk of bias	Intervention Mean annual number ± SD or 95% CI	Comparator Mean annual number ± SD or 95% CI	Absolute or relative difference MD or RR (95% CI)
RAPID (Chapman et al. 2015)	24 months	Low	1.7 (1.51 to 1.89)	1.42 (1.23 to 1.61)	RR = 1.26 (0.92 to 1.74)
EXACTLE (Dirksen et al. 2009)	<30 months	Low	2.55 ± 2.14	2.19 ±1.33	MD = 0.36 (-0.44 to 1.16)

Abbreviations: **CI** = confidence interval, **MD** = mean difference, **RR** = relative risk, **SD** = standard deviation.

Non-randomised controlled trials

One study reported the number of COPD exacerbations in 127 patients 18 months before, and 18 months after commencing augmentation therapy (Barros-Tizon et al. 2012). There was a significant difference in the number of exacerbations (Table 30) and the per cent of patients experiencing exacerbations following augmentation therapy (59.1 vs 44.1% (before and after respectively) $p < 0.005$). However, the magnitude of the effect was relatively small, with the mean number of exacerbations decreasing by 0.2 per patient. Furthermore, the number of severe exacerbations did not differ significantly between the two groups. The authors noted that the multivariate analysis was likely biased favouring the use of augmentation therapy.

Table 30 Results of exacerbations across the non-randomised trials

Study ID	Follow-up	Risk of bias	Intervention Mean number ± SEM	Comparator Mean number ± SEM
Barros-Tizon et al. 2012	36 months	High	1.2 ± 1.6	1 ± 2.2*

Abbreviation: **SEM** = standard error of mean.
$p < 0.01$

HOSPITALISATION DUE TO COPD EXACERBATIONS

The RAPID and EXACTLE trials recorded hospitalisation rates due to exacerbations of COPD at 24 and 30 months respectively (Chapman et al. 2015; Dirksen et al. 2009). Data were not meta-analysed due to the difference in follow-up duration across studies. Both trials reported the overall number of

patients requiring hospitalisation due to an exacerbation of COPD, however, the total number of events experienced and hospitalisation days were not reported consistently. The estimated relative differences showed conflicting directions of effect across the included studies; however, neither study demonstrated a statistically significant difference between treatment groups. Across the two studies, three patients had two, three, and more than three hospitalisations in the treatment arm; in the comparator arm one patient had two and three patients had three hospitalisations. A summary of results of hospitalisations across the direct randomised controlled trials is presented in Table 31.

Table 31 Results of hospitalisations across the direct randomised controlled trials

Study ID	Risk of bias	Follow-up	Intervention n with event/N (%)	Comparator n with event/N (%)	Relative difference RR (95% CI)
RAPID* (Chapman et al. 2015)	High	24 months	13/93 (14.0%) patients	9/87 (10.3%) patients	1.35 (0.61 to 3.00)
EXACTLE (Dirksen et al. 2009)	Low	<30 months	6/38 (15.8%) patients	11/39 (28.2%) patients	0.56 (0.23 to 1.36)

Abbreviations: **CI** = confidence interval, **N** = total number of patients.
* Results from the RAPID trial were sourced from clinicaltrials.gov.

QUALITY OF LIFE

Randomised controlled trials

Quality of life was reported in two of the included RCTs, with a total sample size of 248 patients (Chapman et al. 2015; Dirksen et al. 2009). The individual results of each study are presented in Table 32. The forest plot for the meta-analysis of QoL is presented in Figure 12, showing no evidence of heterogeneity. The primary studies and pooled estimate showed a slightly lower increase in SGRQ score at 24/30 months, corresponding to a slightly slower decline in QoL. This favours A1PI, however, this difference was not statistically significant.

Table 32 Results of quality of life across the direct randomised controlled trials†

Study ID	Follow-up	Risk of bias	Intervention Mean change ± SD	Comparator Mean change ± SD	Mean difference (95% CI)
RAPID (Chapman et al. 2015)	24 months	Low	1.4 ± 11.1	2.2 ± 11.7	-0.80 (-4.14 to 2.54)
EXACTLE (Dirksen et al. 2009)	<30 months	Low	1.48 ± 9.24*	2.37 ± 9.24*	-0.89 (-5.28 to 3.50)

Abbreviations: **CI** = confidence interval, **SD** = standard deviation.
† Quality of life was measured using the St Georges Respiratory Questionnaire, which measures quality of life related to obstructive airway disease on a scale from 0 to 100, with higher scores indicating greater limitations.
* An average SD for both study arms was calculated from available p scores.

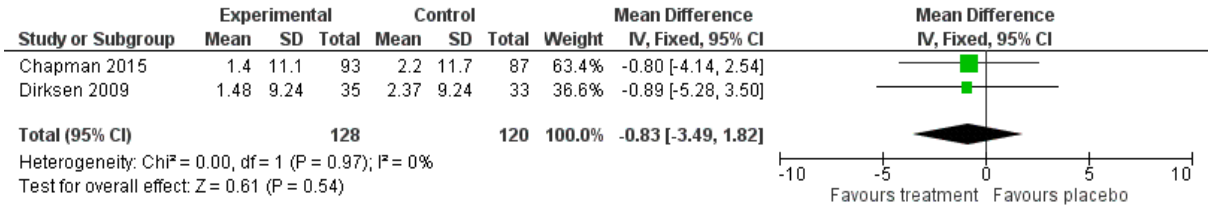


Figure 12 **Forest plot indicating mean changes in St George's Respiratory Questionnaire results for A1PI compared to placebo**

Non-randomised controlled trials

Health-related quality of life was reported in one non-RCT examining patients from the German multicentre COPD cohort COSYCONET (Karl et al. 2017). A total of COPD patients (n=106) and without (n=25) A1PI augmentation were compared. The analysis was adjusted for GOLD grade, age, gender, smoking status, education, and body mass index. It was unclear at what time point health-related quality of life was measured. Overall, there were no significant differences in health-related quality of life when assessed by CAT, SGRQ or ED-5Q-3 L in COPD, AATD and AATD patients receiving augmentation therapy. However, significant differences were found in SGRQ and EQ-5D VAS scores when comparing AATD patients who received augmentation therapy to those who did not ($p < 0.05$).

Lieberman (2000) indirectly assessed quality of life in an internet survey of AATD patients. Eighty three, fourteen and three per cent of patients reported a benefit, unknown and no benefit following augmentation therapy respectively. The perceived benefit from augmentation therapy was attributable to the reduction in number of lung infections. However, it is unclear whether patient demographics differed among the groups. The results in each non-randomised controlled trial are given in Table 33.

Table 33 **Results of quality of life across the non-randomised controlled trials†**

Study ID	Risk of bias	Quality of life measure	Intervention Mean change ± SD or n (%)	Comparator Mean change ± SD or n (%)	Mean difference (95% CI)
Karl et al. 2017	Serious	SGRQ CAT EQ-5D-3 L utility EQ-5D VAS	46.6 ± 16.4 18.9 ± 6.6 83.0 ± 19.1 54.4 ± 18.8	37.5 ± 20.2 17.2 ± 7.3 83.9 ± 19.4 63.6 ± 18.8	-9.1 (-16.7, -1.6)* -1.7 (-4.7, -1.3) 0.9 (-7.5, 9.3) 9.2 (0.9, 17.5)*
Lieberman 2000	Serious	Perceived benefit No benefit Did not know	74/89 (83%) 12/89 (14%) 3/89 (3%)	NR	NR

Abbreviations: **CAT** = COPD assessment questionnaire, **CI** = confidence interval, **EQ-5D-3 L** = Euroqol group 5 domain questionnaire, **EQ-5D VAS** = Euroqol group 5 domain questionnaire including visual analogue scale, **NR** = not reported, **SD** = standard deviation, **SGRQ** = St George Respiratory Questionnaire.
*p < 0.05. mean difference was significant between AT versus no AT.

EXERCISE CAPACITY

One RCT investigated exercise capacity, as measured by incremental shuttle walk distance at 24 months (Chapman et al. 2015). The results are presented in Table 34. Due to reporting limitations, it is unclear whether the change in walking distance (i.e. results showing an increase in walking distance), or total walking distance (i.e. results showing a severe reduction in walking distance) at 24 months was reported. Based on data entered into clinicaltrials.gov it appears to be the change in exercise capacity, in which case both groups reported an increase in exercise capacity at 24 months. Nevertheless, the mean difference in exercise capacity was not statistically significant between treatment groups.

Table 34 Results of shuttle walk distance (metres) in the direct randomised controlled trial

Study ID	Follow-up	Risk of bias	Intervention baseline mean ± SD	Intervention 24 months mean ± SD	Comparator baseline mean ± SD	Comparator 24 months mean ± SD	Mean difference (95% CI)
RAPID (Chapman et al. 2015)	24 months	Low	424.5 ± 183.0	10.8 ± 139.8	435.1 ± 199.7	16.1 ± 101.6	-13.09 (NR) *p* = 0.48*

Abbreviations: **CI** = confidence interval, **NR** = not reported, **SD** = standard deviation.
*Adjusted for country, treatment group, and baseline values.

DYSPNOEA

None of the identified RCTs evaluated dyspnoea as a functional outcome. Instead, the RCTs reported acute episodes of dyspnoea as adverse events (see Section B.6 Dyspnoea).

RESPIRATORY FUNCTION: CHANGE IN FEV_1 (ML OR % PREDICTED)

Randomised controlled trials

FEV_1 was reported variably across the three included RCTs as either FEV_1 (mL) or FEV_1 % predicted, and as either an annualised difference, or an overall difference at last follow-up. Standardised mean differences were calculated in order to pool FEV_1 outcomes from the three studies. Data from the pooled analysis are reported in Table 35 and Figure 13.

The analysis for this report included two studies that reported changes in FEV_1 (mL) (Dirksen et al. 1999; Dirksen et al. 2009), and one study that reported a change in FEV_1 % predicted (Chapman et al. 2015). The analysis is similar to that conducted in the Cochrane review (Gotzsche and Johansen 2016), with the exception of denominators for the RAPID trial—the analysis for this report included the reported ITT population, whereas the Cochrane review reported the per-protocol analysis minus three patients without CT lung density scan data.

The forest plot for the meta-analysis of FEV_1 (Figure 13) shows no evidence of heterogeneity. FEV_1, measured by both mL and % predicted, declined in both treatment arms across the included RCTs.

The reported extent of decline in FEV_1 was lower in patients treated with placebo, however, the estimated differences were not statistically significant.

Table 35 Results of change in FEV_1 (% predicted or mL) across the direct randomised controlled trials†

Study ID	Follow-up	Risk of bias	Intervention mean ± SD	Comparator mean ± SD	Std. mean difference (95% CI)
RAPID (Chapman et al. 2015)	24 months	Low	-3.1% ± 10.7%	-2.3% ± 13.1%	-0.07 (-0.36 to 0.23)
EXACTLE* (Dirksen et al. 2009)	<30 months	Low	-43mL ± 60.1 mL	-23mL ± 60.9mL	-0.33 (-0.78 to 0.12)
DIRKSEN99 (Dirksen et al. 1999)	>36 months	High	-78.9mL ± 63.5mL	-59.1mL ± 63 mL	-0.31 (-0.84 to 0.22)

Abbreviations: **CI** = confidence interval, **SD** = standard deviation.
† FEV_1 is a measure of the amount of air a person can forcibly expire in one second, with lower mL and % predicted values indicating more severe lung disease. A decline in FEV_1 mL or % predicted represents a worsening of lung function.
* EXACTLE also reported % predicted. Changing the analysis to include FEV_1 % predicted for this study instead of FEV_1 mL does not change the result.

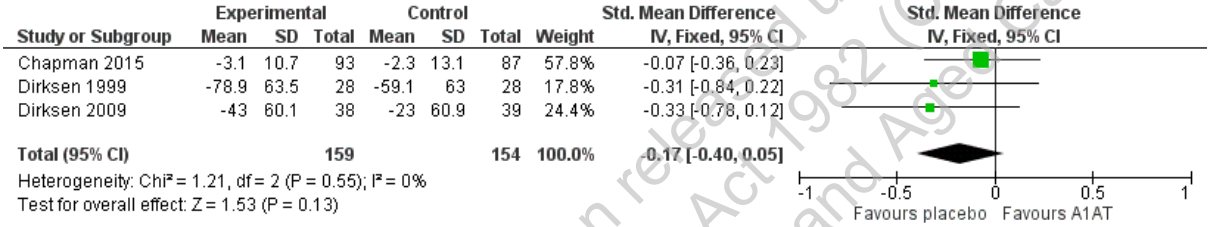


Figure 13 Forest plot indicating standardised mean differnces in FEV_1 for A1PI compared to placebo

Non-randomised controlled trials

The annual change FEV_1 (mL/year) was reported in five studies corresponding to 1609 patients (Barros-Tizon et al. 2012, Tonelli et al. 2009, Wencker et al. 1998, Alpha-1-Antitrypsin Deficiency Registry Study Group 1998, Seersholm et al. 1997) (Table 36). Two studies compared the effects of augmentation within the same patient population (pre- post-intervention design) (Barros-Tizon et al. 2012, Wencker et al. 1998). Three studies retrospectively analysed registry data and compared patients who received augmentation to those who did not (Tonelli et al. 2009, Alpha-1-Antitrypsin Deficiency Registry Study Group 1998, Seersholm et al. 1997). Different methodologies were used to measure FEV_1. For example, some studies recorded FEV_1 measurements before and after bronchodilator use, while others only recorded after. Further, the type of analysis and the covariates adjusted for in each study differed.

The largest non-randomised study concluded there was no statistical difference in annual FEV_1 decline between patients who were treated with and not treated with augmentation therapy (p =0.4) after correcting for gender, smoking status, age, bronchodilator responsiveness and FEV_1 % predicted in a multivariate analysis (Alpha-1-Antitrypsin Deficiency Registry Study Group 1998, n = 927). However, the smaller trials (Barros-Tizon et al. 2012, Tonelli et al. 2009, Wencker et al. 1998 and Seersholm et al. 1997) all reported a significant difference between the augmentation therapy and no augmentation therapy groups (p < 0.05, = 0.05, 0.02 and 0.02 respectively). Differences in the

patient population (and thus the medical strategy used to treat AATD), the method of analysis and the co-variates adjusted for, likely underscore the difference between the differing results studies.

Interestingly, the effects of augmentation therapy appeared most pronounced in patients with a predicted FEV_1 of 30–65% and >65%. Two studies found significant group differences in patients with FEV_1 between 30–65% (Alpha-1 registry study group 1998, and Seersholm et al. 1997, $p = 0.03$ and 0.04 respectively) and $FEV_1 > 65\%$ (Tonelli et al. 2009, Wencker et al. 1998, $p < 0.01$ and 0.05 respectively). In all studies, there was no statistical difference between augmentation therapy and the no augmentation therapy group when FEV_1 was ≤ 30%.

Table 36 Results of change in FEV_1 (% predicted or mL) across the non-randomised controlled trials

Study ID	Risk of bias	Patient population	Intervention Mean change ± SEM	Comparator Mean change ± SEM	Mean difference (95% CI)
Barros-Tizon et al. 2012	Serious	All patients	#1.25 ± 0.5	1.19 ± 0.5*	-0.06 (-0.18, 0.06)
Tonelli et al. 2009	Serious	All subjects FEV_1 < 30% FEV_1 30 – 65 % FEV_1 > 65%	10.6 ± 21.4 0.9 ± 17.6 2.08 ± 24.0 -108.7 ± 17.3	37.0 ± 12.1* 20.1 ± 31.1 -51.9 ± 18.1 -29.2 ± 15.3**	26.4 (-49.4, 102.2) 19.2 (-97.1, 135.6) 49.9 (-85.5, 185.1) -79 (-128.5, -30.5)
Wencker et al. 1998	Serious	All subjects FEV1 < 30% FEV1 30 – 65% FEV1 > 65%	#-49.2 ± 60.8 -15.3 ± 38.5 -49.3 ± 43.4 -122.5 ± 108.4	-34.3 ± 29.7* -19.0 ± 18.0 -37.8 ± 25.0 -48.9 ± 54.9*	14.9 (1.3, 28.5) -3.7 (-20.8, 13.4) 11.5 (-1.3, 24.3) 73.6 (-2.8, 150.0)
Alpha-1-Antitrypsin Deficiency Registry Study Group 1998	Serious	All patients FEV_1 < 35% FEV_1 35 – 49% FEV_1 50 – 79% FEV_1 ≥ 80%	-51.8 ± 2.7 -43.9 ± 3.4 -66.4 ± 5.0 -73.7 ± 6.8 -63.0 ± 12.8	-56.0 ± 3.8 -46.5 ± 6.2 -93.2 ± 11.1 -81.2 ± 8.9 -39.2 ± 5.6	4.2 (-5.7, 14.2) 2.6 (-11.3, 16.5) 26.8 (2.8, 50.9)* 7.5 (-14.7, 29.6) -23.8 (-50.9, 3.3)
Seersholm et al. 1997	Serious	All subjects FEV1 ≤ 30% FEV1 31 – 65% FEV1 > 65%	#53.0 ± 37.6 24.2 ± 23.3 61.8 ± 25.3 162 ± 28.7	74.5 ± 59.6* 30.9 ± 36.3 82.8 ± 49.3* 140 ± 83.2	21.5 (-112.3, 155.3) 6.7 (-82.6, 96.0) 21.0 (-77.5, 119.5) -22.0 (-212.0, 168.0)

Abbreviations: **CI** = confidence interval, **FEV_1** = forced expiratory volume in 1 second, **SEM** = standard error of mean, **SD** = standard deviation.
data presented as SD not SEM.
*$p \leq 0.05$, **$p < 0.001$.

CT-MEASURED LUNG DENSITY

CT lung density decline was the primary outcome in two of the included RCTs (Chapman et al. 2015; Dirksen et al. 2009) and a secondary outcome in the third (Dirksen et al. 1999). The results of the individual studies are presented in Table 37. The EXACTLE trial reported four methods for measuring CT lung density. We used the 24-month data from the first method (physiological adjustment), as both the DIRKSEN99 and RAPID trials used a similar method of physiological adjustment. The Cochrane review included an average of the four methods, which yielded almost identical results (MD 0.86, 95% CI 0.31 to 1.42) to the current meta-analysis review (Gotzsche and Johansen 2016).

The results of the meta-analysis are presented in Figure 14. The pooled estimate demonstrated a slower rate of decline in CT-measured lung density across the included studies for A1PI patients (MD 0.87, 95% CI 0.31 to 1.42), with no evidence of heterogeneity (Chi^2=0.51, I^2=0%, P=0.78). The clinical significance of this result is difficult to ascertain, as discussed in Section B.5.

Table 37 Results of CT-measured lung density (total lung capacity, g/L per year) across the direct randomised controlled trials

Study ID	Risk of bias	Intervention mean ± SD	Comparator mean ± SD	Mean difference and 95% CI
RAPID (Chapman et al. 2015)	Low	-1.45 ± 2.20	-2.19 ± 2.30	0.74 (0.07 to 1.41)
EXACTLE (Dirksen et al. 2009)	Low	-2.83 ± 5.01	-4.21 ± 3.45	1.38 (-0.63 to 3.39)
DIRKSEN99* (Dirksen et al. 1999)	High	-1.50 ± 2.17	-2.57 ± 2.17	1.07 (-0.07 to 2.221)

Abbreviations: **CI** = confidence interval, **SD** = standard deviation.
*Whole lung CT, g/L

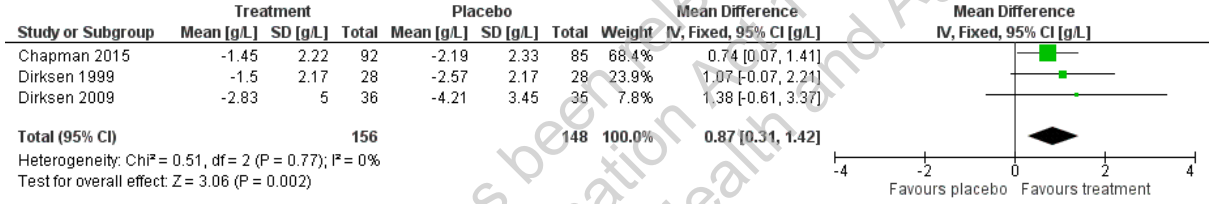


Figure 14 Forest plot indicating changes in CT-measured lung density (g/mL) in A1PI compared to placebo measured at 24 to 30 months follow-up. (Chapman 2015 and Dirksen 1999 reported an annualised rate, whereas Dirksen 2009 reported the change from baseline at 24 months.)

CARBON MONOXIDE DIFFUSING CAPACITY

Randomised controlled trials

All three RCTs investigated carbon monoxide diffusing capacity (D_{LCO}) (Chapman et al. 2015; Dirksen et al. 1999; Dirksen et al. 2009). Results for each study are presented in Table 38 and the forest plot is presented in Figure 15. Different units of measurement were used across studies, therefore standardised mean differences were calculated in order to pool the results. Across the included RCTs, D_{LCO} deteriorated to a greater extent in the A1PI patients. This favoured placebo, however, the difference was not statistically significant. There was no evidence of heterogeneity in the pooled estimate (Chi^2 = 0.66, I^2 = 0%, P = 0.72). This analysis produced almost identical results to that conducted in the Cochrane review (standardised mean difference (SMD) -0.11, 95% CI -0.35 to 0.12), as it utilised the same primary data and analytical method review (Gotzsche and Johansen 2016). The only difference was in the reported population size, whereby we included the ITT population of the RAPID trial as reported in the manuscript, and the Cochrane review included the per-protocol population minus patients without CT scan data (A1PI n=83, placebo n=67).

Table 38 Results of carbon monoxide diffusing capacity across the direct randomised controlled trials

Study ID	Risk of bias	Intervention mean ± SD	Comparator mean ± SD	Standardised mean difference (95% CI)
RAPID [A] (Chapman et al. 2015)	Low	-2.2 ± 18.2	-1.5 ± 19.5	-0.04 (-0.34 to 0.26)
EXACTLE [B] (Dirksen et al. 2009)	Low	-0.46 ± 0.45	-0.34 ± 0.47	-0.14 (-0.67 to 0.38)
DIRKSEN99 [C] (Dirksen et al. 2009)	High	-0.19 ± 0.25	-0.16 ± 0.25	-0.26 (-0.71 to 0.19)

Abbreviations: **CI** = confidence interval, **SD** = standard deviation.
[A] D_{LCO} measured in mL/mm Hg per min, %
[B] D_{LCO} measured in mmol/min/kPa
[C] D_{LCO} measured in mmol/min/kPa/L

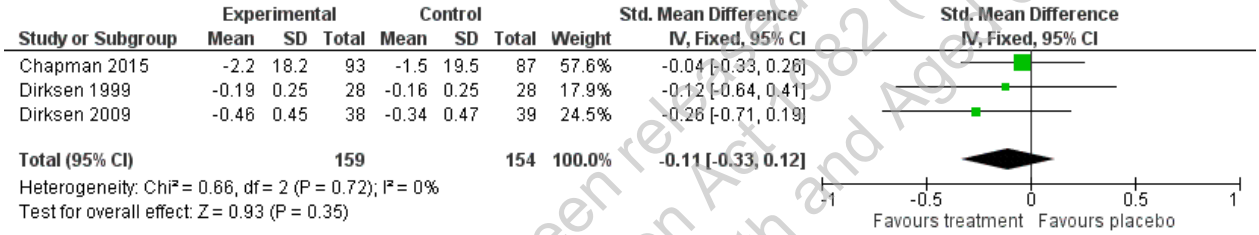


Figure 15 Forest plot indicating the standardised mean difference in carbon monoxide diffusing capacity (D_{LCO}) for A1PI compared to placebo

Non-randomised controlled trials

One study compared D_{LCO} in patients before and after they had received augmentation therapy (Barros-Tizon et al. 2012). Results are presented in Table 39.There was no statistical difference between the two groups. The authors further compared D_{LCO} to a normal healthy Spanish population adjusted for age, sex, height and weight. There were no differences in the decrease of D_{LCO} between the healthy population and the study population. The authors reported this comparison narratively and did not show the precise data or the statistical tests used to assess group differences.

Table 39 Results of carbon monoxide diffusing capacity across the non-randomised controlled trials

Study ID	Risk of bias	Patient population	Intervention Mean change ± SD	Comparator Mean change ± SD	Mean difference (95% CI)
Barros-Tizon et al. 2012	Serious	All patients	69.1 ± 69.2	58.9 ± 26.3	-10.2 (-23.1, 2.7)

Abbreviations: **CI** = confidence interval, **SD** = standard deviation.

BODE Index for COPD survival prediction

No evidence was identified that investigated the BODE index in AT patients compared to BSC or placebo.

Non-randomised controlled trials

Lieberman (2000) assessed the rate of self-reported lung infections in 89 and 47 AATD patients who had and had not received augmentation therapy for > 1 year respectively (Table 40). Within-patients, there was a significant difference in the number of lung infections after receiving augmentation therapy compared to before (p < 0.001). Additionally, there was significant differences between patients who received augmentation therapy to those who did not (p < 0.001). However, the analysis did not adjust for differences in patient demographics such as smoking status, comorbidities and concurrent medical treatments.

Table 40 Results of lung infections in non-randomised controlled trials

Study ID	Risk of bias	Quality of life measure	Before intervention N (%)	After intervention N (%)	Never received intervention N (%)
Lieberman 2000	Serious	Lung infection < 2 Lung infection ≥ 2	27/89 (30%)* 62/89 (70%)*	73/89 (82%) 16/89 (18%)	21/47 (45%)* 26/47 (55%)*

p < 0.001 when compared to after intervention.

AVERAGE HOSPITALISATION

Non-randomised controlled trials

Two studies reported the average hospital stay between patients receiving and not receiving augmentation therapy (Karl et al. 2017; Barros-Tizon et al. 2012) (Table 41). In general, patients who received augmentation therapy reported less time spent in hospital compared to patients who did not receive augmentation therapy. The difference was less than a day and statistical analysis comparing the two groups were not performed in both studies.

Table 41 Results of hospitalisation days in non-randomised controlled trials

Study ID	Risk of bias	Intervention mean ± SD	Comparator mean ± SD	Mean difference (95% CI)
Karl et al. 2017	Serious	2.2 ± 5.7	2.7 ± 6.3	0.5 (-2.1, 3.1)
Barros-Tizon et al. 2012	Serious	3.9 ± NR	3.0 ± NR	NR

Abbreviations: **CI** = confidence interval, **NR** = not reported, **SD** = standard deviation.

B.7. EXTENDED ASSESSMENT OF HARMS

The search strategy used to identify post-marketing harms is documented in Appendix B. Searches were targeted to identify any warning or recalls issued by the medical device and intervention regulating authorities of Australia, New Zealand and the United States. In addition, the product information sheets provided by the manufacturers of Zemaira and PROLASTIN-C (CSL Behring and Grifols Therapeutics, respectively) were reviewed for any concerns not identified elsewhere. In both documents it was noted that the therapies are contraindicated for patients with a known sensitivity to A1PI products, and patients with immunoglobulin A (IgA) deficiency and antibodies against IgA.

Post-market adverse drug reactions to PROLASTIN-C are reported as occasional flu-like symptoms, allergic-like reactions, dyspnoea, tachycardia, shortness of breath, bronchospasm, wheezing, urticaria, back pain, clamminess, sweating, diarrhoea, and fatigue. Less frequently hypotension, anxiety, cyanosis, swelling of hands and feet, angio-oedema, facial and lip oedema, nasal congestion, sinusitis, abdominal pains or cramps, pallor, and weakness have also been reported. Cases of transient increase in blood pressure or hypertension and chest pain have also been reported, but these were rare Karl et al. (2017). Numbers of patients experiencing these events were not reported.

No post-marketing data on long-term adverse event rates was identified for Zemaira (2003), perhaps due to the more recent entry of this product to the market.

B.8. INTERPRETATION OF THE CLINICAL EVIDENCE

It is important to classify the therapeutic profile of AT in relation to BSC or placebo, that is, whether it is therapeutically superior, inferior or equivalent to the comparator.

On the basis of the evidence profile (summarised in Table 42), **it is suggested that, relative to BSC, AT has inferior safety and uncertain effectiveness; however, relative to placebo, there were no important differences in safety outcomes.** A summary of the clinical evidence from the observational studies is provided in Appendix D, Table 106.

Seventeen trials were available for safety outcomes, of which three studies were placebo-controlled RCTs (level II), four were non-randomised studies comparing doses of AT (Level III-II), and 10 were single-arm studies of AT (Level IV). The quality of the single-arm trials was poor, with most appraised as having a high risk of bias. Overall, the populations in the included evidence base had good applicability to the proposed population in Australian practice, noting that the study populations were largely Caucasian.

The conclusion of inferior safety is predicated on the understanding that the intervention is proposed as an additional intervention to BSC, carrying a small risk of severe adverse events. It should be noted that most adverse events associated with the intervention were mild, and severe adverse events were not significantly different across treatment and placebo arms in the RCTs. The direct RCTs did not demonstrate a significant difference in severe adverse events, or discontinuation due to adverse events between treatment groups. Further, no treatment-related deaths were identified in any of the included studies.

Three direct RCTs evaluated the relative effectiveness of AT compared to placebo, with a total of 313 randomised patients. The overall quality of the included RCTs was mostly good, with the exception of DIRKSEN99 which was poorly reported. The key uncertainties around the clinical trials were in relation to allocation concealment, and the key risks of bias were in relation to conflicts of interest of the study authors. All of the RCTs were supported by industry. The key trials note a lack of power to

detect a change, which is accurate, however, power calculations are based on an assumption of an estimated effect direction and size.

The only significant treatment effect observed was for CT-measured lung density. All other effectiveness outcomes reported non-significant differences. Minimum clinically important differences for the primary outcome, that of CT-measured lung density, are not currently available. Evidence suggests that there is a correlation between CT-measured lung density and mortality, but quantifying the importance of the observed effect is not currently possible. As a result, the clinical benefit of the reported reduction in CT-measured lung density decline is uncertain.

Due to the rarity of the disease, it is challenging to recruit a sample size large enough to adequately power a study to detect significant differences in the secondary outcomes, e.g. mortality. However, it is not appropriate to attribute the non-significant findings of the secondary outcomes to the lack of power in the studies.

Table 42 Balance of clinical benefits and harms of A1PI relative to placebo as measured by the critical patient-relevant outcomes in the key studies

Outcomes (units) Follow-up	Risk with placebo	Risk with A1PI (95% CI)	Relative effect (95% CI)	Participants (studies)	Quality of evidence (GRADE)	Comments
Mortality F/U 24 months	34 per 1,000	12 per 1,000 (2 to 78)	RR 0.35 (0.05 to 2.27)	180 (1 RCT)	⊕⊕⊕⊙ MODERATE	Uncertain due to low event rate, RR subject to error
Quality of life (SGRQ) F/U 24 to 30 months	-	MD 0.83 points lower (3.49 points lower to 1.82 points higher)	-	248 (2 RCT)	⊕⊕⊙⊙ LOW	Direction favours placebo; not statistically significant
Annual exacerbation rate F/U 24 to 30 months	-	-	Higher reported RR (1.26, 95% CI 0.92 to 1.74), MD (0.36, 95% CI -0.44 to 1.16) in A1PI group	257 (2 RCT)	⊕⊕⊕⊙ MODERATE	Direction favours placebo; not statistically significant
CT-measured lung density F/U 24 to 30 months	-	SMD 0.87 g/L higher (0.31 higher to 1.42 higher)	-	304 (3 RCT)	⊕⊕⊕⊕ HIGH	Direction favours A1PI; statistically significant
Mortality due to treatment-related adverse events F/U 24 months	No treatment-related deaths were reported			180 (1 RCT)	⊕⊕⊕⊙ MODERATE	No reported deaths due to treatment-related adverse events
Severe adverse events F/U 24 to 30 months	341 per 1,000	283 per 1,000 (195 to 406)	RR 0.83 (0.57 to 1.19)	257 (2 RCT)	⊕⊕⊕⊕ HIGH	Direction favours A1PI; not statistically significant
Discontinuation due to adverse events F/U 24 to 30 months	48 per 1,000	10 per 1,000 (2 to 62)	RR 0.22 (0.04 to 1.30)	248 (2 RCT)	⊕⊕⊕⊙ MODERATE	Direction favours A1PI; not statistically significant
Hospitalisation due to adverse events F/U 3 to 6 years	Median rate 1.4% (range 0.0% to 14.3%)			497 (4 observational studies)	⊕⊕⊙⊙ LOW	-

Abbreviations: **A1PI** = alpha-1 proteinase inhibitor, **CI** = confidence interval, **CT** = computed tomography, **F/U** = follow-up, **MD** = mean difference, **RCT** = randomised controlled trial, **RR** = relative risk, **SGRQ** = St George's Respiratory Questionnaire, **SMD** = standardised mean difference.

a GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality**: We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

SECTION C TRANSLATION ISSUES

C.1. OVERVIEW

Three key issues arise in translating the evidence provided in Section B to an economic model presented in Section D. The first, relates to the applicability of the populations in the pivotal RAPID trial to clinical practice in Australia; the second, involves selection of utilities; and the third, relates to the extrapolation of trial evidence beyond the maximum follow-up of the trial. Each issue is addressed in separate pre-modelling studies in Sections C.2, C.3 and C.4 (Table 43). Each section provides an overview of the issue to be addressed, the pre-modelling methodology to translate trial data into assumptions for economic modelling, and how results are used in Section D.

Table 43 Outline of Section C issues being addressed

Section	Issue
C.2	Applicability of the trial-based evidence to the proposed NBA listing population
C.3	Selection of utilities
C.4	Extrapolation of trial-based evidence

Abbreviations: **NBA** = National Blood Authority.

C.2. APPLICABILITY TRANSLATION ISSUES

C.2.1. APPLICABILITY OF THE TRIAL-BASED EVIDENCE TO THE PROPOSED MBS POPULATION

C.2.1.1 Identification of issue that needs to be addressed

Applicability relates to any ways in which the participants and circumstances of use in the key RAPID trial presented in Section B, differ from the proposed population for treatment (Chapman et al. 2015). This pre-modelling study addresses whether the definition of the trial population is representative of Australian patients, and whether the circumstances of use of the proposed medical service in the trial is representative of how the service will be used in Australian clinical practice.

C.2.1.2 FOCUSED ANALYTICAL PLAN

Patient demographic characteristics, along with inclusion and exclusion criteria of included clinical trials, are reviewed and compared with the proposed NBA-listing eligibility. Inclusion criteria cover age, and clinical characteristics such as A1PI serum levels ≤11 µM and emphysema defined by FEV_1.

C.2.1.3 RESULTS OF PRE-MODELLING STUDY

Ex or never-smoking individuals with severe A1PI deficiency (serum levels ≤11 µM) and emphysema (FEV_1 <80%) are eligible for AT under eligibility criteria in the PICO Confirmation (DoH, 2016). These criteria are in line with those currently proposed by the Canadian Thoracic Society (2012)[1] and American Thoracic Society/European Respiratory Society (2003), which recommend that intravenous AT be commenced for those patients with established airflow obstruction i.e. FEV_1 35%-60% predicted (American Thoracic and European Respiratory Society, 2003; Sandhaus et al. 2016). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2017) suggested that never- or ex-smokers with an FEV_1 of 25%-60% predicted are those most suitable for AT, and that AT should be provided to those with FEV_1 > 65% with a careful analysis of costs.

A range of tests is generally performed to confirm eligibility, including A1PI serum levels and genotype, spirometry, and computed tomography of the lung to assess emphysema. Tests are undertaken to exclude other conditions. This includes monitoring compliance with smoking cessation, arterial blood gases analysis, sputum examination, and other respiratory function investigations. The American Thoracic and European Respiratory (2003) indicated that there is limited evidence to support the use of AT in lung transplant recipients. The demographic and clinical characteristics of patients in the RAPID study, RAPID-OLE study, and the UK AATD registry populations are provided in this section. Alignment of patient characteristics with the proposed listing criteria is described.

RAPID AND RAPID OLE

The RAPID trial (Chapman et al. 2015) is the largest AT trial undertaken to date. The trial examined the efficacy and safety of weekly intravenous administration (60mg/kg) of Zemaira compared with placebo over two years in AATD subjects with emphysema (n=180) that were randomised and treated at 28 trial sites. After the first two years, an open-label extension was undertaken for non-US patients, which is referred to as RAPID-OLE (McElvaney et al. 2017).

The RAPID trial recruited male and female patients, aged 18–65 years, with serum AAT concentration of ≤11 µM and an FEV_1 of 35%–70% of predicted value. Only patients with symptoms of emphysema were included. The average patient age was 53 years, and equal numbers of males and females were recruited. These characteristics are consistent with the proposed listing criteria. Serum concentration of AAT was below 11 µM and FEV_1 % predicted was 47% for both the AT and BSC arms. Patients who were smokers within six months of recruitment, were lung transplantation recipients or candidates, had selective IgA deficiency, or were receiving other augmentation treatments were excluded. The smoking exclusion is in line with the PICO criteria, while lung

[1] Non-smoking or ex-smoking patients with COPD (FEV_1 25% to 80% predicted) attributable to emphysema and documented A1PI deficiency (11 mol/L)

transplantation exclusion is in line with international guidance. A comparison of the RAPID trial's patient population and the proposed listing is presented in Table 44.

Table 44 Comparison of the RAPID trial's patient population and the proposed listing (Chapman et al. 2015)

		Chapman patient baseline characteristics			
Patient characteristics	**Chapman inclusion criteria**	**Characteristic**	**Zemaira N = 93**	**Placebo N = 87**	**Proposed listing**
Age	18 to 65 years	Baseline age: mean (SD):	53.8 (6.9)	52.4 (7.8)	18 years or older
Gender	No restriction	Male	52%	57%	No restriction
Baseline CT lung density (g/L)	No restriction	TLC	45.5 (15.8)	48.9 (15.5)	No restriction
		FRC	47.6 (15.7)	50.7 (15.0)	
		Combined	46.6 (15.6)	49.8 (15.1)	
Gender	No restriction	Male (%)	48 (52%)	50 (57%)	No restriction
Ethnicity	No restriction	White (%)	93 (100%)	87 (100%)	No restriction
FEV_1 predicted (%)	35–70%	FEV_1 predicted (%)	47.4% (12.1)	47.2% (11.1)	FEV_1 <80%.
A1PI serum concentration (μM)	<11μM	A1PI serum concentration (μM)	6.38 (4.62)	5.94 (2.42)	≤11 μM
Smoking	No smoking in previous 6 months				Ex- or never-smoking individuals
Lung transplant	Waiting list or previous lung transplantation, lobectomy, or lung-volume reduction surgery				No restriction
Selective IgA deficiency	No selective IgA deficiency				No restriction
Circumstances of use					
Regimen	Dose regimen: Intravenously 60mg/kg Frequency/duration: Once per week				Not stated

Abbreviations: **A1PI** = alpha-1 proteinase inhibitor, **CT** = computed tomography, **FEV_1** = forced expiratory volume in 1 second, **FRC** = functional residual capacity, **IgA** = immunoglobulin A, **μM** = micromolar, **SD** = standard deviation, **TLC** = total lung capacity.

The circumstances of use are in line with the proposed listing. RAPID patients were randomised to receive AT at 60mg/kg every week. The dosing is consistent with the dose approved in the Australian Product Information (PI). The comparator for AT in the RAPID trial was described as best supportive care, those therapies recommended by published treatment guidelines to manage the symptoms associated with emphysema. BSC encompasses a range of interventions including pharmacological (e.g. bronchodilators, systemic corticosteroids), non-pharmacological (e.g. oxygen therapy) and preventative measures such as vaccinations. The optimal mix of therapies varies amongst patients who are stable and those experiencing acute exacerbation. BSC was provided on the placebo arm of the RAPID trial, and in addition to AT on the intervention arm.

Other Augmentation Therapy Trials

Dirksen et al. (1999) recruited patients from the Danish AAT Deficiency registry from 1991 to 1995 and from the Dutch Registry from 1993 to 1997. The study included 56 patients (26 Danish and 30 Dutch) who were ex-smokers with PI*ZZ genotype-A1PI deficiency and moderate emphysema (FEV_1 30%-80% of predicted). AT (PROLASTIN-C, 250mg/kg) was infused every four weeks. This dosing of 62.5mg/kg/week is slightly higher than the listing of 60mg/kg/week. Patients recruited in the study were in line with the listing (>18 years) and had average ages of 50.4 (Danish) and 45.1 (Dutch) years, which is similar to the RAPID trial. Average FEV_1 % predicted was less than 80%, which aligns with the proposed listing. The average was 49.4% for Danish subjects and 47.1% for Dutch. This also compares with the RAPID trial.

Table 45 Comparison of Dirksen and EXACTLE patient population and the proposed listing

	Dirksen et al. (1999)		EXACTLE		
Characteristics and demographics	**Danish Subjects N = 26**	**Dutch Subjects N = 30**	**PROLASTIN-C N = 38**	**Placebo N = 39**	**Proposed listing**
Age, years mean (SD)	50.4 (1.62)	45.1 (1.17)	54.7 (8.41)	55.3 (9.80)	>18 years
Sex, male/female %	14/12	20/10	65.8/34.2	41/59.0	None
Smoking pack years mean (SD)	20.0 (2.39)	17.1 (1.90)			Non smoker
FEV_1, mean (SD), % predicted	49.4 (2.75)	47.1 (2.58)	46.33 (19.59)	46.55 (21.05)	FEV_1 <80%.
FVC % predicted mean (SD)	110 (3.53)	101 (2.92)			None
Baseline serum AAT µM			4.62 (1.59)	4.55 (1.68)	≤11 µM
DL_{CO}, mmol/min/kPa % predicted mean (SD)	59.5 (3.28)	61.2 (2.98)			None
CT, whole lung, g/L mean (SD)	76.7 (6.15)	70.5 (2.14)			None
Percentile of lung density [g/L]			46.54 (19.61)	46.84 (17.02)	None

Abbreviations: **AAT** = alpha-1 antitrypsin, **CT** = computed tomography, **D_{LCO}** = Pulmonary diffusing capacity for carbon monoxide, **FEV_1** = forced expired volume in 1 second, **FVC** = forced vital capacity, **SD** = standard deviation.
Source: Dirksen et al. 1999, Table 1 p 1469. EXACTLE CSR Section 11.2 p 64 Table 9 p 65.

The EXACTLE trial was a randomised, double-blind clinical trial that included 77 patients and had a follow-up of two years. Average patient age was 55 years, with a higher proportion of male patients randomised to AT. Most patients had moderate to severe COPD, based on the GOLD classification system. For inclusion, patients had a clinical diagnosis of AATD (serum AAT levels < 11 µM) with a specific genotype and FEV_1 % predicted less than 80% at baseline. These characteristics are in line with the proposed listing and the RAPID patient population. AT dosing in EXACTLE was consistent with that approved in Australia. A comparison of the Dirksen and EXACTLE patient population and the proposed listing is presented in Table 45.

UK Anti-trypsin Deficiency Assessment and Program for Treatment (ADAPT), Registry

The UK registry for alpha-1-antitrypsin (AAT) deficiency was established in 1996 and recruitment started in 1997. Stockley et al. (2015) reported that there were 930 ZZ phenotype and 135 SZ phenotype highly characterised patients on the database. The author noted that patients have typically been followed-up on an annual basis, with measurement of health outcomes including

health status questionnaires, post-bronchodilator lung-function testing, CT scanning, routine bloods for haematology and liver function, research bloods for potential biomarkers, whole blood for DNA, sputum for quantitative culture, and diary cards for monitoring exacerbations. Reported patient characteristics (Green et al. 2016) are outlined in Table 46. Average patient age of 52.1 years is similar to the RAPID trial and other previously outlined clinical trials. FEV_1 (% predicted) is also in line with the RAPID trial.

Table 46 Comparison of the UK registry patient population and the proposed listing

Characteristic	All Value N= 76	Proposed listing
Male patients	44 (57.9)	No restriction
Age (years)	52.1 (14.8)	No restriction
Median follow up (years)	7.2 (1.6)	No restriction
FEV_1 (% predicted)	45.3 (29.6)	FEV_1 <80%.
FEV_1/FVC	34.0 (23.0)	No restriction
D_{LCO} (% predicted)	64.9 (38.4)	No restriction
K_{CO} (% predicted)	60.5 (28.3)	No restriction
Chronic bronchitis	31 (40.8)	No restriction
Baseline density (g/l)	46.2 (28.7)	No restriction
Change in density/year	-2.13 (4.08)	No restriction
Density declining	65 (85.8)	No restriction
UZ density	30.33 (26.49)	No restriction
LZ density	49.29 (27.58)	No restriction
UZ density decline/year	-1.72 (3.03)	No restriction
LZ density decline/year	-1.45 (5.28)	No restriction
UZ density declining	54 (77.1)	No restriction
LZ density declining	52 (74.3)	No restriction
SGRQ	44.6 (31.2)	No restriction

Abbreviations: **D_{LCO}** = Pulmonary diffusing capacity for carbon monoxide, **FEV_1** = Forced expired volume in 1 second, **FVC** = forced vital capacity, **K_{CO}** = Transfer factor of carbon monoxide, **LZ** = lower zone, **SGRQ** = Saint Georges Respiratory Questionnaire, **UZ** = upper zone.
Source: Green et al. 2016, Table 1, p. 83.

C.2.1.4 RELATIONSHIP OF PRE-MODELLING STUDY TO THE ECONOMIC EVALUATION

Tonelli and Brantly et al. (2010) indicated that there has been variation in the characteristics of patients selected to receive AT and discordant views on the benefit of such treatment. The circumstances of use in RAPID, Dirksen, EXACTLE trials and the UK registry are largely consistent with the target patient population for AT in Australia. The eligibility criteria of FEV_1<80% in the draft PICO corresponds with FEV_1 of 35%–70% of the predicted normal value used in the RAPID trial. Dosing regimens and settings for service delivery used in the RAPID trial are the same as what would be used in Australian clinical practice. BSC covers a range of lifestyle and pharmacological interventions. The economic model compares AT plus BSC, with BSC alone, so uncertainty is present on both arms of the comparison and is likely to have an impact on effectiveness. Mortality and morbidity severity

(proportions hospitalised by COPD state) are subject to sensitivity analysis to gauge how this uncertainty could affect the estimated ICER.

C.3. SELECTION OF UTILITY VALUE ISSUES

C.3.1 IDENTIFICATION OF ISSUE THAT NEEDS TO BE ADDRESSED

A1PI deficiency impacts patient quality of life. For example, Dirksen et al. (2009) reported that the QoL of patients at baseline in the EXACTLE study was significantly impaired, as measured by the St Georges' Respiratory Questionnaire (SGRQ). Generic measures of QoL, such as EuroQol Group 5 domain questionnaire (EQ-5D), were not reported in the RAPID trial as the trial was powered to measure treatment effect on changes in CT-scan lung density and pulmonary function tests. Larger numbers of patients would be required to measure outcomes using this approach. Cost-utility analysis requires the derivation of quality of life outcomes, as measured by instruments such as EQ-5D, or other generic questionnaires.

C.3.2 FOCUSED ANALYTICAL PLAN

The literature was reviewed to determine EQ-5D values for AATD patients suffering COPD of differing severity. Specifically, values were sought where COPD had been stratified by FEV_1% predicted. QoL data is derived from these sources for inclusion as utility values in the economic model.

C.3.3 RESULTS OF PRE-MODELLING STUDY

Literature search for FEV_1% Predicted Health States

There is limited published data on AATD survival and quality of life because of the rare nature of the disease. A literature search was conducted in EMBASE, Cochrane Library, and HTA agency websites including CADTH and NICE on 20 June 2018 to identify published quality of life analyses for AATD patients. The search strategy involved the search terms included in Table 47. Titles and abstracts were reviewed and a manual search was performed.

Table 47 Search strategy for AATD utility literature review

Search	Terms
1	[AATD] OR [alpha-1 antitrypsin deficiency] OR [antitrypsin deficiency]
2	[AQoL] OR [Australian quality of life] OR QALY
3	[EQ-5D] OR [SGRQ] or [HRQL]
4	[SF-6D] OR [short form 6D]
5	[Time trade off] OR [TTO] OR [Standard gamble]
6	[Health utilities] OR [utility values] OR [utility scores]
7	[2] OR [3] OR [4] OR [5] OR [6] OR [7]
8	[1] AND [8]

Table 48 Results of AATD utility literature review

	EMBASE	Other HTA websites [a]	Cochrane Library
Number of titles and abstracts reviewed after search	53		1
TOTAL number of exclusions	49		0
Number of AATD utility studies included	4		1
Consolidated number of studies excluding duplicates	5		

[a] HTA agencies included: NICE, CADTH.

As expected, there were a limited number of publications reporting on studies assessing the impact of AATD on patient QoL. Five relevant publications were identified (Table 48). A number of reviews of COPD economic models have recently been conducted (Table 49). These models also assess QoL in relation to FEV_1 severity. This is relevant to AATD, even though AATD is related to severe emphysema, rather than a broader range of conditions under the COPD classification of lung disease. Two of these recent COPD utility reviews are also included in this section as background.

Table 49 Studies identified outlining utilities for AATD and COPD states

Study	Reference
Utilities for AATD	
Ejiofor and Stockley 2015	Ejiofor & Stockley, Health status measurements in AATD. European Respiratory Journal 2015 46: PA1032; DOI: 10.1183/13993003.congress-2015.PA1032
Manca et al. 2014	Manca S, Rodriguez E, Huerta A, Torres M, Lazaro L, Curi S, Pirina P, Miravitlles M. Usefulness of the CAT, LCOPD, EQ-5D and COPDSS scales in understanding the impact of lung disease in patients with alpha-1 antitrypsin deficiency. COPD. 2014 Sep;11(5):480-8. doi: 10.3109/15412555.2014.898030.
Gøtzsche and Johansen 2016	Gøtzsche and Johansen 2016 Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease[2], Cochrane Database of Systematic Reviews
Bernhard et al. 2017	Bernhard N.; Lepper P.M.; Vogelmeier C.; Seibert M.; Wagenpfeil S.; Bals R.; Fahndrich S. Deterioration of quality of life is associated with the exacerbation frequency in individuals with alpha-1-antitrypsin deficiency - Analysis from the German registry. International Journal of COPD. 12 (pp 1427-1437), 2017. Date of Publication: 12 May 2017.
Carone et al. 2011	Carone M.; Bruletti G.; Bertella E.; Balestroni G.; Gatta N.; Corda L.; Luisetti M.; Balbi B. Quality of life evaluation in patients with alpha-1-anti-trypsin deficiency: A 3-year prospective study. European Respiratory Journal. Conference: European Respiratory Society Annual Congress 2011. Amsterdam Netherlands. Conference Publication: (var.pagings). 38 (SUPPL. 55) (no pagination), 2011. Date of Publication: 01 Sep 2011.
Utilities for COPD models – recent reviews	
Moayeri et al. 2016	Moayeri F, Hsueh YS, Clarke P, Hua X, Dunt D. Health State Utility Value in Chronic Obstructive Pulmonary Disease (COPD); The Challenge of Heterogeneity: A Systematic Review and Meta-Analysis. COPD. 2016 Jun;13(3):380-98. doi: 10.3109/15412555.2015.1092953.
Hoogendoorn et al. 2016.	Hoogendoorn M, Feenstra TL, Asukai Y, Briggs AH, Borg S, Dal Negro RW, Hansen RN, Jansson SA, Leidl R, Risebrough N, Samyshkin Y, Wacker ME, Rutten-van Mölken MPMH Patient Heterogeneity in Health Economic Decision Models for Chronic Obstructive Pulmonary Disease: Are Current Models Suitable to Evaluate Personalized Medicine? Value Health. 2016 Sep - Oct;19(6):800-810. doi: 10.1016/j.jval.2016.04.002

Abbreviations: **AATD** = alpha-1 anti-trypsin deficiency, **COPD** = chronic obstructive pulmonary disease.

[2] http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD007851.pub3/full

Utilities for AATD

Ejiofor and Stockley 2015

CSL Behring presented the health-related QoL data prepared by Ejiofor and Stockley (2015) for 244 patients not receiving AT in the UK ADAPT programme in 2014. The data records post-bronchodilator FEV_1 and the EQ-5D utility values. Results are presented in Table 50, with the EQ-5D ranging from 0.51 for those with FEV_1<30% predicted, to 0.79 for FEV_1>50%. Limited information is provided about how EQ-5D values were derived, although it is evident that patients with FEV_1>50 comprised 65% of the patient population.

s45, s47(1)(b)

Data plots were also provided in the Ejiofor and Stockley (2015) study, where the relationships between EQ-5D, SGRQ and FEV_1 predicted values were examined. EQ-5D data correlated with the results for the SGRQ (R=-0.772 p<0.001). FEV_1 was considered to explain approximately 43% of the variation in health status as assessed by these instruments, thus factors other than FEV_1 also have an important impact on health status (Ejiofor and Stockley, 2015).

SGRQ was also measured in the RAPID trial. The small sample size appears to confound any possible changes in QoL as measured by this instrument. The authors concluded that, "unsurprisingly, findings from our study did not show significant differences between active and placebo treatment in conventional pulmonary function and clinical endpoints; the study was not designed with sufficient power to detect such changes" (Chapman et al. 2015 p. 366). This lack of significance limits the QoL assessment measured in the RAPID trial being related back to EQ-5D-SGRQ correlations observed by Ejiofor and Stockley (2015).

Manca et al. 2014

The authors aimed to assess the usefulness of different instruments to evaluate QoL in COPD patients with and without AATD. A total of 96 patients were included, 35 with AATD (average age 56.5 years and mean FEV_1% 48.7%) and 61 with non-AATD COPD (70.3 years and FEV_1% 47%). All patients completed the COPD severity score (COPDSS), the EQ-5D, the Living with COPD (LCOPD) and

the COPD Assessment Test (CAT) questionnaires. Questionnaire scores were similar for non-AATD COPD and AATD patients. For example, the average EQ-5D index score was 0.74 for AATD and 0.72 for non-AATD COPD patients. In general, the correlations of scores with FEV_1(%) were higher for AATD patients compared with non-AATD COPD patients. Those with AATD were usually younger, with fewer co-morbidities, and less likely to be smokers.

Bernhard et al. 2017

The aim of this study was to provide information about the deterioration in QoL over a maximum follow-up period of seven years (median follow-up 3.33 years) in AATD patients. Data from the German AATD registry was mined in relation to SGRQ score, exacerbation frequency, smoking history, FEV_1 and D_{LCO} across 868 individuals with PiZZ genotypes. Average patient age was 52.6 years and average SGRQ score was 45.7. SGRQ was correlated with exacerbation frequency, FEV1, smoking and age. Mean annual decrease of SGRQ score in 286 followed-up patients was 1.21 points per year. Worsening of SGRQ was associated with exacerbation frequency in individuals with PiZZ AATD

Gøtzsche and Johansen 2016

These authors reviewed the benefits and harms of AT using the Cochrane Central Register of Controlled Trials, PubMed and ClinicalTrials.gov to March 2016. Data for QoL was limited, with the authors only identifying two trials that reported QoL using the SGRQ. The annual rate of exacerbations could not be included in meta-analysis, as the distribution of the values was highly skewed.

Carone et al. 2011

The aim of this study was to evaluate QoL in relation to AT use (25 patients) and non-AT (7 patients) as part of a three-year prospective analysis of 32 patients (average age 54 years and FEV_1 48% predicted). The SGRQ and EQ-5D questionnaires were administered at baseline and yearly for three years. After three years, the decrease in FEV_1 in the AT group was 125 ml (4%), whereas in the non-AT group the decrease was 610 ml (41%), ($p<0.02$). SGRQ changes were significantly different. The AT arm showed a 7.8-unit improvement, whereas in the non-AT arm QoL decreased by 7.9 units. Changes in health status between the two groups were not significant using EQ-5D.

Utilities for COPD models

Only a limited number of AATD studies were identified that reported quality of life. Given the small number of AATD-specific studies, some recent reviews of utilities employed in COPD economic models are also included in this section as further background.

Moayeri et al. 2016

Moayeri and colleagues undertook a systematic review[3] to estimate mean utility values for COPD using meta-analysis and explored the degree of heterogeneity in the utility values across a variety of clinical studies. Simulation-based studies were not included. The authors limited their analysis to studies using EQ-5D to estimate utility values because it is the most widely used generic measure across all diseases and includes dimensions of mobility, self-care, usual activities, pain and anxiety, which are converted to a single index using preference weights. Country-specific algorithms or tariffs have been generated (Dolan, 1997, Tsuchiya et al. 2002) for this weighting and a minimally important clinical difference for the EQ-5D Index has been estimated to be 0.074 (Walters & Brazier 2005).

The authors identified 32 COPD studies using EQ-5D with 49 observations. Seventeen studies reported utility values by severity of COPD stage. Utility values are outlined in Table 51 (Taken from Table 3, p. 388) for studies were utilities were reported for 3, or more states. They ranged from 0.91 for stage I to 0.41 for stage IV. GOLD stage 1 (very mild COPD with FEV1>80% predicted) utility values ranged from 0.73 to 0.91, while GOLD stage 4 (severe emphysema with FEV1 <30 % predicted) utilities ranged from 0.52 to 0.78. The average values for COPD Stages 1-2 (0.78) and Stages 3-4 (0.67) are similar to that for AATD-specific COPD reported by Ejiofor and Stockley, (2015) for Stages 1-2 of 0.79 and more than 0.59 for Stages 3-4. Results of the Fourth and Fifth Korea National Health and Nutrition Examination Survey reported by Kim et al. (2014) skew COPD results for Stages 3-4. Average utilities are similar for most stages despite COPD relating to more conditions than emphysema. Manca et al. 2014 reported QoL measurement instrument[4] scores for AATD and non-AATD COPD patients to be similar.

Table 51 Selected EQ-5D values stratified by GOLD (FEV_1%) states from Moayeri et al. 2016

Study	Staging	Scores	Method
Wu et al. 2015	GOLD Stage	I 0.786 II 0.734 III 0.691 IV 0.655	This 2011 study included a cross-sectional survey of 678 COPD patients in China using the EQ-5D questionnaire. The authors found that age, gender and disease severity were significantly associated with quality of life after taking other covariates into consideration.
Kim et al. 2014	GOLD Stage	I 0.83 II 0.88 III 0.81 IV 0.60	The EQ-5D and Clinical COPD questionnaires were completed by 200 Korean patients with COPD in one tertiary hospital.
Kim et al. 2014[5]	GOLD Stage	I 0.906 II 0.912 III 0.857 IV 0.780	The Fourth and Fifth Korea National Health and Nutrition Examination Survey was used which included 20,261 adults above 40 years. Mean utility of COPD patients was 0.906(SE 0.004) compared to 0.922(SE 0.001) in the non-COPD control group.

[3] MEDLINE, EMBASE, Web of Science, CINAHL, ProQuest, Cochrane Library, Health Technology Assessment Database, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Google Scholar

[4] COPD severity score (COPDSS), the EuroQoL 5-Dimensions (EQ-5D), the Living with COPD (LCOPD) and the COPD Assessment Test (CAT) questionnaire

[5] Kim ES, Lee BJ, Lee GW, Jung AR, Hwang HS. Health status in adult patients with COPD in Korea. Value Health 2014; 17(7):A779–A780

Study	Staging	Scores	Method
Asukai et al. 2012	GOLD Stage	I 0.82 II 0.801 III 0.774 IV 0.743	EQ-5D questionnaires were implemented in three indacaterol phase III clinical trials at baseline, and weeks 12 and 26 (end of the studies). The EQ-5D questionnaire was completed at the same time as pre-bronchodilator FEV_1 assessment. Around 11,000 EQ-5D questionnaires were pooled and analysed.
Fletcheret al. 2011	BTS	Mild 0.84; Moderate 0.58; Severe 0.41	2426 participants aged 45-67 were recruited to a multi-country study (Brazil, China, Germany, Turkey, US, UK) and cross-sectional survey undertaken. Two thirds of patients had either moderate or severe COPD.
Pickard et al. 2011	GOLD Stage	I 0.73 II 0.59 III 0.63 IV 0.63	120 hospitalised COPD patients self-completed EQ-5D and SF-36 surveys and the disease-specific SGRQ. EQ-5D were transformed using UK tariffs.
Starkie et al. 2011	GOLD Stage	II 0.752 III 0.708 IV 0.672	The study collected QoL data as part of the TORCH (Towards a Revolution in COPD Health) trial. SGRQ and EQ-5D surveys were implemented at baseline and every 24 weeks for 3 years. The study included 6112 participants (4236 completed EQ-5D surveys).
Punekar et al. 2007	GOLD Stage	I 0.68-0.77 II 0.68-0.72 III 0.62-0.64 IV 0.655	This cross sectional multi-country (five EU countries and USA) survey included 2703 patients and their clinicians (1381 in primary and 1322 in specialty care).
Rutten van Moleken et al. 2006	GOLD Stage UK value set	II 0.787 III 0.75 IV 0.647	QoL was measured using EQ-5D visual analogue scale (VAS) scores, EQ-5D utility scores, and SGRQ from patients in a 4-year Tiotropium trial. 1,235 patients participated from 13 countries. The authors noted EQ-5D VAS and utility scores differed significantly among patients in GOLD stages 2, 3, and 4, also after correction for age, sex, smoking, body mass index (BMI), and comorbidity ($p < 0.001$).
Stahl et al. 2003	GOLD Stage	I 0.84 II 0.73 III 0.74 IV 0.52	174 COPD patients from Sweden self-completed Short Form 36 (SF-36), SGRQ, EQ-5D, Health States-COPD (HS-COPD), and Work Productivity and Activity Impairment Questionnaire for COPD (WPAI-COPD) questionnaires.
Borg et al. (2005)	GOLD Stage	I 0.8971 II 0.7551 III 0.7481 IV 0.5493	The study used a cost-of-illness study in northern Sweden and expert derived from a study of asthma in the UK.

Abbreviations: **BMI** = body mass index, **COPD** = Chronic Obstructive Pulmonary Disease, **EQ-5D** = euroqol group 5 domain questionnaire, **FEV_1** = Forced expired volume in 1 second, **GOLD** = global initiative for chronic obstructive lung disease, **QoL** = quality of life, **SGRQ** = Saint Georges Respiratory Questionnaire, **VAS** = visual analogue scale.

Many of the identified COPD simulation models described in the economic model background section of this report include utility values from a number of key trials. A selection of these models is summarised in Table 52. Many of the economic models were developed as part of evaluations associated with the trial. Most models estimate utility by FEV_1-defined COPD states under stable disease and also during exacerbation. For example, in the Asukai Markov model, the indacaterol phase III clinical trial program collected EQ-5D data during selected patient visits.[6]This data was mapped back to FEV_1 mild to severe categories, with mild being assigned 0.82, moderate 0.80,

[6] Whenever an EQ-5D questionnaire was completed at a time for which a pre-bronchodilator FEV_1 value was available

severe 0.77 and very severe 0.74. No utility data were available from the trials to describe an exacerbation and therefore these values were based on the literature.

Table 52 Selected utility values from COPD models outlined by Hoogendoorn et al. 2017

Study	Utilities during Stable disease specified by	Values	Utilities during exacerbations specified by	Values	Study Design, age
Asukai Markov Price et al. 2011	FEV_1% pred	Mild 0.82 Moderate 0.80 Severe 0.77 Very severe 0.74	Exacerbation severity	Non-severe exacerbation -0.01 Severe exacerbation -0.08	EQ-5D was completed at a time for which a pre-bronchodilator FEV_1 value was available, EQ-5D score was labelled as describing the corresponding disease severity. No utility data were available from the trials to describe an exacerbation
Borg et al. 2004	FEV_1% pred	COPD I 0.8971 COPD IIA 0.7551 COPD IIB 0.7481 COPD III 0.5493	Exacerbation severity, FEV_1% pred*	Mild U x 0.95 Moderate U x 0.85 Severe U x 0.3	QALY weights at exacerbations were expressed as a fraction of the exacerbation-free weight by COPD severity
Hoogendoorn et al. 2011	FEV_1% pred	Mild 0.8971 Moderate 0.7551 Severe 0.7481 Very Severe 0.5493	Exacerbation severity	n/a	EQ-5D utility weights were specified by COPD severity from Borg et al. 2004. O'Reilley et al. presented utility values at admission and discharge for a COPD hospitalization based on the UK for severe exaberations and Goosens for moderate.
Samyshkin et al. 2014	FEV_1% pred	Severe COPD 0.751 Very severe 0.657	Exacerbation severity	-0.12 for 1 month (moderate exacerbation of 0.01) and 0.504 (representing a loss of QALY per severe exacerbation of 0.042)	Selected subgroup analyses for patients with at least two COPD exacerbations in the previous year.

Abbreviations: **COPD** = Chronic Obstructive Pulmonary Disease, **EQ-5D** = euroqol group 5 domain questionnaire, **FEV_1** = Forced expired volume in 1 second, ***pred** = predicted **QALY** = quality-adjusted life year, **UK** = United Kingdom.

The Borg et al. (2004) model took a similar approach. Results of a EQ-5D quality-of-life questionnaire from a cost-of-illness study were used for quality-adjusted life-years (QALY) weights. Hoogendoorn et al. (2011) used the same approach, with the annual number of QALYs being calculated as the

annual number of life years using Q-5D utility weights specified by COPD severity (Borg et al. 2004). For each exacerbation a decrement in utility weights was applied.

Samyshkin et al. (2014) also employed health-related utilities for stable disease and exacerbations in their model. The severe COPD and very severe COPD states were associated with utility values of 0.751 and 0.657, respectively. Hospital-treated exacerbations and community-treated exacerbations were translated into loss of QALY per an event of exacerbation. Hoogendoorn et al. (2017) noted COPD models employ differing utility values to similar COPD stages and utility decrements assigned to exacerbations. For instance, the reported average utility values for stage II COPD range from 0.579 (Fletcher et al. 2011) to 0.929 (Rutten et al. 2009). Different methods of utility elicitation measures were thought to explain this variability.

Stage 1-2 and 3-4 COPD stage utility values appear to be broadly aligned in many of the AATD and COPD studies listed in this review. Hesselink et al. 2006 reported that changes in FEV_1% predicted weakly correlated with utility changes during a two-year follow-up of COPD patients, implying that clinical measures such as FEV_1% predicted provide limited information about health condition and are not well correlated with health status of COPD patients. The updated 2014 GOLD report suggests that progression and severity is best measured by a combined COPD assessment, including spirometric test, risk of exacerbations and COPD Assessment Test (CAT) or COPD Control Questionnaire (CCQ).

The SGRQ is a QoL measurement tool that captures three health domains of symptoms, activity and impact on daily life. As part of the TORCH (Towards a Revolution in COPD Health) trial the SGRQ and EQ-5D were measured every 24 weeks for three years. Around 18,505 observations included EQ-5D index and SGRQ scores. A simple algorithm was developed to transform SGRQ into EQ-5D values. The SGRQ was administered as part of the RAPID trial, however, no differences were found in SGRQ between treatment arms possibly due to limited patient numbers. Estimation of EQ-5D differences from SGRQ results in RAPID is therefore not possible, however, difference in utilities between AT and BSC arms are unlikely to be substantial, given RAPID's SGRQ findings.

Utilities for Lung Transplantation Health State

A literature search to identify published QoL analyses associated with lung transplant was conducted on 20 June 2018 in EMBASE, Cochrane Library, and HTA agency websites including CADTH and and NICE. The search strategy involved the search terms included in Table 47, except that AATD was substituted by lung transplant and lung transplantation. Titles and abstracts were reviewed and a manual search was performed. A total of 59 titles were identified, with six being deemed as relevant (see Table 53).

Table 53 Utilities for lung transplantation

Study	Reference
Utilities for lung transplant	
TenVergert et al. 1998	TenVergert EM, Essink-Bot ML, Geertsma A, van Enckevort PJ, de Boer WJ, van der BW. The effect of lung transplantation on health-related quality of life: a longitudinal study. Chest 1998; 113: 358–364
van Den Berg et al. 2000	van Den Berg JW, Geertsma A, van Der BIJ, et al. Bronchiolitis obliterans syndrome after lung transplantation and health-related quality of life. Am J Respir Crit Care Med 2000; 161: 1937–1941
Groen et al. 2004	AC, McGuire, A, Rogers, CA & Murday, AJ, 2004. Cost-Effectiveness of Lung Transplantation in Relation to Type of End-Stage Pulmonary Disease. American Journal of Transplantation, 4(7), pp. 1155-62.
Anyanwu et al. 2001	Anyanwu, AC, McGuire, A, Rogers, CA & Murday, AJ, 2001. Assessment of quality of life in lung transplantation using a simple generic tool. Thorax, Volume 56, pp. 218-22.
Singer et al. 2009	Singer L.G.; Chowdhury N.; Chaparro C.; Hutcheon M.A. 2009. Post-lung transplant health-related quality of life: Perception and reality, Journal of Heart and Lung Transplantation. Conference: 29th Annual Meeting and Scientific Sessions of the International Society for Heart and Lung Transplantation. Paris France. Conference Publication: (var.pagings). 28 (2 SUPPL. 1) (pp S127), 2009
Singer et al. 2015	Singer L.G.; Chowdhury N.A.; Faughnan M.E.; Granton J.; Keshavjee S.; Marras T.K.; Tullis D.E.; Waddell T.K.; Tomlinson G.2015, Effects of recipient age and diagnosis on health-related quality-of-life benefit of lung transplantation, American Journal of Respiratory and Critical Care Medicine. 192 (8) (pp 965-973), 2015.

TenVergert et al. 1998

The aim of this study was to assess the change in health-related quality of life (HRQL) among 24 Dutch lung transplant patients before and after transplantation to treat emphysema. Patients self-completed questionnaires[7] before transplantation, and at 1, 4, 7, 13, and 19 months after transplantation. Transplantation improved mobility, energy and depression. This benefit was maintained for 19 months post-transplantation. Bronchiolitis obliterans (BOS) was highlighted as the most frequent cause of late morbidity in lung transplant recipients. Of the 24 patients included in the present study, six patients developed BOS within 19 months.

Singer et al. 2009

These authors calculated the difference between mean pre-transplant and post-transplant utilities across 252 patients, for both Standard Gamble (SG) and Visual Analogue Scores (VAS). Utility improved with transplant, even for those with BOS. The mean SG utility pre-transplant was 0.4, which increased to 0.88 without BOS and 0.75 with BOS. VAS pre-transplant was 36 and increased to 77 without BOS and 63 with BOS. The authors concluded that lung transplantation significantly improves utility, even with BOS.

van Den Berg et al. 2000

[7] Nottingham health profile (NHP), the State-trait Anxiety Inventory, the Self-Rating Depression Scale-Zung, the Karnofsky Performance index, the index of well-being, and activities of daily living (ADL)

The aim of the study was to assess the relationship between health-related QoL and BOS in the Groningen Lung Transplant Program. The study involved cross-sectional comparison of those with and without BOS, and a longitudinal analysis of 22 patients. It that found lung transplant patients with BOS had lower QoL, which persisted for two to three years post-transplantation.

Singer et al. 2015

QoL was assessed on 430 patients using the SGRQ, EQ-5D, SG, VAS and 36-Item Short-Form Health Survey (SF-36). Transplantation conferred large improvements across all instruments. The SGRQ decreased 247 units, EQ-5D improved by 0.27, SG by 0.48, and VAS by 44. Age was not associated with significant differences in QoL benefits.

Groen et al. 2004

QoL data was sourced from the Dutch lung transplantation program between 1991 and 1995 using EuroQol questionnaires taken every three months for patients on the transplant waiting list, along with one, four and seven months post-transplantation, and then every six months. For those on the waiting list, average utility values of 0.55 during the first six months, 0.50 between six and nine months, 0.45 between nine and 12 months, and 0.40 after one year. Post-transplantation mean utility values ranged from 0.69 at one month post-transplantation to 0.83-0.85 at three-12 months after transplantation. Utility increased to 0.91 in the following year.

Anwanyu et al. 2001

The authors calculated utility scores in a cross-sectional sample of 87 patients waiting for transplantation and 255 lung transplant recipient in the UK. Mean patient age was 39 years, with 28 single lung transplants, 24 bilateral and 34 heart-lung transplants. Utility was measured using a self-completed EQ-5D questionnaire. The mean utility value of patients on the waiting list was 0.31. Average utility values for recipients three years post-transplantation were 0.61 for single, 0.82 for bilateral, and 0.87 for heart-lung transplants. These values are higher than at 0-6-months post-transplant, where 0.69 for single, 0.75 for bilateral, and 0.67 for heart-lung transplants were reported.

C.3. 4. RELATIONSHIP OF PRE-MODELLING STUDY TO THE ECONOMIC EVALUATION

Utilities for FEV_1 Health States

Both AATD and non-AATD COPD patients have taken part in studies where QoL has been elicited using a range of methods including SGRQ, SF-36, EQ-5D, SG, and VAS. Utility data is only available by FEV_1% predicted values from the UK registry for AATD patients provided in the Ejiofor and Stockley (2015) study. QoL assessment is problematic as there was weak FEV_1 and EQ-5D-SGRQ correlation observed by Ejiofor and Stockley (2015). The COPD literature also noted that FEV_1 was a relatively poor indicator of QoL, and composite instruments such as CAT or SQRQ tools should be combined

with spirometry to assess QoL. The RAPID trial implemented SQRQ, however, no significant differences between treatment arms were found.

Given the paucity of available data and limited accuracy of mapping EQ-5D by FEV_1 predicted, utility values are assigned for patients with FEV_1 above and below 50% predicted. GOLD Stages 1-2 EQ-5D utilities averaged around 0.7-0.9 among the reviewed COPD studies and 0.5-0.8 for GOLD Stages 3-4. Similar averages were evident in Ejiofor and Stockley (2015) for COPD patients with AATD and are used in the economic mode. Table 54 presents the health state utility values applied in Section D cost-effectiveness model.

The Ejiofor and Stockley (2015) average of 0.79 for FEV>50% predicted and 0.59 for patients with FEV<50% are used. This approach does not attempt to include disutility associated with exacerbation frequency. Given this uncertainty, sensitivity analysis is undertaken in the concluding part of Section D to understand the sensitivity of ICER results to changes in utility/FEV_1 assumptions. It is evident that model results are relatively robust, and that much of the economic benefit is driven by increases in life expectancy associated with AT.

Table 54 Summary of utility inputs for the Section D cost-effectiveness mode

Health state	Utility	Nature of estimate	Source	Alternative estimates of utility value	Source
FEV_1 ≥50% predicted (all rates of lung density decline)	0.79	EQ-5D data	Mean utility score based on UK Registry data (Ejiofor	+/- 5%	Sensitivity analysis
FEV_1 <50% predicted (all rates of lung density decline)	0.59	EQ-5D data	Mean utility score based on UK Registry data (Ejiofor	+/- 5%	Sensitivity analysis
First year of lung transplant	0.74	EuroQoL data	Mean EuroQoL score (mos 0-18), Anwanyu 2001	+/- 5%	Sensitivity analysis
Subsequent years following lung transplant	0.77	EuroQoL data	Mean EuroQoL score (mos 19-36+ months), Anwanyu 2001	+/- 5%	Sensitivity analysis

Abbreviations: **EQ-5D** = euroqol group 5 domain questionnaire, **FEV_1** = Forced expired volume in 1 second, **NR** = not reported.

Utilities for Lung transplant

Lung transplant utility results reported by Groen et al. (2004) and Anyanwu et al. (2001) indicate that utility increases substantially after transplantation. The data from Anyanwu et al. (2001) are used in the base case (provided in Table 54), as limited detail is provided about the small sample of patients used in the Groen et al. (2004) study. Average utilities for single, double and heart-lung (from Table 2, p. 413) of 0.74 for 0-18 months and 0.77 for 19-36 months+ are included. Utility values were shown to be age insensitive by Singer et al. (2015). The incidence of BOS appeared to be a key driver

of estimated utility. The values are subject to sensitivity analysis to ascertain the robustness of results to transplant QoL assumptions.

C.4. EXTRAPOLATION TRANSLATION ISSUES

C.4.1 IDENTIFICATION OF ISSUE THAT NEEDS TO BE ADDRESSED

This pre-modelling study addresses the method for extrapolating data from the four-year RAPID trial period as an input into the lifetime economic evaluation. This includes transition probabilities between FEV_1 and CT-scan lung density states, and survival.

C.4.2 FOCUSED ANALYTICAL PLAN

Patient transition between health states in the RAPID trial are used for the first four years of the model timeframe for AT and for two years for BSC, as the RAPID-OLE extension was confined to the AT arm. Discussions with clinical experts indicate that AATD patients stabilise after four years. It is assumed that after the first four years of the modelling timeframe, patients will remain on either no decline, slow or rapid decline CT-scan lung density pathways over the 26-year lifetime projection. Parametric survival models are fitted to UK registry data to project survival for patients in each health state from Year five over the lifetime projection.

C.4.3 RESULTS OF PRE-MODELLING STUDY

Transition between FEV_1 and lung density decline states

s45, s47(1)(b)

s45, s47(1)(b) [redacted] The average decline in FEV_1% predicted for 406 A1PI deficiency patients was 1.45% per year in the UK registry (Stockley 2015).

s45, s47(1)(b) [redacted]

A slower rate of progression is possible for patients using AT. s45, s47(1)(b) [redacted]

Survival

Survival estimates in the RAPID trial are the primary clinical inputs in the economic evaluation and the basis from which extrapolation occurs. Annual mortalities on the BSC and AT arms of the RAPID and RAPID-OLE studies were used for the first two and four years of the model, respectively. Extrapolation of survival after two and four years for the BSC and AT arms was required to estimate the proportion of patients in each health state across the time horizon of the model.

s45, s47(1)(b) [redacted]. A number of studies have shown FEV_1 to be an important predictor of survival in patients with emphysema. Two-year mortality increases exponentially once FEV_1 falls below one-third of predicted, at which point two-year mortality reaches 50% in patients with FEV_1 of 15% of predicted (Seersholm et al. 1994). Annual probabilities

of survival derived from parametric model extrapolations were assumed to be the same for each health state regardless of treatment arm.

FEV_1 >50 survival

Green et al. (2016) presented AATD patient subgroup survival analyses based on FEV_1 which "showed an apparent separation of curves on Kaplan Meier plots suggesting that there may be an effect on mortality in the patients with a presentation FEV1>30% predicted. The analysis was not statistically significant presumably due to inadequate power- as the number of deaths per group was low" (ibid, p. 86). s45, s47(1)(b)

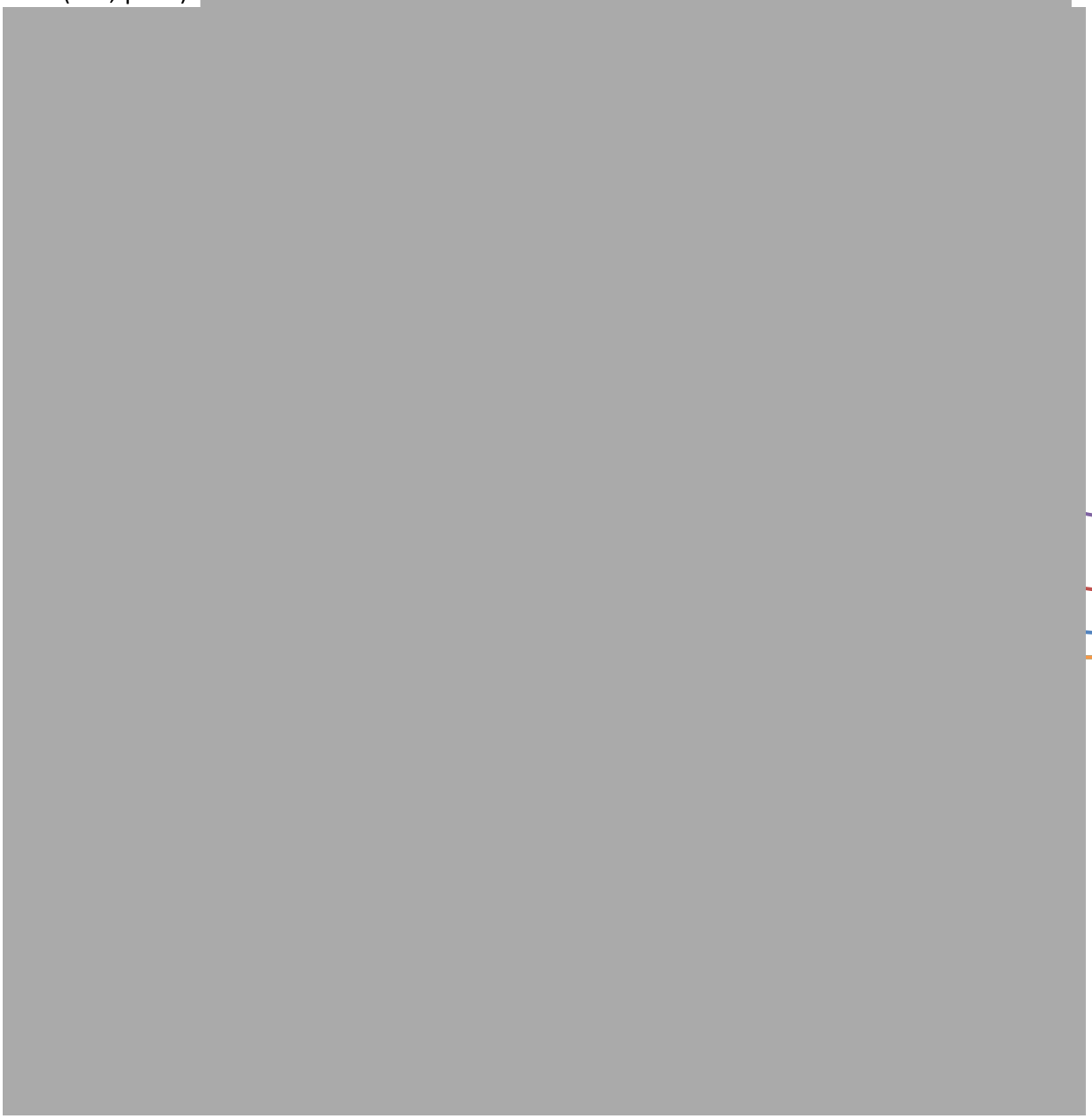


Table 55 Goodness of fit and parameters for FEV 1 >50 survival models

Parametric model	AIC	Shape (meanlog) (mu)	Scale (sdlog) (sigma)	Other (Q)
Weibull	88.76	2.5700	15.5650	
Exponential	93.68	0.02776		
Lognormal	90.89	2.865	0.848	
Generalised gamma	90.21	2.73E+00	1.56E-01	2.61E+00
Gompertz	86.84	3.98E-01	2.69E-03	
Log-logistic	89.30	2.681	14.652	

Abbreviations: **AIC** = Akaike's information criteria.

FEV1 <50 no decline

The Weibull survival function corresponds to a mortality rate that increases with time. The mathematical properties of this distribution matches the underlying scientific assumptions, as the decline is not as rapid as that for the Gompertz model and doesn't appear to have the large right hand tail of the exponential model. By 10 years of follow-up, cumulative survival is about 55%, so a large proportion of the patients in the group have succumbed to AATD. An illustration of the fit of the models compared with digitised survival data is presented in Figure 17.

s45, s47(1)(b)

A summary of the goodness-of-fit statistics (Akaike's Information Criteria—AIC) reported for each of the distributions is presented in Table 56.

Table 56 Goodness of fit and parameters for FEV 1 <50 no decline survival models

Parametric model	AIC	Shape (meanlog) (mu)	Scale (sdlog) (sigma)	Other (Q)
Weibull	17.82	3.6440	11.6210	
Exponential	18.31	0.046		
Lognormal	17.86	2.389	0.457	
Generalised gamma	19.86	2.39E+00	4.54E-01	2.43E-02
Gompertz	17.83	4.79E-01	2.45E-03	
Log-logistic	17.94	3.89	10.85	

Abbreviations: **AIC** = Akaike's information criteria.

FEV_1 <50 slow decline

An illustration of the fit of the models compared with digitised survival data is presented in Figure 18, using analysis provided by s47G (2017).

s45, s47(1)(b)

s45, s47(1)(b)

As for other survival extrapolations, sensitivity analysis provided at the end of Section D includes use of all of the models to gauge sensitivity of the estimated ICER to the parametric model.

s45, s47(1)(b)

[redacted]

FEV<50 rapid decline

Dawkins et al. (2009) provided Kaplan-Meier plots of cumulative hazard for mortality across nine years of follow-up for the UK AATD registry. When categorised by FEV1% predicted, "the group with severe impairment had increased mortality (pZ<0.001) compared with the mild group and there was a direct relationship between severity and mortality. Cox regression analyses indicated that these relationships remained when corrected for age." (ibid, p. 1540). s45, s47(1)(b)

[redacted]

s45

C.4. 4 RELATIONSHIP OF PRE-MODELLING STUDY TO THE ECONOMIC EVALUATION

Patient data from the four years of RAPID/RAPID-OLE are used to model AT transition during the trial period, and two years for BSC. A stepped analysis is included, where benefits are extrapolated from Year four for 26 years (30-year total model projection) to reflect a patient lifetime. Patients are assumed to stay on no decline, slow and rapid decline tracks for the remaining 26 years of the projection. Annual mortality during the RAPID trial is used for the trial period, after which extrapolation of survival is undertaken using parametric models fitted to the UK registry data using the analysis by CSL Behring (2017). For consistency, the Gompertz model was used for all health states, as this model had the best fit across most sub-populations. Different models are included in sensitivity analyses.

C.5 RELATIONSHIP OF EACH PRE-MODELLING STUDY TO THE ECONOMIC EVALUATION

Section C included three pre-modelling studies addressing issues related to applicability and extrapolation, which have implications for the economic model presented in Section D. A summary of the results and implications is provided in Table 59.

Table 59 Summary of results of pre-modelling studies and their uses in the economic evaluation

Section	Pre-modelling study	Results used in Section D	Cross-reference	Results used in sensitivity analyses	Cross-reference
Applicability of the trial-based evidence to the proposed MBS population	Study C.2	The population described in Section B is the same as that used in the economic model.	Section D.2.	NA	NA

Selection of utilities	Study C.3	FEV_1 stratified utilities were taken from the UK registry and applied health states with FEV_1<50 and FEV_1>50	Section D.4. 1.		
Extrapolation of trial-based evidence	Study C.4	Extrapolation from 4-year trial period for 30 years in a stepped analysis.	Section D.4.1.	NA	NA

Abbreviations: **FEV_1** = forced expiratory volume in 1 second, **MBS** = Medicare Benefits Schedule, **NA** = not applicable.

SECTION D ECONOMIC EVALUATION

D.1. OVERVIEW

A1PI maintenance therapy has the aim of slowing the progression of emphysema in adults with AATD (A1PI<11µM). An economic evaluation has been undertaken in this assessment using a cost-utility approach. The model estimates cost per year of life and cost per QALY as an incremental cost-effectiveness ratio (ICER). The model compares A1PI AT with optimal pharmacologic and non-pharmacologic treatment (BSC), compared to BSC alone. Lung transplantation is not included as a comparator, however, it is included in the clinical pathway for each arm of the model. A proportion of patients who reach FEV_1<50 with rapid or slow decline CT-measured lung density are assumed to receive lung transplantation.

Results of the economic model are presented in two steps. The first step outlines cost-effectiveness results for the trial period of four years. This length of follow-up reflects maximum follow-up of the RAPID trial (Chapman et al. 2015) and the open-label extension study (RAPID-OLE) (McElvaney et al. 2017) trials. An average hypothetical cohort of 1,000 patients progresses between FEV_1% and CT-measured lung density decline states based on results of the trial within a cohort-based semi-Markov model. Mortality data were taken from the RAPID-OLE and RAPID studies for the first two and four years, respectively (McElvaney et al. 2017); (Chapman et al. 2015).

The efficacy benefit associated with treatment that leads to improvements in patient morbidity are captured in the model using RAPID trial data, with the primary analysis being expressed as the incremental cost per additional QALY gained. Resource use is attached to each state using proposed A1PI maintenance therapy product costs and MBS item costs. Australian Refined Diagnosis Related Groups (AR-DRG) costs are applied to the frequency of GP and hospital presentations for UK COPD patients of differing severity (Thomas et al. 2014) to estimate AATD disease management costs.

The second step involves extrapolating RAPID transition data over an additional 26 years (lifetime). It was assumed that transitions between health states with varying rates of lung density decline occurred during the follow-up of the RAPID and RAPID-OLE studies and that patients stayed on no, slow or rapid decline tracks for the remaining 26 years. Mortality data for the remainder of the model's lifelong time-horizon were based on observations from 10 years of followed-up patients in the UK AATD registry. A number of parametric models were fitted to the UK registry data to extrapolate observational data for the lifetime projection. A range of sensitivity analyses were undertaken to test the robustness of the results of the modelled economic evaluation. This includes changes in baseline distributions of individuals with emphysema or COPD stratified according to airflow obstruction, being mild, moderate, or severe.

D.2. POPULATIONS AND SETTINGS

D.2.1. POPULATION

The modelled patient population is aligned with the proposed listing. Patient-level data was derived from the RAPID trial with eligible patients having AATD (A1PI<11μM), FEV_1 of 35%–70% (predicted) and being non-smokers. The PICO notes patient eligibility as being ex- or never-smoking individuals with severe A1PI deficiency (serum levels ≤11 μM) and emphysema with FEV_1 <80%. The inclusion criteria for the RAPID trial largely corresponds with the listing PICO, although a FEV_1 of 35%–70% (predicted) was included in the RAPID trial compared to FEV_1 <80% for the proposed listing (See Table 60).

Table 60 Comparison between eligibility criteria in the RAPID study and circumstances of use

Characteristic	RAPID Study	Proposed listing
Inclusion criteria	Severe A1PI deficiency (serum concentration <11μM) with a FEV_1 of 35–70% (predicted).	A1PI deficiency (serum levels ≤11 μM) and emphysema with FEV_1 <80%.
Exclusion criteria	Aged over 65 years; Smoked tobacco within 6 months before recruitment; Waiting list or previous lung transplantation, lobectomy, or lung volume-reduction surgery; or selective IgA deficiency.	Smokers (only ex- or never-smoking individuals eligible)
Dose regimen	Intravenously 60mg/kg	Intravenously 60mg/kg
Treatment frequency/duration	Once per week up to 48 months	Once per week

Abbreviations = **A1PI** = alpha-1 proteinase inhibitor, **FEV_1** = forced expiratory volume in 1 second, **μM** = micromolar.

Baseline patient data from the RAPID trial informs cohort age and disease severity at entry into the model, whilst a post-hoc analysis of Individual Participant Data (IPD) was performed by CSL Behring (2017) to produce transition matrices informing health state transitions over the trial period. Trial data are available to four years, after which the available within-trial data are extrapolated over a lifetime (further 26 years).

The distribution of patients across health states at the beginning of the model (Table 61) was based on the first year BSC patient profile from the RAPID study (Table 6; Table 7). s45, s47(1)(b) [redacted]. Based on the RAPID data, the baseline age was assumed to be 53 years. This variable is relevant to length of the lifetime projection and has no impact on the treatment effectiveness or natural history of the disease in the model.

Table 61 Baseline disease severity – RAPID population; baseline disease severity in the model

Baseline FEV_1 and lung density decline		AT	BSC N= 85 (death 2)	BSC (%)
RAPID				
FEV_1>50 no decline	N (%)	Not reported	6	7%
FEV_1>50 slow decline	N (%)	Not reported	11	13%
FEV_1>50 rapid decline	N (%)	Not reported	17	20%
FEV_1<50 no decline	N (%)	Not reported	7	8%
FEV_1<50 slow decline	N (%)	Not reported	29	34%
FEV_1<50 rapid decline	N (%)	Not reported	15	18%
Modelled population				
FEV_1>50 no decline (%)	(%)	BSC from RAPID	7%	
FEV_1>50 slow decline (%)	(%)	BSC from RAPID	13%	
FEV_1>50 rapid decline (%)	(%)	BSC from RAPID	20%	
FEV_1<50 no decline (%)	(%)	BSC from RAPID	8%	
FEV_1<50 slow decline (%)	(%)	BSC from RAPID	34%	
FEV_1<50 rapid decline (%)	(%)	BSC from RAPID	18%	

Abbreviations: **BSC** = best supportive care, **FEV_1**= forced expiratory volume in 1 second.

Survival models were derived from UK registry populations. The RAPID and UK registry populations appear to have similar characteristics. The average patient age in the UK was 52 years, with males comprising 58% of the population (Green et al. 2016). FEV_1 (% predicted) was 45.3%, which is slightly lower than that reported for baseline patients in the RAPID trial of 47.4% and 47.2% for the intervention and comparator arms, respectively. Baseline density (g/l) in the UK registry was 46.2, compared to 45·5 and 48·9 on each of the RAPID arms.

D.2.2. SETTINGS

The economic model assumes an Australian health care setting, with the modelled population representing adults with documented severe A1PI deficiency. The RAPID study from which much of the data is derived is relevant and applicable to this setting. The RAPID trial was global and included a small number of Australian patients. Australia contributed 9.7%-12.6% of patients to the intervention and comparator arms, respectively, while Europe contributed 32.3%-27.6%, North America 25.8%-25.3%, and Nordic countries 32.3%-34.5%. Dosing followed that recommended for maintenance therapy of 60mg/kg by once-weekly infusion (Zemaira product information, PROLASTIN-C product information; Appendix 1.). This infusion would be provided in an outpatient setting.

The administration cost of $65.05 for each infusion was based on MBS item number 13915. It is noted that patients could possibly be trained to self-infuse at home, which would reduce administration costs. This possibility is included as a sensitivity analysis (see Section D). It does not have a significant impact on the estimated ICER, but would potentially help with convenience and overall patient adherence. Assumed average weight in the RAPID study of 76kg was used to estimate

product costs, resulting in an average use of 4.55 vials (1,000 ml) per week. This was multiplied by the average compliance from the RAPID study of 93.9%, resulting in an average use of 4.28 vials per week (Chapman et al. 2015). Fractional vials are rounded to whole numbers (i.e. five vials) and vial usage per week is multiplied by 52 to estimate annual product usage costs. AT product costs account for more than 90% of the estimated resource use in the lifetime model and is the key driver of the calculated ICER.

BSC encompasses a range of interventions including pharmacological (e.g. bronchodilators, systemic corticosteroids), non-pharmacological (e.g. oxygen therapy), and preventative measures such as vaccinations. AATD disease management costs are derived from Thomas et al. (2014). This study was a retrospective, observational study undertaken in 10 General Practices in England, using routine clinical records of 511 patients with COPD. It reported the frequency of hospital and GP visits stratified by COPD severity, based on each patient's FEV_1 measurement recorded during 2007. The study included 314 (61%) mild-moderate patients (≥50% predicted FEV_1), 145 (28%) severe (30–49% predicted FEV_1) and 52 (10%) very severe (<30% predicted FEV_1) patients. Costs by severity are applied to patients who transition through the Markov model according to probabilities estimated for the intervention and comparator arms. Differences in costs are captured in the incremental cost per QALY calculation, which summarised cost-effectiveness results.

D.3. STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A cost-utility analysis was undertaken to determine the value of AT in addition to optimal pharmacological treatment and supportive care. Table 62 summarises the key characteristics of the economic evaluation.

Table 62 Summary of the economic evaluation

Perspective	This economic evaluation was conducted from the perspective of the Australian health system. It includes resource use supported by government and patients, along with health outcomes applicable to the treatment of patients with emphysema due to A1PI deficiency.
Intervention	Augmentation therapy in addition to optimal pharmacological treatment and supportive care.
Comparator	Best Supportive Care. Optimal pharmacological treatment and supportive care
Type of economic evaluation	Cost-utility analysis
Sources of evidence	RAPID study, RAPID-OLE study, UK Registry data
Time horizon	30-year time horizon in the base case Sensitivity analyses include a time horizon of 20 years and 40 years
Outcomes	Quality-adjusted life years/ life-years gained
Methods used to generate results	Cohort expected value analysis
Health states	1. FEV_1≥50% predicted, no lung density decline 2. FEV_1≥50% predicted, slow lung density decline 3. FEV_1≥50% predicted, rapid lung density decline 4. FEV_1<50% predicted, no lung density decline

	5. FEV_1<50% predicted, slow lung density decline 6. FEV_1<50% predicted, rapid lung density decline 7. Lung transplant 8. Dead
Cycle length	1 year
Discount rate	5% used for base and 3.5% and 7% sensitivity analyses
Software packages used	Microsoft Excel 2010

Abbreviations: A1PI = alpha-1 proteinase inhibitor; **FEV_1** = forced expiratory volume in 1 second.

As noted, a stepped evaluation was undertaken. The first step captures costs and health outcomes over four years, the maximum number of years of follow up in the RAPID-OLE trial. AT is expected to have longer term benefits such as prolonging life and delaying the need for lung transplantation. Correspondingly, a lifetime extrapolation is also included as a second step. The extrapolation is carried forward over 26 years, thus the overall modelling period is 30 years.

This timeframe is selected to align with the patient population in the RAPID trial. The age at baseline was 53.8 years in the RAPID trial (Chapman et al. 2015). Average life expectancy in Australia for a male aged 54 is 28.9 years, and 32.1 years for females (ABS 2016). Sensitivity analyses were conducted for scenarios where the time horizon was varied to 20 years and 40 years. The ICER is relatively insensitive to these changes as a large proportion of the patients in each arm of the model are expected to suffer mortality within the first 20 years of the projection.

D.3.1. LITERATURE REVIEW

A1PI deficiency

A literature review was conducted in June 2018 using the search terms provided in Table 63 to identify cost-effectiveness studies for treatment of A1PI deficiency. The search included EMBASE (1947-), other HTA websites (Canadian Agency for Drugs and Technologies in Health—CADTH; Health Technology Assessment—HTA, National Institute for Clinical Excellence—NICE) and the Cochrane Library.

Table 63 Search terms used

Element of clinical question	Search terms
Population	AATD.mp OR alpha-1 antitrypsin deficiency.mp OR antitrypsin deficiency.mp OR proteinase inhibitor OR Prolastin OR Aralast OR Zemaira OR Trypsone
Intervention	Not applicable
Comparator (if applicable)	Not applicable
Outcomes (if applicable)	Not applicable
Other	Health economics OR economic aspect OR economics OR biomedical technology assessment OR economic evaluation OR health care cost OR technology assessment OR cost effectiveness analysis OR cost minimisation analysis OR cost minimization analysis OR cost minimization analysis OR cost utility analysis

Element of clinical question	Search terms
Limits	English language Remove duplicates 1990-2018

Table 64 Summary of the process used to identify and select studies for the economic evaluation

	EMBASE	Other HTA websites[a]	Cochrane Library
Number of titles and abstracts reviewed after search	1073		
TOTAL number of exclusions	1062		
Number of HTA reports/cost-effectiveness outcomes reported	11	2	
Consolidated number of studies excluding duplicates	13		

[a] HTA agencies included: NICE, CADTH. **Abbreviations**: CADTH, Canadian Agency for Drugs and Technologies in Health; HTA, Health Technology Assessment, NICE, National Institute for Clinical Excellence

Of 113 studies screened, only five published economic studies for A1PI deficiency treatment were identified. Table 65 lists the publications included in the review of economic evaluations.

Table 65 Economic models assessing A1PI deficiency treatment

Published economic models assessing A1PI deficiency treatment	
Study	**Reference**
Hay and Robin 1991	Hay JW, Robin ED. Cost-effectiveness of alpha-1 antitrypsin replacement therapy in treatment of congenital chronic obstructive pulmonary disease. Am J Public Health 1991; 81:427–433
Alkins and O'Malley 2000	Alkins SA, O'Malley P. Should health-care systems pay for replacement therapy in patients with alpha (1)-antitrypsin deficiency? A critical review and cost-effectiveness analysis. Chest 2000; 117:875–880
Gildea et al. 2003	Gildea, et al. 2003. Cost-effectiveness Analysis of Augmentation Therapy for Severe Alpha 1-Antitrypsin Deficiency. American Journal of Respiratory and Critical Care Medicine, pp. 1387-92
Shermock et al. 2005	Shermock KM, Gildea TR, Singer M, Stoller JK. Cost-effectiveness of population screening for alpha-1 antitrypsin deficiency: a decision analysis. COPD. 2005;2: 411–8
Sclar et al. 2012	Sclar DA, Evans MA, Robison LM, Skaer TL. Alpha1-Proteinase inhibitor (human) in the treatment of hereditary emphysema secondary to alpha1-antitrypsin deficiency: number and costs of years of life gained. Clin Drug Investig. 2012; 32:353–60
Other economic studies	
Mullins et al. 2001	Mullins CD, Huang Z, Merchant S, et al. The direct medical cost of alpha (1)-antitrypsin deficiency. Chest 2001; 119: 745-52
Mullins et al. 2003	Mullins CD, Wang J, Stoller JK. Major components of the direct medical costs of alpha1-antitrypsin deficiency. Chest. 2003; 124:826–31
Barros-Tizón et al. 2012.	Barros-Tizón JC, Torres ML, Blanco I, Martínez MT; Investigators of the rEXA study group. Reduction of severe exacerbations and hospitalization-derived costs in alpha-1-antitrypsin-deficient patients treated with alpha-1-antitrypsin augmentation therapy. Ther Adv Respir Dis. 2012 Apr;6(2):67-78. doi: 10.1177/1753465812438387. Epub 2012 Feb 21
Campos. et al. 2015	Campos, M. et al. 2015. Utilization and Costs Associated with the Prolastin Direct Alpha 1 Proteinase Inhibitor Patient Management Program. Obstructive Lung Diseases, October 2015

Published economic models assessing A1PI deficiency treatment	
Study	**Reference**
Zacherle et al. 2015	Zacherle, JM Noone, MC Runken, CM Blanchette 2015. PSY35 - Health Care Cost and Utilization Associated with Alpha-1 Antitrypsin Deficiency Among a Cohort of Medicare Beneficiaries with COPD. Value in Health, Volume 18, Issue 7, November 2015, Page A664 E
Karl et al. 2017	Karl, F. et al. 2017. Costs and health-related quality of life in Alpha-1-Antitrypsin Deficient COPD patients. Respiratory Research 2017 18:60 DOI 10.1186/s12931-017-0543-8
CADTH 2017	Alpha1-Proteinase Inhibitors for the Treatment of Alpha1Antitrypsin Deficiency: A Review of Clinical Effectiveness, Cost Effectiveness, and Guidelines
NICE 2010	Human alpha1-proteinase inhibitor for treating emphysema ID856, in development [GID-HST10017] Expected publication date: 13 February 2019

Abbreviations: **COPD** = chronic obstructive pulmonary disease.

Hay and Robin 1991

Hay and Robin (1991) undertook a cost-effectiveness analysis of AT costs relative to years of life saved. Clinical benefits were based on 14 years of disease progression follow-up in 246 Swedish AATD patients, applied to the adult US population. A non-smoking 50-year-old male was estimated to have an additional 7.12 years life expectancy with AT. The cost per life year estimates ranged from US$28-39 thousand for smoking males and females, and US$41-72 thousand for non-smokers. The relatively cost-effective results appear to be driven by the estimated increase in life expectancy associated with AT. The base model assumed life expectancy increases of around 14 years and seven years for non-smoking 50-year-old women and men, respectively. The non-smoking male life expectancy benefit is double that estimated in this assessment of AT benefits in Australia of three years (in this assessment) for someone in their early 50s using RAPID and UK AATD registry data.

Alkins and O'Malley 2000

Cost effectiveness analysis was undertaken for AT replacement therapy among individuals with severe COPD (FEV_1 < 50% of predicted). The study examined a payer perspective based on Medicare reimbursement rates. Annual AT costs were estimated to be US$51,948 based on a dosage of 60mg/kg, meaning a 70-kg patient would require nine 500-mg vials each week. A systematic review of AT effectiveness studies in MEDLINE and EMBASE between 1980-1998 was used to define absolute risk differences. NIH Registry data was identified that found the five-year mortality rate in patients (FEV_1 < 50%) ranged from 33% in the BSC arm to 15% in the AT arm. The incremental cost per year of life saved for AT replacement therapy was US$13,971. The large gain in life expectancy underpins this result. The authors noted that results depend substantially on the mortality rate reduction. When the effect size was changed from 10% to 70%, the incremental cost per year of life saved ranged from US$152,941 to US$7,330.

Gildea et al. 2003

Gildea et al. 2003 developed a five-state Markov model, based on FEV_1% predicted, to compare AT with BSC. The analysis took a health care system perspective. Health states were defined as FEV_1

50% to 79% predicted, FEV_1 35% to 49% predicted, FEV_1 below 35% predicted, lung transplantation, and death. Patients transitioned through the model based on probabilities largely derived from the NHLBI Registry (AATD Registry Study Group, 1998).

It was assumed that 19% of patients with an FEV_1 below 15% predicted underwent lung transplantation. The model population had a baseline age of 46 years, 50% male and a FEV_1 of 49% predicted. Except for age, these characteristics are similar to that in the RAPID trial. Resource usage was assigned to each state using a retrospective cost analysis of COPD management in the USA (Hilleman et al. 2000). Resources included the cost of medications, oxygen therapy, laboratory and diagnostic tests, clinic and emergency department visits, and hospitalizations. The annual cost of Stage I COPD was US$1,966, Stage II COPD US$5,892 and Stage III COPD US$12,647. Transplantation and post-transplantation resources were taken from cost studies of lung transplant patients (Sharples et al. 2001, Ramsey et al. 1995), where the cost of lung transplantation was estimated at US$328,222, along with annual maintenance costs of US$59,918. The annual cost of AT was calculated to be US$54,765.

Pulmonologists who treat AAT deficiency (n=14) were surveyed using the health utilities index (Mark III) (Crystal et al. 1989) to estimate utility values. The utility assigned for Stage I COPD was 0.93, Stage II COPD 0.75 and Stage III COPD 0.26. The economic model compared AT with no AT, AT for life, and using AT when FEV_1 falls below 35% predicted. The ICER was $207,841/QALY for AT until FEV_1 is below 35% predicted and $312,511/QALY for the AT strategy.

Shermock et al. 2005

The Shermock study used the same model as that in Gildea et al. 2003, however, it was extended to assess the economic attractiveness of AATD screening strategies in all newborns, in all 10-year-old children, and no screening for PI∗ZZ AAT deficiency. The benefit of screening was that information about presence of AATD resulted in a lower likelihood of smoking. Screening all newborns had an ICER of US$422,000 per QALY gained.

Sclar et al. 2012

Sclar and colleagues used Monte Carlo simulation to estimate the number of years of life gained, and health service expenditures per year of life gained, for AT. The authors formulated algorithms (regression model) for the annual decline in FEV_1, predicted FEV_1 and mortality, from data held by the AATD Registry Study Group (AATD Registry Study Group 1998, McElvaney et al. 1997).

Patients were deemed eligible for AT when predicted FEV_1 fell below 70%. Expenditures for AT were estimated using a dose of 60mg/kg, a once-weekly administration schedule, and an administration fee of US$36.73 (Mullins et al. 2001). Patients were eligible for lung transplant when predicted FEV_1 was below 40% (Crapo et al. 1981). The annual probability of lung transplant when eligible was

assumed to be 0.155 (Larsson 1978, Stoller et al. 1994). The cost of lung transplantation was US$67,000 per year for three years.

AT therapy was estimated to result in a significant increase in years of life. Female non-smokers gained an average of 9.19 years, at a cost of US$160,502 per year, and male non-smokers gained 10.60 years at US$59,234 per year. Again, these increases in life expectancy for AT therapy are higher than those estimated in this assessment using RAPID trial data and parametric models fitted to UK registry data.

Mullins et al. 2001

Mullins and colleagues undertook a literature search on the pharmacoeconomics of AAT deficiency in Medline, Health STAR, International Pharmaceutical Abstracts and Ovid. Keywords included 'α1-antitrypsin deficiency', 'late diagnosis', 'early diagnosis', 'aerosol therapy', 'product shortage', 'epidemiology' and 'economics'. A total of 106 papers were identified and collated on the basis of being 'of interest', 'considerable interest', 'good overview of clinical aspects of AAT-deficiency', 'addresses the impact of FEV_1 values', 'cost-effectiveness analysis of AAT deficiency replacement therapy', 'burden of illness of AAT deficiency' and 'describes potential for aerosol augmentation therapy'. The papers by Hay and Robins (1991) plus Alkins and O'Malley (2000) were identified in the economics section. The issue of the lack of statistical power given the rare nature of AATD was noted. The review revealed a limited economic evidence base, with key papers provided in this assessment.

Mullins et al. 2003

Mullins et al. performed a cost analysis on AATD patients in 1998 using a mail survey. Responses were collated from 292 of the 688 individuals. The response rates for PI*ZZ individuals was 42.7% versus 41.8% for non-PI*ZZ subject. The mean age of subjects was 52.0 years. The average costs per year for hospital and outpatient services were US$4,497 and US$2,299. Prolastin and other medicines cost $28, 075 and $6,456 per year. The Australian and US health settings are different, as one is insurance-based and the other largely involves publicly delivered services. These results are of limited applicability to the current assessment

Barros-Tizón et al. 2012

This observational study was undertaken in Spain to evaluate the effect of 18 months of AT therapy in reducing the incidence of exacerbations. The numbers of mild and severe exacerbations were compared and hospitalization-related costs estimated. The total of 127 patients had an average age of 51.7 years and 63.3% were male. "The average number of days of admission was 3.9 before treatment and 3.0 in the treatment period, while in the population with exacerbations the values were 6.7 and 4.6 days, respectively" (ibid, p. 74). Hospital costs were reduced by €416.76 per subject

in the total patient population after 18 months of AT augmentation therapy. The AT arm in RAPID was not associated with a reduction in exacerbations.

Campos et al. 2015

The Campos analysis assessed the costs of 213 patients in the Prolastin Direct A1PI Patient Management Program compared with 232 patient costs of augmentation therapy with other alpha-1-proteinase inhibitors A1PI. The Prolastin Direct program was noted by the authors as a program providing coordinated augmentation therapy services (reimbursement, pharmacy, infusion) in conjunction with Prolastin. Similar demographic patient characteristics too RAPID were observed. Patients were 51% male with mean age of 55.5 years. Mean total monthly costs were US$ 11,705 for PD patients and US$ 13,803 in the comparator. Mean monthly augmentation therapy costs were $9,901, therefore AT comprised 70%+ of total health care costs.

Zacherle et al. 2015

Zacherle and colleagues assessed one-year patient costs in the USA following confirmed COPD or AATD diagnosis for AATD-COPD patients (n=279) and COPD patients (n=183,832) using 2011-2013 Medicare data. Mean age of COPD and AATD cohorts were 72.6 years and 64.6 years, respectively. AATD patients presented more frequency in ER and as inpatient, with total healthcare costs (per patient) being US$ 27,674 higher than COPD total costs. It was noted that AATD patient costs were not adjusted for differences in COPD severity. Many of the AT economic models use COPD severity to cost resource use. Sensitivity analysis, which includes changed resource-cost assumptions for FEV_1-related health states used in the base analysis, is included in the concluding section of this economic assessment. Changes do not have a large impact on the estimated ICER, as the majority of resource use is associated with AT product costs.

Karl et al. 2017

Karl and colleagues calculated direct and indirect patient costs, and QoL using the German multicentre COPD cohort COSYCONET study (German COPD and Systemic Consequences – Comorbidities Network). Health-related QoL (HRQL, as assessed by SGRQ, CAT, and EQ-5D-3 L) was compared between 131 AATD and 2,049 COPD patients. AATD patients were younger (60.3 years vs 65.4 years), more of them never smoked (23.7% vs 5.4%) and they were in higher GOLD grades than the COPD patients. The association of AATD with costs and QoL was examined using generalised linear regression modelling (GLM) adjusted for age, sex, GOLD grade, BMI, smoking status, education and comorbidities. The costs of AT products were excluded.

The regression analysis found that AATD patients (with and without AT), tended to have lower total costs compared to COPD patients without AATD, but these differences were not statistically significant. These results differ to Zacherle et al. 2015 who found AATD-COPD patients had higher costs than COPD patients. The higher number of outpatient visits for AT receiving AATD patients was

thought to be a result of infusions. These costs were not separated in Zacherle et al. 2015. Average direct annual costs were €6,099 in AATD patients without AT, €7,117 in AATD patients with AT (excluding AT medicines), and €7,460 in COPD patients without.

Participants completed the SGRQ, (Jones et al. 1992) the COPD Assessment Test (CAT) (Jones et al. 2011) and the generic EuroQol 5 dimensions (EQ-5D-3L) questionnaire including VAS. There were no significant differences between groups regarding QoL. This result is in line with the study by Manca et al. (2014) who found no QoL differences between AATD/COPD patients and COPD patients without AATD.

CADTH, 2017

CADTH undertook a systematic review of RCTs comparing A1PI with placebo. They concluded that the impact of A1PI on the rate of decline in FEV_1 and rates of exacerbations is variable. They noted that AT therapy has not been demonstrated to lead to an improvement in patient QoL compared to placebo. No studies met the inclusion criteria to address the cost effectiveness of A1PI for the treatment of adults with AATD.

NICE, 2018

NICE are currently undertaking a review of AT therapy effectiveness and guidelines. They note that 670 people in England have emphysema caused by AATD (Miravitlles et al. 2010) and about 540 of these people (80%) will have clinically significant emphysema requiring treatment (NIHR Horizon Scanning Centre 2014). They note that the epidemiology, disease characteristics and disease progression of emphyema in patients with AATD differs from that in usual COPD. Consequently, it is inappropriate to include AATD within the umbrella of what is generally termed 'usual' COPD.[8]

Chronic Pulmonary Obstructive Disease (COPD)

Only a limited number of economic models have been developed to assess AT therapy. Some use COPD states for utility and disease-management cost calculations. The economic literature review was expanded to include some recent COPD economic modelling reviews.

Boland et al. 2013

The review by Boland and colleagues (2013) aimed to identify cost-effectiveness studies of COPD management programs. MEDLINE, the economic evaluation database of the UK National Health System (NHS-EED) and the EUROpean Network of Health Economic Evaluation Database

[8] https://www.nice.org.uk/guidance/gid-hst10017/documents/scope-consultation-comments-and-responses

(EURONHEED) were searched in July 2011. Sixteen papers describing 11 studies were identified. Changes in health related QoL were reported using SGRQ in six studies. Five reported an improved QoL, however, the reduction did not exceed the clinically relevant improvement of four points (Jones et al. 2005). Three studies measured health-related QoL on a VAS and only one study measured the EQ-5D.

Zafari et al. 2017

This study is the most recent published review. It included a systematic search for decision-analytic modelling in COPD using MEDLINE, Embase, and citations within reviewed articles. The search resulted in 4054 references, excluding duplicates. After full-text review, 49 publications met the inclusion criteria. Decision trees and Markov models were the most popular approaches (43 studies) and disease progression was modelled through clinical staging in most studies. A range of methods was used to model COPD progression, some directly via the continuum of lung function (eg. FEV_1), others in discrete clinical states defined by the GOLD grades. Four Markov models used exacerbation status in defining model states. In general, effectiveness was modelled as a direct reduction in exacerbation rate.

Forty of the models were developed for the purpose of economic evaluation, either of alterative COPD treatments or of a COPD management program. The Markov model developed by Oostenbrink et al. (2005) was the most widely adopted model structure, which has been used in eight subsequent studies. Other widely adopted model structures were from Borg et al. (2004), Price et al. (2011), Spencer et al. (2005), Hoogendoorn et al. (2005), Sin et al. (2004), Buist et al. (2005), and Asukai et al. (2013). The features of these widely adopted models were summarised as part of the European consortium review outlined in Hoogendoorn et al. (2016).

Hoogendoorn et al. 2016

The consortium of COPD modelling groups reviewed nine recent COPD economic models and reported patient characteristics, disease progression, mortality, QALYs, and costs for hypothetical subgroups of patients. The consortium reviewed how they differed and how model outcomes for exacerbations and mortality were validated. Features of the models are summarised in Table 66.

Table 66 Summary of COPD economic model progression and mortality characteristics

Study	Disease progression specified by	Exacerbation frequency specified by	Mortality specified by
Asukai Markov	Sex, age, smoking	FEV_1% pred	Sex, age, FEV_1% pred
Asukai simulation	Sex, age, smoking, FEV_1	FEV_1% pred	Sex, age, FEV_1% pred
Borg	Age, FEV_1, rapid decline	FEV_1% pred, frequent exacerbations	Age, FEV_1% pred
Briggs	Sex, age, smoking	Sex, age, smoking, FEV_1% pred	Sex, age, smoking, FEV_1% pred

			all other listed
Dal Negro	Sex, age, RV, D_{LCO}, BODE, % FEV decline, comorbidities	Age, RV, D_{LCO}, BODE, % FEV decline, comorbidities	Age, RV, D_{LCO}, BODE, % FEV decline, comorbidities
Hansen	Smoking, FEV_1% pred	FEV_1% pred	Age, FEV_1% pred.
Hoogendoorn	Sex, age, smoking	FEV_1% pred	Sex, age, smoking FEV_1% pred
Samyshkin	Sex, age, FEV_1% pred	FEV_1% pred	Sex, age, FEV_1% pred
Wacker	Smoking, FEV_1% pred	FEV_1% pred, lung transplant	Sex, age, smoking, FEV_1% pred, lung transplant

Abbreviations: **BODE** = body mass index, airflow obstruction, dyspnoea and exercise index, **D_{LCO}** = diffusing capacity for carbon monoxide, **FEV_1** = Forced expired volume in 1 second, **pred** = predicted, **RV** = residual volume.

In all models except the Markov model of Asukai, disease progression was specified by FEV_1% predicted. Most of the nine models use a series of discrete COPD health states. For example, the Asukai Markov has mild, moderate, severe, and very severe COPD states, based on pre-bronchodilator FEV_1 measures reported in the Indacaterol clinical trials, and death. Cut-off points adopted to define severity were the same as for GOLD. Transition probabilities used in the model were based on patient movement in trials. Borg also defined disease severity by lung function (FEV_1, as a percentage of predicted) divided into four different states using the GOLD guidelines. Hansen developed an Excel-based Markov model with four health states representing the Global Initiative for Chronic Lung Disease (GOLD) disease severity classification. Within each GOLD stage, three sub-states were included to model stable disease with three levels of COPD exacerbation.

All models used FEV1% predicted to specify exacerbation frequency, mortality, utilities, and disease management maintenance costs. Exacerbation costs were specified by FEV1% predicted by four models (Hoogendoorn et al. 2016).

Lung transplant

A literature review was conducted in June 2018 using the search terms 'Lung transplant or lung transplantation' and economic terms provided in Table 63 to identify cost-effectiveness studies on treatments for lung transplantation. The search included EMBASE (1947-), other HTA websites (Canadian Agency for Drugs and Technologies in Health—CADTH, Health Technology Assessment—HTA, National Institute for Clinical Excellence—NICE) and the Cochrane Library. The studies identified in the search are summarised in Table 67.

Table 67 Summary of the process used to identify and select lung transplant studies for the economic evaluation

	EMBASE	Other HTA websites [a]	Cochrane Library
Number of titles and abstracts reviewed after search	474		
Total number of exclusions	468		
Number of HTA reports/cost-effectiveness outcomes reported	6		

	EMBASE	Other HTA websites [a]	Cochrane Library
Consolidated number of studies excluding duplicates	6		

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; HTA, Health Technology Assessment, NICE, National Institute for Clinical Excellence.
[a] HTA agencies included: NICE, CADTH.

Of 474 studies screened, only five published economic models for lung transplant were identified. Table 65 and Table 68 list the publications included in the review of economic evaluations.

Table 68 Economic evaluations of lung transplantation

Published economic models assessing lung transplantation	
Study	**Reference**
Al et al. 1998	Al MJ, Koopmanschap MA, van Enckevort PJ, Geertsma A, van der Bij W, de Boer WJ, et al. Cost-effectiveness of lung transplantation in The Netherlands: a scenario analysis. Chest. 1998; 113:124-30
Ramsey et al. 1995	Ramsey SD, Patrick DL, Albert RK, Larson EB,Wood DE, Raghu G. The cost-effectiveness of lung transplantation: a pilot study. University of Washington Medical Center Lung Transplant Study Group. Chest. 1995;108: 1594-601
Sharples et al. 2000	Sharples LD, Taylor GJ, Karnon J, Caine N, Buxton M, McNeil K, Wallwork J. A model for analyzing the cost of the main clinical events after lung transplantation. J Heart Lung Transplant. 2001 Apr;20 (4):474-82.
Vasiliadis et al. 2005	Vasiliadis HM, Collet JP, Penrod JR, Ferraro P, Poirier C. A cost-effectiveness and cost-utility study of lung transplantation, J Heart Lung Transplant. 2005 Sep;24(9):1275-83.
Anyanwu et al. 2000	Anyanwu AC, Rogers CA, Murday J. Where are we today with pulmonary transplantation? Current results from a national cohort. UK Cardiothoracic Transplant Audit Steering Group. Transpl Int. 2000;13 Suppl 1:S245-6
Groen, et al. 2004	Groen, H., 2004. Cost-Effectiveness of Lung Transplantation in Relation to Type of End-Stage Pulmonary Disease. American Journal of Transplantation, 4(7), pp. 1155-62.
Other studies	
Paraskeva et al. 2018	Paraskeva, M. et al. Lung transplantation in Australia, 1986-2018: more than 30 years in the making. MJA, 2018, Narrative Review (10) 4 June 2018

Al et al. 1998

Al et al. (1998) developed a microsimulation model based on Dutch lung transplantation data from 1990 to 1995 to estimate QoL and costs with and without transplantation. The data set included 425 patients referred for lung transplantation, 57 of whom underwent transplantation. The model estimated survival with and without transplantation using a Weibull parametric model.

Health-related QoL was elicited using a self-administered questionnaire. It contained domains covering wellbeing, depression, anxiety and daily activities, along with EuroQol and Nottingham health profile generic instruments. Patients completed the questionnaire at outpatient screening phase, then every three months. Following transplantation, QoL was measured at one, four, and seven months, then every six months.

QALY were calculated from the EuroQol responses. Average patient utility on the waiting list varied from 0.55 at six months or less, to 0.4 for more than 15 months. Utility of 0.52 at screening, declined

the longer that patients awaited transplantation. Utility increased after transplantation from 0.53 at one to three months post-transplant, to 0.9 by 25 months or more. For the baseline scenario, the costs per life-year gained are G194,000 (G = Netherlands guilders) and the costs per QALY gained are G167,000.

Ramsey et al. 1995

Ramsey and colleagues undertook a cost-effectiveness analysis of lung transplantation among 25 patients in a pilot study in the USA. Inpatient and outpatient costs were identified from the hospital billing service and home health agencies. QALY scores were computed using utility scores obtained through SG interviews. The post-transplant mean utility score of 0.8 was significantly higher than the mean waiting-list score of 0.68. Survival data was sourced from an international lung transplant registry and from studies of patients on lung transplant waiting lists (Deng et al. 2009). Transplantation cost was US$164,989, with follow-on post-transplant monthly costs of US$11,917. Life expectancy was not significantly increased for lung transplant patients 5.89 years compared to waiting-list patients 5.32 years, although quality-adjusted life expectancy did improve. The incremental cost per QALY gained for post-transplant compared with waiting-list patients was US$176,817.

Sharples et al. 2000

A Markov model was developed using a retrospective analysis of 359 patients in the UK to estimate post-transplant complications patient costs. BOS was found to be a key cost driver. Acute events such as rejection and CMV infections also influenced cost. At the end of five years, 52.1% of the lung transplant recipients had died.

Vasiliadis et al. 2005

Lung transplantation cost-effectiveness analysis was undertaken using 124 patients in Quebec between 1997 and 2001. Survival was presented in mean life-years and utility was assessed by the standard gamble approach (Von Neumann 1944) across 34 candidates and 71 recipients. During the interview, the standard gamble was supplemented with the use of a probability wheel (Torrance 1976). The average utility assigned to the post-transplant period was calculated yearly up to year four and an average score applied for beyond four years. For 37 patients, the annual mean difference utilities were 0.63, 0.7, 0.48, 0.77 and 0.45. The waiting list average utility was 0.17. Forty of the transplants were single and 36 double. The mean life years and QALYs gained were 0.57 and 0.62, respectively. The cost per patient without transplantation was US$1,102 per month. The cost of the transplant was US$31,815, with a four years average post-transplant cost per month around US$1,156 (range from US$626 to US$1,809).

Anyanwu et al. 2000

This UK economic analysis included data from seven transplantation units, and survival data from 677 lung transplants, which is higher than some of the earlier cited studies. Data from the national UK Cardiothoracic Transplant Audit database (Anyanwu et al. 2000) was used to compute survivals. Four-year national survival data were extrapolated to 15 years by using parametric modelling. Survival gain in this study (from 2.0 to 2.5 years for 15 years) was less than that found in the Dutch study (Van Enckovert et al. 1998), which yielded a gain of 4.4 years.

Health utility and health-related quality of life (HRQoL) were measured using the EQ-5D questionnaire (Anyanwu et al. 2001). The survey was undertaken across 87 patients waiting for lung transplantation and on 255 transplant recipients. These utilities were described earlier. The average costs were $176,640, $180,528, and $178,387 for single-lung, double-lung, and heart-lung transplantation. The ICERS were $48,241 for single-lung, $32,803 for double-lung, and $29,285 per QALY gained for heart-lung transplantation.

Across a 15-year period, lung transplantation yielded mean benefits (relative to medical treatment) of 2.1, 3.3 and 3.6 QALY for single-lung, double-lung and heart-lung transplantation, respectively. During the same period, the mean cost of medical treatment was estimated at $73,564, compared with $176,640 for single-lung, $180,528 for double-lung, and $178,387 for heart-lung transplantation. The costs per QALY gained were $48,241 for single-lung, $32,803 for double-lung, and $29,285 for heart-lung transplantation.

Groen et al. 2004

A microsimulation model was developed using performance data from the lung transplantation program in the Netherlands. There was variation in ICERs between interventions. The variations were driven by differences in survival and in quality of life. ICERS varied from 77 to 90 at a 5% discount rate. The authors concluded "as a result of relatively small numbers of patients, the confidence intervals of survival estimates for some diagnoses are rather wide. Despite this limitation in the source data, closely fitting survival functions could be constructed for all diagnoses "(ibid, p. 1161).

Paraskeva et al. 2018

Paraskeva and colleagues reviewed lung transplant waiting times and survival in Australia in early 2018. They noted that lung transplantation remains limited by donor supply, with 15%-20% of lung transplant candidates dying while on a waitlist. Age-related eligibility was highlighted as a consideration, with candidates of more than 65 years being considered with minimal comorbidities. Most lung transplants in Australia are bilateral, with 203 conducted in 2016 (Australia and New Zealand Cardiothoracic Organ Transplant Registry. 2016) Survival of bilateral lung transplant recipients at one, three and five years has been estimated at 90%, 74% and 68%, respectively, which are higher than international survival rates of 82%, 69% and 59% (Chambers et al. 2017). Given that Australian survival is higher; a sensitivity analysis is included with lower rate of mortality following a

lung transplant. Given that only a small proportion of patients receive transplantation, this sensitivity analysis has a limited impact on the estimated ICER.

Summary

Only a limited number of economics studies relating to AT cost-effectiveness were identified. Two (Hay & Robin 1991, Alkins & O'Malley 2000) related resource use to expected life gain using USA registry data. High incremental expected survival of more than seven years in non-smokers resulted in AT appearing relatively cost-effective. Gildea and colleagues developed a model where health states were stratified by COPD severity using FEV_1-defined ranges. This approach is also adopted in COPD modelling more broadly. The RAPID trial was powered to detect changes in CT-scanned lung density. Correspondingly, the patient-level data and model developed by s47G defined health states by FEV_1 predicted and CT lung density decline tracks. This approach is followed in this assessment. A number of economic models have also been developed to assess the economic attractiveness and costs of lung transplantation. The two major studies are from the UK and the Netherlands. Given that the UK study had larger patient numbers, assumptions for this assessment are drawn from that study.

D.3.2. STRUCTURE OF THE ECONOMIC EVALUATION

A cost-utility model based on the decision tree in s47G was developed to estimate the expected costs and QALYs associated with AT compared to BSC. The Markov model was developed using Microsoft Excel 2010 and is included as an attachment to this assessment. There are eight health states in the model, which are defined using FEV_1 and CT-scan lung density decline. The $FEV_1 \geq 50\%$ and $FEV_1 < 50\%$ states were stratified by lung density decline, categorised as no lung density decline (<0 g/l/year), slow lung density decline (0-2 g/l/year) and rapid lung density decline health state (>2 g/l/year).

s45, s47(1)(b) [redacted]

1. $FEV_1 \geq 50\%$ predicted, no lung density decline
2. $FEV_1 \geq 50\%$ predicted, slow lung density decline
3. $FEV_1 \geq 50\%$ predicted, rapid lung density decline
4. $FEV_1 < 50\%$ predicted, no lung density decline
5. $FEV_1 < 50\%$ predicted, slow lung density decline
6. $FEV_1 < 50\%$ predicted, rapid lung density decline
7. Lung transplant
8. Dead

The additional two states of lung transplant and death are also included in the model structure. Patients were only eligible for lung transplantation at the later stages of disease progression, defined as $FEV_1 < 50\%$ predicted and either slow or rapid decline in lung density. s45, s47(1)(b) [redacted]

s45, s47(1)(b) [redacted]

The baseline distribution of patients was based on the BSC arm in the RAPID trial. A cohort of 1,000 patients was allocated to each of the states, and results of the economic evaluation were generated as cohort-expected value analysis for this population of 1,000. The model's baseline year was 2019. All future costs and health benefits are discounted back to this year using a rate of 5%, which is standard MSAC economic evaluation practice. Higher and lower discount rates are included in a sensitivity analysis at the conclusion of Section D.

D3.3 ASSUMPTIONS INCORPORATED INTO THE MODEL STRUCTURE

Assumptions incorporated into the economic evaluation (summarised in Table 62) relate to the model's perspective and type of economic evaluation, along with the sources of evidence, time horizon, and outcomes used to measure the intervention and comparator.

Type of economic evaluation

Given the claim of superiority, a cost-utility economic model has been developed. It is presented as a stepped analysis. The first step estimates costs and clinical benefits over the maximum follow-up period for which clinical outcomes have been reported, which is the four-year RAPID trial. As AATD is a chronic condition, AT therapy is likely to have longer term costs and benefits. The second step of the economic modelling approach extrapolates the period of analysis for a further 26 years. This corresponds with an overall time horizon of 30 years, which corresponds to life expectancy at 54 years in Australia. Incremental costs and clinical benefits (life years and QALYS) are estimated to calculate ICER.

Sources of evidence

The RAPID trial is the key source of clinical evidence, however, the population was limited and the trial was powered to report lung density decline rather than FEV_1. Patients in the model are assumed to transition between states characterised by FEV_1 and CT-scan defined lung density. A transition matrix from individual patients in the RAPID trial was provided by s47G [redacted]

Given that no significant change in FEV_1 was measured in RAPID, the proportions falling into each state in the small RAPID trial are uncertain at the population level. s45, s47(1)(b) [redacted]

Annual transition probabilities were defined for the AT and BSC arms. These parameters were estimated using results of the RAPID/RAPID OLE trials for the first four years for AT and for the first two years for BSC. Patients could move between any states as defined by the results of patient outcome reporting within the RAPID and RAPID-OLE period using patient-level data supplied by CSL Behring (2017). The rate of CT-scan density decline is a relative measure rather than an absolute definition of a state. It is likely to stabilise after four years of AT or BSC, therefore patients were assumed to remain on the same no decline, slow decline or fast decline tracks from year four until the end of the lifetime projection in the stepped analysis. Patients were assumed to progress from $FEV_1 \geq 50\%$ to $FEV_1 < 50\%$ based on average patient FEV_1 progression in the ADAPT UK registry for BSC, and an adjusted slower decline for AT patients using the meta-analysis of Chapman et al. (2009). Patients in the $FEV_1 < 50$ slow and rapid decline states transition to lung transplantation at a fixed proportion using UK transplantation rates.

To define longer-term survival, parametric models were fitted to patient data from the UK registry, grouped by FEV_1 and no, slow and rapid decline pathways. The annual probabilities of death for each health state after the four-year follow-up of the RAPID trial, were based on these models. The methods used to measure CT lung-density decline in the registry, were noted as being comparable to the methods used to measure CT lung density in the RAPID trial. Patients join the year of follow-up of the ADAPT UK registry best matched to cumulative survival on each arm at the end of the RAPID trial. Annual rates of mortality for each FEV_1/lung density decline state then follow the slope of the parametric model.

Patients transitioning from $FEV_1 > 50$, to $FEV_1 < 50$ at later years of follow-up are likely to have overstated annual mortality. This bias is likely to favour the intervention, however, the exact magnitude of the error is difficult to predict because survival data is not provided by age in the UK registry dataset. Given that only limited numbers of patients transition between FEV>50 and FEV<50 after maximum RAPID follow-up, the impact on ICER is likely to be limited. Sensitivity analysis is included at the end of Section D, demonstrating the robustness of the estimated ICER to parametric model selection. Given high rates of annual mortality for FEV<50/rapid decline, the type of model selected to extrapolate survival for this patient group has the largest impact on economic results.

Perspective

The economic analysis takes the perspective of the Australian health system. Health service costs are valued at 100% of fee value for MBS items. This perspective is taken by the Federal Government of Australia and the National Blood Authority (NBA). Budget impact analysis provided in Section E takes MBS, Pharmaceutical Benefits Advisory Committee (PBAC), state government and private payer perspectives.

Time horizon

The base case of the economic evaluation is generated by a trial-period follow-up period using the four-year RAPID trial. Due to the chronic nature of A1PI deficiency, an extrapolated time horizon (additional 26 years) was also included to reflect a patient lifetime. The age at baseline was 53.8 years, which aligns with the RAPID study (Chapman et al. 2015).

The model evaluated AT over 30 years to capture all possible differences in costs and outcomes (life year and QALY) between the modelled cohorts, given that the average life expectancy of Australian males and females is around 30 years for a 54-year-old. In the sensitivity analysis, the time horizon was varied to 20 years and 40 years. Given that the median survival time from diagnosis as a severe A1PI deficient patient treated with BSC is less than 10 years (Tanash et al. 2010), sensitivity analyses on time horizons at 30 years and 40 years have limited impact on the estimated ICER.

Outcomes

QoL, generally assessed by EQ-5D, is the main outcome of cost-utility analysis. Measures of QoL that could be transformed into utility were not reported in the RAPID study. CSL Behring (2017) presented EQ-5D values stratified by FEV_1% predicted from the UK ADAPT registry using data from 244 patients not receiving maintenance therapy (Ejiofor and Stockley, 2015). A weighted average of the utilities in patients with a FEV_1% <30, 30-35, 35-40, 40-45 and 45-50 was calculated to derive the utility for the FEV_1 <50% predicted group health state. The utility value for FEV_1 >50% was taken from the dataset. These values are used in this assessment. Lung transplant utility values were taken from the UK. Results reported by Groen et al. (2004) in The Netherlands and Anyanwu et al. (2001) in the UK indicate that utility increases substantially after transplantation. The data from Anyanwu et al. (2001) are used in the base case, as Groen et al. (2004) reported a smaller transplant patient population.

Methods used to generate results

The economic model used to generate the results is an expected value cohort analysis for 1,000 patients. A Markov model was developed, through which patients transition between each state based on annual transition probabilities. As indicated, these were defined for the first four years of AT using RAPID/RAPID OLE and for the first two years of BSC using RAPID. Patients are assumed to remain on the no, slow or rapid decline track for the extrapolated lifetime analysis. Patients move between FEV_1>50 and FEV_1<50 based on the average annual FEV_1 decline rate observed in the UK AATD registry. Transitions to mortality are defined by parametric survival models for each health state. A fixed fraction of FEV_1<50 slow and rapid decline patients are assumed to receive transplantation. The simulation began with the hypothetical cohort of 1,000 patients in one of the six FEV_1% predicted/density decline health states (according to the distribution of patients from the BSC arm of the RAPID trial), and ran for four years (trial) or 30 years (lifetime). The evaluation then compares the expected costs and clinical outcomes (life years, QALYs) between the treatment options.

Health states

The model includes eight states based on FEV and CT scan-measured lung density decline (presented in Table 69). Death is a state from which patients could not transition, and lung transplant patients could only transition to death. Patients could not transition between the no decline, slow decline and rapid decline health states after four years, but they could progress from $FEV_1 \geq 50\%$ to $FEV_1 < 50\%$ based on a background rate of decline for BSC and adjusted slower progression for AT.

Table 69 Economic model health states

Health state	Description	Possible transitions to other health states
$FEV_1 \geq 50\%$ predicted, no lung density decline	No lung density decline is defined as <0 g/l/year, slow lung density decline as 0-2 g/l/year and rapid lung density decline as >2 g/l/year	Patients could not transition between the no decline, slow decline, but rapid decline health states after 4 years and could simultaneously progress from FEV1≥50% to FEV1<50%. Parametric models are used to extrapolate annual mortality after 4 years. RAPID trial data is used in the trial period.
$FEV_1 \geq 50\%$ predicted, slow lung density decline		
$FEV_1 \geq 50\%$ predicted, rapid lung density decline		
$FEV_1 < 50\%$ predicted, no lung density decline		
$FEV_1 < 50\%$ predicted, slow lung density decline		
$FEV_1 < 50\%$ predicted, rapid lung density decline		
Lung transplant	A fraction of $FEV_1 < 50\%$ predicted, rapid and slow lung density decline transition to this state.	Lung transplant, Death
Death	The proportion of the cohort that die from any cause, even those that are unrelated to morbidity, transition into this health state. No costs or benefits are accrued in this health state.	None (this is an absorbing health state)

Abbreviations: FEV_1 = Forced expired volume in 1 second.

Cycle length

The economic model employs a cycle length of one year. This step was chosen as s47G provided AT and BSC patient-transition data on an annual basis, along with parametric model for survival derived from the UK registry.

Discount rate

Costs and clinical benefits (difference in QALYs between AT and BSC) are discounted at 5% per annum. The impact of discounting is explored in sensitivity analyses. A half-cycle correction is applied.

Comparator

The main comparator for AT is BSC, described as a range of interventions including pharmacological (e.g. bronchodilators, systemic corticosteroids), non-pharmacological (e.g. oxygen therapy) and preventative measures such as vaccinations.

D.4. INPUTS TO THE ECONOMIC EVALUATION

The following sections summarise the clinical and economic input parameters included in the economic evaluation.

D.4.1. CLINICAL INPUT PARAMETERS

Baseline patient demographics

Table 70 summarises baseline patient characteristics of the modelled patient population. Age affects the modelling time frame, given that a patient with a base age of 54 has a life expectancy of 30 years. This variable does not affect the treatment effectiveness or natural history of the disease in the model. The distribution among health states at commencement was taken from the patient profile in the RAPID trial.

Table 70 Baseline patient and disease characteristics of the modelled patient cohort

Parameter	Input	Source
Age of population at baseline	53 years	RAPID
FEV_1 and lung sensitivity decline state at baseline		
FEV_1>50 no decline (%)	7%	RAPID
FEV_1>50 slow decline (%)	13%	RAPID
FEV_1>50 rapid decline (%)	20%	RAPID
FEV_1<50 no decline (%)	8%	RAPID
FEV_1<50 slow decline (%)	34%	RAPID
FEV_1<50 rapid decline (%)	18%	RAPID

Abbreviations: FEV_1 = Forced expired volume in 1 second.

As described in Section D.2 above, the model is built to perform a Markov process, so patient transition into different states over the course of the model projection period. There were only eight Australian patients the RAPID multicentre global trial, so there is uncertainty about the proportions of Australian populations allocated to each health state. These proportions are varied in a sensitivity analysis, with all patients being assumed to commence as FEV_1>50, and all FEV_1<50 equally distributed among lung density decline groups. Changing the baseline patient distribution only has a small impact on the estimated ICER.

Transition probabilities – effectiveness of AT and BSC as captured in the model

Transition probabilities are derived from RAPID IPD, provided by CSL Behring (2017). Patients move between FEV_1<50 and >50 CT-scan lung density decline states according to that observed over four

years for AT (RAPID and RAPID OLE), and two years for BSC (RAPID). Annual probabilities are provided in Table 71. A constant proportion of FEV_1<50 slow and rapid CT-scan lung decline patients are assumed to receive lung transplantation.

s47(1)(b)

After four years, patients can only transition between FEV_1>50 and FEV_1<50 states that match their no decline, slow decline and rapid decline pathway. Patients cannot revert back to FEV_1>50, once they have transitioned to FEV_1<50. The baseline rate of FEV_1 decline was derived from the UK registry and was assumed to be the same for all FEV_1>50 states.

s45, s47(1)(b)

Table 72 Health state transition probabilities – Years >4 years

	FEV_1>50 no decline	FEV_1>50 slow decline	FEV_1>50 rapid decline	FEV_1<50 no decline	FEV_1<50 slow decline	FEV_1<50 rapid decline
BSC						
s45, s47(1)(b)						
AT						
s45, s47(1)(b)						

Abbreviations: **AT** = augmentation therapy, **BSC** = best supportive care, **FEV_1** = Forced expired volume in 1 second.

Trial mortality

Annual mortality probabilities are trial mortalities taken from four years of RAPID/RAPID OLE for AT, and two years for BSC from RAPID - s47G Death is assumed to be the same for all patients in each arm of the model regardless of health state. Annual rates are provided in Table 73.

Table 73 Health state dispositions at month 24 and month 30 and associated transition probabilities – patients with severe depression at baseline

	Annual probability of death		Cumulative survival	
	AT	BSC	AT	BSC
Year 1	1.08%	2.30%	98.92%	97.70%
Year 2	0.00%	1.18%	98.92%	96.55%
Year 3	0.71%		98.22%	
Year 4	0.00%		98.22%	

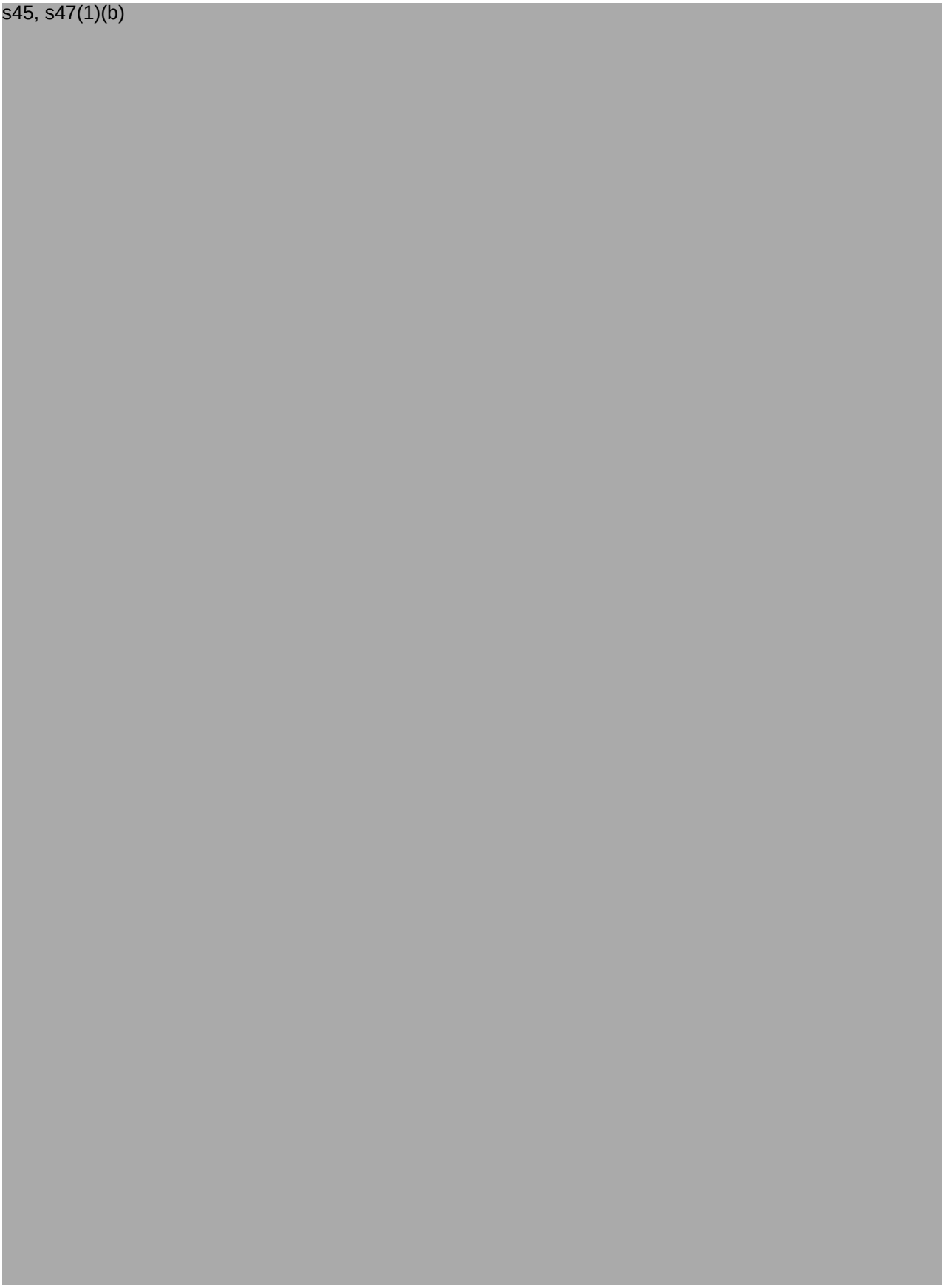
Abbreviations: **AT** = augmentation therapy, **BSC** = best supportive care, **FEV_1** = Forced expired volume in 1 second.

Extrapolation of mortality after the trial period

As outlined in Section C, a series of parametric survival models provided by s47G are used to model survival (Figures 21, 22 & 23). Results of the extrapolations are presented as a series of Markov traces for the AT and BSC arms, along with a trace showing the difference in patient numbers by state as a result of AT delivery. For both AT and BSC it is evident that large numbers of patients transition out of FEV_1>50 rapid decline and FEV_1<50 slow decline in the early years of the model projection. The key difference between AT and BSC, is that larger numbers of patients are retained in the FEV_1<50 slow decline state compared to the FEV_1<50 rapid decline state, as a result

of AT. The effective annual rate of death across the AT arm is less than that of BSC, resulting in an increase of three life years for an average patient.

s45, s47(1)(b)



s45, s47(1)(b)

D.4.2. ECONOMIC INPUT PARAMETERS

AT is expected to change resource use in the healthcare system due to cost of the product and change in costs associated with ongoing disease management (Table 74).

Cost of Intervention

AT product and delivery services

AT delivery involves costs of the product and medical services. These costs are provided in Table 74.

Table 74 Resources associated with AT and disease management costs by COPD severity

MBS Item	Provider of resource	Price per unit of resource (AU$)	Number of vials or services per year	Proportion availing service / product (%)	Total annual cost (AU$)	Source
AT product cost and delivery						
s45, s47(1)(b)						Based on 60mg/kg, 1,000ml vial, adherence 94% and weight 76 kg
Costs of infusion	MBS	65.05	52.00	1.00	3,382.60	MBS item, 13915
Subtotal					s45, s47(1)(b)	

Mild-Moderate COPD >FEV_1 50						
GP consultations	General Practioner	37.60	2.33	1.00	87.61	MBS item 23, Level B using Thomas et al. 2014
Hospital Services	Hospital	7,017.54	1.00	0.04	280.70	Weighted Average costs for DRG items E65A/E65B, using Thomas et al. 2014 for frequency
Subtotal					**368.31**	
Severe COPD						
GP consultations	General Practioner	37.60	3.33	1.00	125.21	MBS item 23, Level B using Thomas et al. 2014
Hospital Services	Hospital	7,017.54	1.00	0.10	701.75	Weighted Average costs for DRG items E65A/E65B, using Thomas et al. 2014 for frequency
Subtotal					**826.96**	
Very Severe COPD						
GP consultations	General Practioner	37.60	3.67	1.00	137.99	MBS item 23, Level B using Thomas et al. 2014
Hospital Services	Hospital	7,017.54	1.00	0.16	1,122.81	Weighted Average costs for DRG items E65A/E65B, using Thomas et al. 2014 for frequency
Subtotal					**1,260.80**	
Weighted Severe COPD (FEV_1<50)				**74%**	**939.76**	Thomas et al. 2014 - assuming 74% of patients had severe COPD and 26% had very severe COPD
Lung transplant costs						
Lung transplant first year	Hospital and MBS	122,332.97	1.00	1.00	153,159.28	AR-DRG A03Z, NHCDC round 18 adjusted by AIHW health price index.
Lung transplant follow-up years	Hospital and MBS	13,837.00	1.00	1.00	14,542.69	Anyanwu 2002 - adjusted by AIHW health price index

Abbreviations: **AIHW** = Australian Institute of Health and Welfare, **AR-DRG** = Australian Refined Diagnosis Related Groups, **AT** = augmentation therapy, **COPD** = chronic obstructive pulmonary disease, **DRG** = diagnosis related groups, **FEV_1** = forced expiratory volume in 1 second, **GP** = general practitioner, **MBS** = Medicare benefits schedule.

COPD Medical Services Costs

The costs of COPD medical services for disease management are taken from the frequencies of GP and hospitalisations by COPD severity stage reported in a UK survey by Thomas et al. (2014). They are indexed to 2018 using the AIHW health price index.[9]

[9] The AIHW price index is reported until 2016 (in July 2018). The value in this year of 1.7 is also used for 2017 and 2018

Utility values

The derivation of utilities was outlined in Section C using UK registry data (Ejiofor & Stockley 2015) provided by CSL Behring (2017). UK registry values are included in the economic model (Table 75).

s45, s47(1)(b)

Of note, the trial-estimated utilities for follow-up lung transplant appear to be higher than those reported from the Australian population. For example, event-free values of 0.80 for 75+ years were found as part of the Queensland 2011 Self-Reported Health Status survey (Clemens et al. 2014), and a value of 0.70 for 71+ years in the short form 6D (SF-6D) as part of the Household, Income and Labour Dynamics in Australia (HILDA) survey (Norman et al. 2013). Given these uncertainties they are subjected to a range of sensitivity analyses presented at the end of Section D.

D.5. Results of the Economic Evaluation

D.5.1. Health Care Costs by Resource Type

The costs per patient for AT and BSC for the trial period analysis and the stepped lifetime horizon are presented in Table 76. Costs presented are averages generated by the model. It is evident that the cost of the AT product and its delivery are the dominant costs for AT, and resources associated with COPD management are minor. Lung transplant costs are small compared to AT product and delivery costs. Costs are greater for the AT arm as AT patients have higher survival than do BSC patients.

Table 76 Health care costs by resource type for base-case analysis (1,000-person cohort)

	AT (AU$)	BSC (AU$)	Incremental Cost (AU$)	% Total Incremental Cost
Trial period	**Undiscounted**	**Undiscounted**	**Undiscounted**	**Undiscounted**
s45, s47(1)(b)				
Mild-Moderate COPD >FEV_1 50	635,831	580,570	55,260	0%
Severe COPD <FEV_1 50	2,747,065	2,635,731	111,334	0%
Lung transplant	17,480,957	17,430,173	50,784	0%
Total	s45, s47(1)(b)			

	AT (AU$)	BSC (AU$)	Incremental Cost (AU$)	% Total Incremental Cost
Lifetime	**Undiscounted**	**Undiscounted**	**Undiscounted**	**Undiscounted**
s45, s47(1)(b)				
Mild-Moderate COPD >FEV_1 50	1,227,205	881,163	346,042	0%
Severe COPD <FEV_1 50	5,460,430	4,013,603	1,446,827	0%
Lung transplant	61,086,623	46,950,532	14,136,091	1%
s45, s47(1)(b)				

Abbreviations: **AT** = augmentation therapy, **BSC** = best supportive care, **COPD** = Chronic Obstructive Pulmonary Disease, **FEV_1** = Forced expired volume in 1 second.

D.5.2. HEALTH OUTCOMES PER PATIENT BY STEP AND BY HEALTH STATE

Table 77 presents the average outcomes (per patient) generated by the economic model for LY or QALY in the trial follow-up period. It is evident that most incremental LYs and QALYs accrue to the FEV<50 slow decline state for AT.

Table 77 Average patient health outcomes by health state and by outcome measure for trial analysis

	AT	BSC	Incremental	% Total Incremental
Trial period				
# LYGs	**Undiscounted**	**Undiscounted**	**Undiscounted**	**Undiscounted**
FEV_1>50 no decline	0.1	0.0	0.1	33%
FEV_1>50 slow decline	1.3	1.2	0.1	48%
FEV_1>50 rapid decline	0.3	0.4	-0.1	-27%
FEV_1<50 no decline	0.3	0.1	0.2	62%
FEV_1<50 slow decline	2.1	1.3	0.8	299%
FEV_1<50 rapid decline	0.5	1.4	-0.9	-313%
Lung transplant - first year	0.1	0.1	0.0	0%
Lung transplant - following years	0.2	0.2	0.0	0%
Total	**4.9**	**4.6**	**0.3**	**100%**
# QALYs	**Undiscounted**	**Undiscounted**	**Undiscounted**	**Undiscounted**
FEV_1>50 no decline	0.1	0.0	0.1	37%
FEV_1>50 slow decline	1.0	0.9	0.1	54%
FEV_1>50 rapid decline	0.2	0.3	-0.1	-31%
FEV_1<50 no decline	0.2	0.0	0.1	52%
FEV_1<50 slow decline	1.3	0.8	0.5	254%
FEV_1<50 rapid decline	0.3	0.8	-0.5	-266%
Lung transplant - first year	0.1	0.1	0.0	0%
Lung transplant - following years	0.1	0.1	0.0	0%
Total	**3.3**	**3.1**	**0.2**	**100%**

Abbreviations: **AT** = augmentation therapy, **BSC** = best supportive care, **FEV_1** = Forced expired volume in 1 second, **LYGs** = life years gained, **QALY** = quality-adjusted life year.

Table 78 presents the average outcomes (per patient) generated by the economic model for LY or QALY in the lifetime period. Again, it is evident that most incremental LYs and QALYs accrue to the FEV<50 slow decline state for AT.

Table 78 Health outcomes by health state and by outcome measure for lifetime analysis (Per patient)

Lifetime	AT	BSC	Incremental	% Total Incremental
# LYGs	**Undiscounted**	**Undiscounted**	**Undiscounted**	**Undiscounted**
FEV_1>50 no decline	0.2	0.0	0.2	6%
FEV_1>50 slow decline	2.6	1.8	0.8	27%
FEV_1>50 rapid decline	0.5	0.5	0.0	-1%
FEV_1<50 no decline	0.5	0.1	0.4	14%
FEV_1<50 slow decline	4.4	2.0	2.3	79%
FEV_1<50 rapid decline	0.9	2.2	-1.2	-41%
Lung transplant - first year	0.2	0.2	0.0	2%
Lung transplant - following years	2.0	1.5	0.4	15%
Total	**11.3**	**8.4**	**3.0**	**100%**
# QALYs	**Undiscounted**	**Undiscounted**	**Undiscounted**	**Undiscounted**
FEV_1>50 no decline	0.2	0.0	0.1	7%
FEV_1>50 slow decline	2.1	1.4	0.6	31%
FEV_1>50 rapid decline	0.4	0.4	0.0	-1%
FEV_1<50 no decline	0.3	0.1	0.2	12%
FEV_1<50 slow decline	2.6	1.2	1.4	68%
FEV_1<50 rapid decline	0.6	1.3	-0.7	-36%
Lung transplant - first year	0.2	0.1	0.0	2%
Lung transplant - following years	1.5	1.2	0.3	17%
Total	**7.8**	**5.7**	**2.0**	**100%**

Abbreviations: **AT** = augmentation therapy, **BSC** = best supportive care, **FEV_1** = Forced expired volume in 1 second, **LYGs** = life years gained, **QALY** = quality-adjusted life year.

D.5.3. Incremental Costs and Effectiveness

The incremental cost and the incremental effectiveness of AT for an average patient are presented in Table 79 for the 1000-person cohort. The ICER is presented as the incremental cost of achieving an additional QALY. It is evident that the life time ICER is s47(1)(b) per QALY and for the trial period is s47(1)(b) .

Table 79 Incremental Cost Effectiveness Ratio (1,000-patient cohort)

	Cost (AU$)	Incremental cost (AU$)	Effectiveness (QALYs)	Incremental effectiveness	ICER
Trial period					
A1PI Augmentation Therapy	s45, s47(1)(b)				
Best Supportive Care	18,531,803		2,822.6		
Lifetime					
A1PI Augmentation Therapy	s45, s47(1)(b)				
Best Supportive Care	37,389,939		4,525.4		

Abbreviations: **A1PI** = Aplha-1 proteinase inhibitor; **ICER** = incremental cost-effectiveness ratio; **QALY** = quality-adjusted life year.

D.6. SENSITIVITY ANALYSES

A trial period (4 years) and lifetime extrapolation (30 years) are included in the economic analysis. Only limited incremental clinical benefits accrue during the trial period, as patients transition to health states during this period. Mortality differences become more evident between the AT and BSC arms over the following five to 20 years of the lifetime projection. Thus, the ICER for the trial period is far greater (i.e. less cost effective) than that of the lifetime projection. Sensitivity analyses are presented for the lifetime analysis using the following univariate changes and scenario analyses (Table 80):

- The average age of entry in the baseline is 53 years (based on RAPID trial participants). A lifetime projection of 30 years is used in the economic model, based on average life expectancy for males and females in Australia. This is decreased to 20 years and increased to 40 years to gauge model results over two lengths of maximum follow-up. It is evident that the ICER is relatively insensitive to this assumption, as most mortality occurs within the first 20 years of the modelling projection.

- The baseline distribution of patients across FEV_1 and CT lung-density decline states was based on the RAPID trial. It is assumed that FEV_1>50 no decline accounts for 7% of the starting patient population, FEV_1>50 slow decline 13%, FEV_1>50 rapid decline 20%, FEV_1<50 no decline 8%, FEV_1<50 slow decline 34%, and FEV_1<50 rapid decline 18%. The RAPID trial was conducted across multiple countries with only eight patients recruited in Australia. There is considerable uncertainty about the characteristics of patients who would be recruited, as limited public data is available about this population in relation to FEV_1 and CT lung-density decline status. Two sensitivity analyses are undertaken. The first, where all patients are assumed to be FEV_1>50 and equally distributed among CT lung-density no decline, slow and rapid decline; and the second, with all patients FEV_1<50 and equally distributed among CT lung-density no decline, slow and rapid decline. It is evident that baseline characteristics only have limited impact on the ICER as patients transition into FEV_1<50 within a few years.

- An average weight of 75.9kg is used in the model (based on RAPID trial participants). This weight is in line with average adult weights in Australia as reported by ABS and a range of other cited trials. Weight is varied to assess ICER impact. The lower bound weight of 68 kg is not sufficient to change the number of vials needed per week, as part-vials are rounded to a whole number (i.e. five vials based on 60mg dosing). The upper weight of 83kg results in six vials required per week. This has a large impact on the estimated ICER as the cost of the AT product is the key driver of the model.

- Lung transplant probability (4.17%) and probability of death resulting from lung transplant (8.53%) are derived from UK data for the base model. Only patients with FEV_1<50 and in slow and rapid decline tracks are assumed to be eligible for lung transplantation. Changes

in these variables have a limited impact on the estimated ICER, as only a small proportion of patients from severe states are assumed to receive a transplant.

- A base discount rate of 5% was used. Higher rates of 7.5% and lower rates of 2.5% are also included. Changes in discount rate have an impact because much of the clinical benefit occurs between years five and 20 of the model projection, where discounting has a large effect on present value. The stepped analysis shows that only a small proportion of avoided mortality and morbidity accrues within the trial period. For example, only 9% of incremental life years gained occur in the four-year trial period, and a similar percentage is estimated for QALYs.

- The rate of FEV_1 decline between BSC and AT patients differed in the meta-analysis conducted by Chapman et al. (2015). FEV_1 decline was estimated to reduce by 26% as a result of AT usage, and this assumption is employed in the model. The base model assumes that patients transition to no, slow and rapid decline pathways during the trial period, then follow these tracks over a lifetime. This assumption is changed in the sensitivity scenario "transitions within RAPID continue for lifetime". This scenario allows patients to keep transitioning between states for 30 years as they did in the four-year RAPID trial period. The estimated ICER from allowing lifetime transition between decline states does not vary substantially because most patients have moved to severe states within the four years of the trial period, then follow defined survival curves for each health state.

- Annual patient mortality is taken from the AT and BSC arms of the RAPID trial and applied to all BSC and AT health states across the four years of AT follow-up and two years of BSC follow-up. After this period, mortality is estimated using parametric models fitted to UK registry data for non-lung transplant FEV_1/CT density decline states. Under the base modelling assumption, patients hinge to the UK survival curves based on year of best match, rather than year of follow-up. As age is not specified in the survival data, the relative risk of mortality by age and disease state is uncertain. If annual patient mortality by year from the UK registry is applied to the AT and BSC arms following the respective years of maximum follow-up (rather than hinging to year of best fit), then the estimated ICER changes considerably. The ICER becomes less cost-effective.

- UK survival data is extrapolated using a range of parametric models fitted using clinical plausibility and AIC criteria provided by CSL Behring (2017). In most cases the Gompertz model is the best fit, hence this model is used across all non-transplant states. The model is varied in sensitivity analyses, which included use of the Log-logistic, Lognormal, Weibull, Exponential and Generalised Gamma specifications. For the FEV_1 >50 and FEV_1 <50 slow decline states, changes in the model lead to an increase in the estimated ICER. The opposite occurred for FEV_1 <50 no decline and FEV_1 <50 rapid decline states. The choice of

model for the FEV_1<50 rapid decline state had the largest impact on the estimated ICER. The use of Lognormal, Generalised Gamma and Weibull models results in the ICER being 10% more cost-effective, while use of the Exponential model resulted in a 10% decrease in cost-effectiveness. Large numbers of patients transition to this state during the trial period, particularly on the BSC arm. Assumptions about annual mortality correspondingly have a large impact on the estimated ICER.

- s47(1)(b) . Changes in the number of vials used or product price is the key driver of cost effectiveness. The base cost of AT assumes a price per 1,000 ml s47(1)(b) This varies from a low value of s47(1)(b) per 1,000ml vial to a high value of s47(1)(b) per 1,000ml vial. The estimated ICER varies considerably between s47(1)(b) and s47(1)(b) . The MBS cost of AT delivery is also varied by 20% from the base cost per infusion of s47(1)(b) This has limited impact on cost-effectiveness results.

- In many reviewed COPD economic models, disease management costs were an aggregate of maintenance and acute care costs during flare ups. The frequency of flare ups was not explicitly modelled in this assessment. RAPID trial results showed a non-significant difference between these occurrences on the BSC and AT arms. As in the s47G model, Thomas and colleague's (2014) collation of COPD costs by GOLD stages was used to estimate disease management costs for health states in the economic model. The Thomas et al. (2014) analysis included acute care proportions for each state. Proportion hospitalised for mild COPD was 4%, for severe COPD 10%, and for very severe COPD 16%. These proportions are uncertain for AT. They are varied by 20% for each COPD state. This variation has limited impact as economic results are governed by AT product costs. The proportion of severe COPD patients who are very severe, assumed to be 74% in the base case, is also varied. Similarly, this scenario had limited impact on the estimated ICER.

- The base cost for lung transplant is estimated to be $153,159, using Australian AR-DRG costs weighted by separations. There is uncertainty about how much this procedure may cost and it is varied in a univariate change of 20%. Given the small number of patients who receive transplantation in the model, and the cost of the procedure relative to AT product costs, this variation has limited impact. Lung transplant follow-up costs of $14,543 per year are also varied by the same magnitude and ICER results do not change significantly.

- Utilities are specified for the patient group over FEV_1 >50 (0.79) and FEV_1 <50 (0.59). There is uncertainty around these estimates, as no account for lung-decline status is included. A sensitivity analysis is included where these values are changed by 5%. It is evident that the ICER does not vary considerably. This is largely because much of the LY and QALY benefits are derived from an increase in the years of life lived. Lung transplant first year and

following year utilities are also varied. Given the small relative patient number, this scenario has a limited impact on the estimated ICER.

Table 80 Sensitivity analysis for lifetime analysis

Parameter	Analysis	Incremental cost	Incremental effect	ICER
Base Case		s47(1)(b)	**1,301**	s47(1)(b)
Background assumptions				
Years of follow-up (30 years)	20		1,274	
	40		1,308	
RAPID baseline distribution by FEV_1	All FEV_1>50		1,511	
	All FEV_1<50		1,182	
Average weight (75.9kg)	68		1,301	
	83		1,301	
Discount rate (5%)	7.5%		1,065	
	2.5%		1,613	
Lung transplant probability (4.17%)	2.1%		1,305	
	6.3%		1,287	
Probability of death - lung transplant (8.53%)	4.3%		1,369	
	12.8%		1,255	
Parameter	**Analysis**	**Incremental cost**	**Incremental effect**	**ICER**
A1PI Augmentation Therapy delivery costs				
s47(1)(b)	s47(1)(b)		1,301	s47(1)(b)
			1,301	
Cost per infusion ($65)			1,301	
			1,301	
Disease management costs				
Mild COPD proportion hospitalised (4%)	3.2%	s47(1)(b)	1,301	s47(1)(b)
	4.8%		1,301	
Severe COPD proportion hospitalised (10%)	8.0%		1,301	
	12.0%		1,301	
Very severe COPD proportion hospitalised (16%)	12.8%		1,301	
	19.2%		1,301	
Proportion of severe COPD patients very severe (74%)	59.2%		1,301	
	88.8%		1,301	
Lung transplant costs ($153,159)	$122,527		1,301	
	$183,791		1,301	
Lung transplant follow-up costs ($14,543)	$11,634		1,301	
	$17,451		1,301	
Effects				
FEV_1 >50 survival model (Gompertz)	Log-logistic		1,281	
	Lognormal		1,292	

	Weibull	s47(1)(b)		1,283	s47(1)(b)
	Exponential			1,308	
	Generalised Gamma			1,287	
FEV_1 <50 no decline survival model (Gompertz)	Log-logistic			1,330	
	Lognormal			1,327	
	Weibull			1,310	
	Exponential			1,417	
	Generalised Gamma			1,326	
FEV_1 <50 slow decline survival model (Gompertz)	Log-logistic			1,224	
	Lognormal			1,190	
	Weibull			1,211	
	Exponential			1,236	
	Generalised Gamma			1,191	
FEV_1 <50 rapid decline survival model (Gompertz)	Log-logistic			1,411	
	Lognormal			1,462	
	Weibull			1,452	
	Exponential			1,177	
	Generalised Gamma			1,468	
Survival model hinged to last year of rapid through best fit	Year of maximum follow-up of each arm			480	
Patients follow same lung density decline after 4 years	Transitions within RAPID continue for lifetime			1,290	
Utilities					
FEV_1 >50 (0.79)	0.83			1,326	
	0.75			1,276	
FEV_1 <50 (0.59)	0.62			1,332	
	0.56			1,271	
Lung transplant – first year (0.74)	0.78			1,302	
	0.70			1,300	
Lung transplant - following year (0.77)	0.81			1,309	
	0.73			1,293	

Abbreviations: **A1PI** = alpha-1 proteinase inhibitor; **AT** = augmentation therapy, **COPD** = chronic obstructive pulmonary disease; **FEV_1** = forced expiratory volume in 1 second; **ICER** = incremental cost-effectiveness ratio; **QALY** = quality-adjusted life year.

Key results from the sensitivity analysis are summarised in Table 81.

Table 81 Key drivers of the economic model

Description	Method/Value	Impact
Cost of the AT product	The average dosing for AT is taken from the RAPID trial and applied to an average weight of 75.9 kg. The number of vials (rounded to a whole number) is multiplied by average, high and low AT product prices	The base cost of AT assumes a price per 1,000 ml s47(1)(b) This is varied by low and high values of s47(1)(b) to s47(1)(b) per 1,000ml vial. The estimated ICER varies considerably between s47(1)(b) and s47(1)(b) per QALY.
Transition between FEV_1 and CT density decline during RAPID drives clinical benefit	There were considerable differences in transition between health states for the AT and BSC arms in the RAPID trials. The economic model assumes movement to no, slow and rapid decline tracks during the trial period is sustained for a lifetime.	A higher number of patients move to the FEV_1<50 decline states on the BSC arm in RAPID. Movement during the trial period drives economic results. Allowing transition between no, slow and rapid tracks after 4 years has limited impact on the estimated ICER.
Selection of extrapolation model for the FEV_1<50 rapid decline group survival	In most cases the Gompertz model is the best fit model to extrapolate survival and this model is used across all non-transplant states. The model is varied as part of sensitivity analyses which included use of the Log-logistic, Lognormal, Weibull, Exponential and Generalised Gamma specifications. Large numbers of patients transition to this state during the trial period, particularly on the BSC arm.	The specification of the FEV<50 rapid decline model had the largest impact on the estimated ICER. The use of Lognormal, Generalised Gamma and Weibull models results in the ICER being 10% more cost-effective, while use of the Exponential model resulted in a 10% decrease in cost-effectiveness.
Disease management costs for COPD	Disease management costs in many reviewed COPD economic models were an aggregate of maintenance and acute-care costs during flare ups. The frequency of flare ups was not explicitly modelled in this assessment. The Thomas et al. 2014 analysis included acute-care proportions for each state. They are varied by 20% for each COPD state	This variation has limited impact as economic results are governed by AT product costs. The proportion of severe COPD patients who are very severe, which is assumed to be 74% in the base cases is also varied. Similarly, this scenario had limited impact on the estimated ICER

Abbreviations: **AT** = augmentation therapy, **BSC** = best supportive care, **COPD** = chronic obstructive pulmonary disease, **CT** = computed tomography, **FEV_1** = forced expiratory volume in 1 second, **ICER**, incremental cost-effectiveness ratio; **QALY**, quality-adjusted life year.

SECTION E FINANCIAL IMPLICATIONS

E.1. JUSTIFICATION OF THE SELECTION OF SOURCES OF DATA

Section E presents the financial budget impact for the potential listing of AT using an epidemiological approach over a six-year period, based on an estimation of the number of patients eligible for treatment. A1PI deficiency is associated with COPD, however, emphysema is typically the main manifestation. Estimating the eligible population for AT has been calculated from the estimated proportion of COPD patients in Australia, combined with an estimated prevalence of ZZ phenotypes and rate of diagnosis.

The data sources used to estimate the number of patients potentially eligible for treatment with AT are provided in Table 82. Toelle et al. (2013) estimated the prevalence of COPD in Australia between 2006 and 2010. The authors undertook a cross-sectional random survey of adults 40 years and older across six purposely selected diverse sites. Interviewees answered a standardised questionnaire and performed FEV_1 and FVC tests. The prevalence of GOLD Stage II or higher COPD was estimated at 7.5% among the 1,620 surveyed men and 1,737 women.

The prevalence of COPD among Australians aged 45 years and older was also reported by the Australian Institute of Health and Welfare as part of Australian Bureau of Statistics National Health Surveys in 2014–15. Surveys indicated that 5.2% of Australians aged 18 years self-reported a diagnosis of COPD, chronic bronchitis or emphysema (AIHW 2018). Age-stratified prevalence varied from 2.5% in 45- to 54-year-old males, to 10% in those aged 75 years or older. The 45- to 54-year-old rate was similar in females, but only 8.1% in those aged 75 years or older. COPD hospitalisations per 100,000 population in 2015–16 were estimated to be 804.7 in males and 666.6 for females. Differences between the Toelle et al. (2013) and AIHW (2018) estimates could be associated with differences in response rate, age groupings and methods of diagnosis.

Using ABS Australian population statistics, the estimated national proportion of 40- to 65-year olds, and an average population growth rate of 1.6% per year, it is estimated that this age group will account for around eight million Australians in 2019. The numbers suffering from COPD (GOLD Stage II or higher) is estimated using the Toelle et al. (2013) study prevalence, along with a lower prevalence estimate (6.8%) being included in a sensitivity analysis.

Table 82 Summary of the key assumptions used in the financial impact assessment

Assumption	Base case	Sensitivity analysis	Reference
Population and incidence			
Australian population	24,770,700		Australian population in December 2017 quarter. ABS (2018). The 2017 estimate is inflated by the growth rate of 1.6% for the 2019 base year.
Australian population aged 40-65 years	7,872,729	13,215,161	The proportion of the Australian population aged 40 to 65 years is used for prevalence estimate given life expectancy for AATD. A higher population estimate is included in a sensitivity analysis based on the 25- to 65-year age group. ABS (2018).
Australian population growth rate	1.6%		Population growth rate for the year ended 31 December 2017, ABS (2018)
COPD prevalence in sufferers 40-65 years old (with symptoms; GOLD Stage II or higher COPD)	7.5%	+/- 10%	The base estimate is from the Toelle et al. (2013) COPD in the Australian burden of lung disease (BOLD) study. A lower and higher estimate is included in a sensitivity analysis.
AATD deficiency genotype (types ZZ or SZ) prevalence among COPD patients	0.63%	+/- 10%	Rahaghi et al. (2012) found 0.63% of 3,152 COPD (> GOLD II, FEV_1/FVC ratio < 0.7, with post-bronchodilator FEV_1<80% predicted) subjects had a severe deficiency genotype.
Adjustment to Rahaghi et al. (2012) to match ethnicity risk profile in for AATD deficiency genotype in the Australian population	90%		The Rahaghi et al. (2012) study included 0.5% Asian subjects who are known to have low AATD deficiency genotype (types ZZ or SZ) prevalence. The Australian population is adjusted for the high-risk group (eg. European decent) to be 90% of the population[10].
AATD 40-65 years old patients with COPD (GOLD II or higher) that are symptomatic and diagnosed (%)	10%	+/- 10%	In the UK around 4.6% of those with the Pi*ZZ genotype were estimated to be symptomatic and diagnosed. There is uncertainty around this parameter in Australia, with market research suggesting 5-10% of those with the Pi*ZZ genotype would be symptomatic and diagnosed. This is equivalent to around10% of 40-65-year-old AATD patients with COPD (GOLD II or higher) given prevalence of the pi-ZZ genotype in Australia has been estimated at approximately 1 in 5,584 by de Serres et al. (2003)
Proportion of 40-65 year old symptomatic patients who are eligible	s47(1)(b)		Estimate based on proportion of non or ceased smokers based on confidential market research
AT product cost			
Product cost			Estimate of average, high and low prices per 1,000ml vial
Vial size	1,000mg		(Zemaira, PROLASTIN-C Information)
Average weight kg	75.9 kg		RAPID trial
Dose	60mg/kg		(Zemaira, PROLASTIN-C Information)

[10] ABS 2018. 3101.0 - Australian Demographic Statistics, December Quarter 2017, June 2018.

Assumption	Base case	Sensitivity analysis	Reference
Adherence	s47(1)(b)		Estimate based on confidential market research 2015
Infusions per year	52		(Zemaira, PROLASTIN-C Information)
Total annual drug cost	s47(1)(b)		Calculated, numbers of vials rounded to whole number
Administration cost			
Administration costs per infusion	$55.3		MBS item number 13915, 85% benefit for outpatient delivery
Total annual treatment costs	s47(1)(b)		Calculated
Treatment uptake			
Proportion of eligible patients treated	s47(1)(b)		Estimate based on confidential market research 2015

Abbreviations: **ABS** = Australian Bureau of Statistics, **AATD** = alpha-1 antitrypsin deficiency, **ABS** = Australian bureau of statistics, **COPD** = chronic obstructive pulmonary disease, **GOLD** = global initiative for chronic obstructive lung disease, **FEV$_1$** = forced expiratory volume in 1 second, **FVC** = forced vital capacity, **MBS** = Medical Benefit Schedule.

There is no estimate available for the number of Australian patients with COPD due to AAT deficiency. Rahaghi and colleagues (2012) estimated the frequency of abnormal AAT genotypes among patients with COPD[11] across 19 centres in the USA. Eligible patients were offered testing for AATD, with 3,457 patients being tested. Deficient patients (ZZ, SZ) accounted for 0.63% of those tested. Deficient patients (ZZ, SZ) constituted 0.63% of those tested, while 10.88% were carriers (MS, MZ). There were lower rates of AAT deficiency among African American subjects and no incidence amongst Asians, although only a very small number of people with Asian background (0.5%) participated in the study.

Around 28% of Australia's population was born overseas. In recent years many residents have been born in Asian countries, with large increases from Japan (24%), China (8%), Malaysia (7%) and India (6%).[12] Immigration estimates only provide an indication of background ethnicity as children are not considered. The census includes questions about 'language spoken at home'. In Australia in 2016, around 300 languages were identified, with about one-fifth of Australians speaking a language other than English. After English, Mandarin was the most frequently used language (2.5% of the total population). In 2016, it appeared that approximately 11% of the population spoke languages from South and East Asia (ABS 2016). Given that the estimated prevalence of Pi*ZZ and associated genotypes is very low in these populations, the estimate of 0.63% of COPD sufferers having AATD (Rahaghi et al, 2012) is adjusted by 90% to align with the AATD higher-risk group in Australia.

In the UK around 4.6% of those with the Pi*ZZ genotype were estimated to be symptomatic and diagnosed (NIHR 2014). There is a high degree of uncertainty about the proportion of COPD (GOLD

11 >GOLD II, FEV1/FVC ratio < 0.7, with post-bronchodilator FEV1<80% predicted
12 http://www.abs.gov.au/AUSSTATS/abs@.nsf/Latestproducts/3412.0Media%20Release12015

Stage II or higher) patients diagnosed with the Pi*ZZ genotype in Australia. Based on confidential market research it is estimated that 5% to 10% of those with the Pi*ZZ genotype are symptomatic and diagnosed, which is equivalent to 10% of COPD (GOLD II or higher) 40-65 years old patients with AATD. The proportion is subject to univariate sensitivity analysis where upper and lower estimates of 9% and 11% are included. Changing this assumption has a significant impact on the financial costs of the listing, although product price changes have a greater impact. It is likely that clinicians would test a larger number of patients in the event that AT were listed, therefore diagnosis rate is an important consideration.

The budget impact approach combines the Australian population (aged 40 to 65 years), with estimated prevalence of diagnosed COPD in patients aged over 40 years and an estimate of AATD patients with diagnosed COPD (GOLD II or higher). Not all diagnosed patients would be eligible, as many could be smokers. It is assumed that around half would be ex- or non-smokers and meet other inclusion criteria. s45, s47(1)(b) Correspondingly s47(1)(b) of AT eligible patients are assumed to be prescribed AT. s47(1)(b)

E.2.1. NUMBER OF PATIENTS WITH THE MEDICAL CONDITION TARGETED BY THE PROPOSED MEDICAL SERVICE

The number of patients eligible for treatment is shown in Table 83. The 25- to 65-year-old Australian population was sourced from the ABS. The prevalence of 7.5% was derived from Toelle et al. (2013) who reported the prevalence of patients in Australia with COPD whose post-bronchodilator FEV_1/FVC ratio < 0.70 and FEV_1 < 80% predicted. Estimates for 2019 predict a total of 604,009 COPD patients in this age group, increasing to 643,603 in 2023 with an Australian population growth rate of 1.6%.

Table 83 Population eligible for augmentation therapy with A1PI in Australia

Description	2019	2020	2021	2022	2023	Source
Australian population	25,167,031	25,569,704	25,978,819	26,394,480	26,816,792	ABS, Australian demographic Statistics
Australian population growth rate	1.6%	1.6%	1.6%	1.6%	1.6%	ABS, Australian demographic Statistics
Australian population 40-65 years old (%)	32.0%	32.0%	32.0%	32.0%	32.0%	ABS, Australian demographic Statistics
Australian population 40-65 years old	8,053,450	8,182,305	8,313,222	8,446,234	8,581,373	Calculated
Australian population with GOLD II or higher COPD (%)	7.5%	7.5%	7.5%	7.5%	7.5%	Toelle et al. (2013) COPD in the Australian

Description	2019	2020	2021	2022	2023	Source
						burden of lung disease (BOLD) study
Australian population 40-65 years with COPD (GOLD II or higher)	604,009	613,673	623,492	633,468	643,603	Calculated
AATD prevalence among COPD (GOLD II or higher) sufferers (%)	0.57%	0.57%	0.57%	0.57%	0.57%	Rahaghi et al. (2012), adjusted by 90%.
COPD (GOLD II or higher) sufferers with AATD	3,425	3,480	3,535	3,592	3,649	Calculated
COPD (GOLD II or higher) patients with AATD that are diagnosed (%)	s45, s47(1)(b)					The estimate is based on 5%-10% of those with PiZZ in Australia (1/5584) being diagnosed. The 5-10% estimate is derived from confidential market research.
Symptomatic COPD (GOLD II or higher) patients with AATD diagnosis	342	348	354	359	365	Calculated
COPD/AATD symptomatic patients who are eligible (%) for AT	s45, s47(1)(b)					Estimate of compliance with inclusion criteria (e.g. non-smoker, emphysema COPD)
AT eligible patients						Calculated

Abbreviations: **AATD** = alpha-1 antitrypsin deficiency, **ABS** = Australian Bureau of Statistics, **AT** = augmentation therapy, **COPD** = Chronic Obstructive Pulmonary Disease, **GOLD** = global initiative for chronic obstructive lung disease.

As noted, genotype prevalence data from Australia is limited. Rahaghi and colleagues estimated the frequency of abnormal AAT genotypes among patients with COPD and found ZZ and SZ genotypes accounted for 0.63% of those tested. When adjusted by 90% to account for the European at-risk population in Australia, a prevalence of 0.57% is estimated. Using these proportions, a total of 3,425 COPD sufferers (Stage II or higher) are estimated to have AATD. This increases to 3,649 with population growth by 2023.

Not all COPD sufferers (Stage II or higher) with AATD are diagnosed. In the UK (NIHR 2014), about 4.6% of those with the Pi*ZZ genotype were estimated to be symptomatic and diagnosed. Market research in Australia suggests that somewhere between s47(1)(b) of those with AATD are diagnosed. De Serres et al. (2003) reported gene frequencies per 1,000 persons from a range of cohort studies conducted in various populations in Australia. PiZZ prevalence was estimated at 1 in 5,584. When

this prevalence is applied to the Australian population in 2019, a total of 4,507 are estimated to carry high-risk genotypes. If s47(1)(b) is applied to this sub-population, then 342 symptomatic COPD (GOLD II or higher) patients with AATD diagnosis are estimated for 2019.

E.2.2. NUMBER WHO WOULD BE ELIGIBLE FOR THE REQUESTED RESTRICTION

The eligible population includes non- or previous smokers with emphysema COPD. It is estimated that these criteria apply to s47(1)(b) of the symptomatic COPD (GOLD II or higher) patients with AATD diagnosis. s47(1)(b)

A total of s47(1)(b) patients are estimated to be eligible for AT in 2019, which increases to s47(1)(b) by 2023.

E.2.3. NUMBER OF PATIENTS LIKELY TO USE THE PROPOSED MEDICAL SERVICE

It is estimated that the uptake of AT will be approximately s47(1)(b) by 2022, as many clinicians have indicated that they would prescribe AT should it become listed. The numbers of patients likely to take up AT over a six-year period are summarised in Table 84. It is estimated that in 2019 a total of s47(1)(b) patients would use AT, increasing to s47(1)(b) patients by 2023. This is equivalent to s47(1)(b) of COPD (GOLD II or higher) sufferers with AATD (i.e. s47(1)(b) of 1,825) in 2023.

s45, s47(1)(b)

E.2.4. NUMBER OF TIMES THE PROPOSED MEDICAL SERVICE IS DELIVERED OVER FIVE YEARS

AT is delivered on a per kilogram basis, at a dose of 60mg/kg/week. The estimated cost per patient is based on the average weight of adult patients (76 kg) in the RAPID trial. This weight is similar to the average adult weight of 77kg in Australia from the ABS (2012).[13] Patient weight, dose per kg recommendations, vial size and adherence assumptions are combined to estimate the number of vials used per week across Australia. These estimates are provided in Table 85.

[13] Australian Health Survey: First Results, 2011-12

Table 85 Estimated AT vial usage in Australia, 2019-2023

	2019	2020	2021	2022	2023
Number of vials					
AT patients across Australia	s45, s47(1)(b)				
Average weight (kg)	76	76	76	76	76
Recommended dose of AT	60	60	60	60	60
Grams of AT per patient per week	4554	4554	4554	4554	4554
Vials per patient per week	5	5	5	5	5
Adherence	s45, s47(1)(b)				
Vials per year across Australia					

Abbreviations: **AT** = augmentation therapy.

It is evident that s47(1)(b) vials are estimated for 2019, increasing to s47(1)(b) by 2023. Vials per patient per week are estimated on a whole number basis as it is assumed that vial fractions cannot be held from week to week or distributed among patients.

E.1. COSTS TO THE NBA OF THE PROPOSED THERAPY OVER FIVE YEARS

The proposed price of PROLASTIN-C is s47(1)(b) and Zemaira s47(1)(b) per 1,000ml vial. An average price of s47(1)(b) is included, with s47(1)(b) and s47(1)(b) used as high and low bounds in sensitivity analyses. The financial impact to the NBA for AT is summarised in Table 86. The estimated cost is presented over the six-year costing proposal period and is based on the s47(1)(b) uptake rate for AT by 2023. Uptake begins at s47(1)(b) and increases by s47(1)(b) per year. The cost to the NBA for the total AT market is estimated to be s47(1)(b) in 2019, increasing to s47(1)(b) in 2023.

Table 86 Estimated financial impact to the National Blood Authority; total augmentation therapy market

	2019	2020	2021	2022	2023
Number of vials					
Number of vials across Australia	s45, s47(1)(b)				
Cost per 1,000ml vial $					
Cost per patient per year $					
Total cost of augmentation therapy $					

E.2. CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

Changes in other MBS-funded medical services likely to be affected by listing the proposed product, are outlined in Table 87. Patients will receive MBS benefits for AT infusions. Each service is costed using MBS item number 13915 at 85% of benefit. This unit cost is multiplied by the number of patients and adherence to calculate aggregate MBS costs for infusion. MBS financial costs increase from $278,000 in 2019, to $443,000 in 2023. Compared to AT product costs, these expenses are minimal. Clinicians are also likely to screen more patients for AATD should AT be listed. Given the rare nature of AATD, these costs are likely to be small.

Table 87 Estimated financial impact to MBS from augmentation therapy listing

	2019	2020	2021	2022	2023
Outpatient AT delivery					
AT eligible patients	s45, s47(1)(b)				
MBS item number 13915 per patient per year	52	52	52	52	52
MBS item number 13915 services per year	5,343	6,333	7,353	8,405	8,539
MBS benefit per service	55.3	55.3	55.3	55.3	55.3
MBS benefit per patient per year	2,876	2,876	2,876	2,876	2,876
Adherence	94%	94%	94%	94%	94%
Infusion delivery MBS costs	277,422	328,838	381,828	436,429	443,412

Abbreviations: **AT** = augmentation therapy, **MBS** = Medical Benefit Schedule.

E.3. OVERALL FINANCIAL IMPLICATIONS

The five-year budget impact underpinned by the assumptions above is presented in Table 88. Costs increase from s47(1)(b) in 2019 to s47(1)(b) in 2023. Listing AT has financial implications for other parts of the Australian Government's health budget, for state and territory government health budgets including public hospitals, and for patients and private insurers. These costs were modelled in the economic analysis in Section D. Disease management costs for COPD are estimated to be minor compared with AT product costs. More than 95% of the incremental resource cost estimated in Section D is associated with AT.

Table 88 Estimated financial impact to government from augmentation therapy listing

	2019	2020	2021	2022	2023
Total government costs					
AT patients	s45, s47(1)(b)				
NBA-supported AT product costs					
MBS-supported infusion service delivery	277,422	328,838	381,828	436,429	443,412
Total costs to government	s45, s47(1)(b)				

Abbreviations: **AT** = augmentation therapy, **MBS** = Medical Benefit Schedule, **NBA** = national blood authority.

E.4. IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

The budget impact model presented in this section provided a base case in which the lower estimate was utilised. Key base assumptions are included in a sensitivity analysis in Table 89. The budget impact is most sensitive to the assumed price for AT and the age grouping of the Australian population. The overall budget varies by 15% under the high- and low-price assumptions. Given the large contribution of the AT product itself to overall resource in the economic model, variations in price have a large impact on both financial and economic attractiveness.

Table 89 Net government cost sensitivity analysis

	Year 1	Year 2	Year 3	Year 4	Year 5
Base case net cost	s45, s47(1)(b)				
s47(1)(b)					
Australian population 25-65 years old, 13,215,161 people					
COPD prevalence in sufferers 40-65 years old (with symptoms; GOLD Stage II or higher COPD), 6.8%					
COPD prevalence in sufferers 40-65 years old (with symptoms; GOLD Stage II or higher COPD), 8.3%					
AATD prevalence among COPD (GOLD II or higher) patients 0.51%					
AATD prevalence among COPD (GOLD II or higher) patients 0.62%					
AATD patients with COPD (GOLD II or higher) that are symptomatic and diagnosed (9%)					
AATD patients with COPD (GOLD II or higher) that are symptomatic and diagnosed (11%)					
COPD/AATD symptomatic patients who are eligible (%) 45%					
COPD/AATD symptomatic patients who are eligible (%) 55%					
s47(1)(b)					

Abbreviations: **AATD** = alpha-1 antitrypsin deficiency; **AT** = augmentation therapy; **COPD** = Chronic Obstructive Pulmonary Disease; **GOLD** = global initiative for chronic obstructive lung disease; **MBS** = Medical Benefit Schedule.

The base budget impact was estimated using the 40- to 65-year-old population in Australia. AATD is likely to present within this age bracket, as the average ages at baseline in most trials have been in the early 50s. Given AATD life expectancy, there are likely to be limited patient numbers above age 65. Some patients may present earlier than 40, therefore COPD/AATD prevalence is also estimated for the 25- to 65-year-old age group. The budget impact is large when this age group is included. This scenario over-estimates the eligible population, given that most patients suffer severe COPD in their 50s. The scenario indicates that usage by younger age groups than that in the base scenario would have significant budget impacts.

Financial impact is also sensitive to varying the prevalence proportions by 10%, however, less so than the upper and lower price estimation. Uptake rate also has an impact. A decrease in year 2022 uptake from s47(1)(b) results in a s47(1)(b) budget requirement in that year. Further sensitivity analyses to parameters used in deriving budget impact estimates presented in this Section can be performed with the attached spreadsheet ('Alpha_Budget Impact_FINAL.xlsx').

SECTION F OTHER RELEVANT CONSIDERATIONS

ACCESS CONSIDERATIONS

The use of blood products is routinely governed/administered through specialised centres, which can limit the availability and access of A1PI to patients living within major metropolitan areas. Further, treatment must be initiated and monitored by a respiratory physician (PROLASTIN®-C product summary), which can impact the ability of rural and remote patients to obtain and use the drug. In order to be tested for AATD and potentially receive A1PI, patients must initially travel to these centres, incurring additional costs such as childcare, accommodation, travel, and time away from work. Clinical feedback suggests that once patients have been deemed eligible for A1PI, they can access the drug via a local pharmacy or outpatient clinic.

The proposed shelf life of lyophilised A1PI is 36 months at ≤ 25C°, with the reconstituted product requiring administration within three hours (Australian Public Assessment Report for A1PI). Consequently, A1PI needs to be transported using a temperature-controlled supply chain (i.e. cold chain), which will incur a cost. It is unclear whether temperature controlled transport is accessible to rural patients. Clinical feedback suggests that no cold supply chains are currently established due to the limited funding of A1PI, but that these challenges are not insurmountable.

Patients can administer A1PI at home or with the assistance of a carer, when deemed appropriate by the treating specialist and after receiving adequate training (PICO Confirmation, page 11). Specific training required to become competent in A1PI self-administration needs to be specified, as this will incur additional costs and resources.

It is unclear whether eligibility to receive A1PI should be granted to AATD patients who have previously received lung transplants. Given that AATD is a genetic disorder, the replaced lungs will be gradually damaged, necessitating another transplant. By granting access to this group of patients, it is anticipated that the transplant's longevity will be increased.

Given the progressive nature of AATD, it is anticipated that early intervention with A1PI would result in greater long-term lung health. However, clinical trial populations have only included severe patients. It is unclear whether less severe patients should have access to this drug as well.

The PICO Confirmation noted that clinical experts advise that cigarette smoking inactivates A1PI, rendering this expensive product useless in smokers. Excluding smoking patients may restrict access of A1PI to specific communities. To mitigate any potential discrimination of usage, it is suggested that smoking patients in specific communities be provided with the resources required to quit, in order to become eligible.

DOSING CONSIDERATIONS

The PROLASTIN-C product summary recommends administering 60mg/kg of the drug intravenously once a week (PROLASTIN-C product summary). However, the precise dose that confers the greatest clinical efficacy is yet to be determined. Several published trials have examined alternate doses of AT with the primary outcome either the number of adverse events or peak/trough concentration of A1PI in serum (Table 90). The only published study comparing different doses of AT concluded that steady-state serum concentration of A1PI was higher following 120mg/kg compared to 60mg/kg and the number of adverse events was similar between the two treatments (Campos et al. 2013). No study has evaluated the clinical efficacy between different doses of AT. A clinical trial (SPARTA) comparing 120mg/kg A1PI, 60mg/kg A1PI and placebo on lung density is expected to finish in 2021.

Table 90 Studies evaluating different doses of A1PI therapies

Study	Location, follow-up, patient numbers	Dose(s)	Adverse events
Single-arm studies			
Piitulainen et al. (2003) Case series Level IV	Sweden 4 weeks N = 5	120mg/kg every 2 weeks	Not reported
Hubbard and Crystal (1988) Case series Level IV	United States 12 months N = 9	250mg/kg every 28 days	No adverse events
Comparative studies			
Sorrells et al. (2015) (SPARTA trials) RCT Level II	15 countries 160 weeks N = 339 (estimated)	120mg/kg vs 60mg/kg vs placebo weekly	Not applicable Ongoing trial
Campos et al. (2013) RCT Cross over Level II	United States 22 weeks N = 30	60mg/kg weekly vs 120mg/kg weekly	69 and 43 TAE in 60 and 120mg/kg respectively
Dirksen et al. (1999) RCT Level II	Denmark and The Netherlands At least 36 months N = 56	250mg/kg vs albumin (625mg/kg) every 4 weeks	No adverse events

Abbreviations: **mg/kg** = milligrams per kilogram of body weight, **RCT** = randomised controlled trials, TAE = treatment emergent adverse events.

ETHICAL CONSIDERATIONS: RULE OF RESCUE

The following four criteria outline eligibility for a service to be considered under the rule of rescue:

1. NO ALTERNATIVE TREATMENT OPTION EXISTS IN AUSTRALIA

There is currently no effective disease-modifying treatment for patients with AATD. Current treatments address the symptoms but not the cause of AATD. AT with A1PI is the only potential treatment for patients with AATD. Therefore, A1PI fulfils this criterion.

2. THE MEDICAL CONDITION IS SEVERE, PROGRESSIVE AND EXPECTED TO LEAD TO PREMATURE DEATH

The pathogenesis of AATD results in the progressive deterioration of an individual's lungs. This causes significant morbidity and premature death among those afflicted with the disorder. A1PI has the potential to slow disease progression in patients with AATD. Therefore, A1PI fulfils this criterion.

3. THE MEDICAL CONDITION APPLIES TO A VERY SMALL NUMBER OF PATIENTS

The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the PBAC's consideration. However, the PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.

Based on estimates by commercial sponsors, the incidence of people meeting the criteria for A1PI in Australia in 2018 was s47(1)(b) (PICO Confirmation page 4). s47(1)(b)

4. THE PROPOSED SERVICE PROVIDES A WORTHWHILE CLINICAL IMPROVEMENT

It is unclear whether A1PI fulfils this criterion. The primary outcome in the included RCTs was change in lung density, inferred by CT densitometry. CT lung density has been suggested to be a more sensitive measure of mortality than FEV_1, thereby requiring smaller sample sizes in order to detect meaningful differences in a clinical trial setting (Schluchter et al. 2000).

Overall, the literature base suggests that lung CT densitometry is correlated to functional outcomes including FEV_1, K_{CO} and mortality. It is less clear whether it is correlated to QoL. However, when these correlations are taken together with the findings from the trials listed in section B, it is unclear whether A1PI fulfils this criterion.

In order to detect statistically significant differences between placebo and AT, both Stockely et al. (2018) and Schluchter et al. (2000) have recommended large sample sizes. Owing to the rarity of AATD it is unclear whether obtaining such numbers would be feasible.

APPENDIX A CLINICAL EXPERTS AND ASSESSMENT GROUP

CLINICAL EXPERTS CONSULTED DURING THE PREPARATION OF THIS REPORT

Name	Expertise
s47F	

ASSESSMENT GROUP

Research and Evaluation incorporating ASERNIP-S, Royal Australasian College of Surgeons, South Australia

Name	Position
s47F	

Noted conflicts of interest

The assessment group has no conflicts of interest to report.

APPENDIX B SEARCH STRATEGIES

Bibliographic databases

Electronic database	Time period searched	Results
Embase	Inception – 23 May 2018	4412
PubMed	Inception – 24 May 2018	3221
The Cochrane Library (CDSR, Central, DARE, HTA, HEED)	Inception – 24 May 2018	67

Additional sources of literature (including websites)

Source	Location	Search date
Clinical trial registries		
ClinicalTrials.gov	https://clinicaltrials.gov/	28 May 2018
Cochrane Central Register of Controlled Trials	http://cochranelibrary-wiley.com/cochranelibrary/search	28 May 2018
EU Clinical Trials Registry	https://www.clinicaltrialsregister.eu/ctr-search/search	29 May 2018
WHO International Clinical Trials Registry Platform (ICTRP)	http://www.who.int/ictrp/en/	29 May 2018
Current Controlled Trials MetaRegister	http://www.isrctn.com	29 May 2018
Australian New Zealand Clinical Trials Registry	http://www.anzctr.org.au/	29 May 2018
Grey literature sources		
New York Academy of Medicine Grey Literature Report	http://www.greylit.org	24 May 2018
Economic studies		
CEA Registry	https://research.tufts-nemc.org/cear4/	13 June 2018
HTA Websites		
National Information Centre of Health Services Research and Health Care Technology (NICHSR)	http://www.nlm.nih.gov/nichsr/	24 May 2018
National Library of Medicine Health Services/Technology Assessment Texts (HSTAT)	http://www.ncbi.nlm.nih.gov	24 May 2018
International Information Network on New and Emerging Health Technologies (EuroScan International Network)	http://euroscan.org.uk/	24 May 2018
Other sources		
National Institute for Heath and Care Excellence (NICE)	http://www.nice.org.uk	24 May 2018
NHS National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta	24 May 2018
Online Mendelian Inheritance in Man	http://omim.org/	24 May 2018
Patient/practitioner societies		
Alpha-1 Foundation	http://www.alpha1.org/Investigators/Resources/Last-Month-on-PubMed	24 May 2018
National Blood Authority	http://www.blood.gov.au	24 May 2018

Source	Location	Search date
Lung Foundation Australia	http://www.lungfoundation.com.au	24 May 2018
Thoracic Society of Australia and New Zealand	http://www.thoracic.org.au/	24 May 2018
Manufacturers		
Grifols	http://www.grifols.com/en/web/international/home#	24 May 2018
CSL Behring	http://www.cslbehring.com.au/	24 May 2018
SHIRE	http://www.shire.com	24 May 2018
Extended assessment of harms		
Medsafe Recall Actions Archive	http://www.medsafe.govt.nz/	16 July 2018
Medsafe Early Warning System Alert Communications	http://www.medsafe.govt.nz/	16 July 2018
MBS Online	http://www.mbsonline.gov.au/	16 July 2018
Therapeutic goods administration (TGA) Current Year Alerts	https://www.tga.gov.au/current-year-alerts	16 July 2018
Therapeutic goods administration (TGA) Recalls	https://www.tga.gov.au/recalls	16 July 2018
The Pharma Letter	https://www.thepharmaletter.com/listing/pharmaceutical/respiratory-and-pulmonary-	16 July 2018
FDA Recalls	https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Recalls/default.htm	16 July 2018
FDA Device Advice	https://www.fda.gov/medicaldevices/deviceregulationandguidance/default.htm	16 July 2018
European Commission Market Surveillance and Vigilance	https://ec.europa.eu/	16 July 2018

Table 91 PubMed Search Strategy

Search	Searched terms	Results
#1	alpha 1-Antitrypsin Deficiency[MeSH Terms]	3221
#2	alpha 1-Antitrypsin Deficiency	4,480
#3	alpha1-proteinase inhibitor deficiency	4,493
#4	#1 or #2 or #3	3,221
#5	Chronic obstructive pulmonary disorder	50,532
#6	Chronic obstructive pulmonary disorder[MeSH]	48,147
#7	COPD	75,911
#8	COPD[MeSH]	48,245
#9	Emphysema	34,561
#10	Emphysema[MeSH]	26,463
#11	#5 or #6 or #7 or #8 or #9 or #10	96,691
#12	#4 and #11	3,221
	Databases searched: PubMed **Restrictions: Humans; English**	

Search	Searched terms	Results
	Date searched: 24 May 2018 **Total results: 3221**	

Table 92 Embase Search Strategy

Search	Searched terms	Results
#1	alpha 1-Antitrypsin Deficiency	11,139
#2	Alpha 1 antritrypsin deficiency	11,148
#3	alpha1-proteinase inhibitor deficiency	32
#4	#1 or #2 or #3	11,167
#5	Chronic obstructive pulmonary disorder	1,134
#6	COPD	160,580
#7	Emphysema	105,210
#8	#5 or #6 or #7	249,005
#9	#4 and #8	4,412
	Databases searched: Ovid Embase; Ovid Medline **Restrictions: Humans; English** **Date searched: 23 May 2018** **Total results: 4412**	

Table 93 Cochrane Search Strategy

Search	Searched terms	Results
	alpha 1-Antitrypsin Deficiency	106
#2	alpha1-proteinase inhibitor deficiency	24
#3	#1 or #2	115
#4	Emphysema	1107
#5	COPD	11127
#6	#4 or #5	12065
#7	#3 and #6	67
	Databases searched: Cochrane Database of Systematic Reviews **Date searched: 24 May 2018** **Total results: 67**	

Table 94 Clinicaltrials.gov Search Strategy

Search	Searched terms	Results
#1	Alpha 1-Antitrypsin Deficiency	76
#2	Zemaira	156

Search	Searched terms	Results
#3	Prolastin	156
#4	#1 and (#2 or #3)	76
	Date searched: 28 May 2018 **Total results: 76**	

Table 95 Cochrane Central Register of Controlled Trials Search Strategy

Search	Searched terms	Results
#1	Alpha 1-Antitrypsin Deficiency	118
	Date searched: 28 May 2018 **Total results: 118**	

Table 96 EU Clinical Trials Registry Search Strategy

Search	Searched terms	Results
#1	Alpha 1-Antitrypsin Deficiency	10
	Date searched: 29 May 2018 **Total results: 10**	

Table 97 WHO International Clinical Trials Registry Platform Search Strategy

Search	Searched terms	Results
#1	Alpha 1-Antitrypsin Deficiency	67
	Date searched: 29 May 2018 **Total results: 67**	

Table 98 Current Controlled Trials MetaRegister Search Strategy

Search	Searched terms	Results
#1	Alpha 1-Antitrypsin Deficiency	8
#2	Zemaira	0
#3	Prolastin	0
	Date searched: 29 May 2018 **Total results: 8**	

Table 99 Australian New Zealand Clinical Trials Registry Search Strategy

Search	Searched terms	Results
#1	Alpha 1-Antitrypsin Deficiency	2
	Date searched: 29 May 2018 **Total results: 2**	

Table 100 CEA Registry Search Strategy

Search	Searched terms	Results
#1	Alpha 1-Antitrypsin Deficiency	8
	Date searched: 13 June 2018 **Total results: 2**	

APPENDIX C STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Table 101 Characteristics of randomised controlled trials included in the systematic review to assess efficacy

Authors Publication Year Study ID	Study design Evidence level	Location Length of follow-up	Study population characteristics (at baseline after randomisation)	Description of Intervention	Description of Comparator	Relevant outcomes assessed	Measurement of outcomes and analysis
Chapman et al. 2015 **RAPID**	RCT Level: IIA	21-centred trial across 13 countries 24 months masked period and up to 48 month extension with open-label	**$n_{\alpha 1\text{-antitrypsin}}$ = 93** **$n_{placebo}$ = 87** **Age** [I] = 53.8 ± 6.9 [C] = 52.4 ± 7.8 **FEV_1 Predicted (%)** [I] = 47.4 ± 12.1 [C] = 47.2 ± 11.1 **Alpha-1 Antitrypsin (µM)** [I] = 6.38 ± 4.62 [C] = 5.94 ± 2.42 **Lung density (g/L)** TLC-[I] = 45.5 ± 15.8 TLC-[C] = 48.9 ± 15.5 FRC-[I] = 47.6 ± 15.7 FRC-[C] =50.7 ± 15.0 Comb-[I] = 46.6 ± 15.6 Comb-[C] = 49.8 ± 15.1 **Genotype (both arms)** PiZZ = 168 (93%)	**Intervention** Intravenous A1PI 60mg/kg per week for 24 months (12 months masked and 12 months opened)	**Comparator** Placebo No further detail provided	**Primary outcome** Lung density reduction rate measured by PD15 for TLC and FRC combined and separately at baseline, 3 months and 12 months **Secondary outcome** • Anthonisen exacerbation • Exacerbation duration and severity • FEV_1 • Single-breath diffusion capacity • A1PI concentration • Incremental shuttle walk test • SGRQ status • BMI • Mortality • TEAE	**Primary outcome** Analysed by GLMM where TLC, FRC, country, time, treatment and treatment-by-time interaction using fixed effects and patients and time-by-patient using random effects

Authors Publication Year Study ID	Study design Evidence level	Location Length of follow-up	Study population characteristics (at baseline after randomisation)	Description of Intervention	Description of Comparator	Relevant outcomes assessed	Measurement of outcomes and analysis
Dirksen et al. 2009 **EXACTLE**	RCT Level: IIA	Denmark, UK and Sweden Up to 30 months	**$n_{\alpha 1\text{-antitrypsin}}$ = 38** **$n_{placebo}$ = 39** **Age** [I] = 54.7 ± 8.4 [C] = 55.3 ± 9.8 **Gender (M:F)** [I] 25:13 [C] 16:23 **FEV_1 Predicted (%)** [I] = 46.3 ± 19.6 [C] = 46.6 ± 21.0 **Alpha-1 Antitrypsin concentration (µM)** [I] = 4.6 ± 1.6 [C] = 4.6 ± 1.7 **Lung density (g/L)** TLC-[I] = 54.55 ± 13.37 TLC-[C] = 53.90 ± 15.97 Comb-[I] = 47.98 ± 19.07 Comb-[C] = 45.48 ± 46.95 **Genotype (both arms)** PiZZ = 77 (100%)	**Intervention** Intravenous A1PI 60mg/kg per week for 24 months	**Placebo** 2% albumin, same dosage to the intervention	**Primary outcome** Lung density reduction rate measured by PD15 via four different methods at 12, 24 and 30 months; **Secondary outcome** • FEV_1 • Diffusion capacities (D_{Lco}) • Transfer coefficient (K_{CO}) • Exacerbation duration and severity defined by Rodriguesz-Roisin criteria • SGRQ status • AE	Four methods were used: • Method 1: GLMM without lung volume variable, this was regarded as the primary outcome among the other three; • GLMM with lung volume variable; • ANCOVA without lung volume as a covariate; • ANCOVA with lung volume as a covariate

Authors Publication Year Study ID	Study design Evidence level	Location Length of follow-up	Study population characteristics (at baseline after randomisation)	Description of Intervention	Description of Comparator	Relevant outcomes assessed	Measurement of outcomes and analysis
Dirksen et al. 1999 **DIRKSEN99**	RCT Level IIA	Denmark and The Netherlands At least 36 months	**$n_{\alpha 1\text{-antitrypsin}}$ = 28** **$n_{placebo}$ = 28** **Age*** Overall mean = 47.56 **Gender (M:F)** Overall = 34:22 **FEV_1 Predicted (%)** [I] = 46.2 ± 11.90 [C] = 50.0 ± 15.93 **Lung density (whole lung, g/L)** [I] = 67.7 ± 22.06 [C] = 73.0 ± 28.29 **Genotype (both arms)** PiZZ = 56 (100%)	Intravenous A1PI 250mg per month for at least 36 months	625mg/kg albumin, same frequency to the intervention	**Lung density parameters including** • Whole lung density by PD15 • Lung density slice 5cm below the carina **Lung function parameters including** • FEV_1 and %predicted • FVC • Diffusion capacities (D_{Lco}) • Transfer coefficient (K_{CO})	GLMM on all outcomes where fixed effects were time, nations, lung volume (log-transformed) and treatment arms, and random effects were patients IDs

Abbreviations: **AE** = adverse events, **ANCOVA** = Analysis of covariance, **BMI** = body mass index, **C** = comparator group, **Comb** = combined, **D_{Lco}** = diffusing capacity for carbon monoxide, **FEV_1** = forced expiratory volume in one second, **FRC** = functional residual capacity, **FVC** = forced vital capacity, **GLMM** = generalised linear mixed model, **I** = intervention group, **K_{CO}** = D_{LCO} divided by alveolar volume, **PD15** = 15th percentile point, **SGRQ** = St George's Respiratory Questionnaire, **TEAE** = Treatment-emergent adverse events, **TLC** = total lung capacity.
* The study reported some baseline parameters by centres, not by arms. Only mean values were calculable from available data and those are only for overall average, not by arms.

Table 102 Characteristics of RCT studies used in the systematic literature review to assess safety

Authors Publication Year Study ID	Study design Evidence level	Location Length of follow-up	Study population characteristics (at baseline after randomisation)	Description of Intervention	Description of Comparator	• Safety outcomes assessed
Chapman et al. 2015 **RAPID**	RCT Level: IIA	21-centred trial across 13 countries 24 months masked period and up to 48 month extension with open-label	***Zemaira* = 93** **Placebo = 87** **Age** [I] = 53.8 ± 6.9 [C] = 52.4 ± 7.8 **FEV_1 Predicted (%)** [I] = 47.4 ± 12.1 [C] = 47.2 ± 11.1 **Alpha-1 Antitrypsin (µM)** [I] = 6.38 ± 4.62 [C] = 5.94 ± 2.42 **Lung density (g/L)** TLC-[I] = 45.5 ± 15.8 TLC-[C] = 48.9 ± 15.5 FRC-[I] = 47.6 ± 15.7 FRC-[C] =50.7 ± 15.0 Comb-[I] = 46.6 ± 15.6 Comb-[C] = 49.8 ± 15.1 **Genotype (both arms)** PiZZ = 168 (93%)	**Intervention** Intravenous A1PI 60mg/kg per week for 24 months (12 months masked and 12 months opened)	**Comparator** Placebo No further detail provided	• Any adverse events • Severe adverse events • Treatment-related adverse events • Dyspnoea • Death due to adverse event • Discontinuation due to adverse events

Authors Publication Year Study ID	Study design Evidence level	Location Length of follow-up	Study population characteristics (at baseline after randomisation)	Description of Intervention	Description of Comparator	• Safety outcomes assessed
Dirksen et al. 2009 **EXACTLE**	RCT Level: IIA	Denmark, UK and Sweden Up to 30 months	***Prolastin* = 38** **Placebo = 39** **Age** [I] = 54.7 ± 8.4 [C] = 55.3 ± 9.8 **Gender (M:F)** [I] 25:13 [C] 16:23 **FEV_1 Predicted (%)** [I] = 46.3 ± 19.6 [C] = 46.6 ± 21.0 **Alpha-1 Antitrypsin concentration (µM)** [I] = 4.6 ± 1.6 [C] = 4.6 ± 1.7 **Lung density (g/L)** TLC-[I] = 54.55 ± 13.37 TLC-[C] = 53.90 ± 15.97 Comb-[I] = 47.98 ± 19.07 Comb-[C] = 45.48 ± 46.95 **Genotype (both arms)** PiZZ = 77 (100%)	**Intervention** Intravenous A1PI 60mg/kg per week for 24 months	**Placebo** 2% albumin, same dosage to the intervention	• Adverse events experienced by >1 patient • Severe adverse events • Treatment-related adverse events • Dyspnoea • Discontinuation due to adverse event

Authors Publication Year Study ID	Study design Evidence level	Location Length of follow-up	Study population characteristics (at baseline after randomisation)	Description of Intervention	Description of Comparator	• Safety outcomes assessed
Dirksen et al. 1999 **DIRKSEN99**	RCT Level: IIA	Denmark and The Netherlands At least 36 months	***Prolastin* = 28** **Placebo = 28** **Age** Overall mean = 47.56 **Gender (M:F)** Overall = 34:22 **FEV_1 Predicted (%)** [I] = 46.2 ± 11.90 [C] = 50.0 ± 15.93 **Lung density (whole lung, g/L)** [I] = 67.7 ± 22.06 [C] = 73.0 ± 28.29 **Genotype (both arms)** PiZZ = 56 (100%)	Intravenous A1PI 250mg/kg per month for at least 36 months	625mg/kg albumin, same frequency to the intervention	• Any adverse events

Abbreviations: **AE** = adverse events, **C** = comparator group, **I** = intervention group, **RCT** = randomised controlled trial, **TEAE** = Treatment-emergent adverse events.

Table 103 Characteristics of non-randomised controlled trials used in the systematic literature review to assess efficacy

Authors Publication Year Study ID	Study design Evidence level	Location Length of follow-up mean (SD)	Study population characteristics (at baseline)	Description of Intervention	Description of Comparator	Relevant outcomes assessed	Measurement of outcomes and analysis
Alpha-1-Antitrypsin Deficiency Registry Study Group 1998	Non-RCT Level III-3	United States Median (range), 52 (12 – 86) months	**Age** 46 ± 11 **Gender (M:F)** 510:417 **Tobacco exposure (both)** Nonsmokers = 198/927 Exsmokers = 655/927 Current smokers = 75/927 **FEV_1 Predicted (%)** 49 ± 30 **Alpha-1 Antitrypsin (µM)** 5.7 ± 1.4	**Intervention** Augmentation therapy No further details provided Always receiving AT N=389 Partly receiving AT N=261	**Comparator** Untreated No further details provided Never receiving AT N=277	**Primary outcomes** • ΔFEV1 • Survival	FEV1: linear mixed effects modelling (covariates: mean FEV1 % predicted) Survival: kaplan-meier, log-rank test, cox proportional hazards regression (covariates: baseline FEV1 % and time)
Barros-Tizón et al. 2012	Non-RCT Level IV (pre- and post-intervention)	Spain Total 36 months 18 months pre- and post-intervention	**Age** 51.7 ± 9.1 **FEV^1 predicted** 46.0 ± 13.4 **AAT serum concentrations** <11 µml (inclusion criteria) **Tobacco exposure** Smokers 4/127 (3%) Exsmokers 100/127 (94%) Nonsmokers 22/127 (17%) **Genotype** PiZZ 118/127 (96%) PiSZ 1/127 (0.8%) Other 7/127 (6%)	**Intervention** Augmentation therapy Mean dose 60.3 (3.8) mg/kg Administered Biweekly, n=22 Weekly, n=8 Every 3 weeks, n=97	**Comparator** No treatment (pre-intervention) No further details provided	**Primary outcome** • Number of exacerbations **Secondary outcomes** • Lung function • Adverse events • Costs associated with hospitalisation	T-test, Wilcoxon signed-rank, ANOVA, multivariate logistics regression

Karl et al. 2017	Non-RCT Level III-2	Germany 1 year	**Number of patients** [I] = 106 [C] = 25 **Age, mean (SD)** [I] = 59.6 (9.9) [C] = 63.1 (10.2) **Gender (M:F)** [I] = 66:40 [C] = 8:17, $p < 0.01$ **COPD GOLD grade** [I] Grade 1 = 4.7%; Grade 2 = 24.5% Grade 3 = 50.9%; Grade 4 = 19.8% [C] Grade 1 = 4%; Grade 2 = 76% Grade 3 = 8%; Grade 4 = 12% **Education** [I] Basic = 33% Secondary = 42.5% Higher = 24.5% [C] Basic = 28% Secondary = 48% Higher = 24% **Tobacco exposure** [I] Never = 20.8% Former = 78.3% Current = 0.9% [C] Never = 36% Former = 64% Current = 0% **BMI (kg/m²)** [I] = 24.6 (4.1) [C] = 24.8 (3.6)	**Intervention** Augmentation therapy No further details provided N=106	**Comparator** Untreated No further details provided N=25	**Primary outcomes** • Direct and indirect health care costs • Health-related quality of life	T-test, chi squared test, Wilcoxon signed-rank tests, generalised linear model (covariates: GOLD grade, age, sex, education, smoking status, BMI, comorbidities)
Alpha-1 proteinase inhibitor augmentation – MSAC CA 1530			**Comorbidities, count mean (SD)** [I] = 3.0 (2.5) [C] = 3.4 (2.3)				160

Lieberman 2000	Non-RCT Level III-2	United States N/A	**Number of patients** [I] = 96 [C] = 47 **Age, median (range)** [I] Male = 50 (36 – 67) Female = 53 (33 – 72) [C] Male = 55 (37 – 70) Female = 45 (33 – 67) **Gender (M:F)** [I] = 50:46 [C] = 24:23 **Phenotype** [I] PiZZ = 95/96; PiSZ = 1/96 [C] PiZZ = 46/47; PiSZ = 1/47 **Tobacco exposure** [I] Exsmokers = 93/96 Never smoked = 3/96 [C] Exsmokers = 35/47 Never smoked = 12/47** **Alpha-1 Antitrypsin (60mg/kg)** **Frequency** Bi weekly = 35 Weekly = 54 Monthly = 7 **Duration** < 1 year = 7 > 1 to < 10 years = 89	**Intervention** Augmentation therapy No further details provided N=96	**Comparator** Untreated No further details provided N=47	**Primary outcome** • Number of infections **Secondary outcomes** • Perceived benefit	Chi squared test

Seersholm et al. 1997	Non-RCT Level III-3	Denmark and Germany 3.2 (1.6) years for AT patients 5.8 (3.4) years for no AT patients	**Number** [I] = 198 [C] = 97 **Gender (M:F)** [I] = 142:56 [C] = 55:42, *p* = 0.01 **Age, mean (SD)** [I] = 46 (8) [C] = 45 (10) **Phenotype** [I] PiZZ = 198/198 [C] PiZZ = 97/97 **FEV_1 predicted %** [I] = 37 (14) [C] = 42 (10), *p* = 0 .02	**Intervention** 60mg/kg per week N=198	**Comparator** Untreated No further details provided N=97	**Primary outcome** • ΔFEV_1 (mL/year)	Random effects modelling (covariates: age at baseline, follow-up time, treatment, gender, initial FEV_1, individual patients)

Tonelli et al. 2009	Non-RCT Level III-3	United States 41.7 (2.6) months	**Number of patients** [I] = 124 [C] = 40 **Age, mean (SE)** [I] = 61.3 (0.7) [C] = 56.1 (1.9), $p = 0.01$ **Gender M:F** [I] = 65:59 [C] = 20:20 **Ethnicity (white)** [I] = 95.2% [C] = 90% **Tobacco exposure** [I] Exsmokers = 84.7% Current = 0% [C] Exsmokers = 62.5%, $p < 0.001$ Current = 5% Comorbidities [I] COPD = 37.1% [C] COPD = 15%, $p = 0.009$ **Baseline FEV_1 (L/m), mean (SE)** [I] = 1.4 (0.1) [C] = 2.4 (0.2), $p < 0.001$ **FEV_1 (% of predicted), mean (SE)** [I] = 43 (2) [C] = 77 (5), $p < 0.001$ **Phenotype** [I] PiZZ = 124/124 [C] PiZZ = 40/40	**Intervention** Augmentation therapy No further details provided N=124	**Comparator** Untreated No further details provided N=40	**Primary outcome** • ΔFEV_1 (mL/year) **Secondary outcomes** • Mortality	T-test, chi squared test, Fisher exact test Random effects modelling (covariates: gender, age at baseline, smoking status, individual patient, follow-up duration) Logistic regression (covariates: age, gender, baseline FEV_1, COPD, smoking status)

Wencker et al. 1998	Non-RCT Level IV (pre- and post-intervention)	Germany 98.9 (36.6) months	**Gender (M:F)** 62:34 **Phenotype** PiZZ = 85/96; PiSZ = 8/96; Other 3/96 **Tobacco exposure** Exsmokers = 70/96 Never smoked = 12/96 Smoker = 14/96 **BMI (kg/m²), mean (SD)** 22.9 (3.6) **FEV_1 (L/s)** 1.43 (0.65) **FEV_1 predicted %** 41 (17.3)	**Intervention** 60mg/kg per week N=96	**Comparator** No treatment (pre-intervention) No further details provided	**Primary outcome** • ΔFEV_1 (mL/year)	T-test, chi squared test, Wilcoxon signed-rank, mixed effects modelling (covariates: treatment, individual patient)

Abbreviations: **AE** = adverse events, **ANCOVA** = Analysis of covariance, **BMI** = body mass index, **C** = comparator group, **Comb** = combined, **D_{Lco}** = diffusing capacity for carbon monoxide, **FEV_1** = forced expiratory volume in one second, **FRC** = functional residual capacity, **FVC** = forced vital capacity, **GLMM** = generalised linear mixed model, **I** = intervention group, **K_{CO}** = D_{LCO} divided by alveolar volume, **PD15** = 15th percentile point, **RCT** = randomised controlled trial, **SGRQ** = St George's Respiratory Questionnaire, SE = **TEAE** = Treatment-emergent adverse events, **TLC** = total lung capacity.
** Significant difference between groups $p < 0.001$.

Table 104 Characteristics of single arm studies used in the systematic literature review to assess safety

Authors Year Study ID	Design Evidence level	Location Length of follow-up Sample size	Baseline population characteristics	Description of patient group/s Intervention	Safety outcomes assessed
McElvaney et al. 2017 RAPID-OLE	Non-RCT, prospective III-2	Ireland 24 months N=140	**Age** [I] = 53.8 ± 6.9 [C] = 52.4 ± 7.8 **FEV_1 Predicted (%)** [I] = 47.4 ± 12.1 [C] = 47.2 ± 11.1 **Alpha-1 Antitrypsin (µM)** [I] = 6.38 ± 4.62 [C] = 5.94 ± 2.42 **Lung density (g/L)** TLC-[I] = 45.5 ± 15.8 TLC-[C] = 48.9 ± 15.5 FRC-[I] = 47.6 ± 15.7 FRC-[C] =50.7 ± 15.0 Comb-[I] = 46.6 ± 15.6 Comb-[C] = 49.8 ± 15.1 **Genotype (both arms)** PiZZ = 168 (93%)	Intervention/Patients Early-start [48m] Intravenous *Zemaira* 60mg/kg per week for 48 months Delayed-start [24m] Intravenous *Zemaira* 60mg/kg per week for 24 months Early-start [48m] = 76 Delayed-start [24m] = 64	• Adverse events • Severe adverse events • Treatment-related adverse events • Dyspnoea
The Alpha-1-Antitrypsin Deficiency Registry Study Group 1998	37-site Observational cohort study (Registry) IV	USA 5 years N=927 (not all treated with intervention)	**Age** 46 ± 11 **Gender (M:F)** 510:417 **Tobacco exposure (both)** Nonsmokers = 198/927 Exsmokers = 655/927 Current smokers = 75/927 **FEV_1 Predicted (%)** 49 ± 30 **Alpha-1 Antitrypsin (µM)** 5.7 ± 1.4	Intervention = *Prolastin* *Patients* = Registry participants never (227), partly (261), and always (389) receiving AT	• Discontinuation due to adverse event
Barker et al. 1994	Retrospective case series IV	USA 48 months N=14	**Age** 50 ± 6 **Gender (M:F)** 10:4 **Tobacco exposure** Nonsmokers = 1 Exsmokers = 13 **FEV_1 Predicted (%)** 0.9 ± 0.4 **AAT mg/dl** 41 ± 8.8 **Phenotype** PiZ	Intervention = *Prolastin* *Patients* = NHLBI Registry for severe AAT deficiency participants 14 1-2 weekly Prolastin infusions of 60mg/kg	• Any adverse events • Hospitalisation due to adverse event • Discontinuation due to adverse event • Death due to adverse event
Barker et al. 1997	Open label, uncontrolled pharmacoki	USA 4 months	**Age** 51.1 ± 7.2	Intervention = A1PI Patients = 23	• Any adverse events • Severe adverse

Authors Year Study ID	Design Evidence level	Location Length of follow-up Sample size	Baseline population characteristics	Description of patient group/s Intervention	Safety outcomes assessed
	netic study IV	N=23	**Pulmonary impairment** Severe 18/23 Other 5/23 **AAT mg/dl** ≤50 **Phenotype** PiZ	2 weekly A1PI infusions of 120 mg/kg for 10 infusions	events • Treatment-related adverse events • Dyspnoea • Death due to adverse event
Barros-Tizón et al. 2012	Multicentre, retrospective case series study IV	Spain 18 months N=27	**Age** 51.7 ± 9.1 **FEV¹ predicted** 46.0 ± 13.4 **AAT serum concentrations** <11 µml (inclusion criteria) **Tobacco exposure** Smokers 4/127 (3%) Exsmokers 100/127 (94%) Nonsmokers 22/127 (17%) **Genotype** PiZZ 118/127 (96%) PiSZ 1/127 (0.8%) Other 7/127 (6%)	Intervention = *Prolastin* or *Trypsone* Patients = 27 1-3 weekly A1PI infusions of 60mg/kg *Prolastin*/*Trypsone*	• Any adverse events • Severe adverse events • Treatment-related adverse events • Discontinuation due to adverse event • Death due to adverse event
Campos et al. 2013	Multicentre, double blind, cross-over study III-3	USA 4 months N=30	**Age** [60] 59.7 ± 6.7 [120] 57.4 ± 6.3 **FEV¹ predicted** <80% both **Phenotype** [60] 13/15 PiZZ, 1/15 null, 1/15 PiZM [120] all PiZZ	Intervention/Patients 60mg/kg *PROLASTIN-C* = 15 120 mg/kg *PROLASTIN-C* = 15 60mg/kg group Weekly *PROLASTIN-C* infusions of 60mg/kg for 8 weeks 120 mg/kg group Patients crossed-over to the other group for a further 8 weeks (swapped)	• Any adverse events • Severe adverse events • Treatment-related adverse events • Discontinuation due to adverse event • Death due to adverse event
Hubbard & Crystal1988	Case series, propsective IV	USA 12 months N=9	**Age** 46 ± 8.0 **Gender (M:F)** 6:3 **Phenotype** PiZZ = 8/9 PiZ null = 1/9 **Tobacco exposure** Nonsmokers = 6/9 Exsmokers = 3/9 **AAT serum levels** 35 ± 10 mg/dL (4.7 µmol)	Intervention =A1PI Patients = 9 A1PI Infusions of 250 mg/kg every 28 days	• Adverse events • Changes in body weight, abnormalities in blood or urine, antibodies against AAT • Infection from treatment

Authors Year Study ID	Design Evidence level	Location Length of follow-up Sample size	Baseline population characteristics	Description of patient group/s Intervention	Safety outcomes assessed
			FEV¹ predicted 78% ± 17%		
Sandhaus et al. 2014	RCT Open label extension III-2	USA 3-site multi centre, first 3 months randomised followed by open label 7 months N=50	**Age** [G] = 55.4 ± 7.7 [P] = 55.7 ± 9.2 **Gender (M:F)** 25:25 **Race** Caucasian = 49 Hispanic = 1 **Phenotype** PiZZ = 43 PiMZ = 2 PiSZ = 2 Unknown = 3 **FEV¹ predicted** [G] 46 ± 17 [P] 47 ± 23 **Alpha-1 Antitrypsin (µM)** [G] 4.8 ± 2 [P] 4.3 ± 1	Intervention/Patients *Glassia* = 33 *Prolastin* = 17 GLASSIA Intravenous A1PI 60mg/kg PROLASTIN Intravenous A1PI 60mg/kg	• Adverse events occurring in >10 % patients • Severe adverse events • Treatment-related adverse events • Discontinuation due to adverse event
Schmidt et al. 1988	Case series, multicentre, unknown if prospective IV	Germany 6 months N=20	**Age** 46.5 ± 7.6 **Gender (M:F)** 15:5 **Phenotype** PiZ = 20/20 **Tobacco exposure** Nonsmokers = 5/20 Exsmokers = 15/20 **FEV¹ one second** 1,094 ± 319	Intervention = A1PI Patients = 20 Weekly A1PI infusions of 60mg/kg for 6 months	• Any adverse events • Severe adverse events
Schwaiblmair et al. 1997	Case series, prospective IV	Germany 36 months N=20	**Age** 48 ± 1.8 **Gender (M:F)** 11:9 **Phenotype** PiZZ = 19/20 PiSZ = 1/20 **Tobacco exposure** Nonskomers = 3/20 Exsmokers = 17/20 **AAT serum levels** 43 ± 4.0 mg/dL **FEV¹ predicted** 41.7 ± 3.1	Intervention = A1PI Patients = 20 Weekly A1PI infusions of 60mg/kg for 36 months	• Adverse events • Hospitalisation due to adverse event • Severe adverse events • Treatment-related adverse events • Death due to adverse event

Authors Year Study ID	Design Evidence level	Location Length of follow-up Sample size	Baseline population characteristics	Description of patient group/s Intervention	Safety outcomes assessed
Stocks et al. 2010	Multicentre, double blind, cross-over study III-3	USA 6 months N=24	**Age** 57.7 ± 8.04 **Gender (M:F)** 14:10 **Phenotype** PiZZ = 23/24 PiSZ = 1/24 **AAT serum levels** 18.7 ± (3.9) **FEV¹ predicted** 43% ± 13.3	Prolastin = 12 PROLASTIN-C = 12 Weekly infusions of 60mg/kg for 6 months	• Any adverse events • Infection from treatment • Severe adverse events • Treatment-related adverse events • Discontinuation due to adverse event • Death due to adverse event
Stoller et al. 2003	Observational cohort study, prospective (Registry) IV	USA 7 years N=747	**Age** Sometimes 47 ± 10 Always 48 ± 9.0 **Gender (M:F)** Sometimes 204:153 Always 226:164 **Tobacco exposure (both)** Nonsmokers = 92/747 Exsmokers = 595/747 Current smokers = 60/747 **FEV_1 Predicted (%)** Sometimes 0.37 ± 0.2 Always 0.37 ± 0.2 **Alpha-1 Antitrypsin (µM)** Sometimes 5.7 ± 1.3 Always 5.7 ± 1.3	Intervention = A1PI Patients Registry participants: Sometimes receiving *Prolastin* AT = 357 Always receiving *Prolastin* AT = 390	• Any adverse events • Severe adverse events • Dyspnoea • Discontinuation due to adverse event • Hospitalisation due to adverse event • Physician visit or new medication due to adverse event
Wencker et al. 1998	Case series, prospective IV	Germany 6 years N=443	**Age** 47 ± 9.0 **Gender (M:F)** 292:151 **Tobacco exposure** Exsmokers = 356 Nonsmokers = 87 **Phenotype** PiZZ = 394 PiSZ = 31 Null = 6 PiFZ = 3 Other/unknown = 9 **FEV_1 Predicted (%)** Ex 35.5 ± 14.8 Non 42.2 ± 18.2	Intervention = *Prolastin* Patients = 443 Weekly infusions of 60mg/kg for 29 months [Exsmokers] and 23 months [Nonsmokers]	• Any adverse events • Severe adverse events • Hospitalisation due to adverse event • Dyspnoea • Discontinuation due to adverse event • Death due to adverse event • Infection from treatment
Wewers et al. 1987	Case series with healthy controls, unknown if	USA 6 months N=21	**Age** 46 ± 8 **Gender (M:F)**	Intervention = A1PI Patients = 21 Weekly infusions of	• Any adverse events • Severe adverse events • Infection from

Authors Year Study ID	Design Evidence level	Location Length of follow-up Sample size	Baseline population characteristics	Description of patient group/s Intervention	Safety outcomes assessed
	prospective III-2		18:3 **Tobacco exposure** Exmokers = 19 Nonsmokers = 2 **Phenotype** PiZZ = 21/21 **FEV_1 Predicted (%)** 37 ± 3 **Alpha-1 Antitrypsin (µM)** 4.2 ± 0.8	60mg/kg for 6 months	treatment

Abbreviations: **AE** = adverse event; **AT** = augmentation therapy; **NHBLI** = National Heart, Lung, and Blood Institute, **RCT** = randomised controlled trial.

APPENDIX D EVIDENCE PROFILE TABLES

Table 105 Evidence profile table of effectivness outcomes for A1PI compared to placebo for patients with severe AATD and emphysema

Outcome (units, follow-up)	No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (e.g. publication bias)	No. of patients in A1PI arm	No. of patients in placebo arm	Relative effect (95%CI)	Absolute effect (95%CI)	Quality	Importance
Mortality (follow up: 24 months)	1 RCT	not serious	not serious	not serious	serious [a]	none	1/93 (1.1%)	3/87 (3.4%)	RR 0.35 (0.05 to 2.27)	MD 22 fewer per 1,000 (from 33 fewer to 44 more)	⊕⊕⊕⊙ Moderate	Critical
Mortality (follow up: median 47 months)	2 Observational studies	serious [d,e,f]	serious [b]	not serious	serious [a]	none	87/774 (11.2%)	25/317 (7.9%)	not pooled	see comment	⊕⊙⊙⊙ Very low	Critical
SGRQ Score (follow up: range 24 to 30 months; Scale from: 0 to 100)	2 RCTs	not serious	serious [b]	not serious	serious [a]	none	128	120	-	MD 0.83 points lower (3.49 lower to 1.83 higher)	⊕⊕⊙⊙ Low	Critical
Quality of life (follow up: 12 months; assessed with: SGRQ score or narrative)	2 Observational studies [g]	serious [d,e,f]	not serious	not serious	serious [a]	none	Increased quality of life was observed in 3/5 measures.	⊕⊙⊙⊙ Very low	Critical	Quality of life (follow up: 12 months; assessed with: SGRQ score or narrative)	2 Observational studies [g]	serious [d,e,f]

Annual exacerbation rate (follow up: range 24 to 30 months)	2 RCTs	not serious	not serious	not serious	serious [a]	none	Higher reported RR (1.26, 95% CI 0.92 to 1.74), MD (0.36, 95% CI -0.44 to 1.16) in A1PI group; these differences were not significant				⊕⊕⊕⊙ Moderate	Critical
Number of exacerbations (follow up: 36 months)	1 Observational study	serious [e,f]	not serious	not serious	serious [a,h]	publication bias strongly suspected [i]	The mean (SD) number of exacerbations decreased from 1.2 (1.6) before AT to 1 (2.2) after AT (p < 0.01)	⊕⊙⊙⊙ Very low	Critical	Number of exacerbations (follow up: 36 months)	1 Observational study	serious [e,f]
CT-measured lung density (follow up: range 24 to 30 months; assessed with: g/mL)	3 RCTs	not serious	not serious	not serious	not serious	none	155	148	-	MD 0.87 g/L higher (0.31 higher to 1.42 higher)	⊕⊕⊕⊕ High	Critical
Hospitalisation due to COPD exacerbation (follow up: range 24 to 30 months)	2 RCTs	not serious	serious [b]	not serious	serious [a]	publication bias suspected [c]	Reported RR ranges from 0.56 (0.23 to 1.36) to 1.41 (0.57 to 3.48)				⊕⊙⊙⊙ Very low	Important

Change in FEV_1 (mL or % predicted) (assessed with: spirometry)	3 RCTs	not serious	not serious	not serious	serious [a]	none	159	154	-	SMD 0.17 SD lower (0.4 lower to 0.05 higher)	⊕⊕⊕⊙ Moderate	Important
Change in FEV_1 (mL or % predicted) (follow up: median 52 months; assessed with: spirometry)	4 Observational studies [g]	serious [d,e,f]	serious [b]	not serious	serious [a]	none	1068	510	-	see comment	⊕⊙⊙⊙ Very low	Important
Carbon monoxide diffusion (D_{LCO}) (follow up: range 24 to 30 months; assessed with: mmol/min/kPa or mL/mm Hg per min; %)	3 RCTs	randomised trials	not serious	not serious	not serious	serious [a]	155	151	-	SMD 0.11 SD lower (0.34 lower to 0.11 higher)	⊕⊕⊕⊙ Moderate	Important
Carbon monoxide diffusion (D_{LCO}) (follow up: range 24 to 30 months; assessed with: %)	1 Observational study	serious [b,c]	not serious	not serious	serious [a,e]	publication bias strongly suspected [d]	127	127	-	MD 10.2 (23.1 lower to 2.7 higher)	⊕⊙⊙⊙ Very low	Important

Lung infection (follow up: range 1 years to 10 years; assessed with: Self-reporting)	1 Observational study [g]	serious [d,f]	not serious	not serious	serious [a]	none	Lung infection < 2 increased from 27/89 to 73/89 Lung infection ≥ 2 decreased from 62/89 to 16/89	⊕⊙⊙⊙ Very low	Important			
Hospitalisation (follow up: median 24 months; assessed with: Number of days spent in hospital)	2 Observational studies [g]	serious [e,f]	not serious	not serious	serious [a,j]	publication bias strongly suspected [i]	The average time spent in hospital decreased on average by a day	⊕⊙⊙⊙ Very low	Important			

Abbreviations: **CI** = Confidence interval, **RR** = Risk ratio, **MD** = Mean difference, **SMD** = Standardised mean difference.

a. Underpowered to detect differences, b. Contradictory results not explained by sensitivity analysis, c. Exacerbations were recorded but not reported in at least one additional trial, d. Baseline population differences, e. Patients excluded from analysis without clear explanations, f. Poorly defined intervention and comparators, g. Before and after studies and cohort studies, h. Fulfils the MCID for exacerbations but the reduction is very small (1.2 to 1), i. Missing data, j. No or poor reporting of statistical analysis

GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 106 Evidence profile table of safety outcomes for A1PI compared to placebo for patients with severe AATD and emphysema

Outcome No. patients Follow-up (median, (range))	No. of studies and study design	Risk of bias	Inconsiste-ncy	Indirectness	Imprecision	Other considerations (publication bias)	Effect				Quality	Importance
Severe AE No. of patients: 257 F/U: 30 months (24 - 36 months)	2 RCTs	not serious	not serious	not serious	not serious	none	37/131 (28.2%)	43/126 (34.1%)	**RR 0.83** (0.57 to 1.19)	**58 fewer per 1,000** (from 65 more to 147 fewer)	⊕⊕⊕⊕ High	Critical
Severe AE No. of patients: F/U: 6 months (3 – 84 months))	11 Observational studies	serious [a]	not serious	not serious	not serious	none	Median occurrence 2.1% (0.0-30.0%)				⊕⊙⊙⊙ Very low	Critical
Death due to AE No. of patients: 180 F/U: 24 months (NA)	1 RCT	not serious	not serious	not serious	serious [b]	none	No treatment-related deaths were reported in any of the included RCTs				⊕⊕⊕⊙ Moderate	Critical
Death due to AE No. of patients: F/U: 18 months (4 – 72 months)	7 Observational studies	serious [a]	not serious	not serious	not serious	none	Median occurrence 0.0% (0.0-7.1%)				⊕⊙⊙⊙ Very low	Critical
Discontinuation due to AE No. of patients: 257 F/U: 27 months (24 – 30 months)	2 RCTs	not serious	not serious	not serious	serious [b]	none	1/131 (0.8%)	6/126 (4.8%)	**RR 0.22** (0.04 to 1.30)	**37 fewer per 1,000** (from 14 more to 46 fewer)	⊕⊕⊕⊙ Moderate	Critical
Discontinuation due to AE No. of patients: F/U: 33 months	8 Observational studies	not serious	not serious	not serious	not serious	none	Median occurrence 0.6% (0.0-7.1%)				⊕⊕⊙⊙ Low	Critical

Outcome No. patients Follow-up (median, (range))	No. of studies and study design	Risk of bias	Inconsiste-ncy	Indirectness	Imprecision	Other considerations (publication bias)	Effect				Quality	Importance
(3 – 84 months)												
Hospitalisation due to AE No. of patients: F/U: 60 months (36 – 84 months)	4 Observational studies	not serious	not serious	not serious	not serious	none	Median occurrence 1.4% (0.0-14.3%)				⊕⊕⊙⊙ Low	Important
Any adverse events No. of patients: 313 F/U: 30 months (24 – 36 months)	3 RCTs	not serious	serious [c]	not serious	not serious	none	129/159 (81.1%)	124/154 (80.5%)	**RR 1.00** (0.97 to 1.03)	**0 fewer per 1,000** (from 24 fewer to 24 more)	⊕⊕⊕⊙ Moderate	Important
Any adverse events No. of patients: 1747 F/U: 12 months (3 – 84 months)	13 Observational studies	serious [a]	not serious	not serious	not serious	none	Median occurrence 24.2% (0.0-100%)				⊕⊙⊙⊙ Very low	Important
Treatment-related adverse events No. of patients: 257 F/U: 27 months (24 – 30 months)	2 RCTs	not serious	not serious	not serious	not serious	none	32/131 (24.4%)	36/126 (28.6%)	**RR 0.86** (0.57 to 1.29)	**40 fewer per 1,000** (from 83 more to 123 fewer)	⊕⊕⊕⊕ High	Important
Treatment-related adverse	7 Observational	serious [a]	not serious	not serious	not serious	none	Median occurrence 10.0% (0.0-28.6%)				⊕⊙⊙⊙ Very low	Important

Outcome No. patients Follow-up (median, (range))	No. of studies and study design	Risk of bias	Inconsiste-ncy	Indirectness	Imprecision	Other considerations (publication bias)	Effect				Quality	Importance
events No. of patients: F/U: 6 months (4 – 48 months)	studies											
Dyspnoea No. of patients: 257 F/U: 27 months (24 – 30 months)	2 RCTs	not serious	serious [c]	not serious	serious [b]	none	17/131 (13.0%)	13/126 (10.3%)	**RR 1.27** (0.59 to 2.71)	**28 more per 1,000** (from 42 fewer to 176 more)	⊕⊕⊙⊙ Low	Important
Dyspnoea No. of patients: F/U: 60 months (4 – 84 months)	4 Observational studies	not serious	not serious	not serious	not serious	none	Median occurrence 18.3% (3.8-34.8%)				⊕⊕⊙⊙ Low	Important

Abbreviations: **AE** = adverse events, **CI** = confidence interval; **F/U** = follow-up, **RR** = risk ratio.
[a] Limited length of follow-up to detect events, outcomes not clearly defined a priori
[b] Small sample size for rare event
[c] Contradictory results across studies
GRADE Working Group grades of evidence (Guyatt et al., 2013)
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 107 Modified quality appraisal of included case series investigations according to the IHE Quality Appraisal of Case Series Studies (Guo et al. 2016)

Study ID	Was the objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in multiple centres?	Were patients recruited consecutively?	Were patient characteristics described?	Were the eligibility criteria clearly stated?	Did patients enter the study at a similar point in the disease?	Was the intervention clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention?	Were outcomes measured using appropriate methods?	Was follow-up long enough to capture important events?	Were losses to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were the adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interests and sources of support reported?
Alpha-1 Registry Group (1998)	✓	✓	✓	×	✓	✓	×	✓	×	×	?	✓	✓	×	•	•	×
Barros-Tizón et al. (2012)	•	×	✓	?	✓	✓	?	✓	✓	×	×	✓	✓	×	✓	?	✓
Barker et al. (1994)	✓	×	✓	×	•	×	×	✓	×	×	×	✓	NA	×	•	✓	×
Barker et al. (1997)	✓	✓	✓	×	✓	✓	×	•	✓	×	✓	×	✓	×	✓	✓	•
Campos et al. (2013)	✓	✓	✓	?	✓	✓	×	✓	•	✓	✓	×	✓	×	•	✓	✓
Hubbard & Crystal (1988)	✓		?	?	✓	?	×	•	✓	×	•	✓	✓	✓	?	✓	×
Sandhaus et al. (2014)	✓	✓	✓	✓	✓	✓	×	✓	•	×	×	×	✓	×	✓	✓	✓
Schmidt et al. (1988)	✓	?	✓	×	✓	•	?	•	•	×	×	×	✓	×	•	✓	×
Schwaiblmair et al. (1997)	✓	?	?	?	•	?	✓	•	×	×	×	✓	✓	×	×	?	•
Stocks et al. (2010)	✓	✓	✓	✓	•	✓	×	✓	✓	✓	•	×	✓	×	✓	✓	✓
Stoller et al. (2003)	✓	✓	✓	×	•	•	×	✓	✓	×	×	✓	✓	×	•	✓	•
Wencker et al. (1998)	✓	✓	✓	✓	•	✓	×	✓	×	×	×	✓	✓	✓	•	✓	×
Wewers et al. (1987)	?	?	?	?	•	•	×	•	?	×	×	×	✓	×	•	✓	×

✓ = Yes; × = No; ? = unclear; • = partial.

Table 108 Risk of bias in non–randomised studies comparing A1PI augmentation therapy and best supportive care or placebo

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias
Alpha-1 registry group 1998	Serious	Moderate	Serious	Low	Serious	Moderate	Serious	Serious
Barros-Tizon et al. 2012	Serious	Moderate	Serious	Low	Serious	Moderate	Serious	Serious
Karl et al. 2017	Serious	Low	Moderate	Low	Low	Moderate	Moderate	Serious
Lieberman 2000	Serious	Serious	Serious	Low	Low	Moderate	Low	Serious
McElvaney et al. 2017	Low	Low	Low	Low	Low	Moderate[14]	Moderate[15]	Moderate
Seersholm et al. 1997	Serious	Moderate	Low	Low	Low	Moderate	Low	Serious
Tonelli et al. 2009	Serious	Serious	Serious	Moderate	Serious	Moderate	Moderate	Serious
Wencker et al. 1998	Serious	Moderate	Serious	Low	Low	Moderate	Moderate	Serious

[14] Assessors not blinded to intervention, outcome of all-cause mortality could be subject to negligible assessor judgement

[15] Outcomes are consistent with an a priori plan, there is no indication of selection of reported patients of analyses

Table 109 Safety outcomes reported in RCT studies

Authors Publication Year Study ID	Adverse events Intervention	Adverse events Control	Severe adverse events	Treatment-related adverse events	Discontinuation/ Hospitalisation / Mortality due to adverse events (state which)
Chapman et al. 2015 **RAPID***	Events Total AE 1298 Patients Total AE 92 (99%) Events Infections/Infestations 334 Respiratory disorders 249 Nervous system 194 Admin site issues 144 COPD 107 GI disorders 104 Headache 98 Lower respiratory 88 MS disorders 68 Aggravation 62 Nasopharyngitis 53 Oropharyngeal pain 36 Cough 31 Dyspnoea 29 Bronchitis 26 Upper respiratory 26 Nausea 23 Sinusitis 17 Pneumonia 15 Pyrexia 15 Influenza 14	Events Total AE 1068 Patients Total AE 86 (99%) Events Infections/Infestations 369 Respiratory disorders 127 Nervous system 134 Admin site issues 101 COPD 53 GI disorders 92 Headache 105 Lower respiratory 72 MS disorders 75 Aggravation 41 Nasopharyngitis 58 Oropharyngeal pain 13 Cough 7 Dyspnoea 11 Bronchitis 16 Upper respiratory 25 Nausea 11 Sinusitis 25 Pneumonia 18 Pyrexia 8 Influenza 12	Patients Intervention: 25/93 (27%) 28/93 (30%)* Patients (n=93) Intervention: COPD 9 (10%) Pneumonia 3 (3%) Condit. aggravated 2 (2%) Lung neoplasm 2 (2%) Dizziness 2 (2%) Pneumothorax 2 (2%) Confusional state 1 (1%) Suicide attempt 1 (1%) Hydronephrosis 1 (1%) Angina 1 (1%) Abdominal pain 1 (1%) Back pain 1 (1%) Bladder cancer 1 (1%) Dyspnoea 1 (1%) GORD 1 (1%) Ileus 1 (1%) Nausea 1 (1%) Small intestinal obstruction 1 (1%) Patients Control: 27/87 (31%) 28/87 (32%)* Patients (n=87) Control: Pneumonia 6 (5%) Lower respiratory 4 (5%) Diverticulitis 2 (2%) COPD 2 (2%) Dyspnoea 2 (2%) Palpitations 1 (1%) Eye inflammation 1 (1%) Intestinal obstruction 1 (1%) Joint injury 1 (1%) Cholelithiasis 1 (1%) Bronchitis 1 (1%) Appendicitis 1 (1%) Cellulitis 1 (1%) Graft infection 1 (1%) Pyelonephritis 1 (1%) Sepsis 1 (1%) Back pain 1 (1%) Lung neoplasm 1 (1%)	Events Intervention: 91 Control: 50 Patients Intervention: 21 (23%) Control: 21 (24%)	Death due to an adverse event Intervention: 1 (1%) respiratory failure Control: 3 (3.5%) sepsis, pneumonia, breast cancer Discontinuation due to an adverse event Intervention: 1/93 (1%) Control: 4/87 (5%)

Authors Publication Year Study ID	Adverse events Intervention		Adverse events Control		Severe adverse events		Treatment-related adverse events	Discontinuation/ Hospitalisation / Mortality due to adverse events (state which)
	Fatigue	14	Fatigue	12	Adhesion 1 (1%)	Muscle spasm 1 (1%)		
	Back pain	12	Back pain	12	Chest pain 1 (1%)	Chest pain 1 (1%)		
					Haemorrhage post treatment 1 (1%)	Breast cancer 1 (1%)		
	Patients (n=93)		Patients (n=87)			Parathyroid tumour benign 1 (1%)		
	Infections/Infestations	77 (83%)	Infections/Infestations	76 (87%)	Hyponatraemia 1 (1%)			
	Respiratory disorders	63 (68%)	Respiratory disorders	49 (56%)	Influenza 1 (1%)	Syncope 1 (1%)		
	Admin site issues	48 (52%)	Admin site issues	42 (48%)	Pyrexia 1 (1%)	Nephrolithiasis 1 (1%)		
	GI disorders	46 (49%)	GI disorders	47 (54%)	Anaphylactic reaction 1 (1%)	Pneumothorax 1 (1%)		
	Nervous system	46 (49%)	Nervous system	43 (49%)		DVT 1 (1%)		
	Headache	37 (40%)	Headache	33 (38%)	Lower respiratory 1 (1%)			
	MS disorders	35 (38%)	MS disorders	37 (43%)	Diverticulitis 1 (1%)			
	Nasopharyngitis	30 (32%)	Nasopharyngitis	26 (30%)	Bronchitis 1 (1%)			
	COPD	30 (32%)	COPD	20 (23%)	Gastroenteritis viral 1 (1%)			
	Oropharyngeal pain	22 (24%)	Oropharyngeal pain	10 (11%)	UTI 1 (1%)			
	Cough	20 (22%)	Cough	7 (8%)	Intervertebral disc protrusion 1 (1%)			
	Aggravation	20 (22%)	Aggravation	14 (16%)	Pulmonary embolism 1 (1%)			
	Lower respiratory	18 (19%)	Lower respiratory	17 (20%)	Respiratory failure 1 (1%)			
	Dyspnoea	17 (18%)	Dyspnoea	10 (11%)	Hypotension 1 (1%)			
	Nausea	15 (16%)	Nausea	8 (9%)				
	Influenza	14 (15%)	Influenza	10 (11%)				
	Upper respiratory	14 (15%)	Upper respiratory	14 (16%)				
	Pyrexia	13 (14%)	Pyrexia	6 (7%)				
	Bronchitis	12 (13%)	Bronchitis	11 (13%)				
	Sinusitis	12 (13%)	Sinusitis	10 (11%)				
	Back pain	12 (13%)	Back pain	10 (11%)				
	Pneumonia	11 (12%)	Pneumonia	12 (14%)				
	Fatigue	8 (9%)	Fatigue	10 (11%)				

Authors Publication Year Study ID	Adverse events Intervention	Adverse events Control	Severe adverse events	Treatment-related adverse events	Discontinuation/ Hospitalisation / Mortality due to adverse events (state which)
Dirksen et al. 2009 EXACTLE*	Adverse events 28 Patients 37 (99%) Patients (n=38) Severe exacerbations 5 (13%) Pneumonia 3 (8%) Pneumothorax 2 (5%) Atrial fibrillation 2 (5%) Biliary colic 1 (3%) Constipation 1 (3%) Epistaxis 1 (3%) Gall bladder disorder 1 (3%) GO reflux 1 (3%) Malaria 1 (3%) Menorrhagia 1 (3%) Psoriasis 1 (3%) TIA 1 (3%) Upper limb fracture 1 (3%) Abdominal pain 0 (0%) IA haemorrhage 0 (0%) Rectal haemorrhage 0 (0%) Nodule 0 (0%) Cholestatic jaundice 0 (0%) Appendicitis 0 (0%) Sepsis 0 (0%) Subcutaneous abscess 0 (0%) UTI 0 (0%) Arthralgia 0 (0%)	Adverse events 40 Patients 38 (99%) Patients (n=39) Severe exacerbations 6 (15%) Pneumonia 4 (10%) Pneumothorax 0 (0%) Atrial fibrillation 0 (0%) Biliary colic 0 (0%) Constipation 0 (0%) Epistaxis 0 (0%) Gall bladder disorder 1 (3%) GO reflux 0 (0%) Malaria 0 (0%) Menorrhagia 0 (0%) Psoriasis 0 (0%) TIA 0 (0%) Upper limb fracture 0 (0%) Abdominal pain 1 (3%) IA haemorrhage 1 (3%) Rectal haemorrhage 1 (3%) Nodule 1 (3%) Cholestatic jaundice 1 (3%) Appendicitis 1 (3%) Sepsis 1 (3%) Subcutaneous abscess 1 (3%) UTI 1 (3%) Arthralgia 1 (3%)	Patients Intervention: 9/38 (24%) Control: 15/39 (38%) Patients (n=38) Pneumonia 3 (8%) Atrial fibrillation 2 (5%) Pneumothorax 2 (5%) Constipation 1 (3%) GORD 1 (3%) Biliary colic 1 (3%) Malaria 1 (3%) Upper limb fracture 1 (3%) Gallbladder disorder 1 (3%) TIA 1 (3%) Menorrhagia 1 (3%) Epixtaxis 1 (3%) Psoriasis 1 (3%) Patients (n=39) Pneumonia 4 (10%) Pulmonary embolism 2 (5%) Abdominal pain 1 (2%) Intra-abdominal haemorrhage 1 (2%) Rectal haemorrhage 1 (2%) Nodule 1 (2%) Gallbladder disorder 1 (2%) Jaundice 1 (2%) Appendicitis 1 (2%) Sepsis 1 (2%) Subcutaneous abscess 1 (2%) UTI 1 (2%) Arthralgia 1 (2%) Osteoarthritis 1 (2%) Breast cancer 1 (2%) COPD 1 (2%) Dyspnoea 1 (2%) Pleural effusion 1	Events Intervention: 14 Control: 35 Patients Intervention: 11 (29%) Control: 15 (38%)	Discontinuation due to an adverse event Intervention: 0 Control: 2

Authors Publication Year Study ID	Adverse events Intervention	Adverse events Control	Severe adverse events	Treatment-related adverse events	Discontinuation/ Hospitalisation / Mortality due to adverse events (state which)
	Osteoarthritis 0 (0%) Breast cancer 0 (0%) COPD 0 (0%) Dyspnoea 0 (0%) Pleural effusion 0 (0%) Pulmonary embolism 0 (0%) Pulmonary oedema 0 (0%) Lichen sclerosus	Osteoarthritis 1 (3%) Breast cancer 1 (3%) COPD 1 (3%) Dyspnoea 1 (3%) Pleural effusion 2 (5%) Pulmonary embolism 1 (3%) Pulmonary oedema 1 (3%) Lichen sclerosus	(2%) Pulmonary oedema 1 (2%) Lichen sclerosus 1 (2%)		
Dirksen et al. 1999 DIRKSEN99	Patients Adverse effects 0/28	Patients Adverse effects 0/28	NR NR	NR	NR

Abbreviations: **AE** = adverse event, **COPD** = chronic obstructive pulmonary disorders, **DVT** = Deep vein thrombosis, **GI** = gastrointestinal, **GO** = gastro-oesophageal, **GORD** = gastrointestinal reflux disease, **IA** = Intra-abdominal, **MS** = musculoskeletal, **TIA** = Transient ischaemic attack, **UTI** = Urinary tract infection. *Some data were obtained from the outcomes tab on www.clinicaltrials.gov

Table 110 Safety outcomes reported in single arm studies

Authors Publication Year Study ID	Adverse events*		Severe adverse events	Treatment-related adverse events Events Patients (%)	Discontinuation/ Hospitalisation / Death due to adverse events
McElvaney et al. 2017 **RAPID-OLE**	Adverse events Patients Patients (n=140) COPD Nasopharyngitis Headache Condition aggravated Lower respiratory tract infection Oropharyngeal pain Dyspnoea Upper respiratory tract infection Influenza Back pain Cough Pneumonia Oral candidiasis Bronchitis Diarrhoea Oedema peripheral Nausea	[48m] 773 [24m] 620 [48m] 76 (100%) [24m] 64 (97%) 56 (40%) 40 (28%) 28 (20%) 27 (19%) 20 (14%) 19 (13%) 18 (13%) 17 (12%) 16 (11%) 15 (11%) 13 (9%) 13 (9%) 13 (9%) 12 (8%) 12 (8%) 12 (8%) 11 (8%)	Patients Early-start [48m] (n=76) 23 (30%) Delayed-start [24m] (n=64) 19 (30%)	Patients Early-start [48m] (n=76) 11 (15%) Delayed-start [24m] (n=64) 7 (11%)	
The Alpha-1-Antitrypsin Deficiency	NR	NR	NR	NR	Discontinuation due to an adverse event 137/1129 (12%)

Authors Publication Year Study ID	Adverse events*		Severe adverse events	Treatment-related adverse events Events Patients (%)	Discontinuation/ Hospitalisation / Death due to adverse events
Registry Study Group 1998					
Barker et al. 1994	Adverse events Patients Patients (n=14) Back pain Headache Shortness of breathe	10 4 (28%) 2 (14%) 4 (28%) 4 (28%)	NR	NR	Hospitalisation due to an adverse event 2/14 (14%) Discontinuation due to an adverse event 1/14 (7%) Death due to an adverse event 1/14 (7%)
Barker et al. 1997	Adverse events Patients Patients (n=23) Headache Fatigue Dyspnoea Cough Chest tightness	27 21 (91%) 10 (43%) 9 (39%) 8 (35%) 2 (8%) 1 (4%)	Patients (n=23) 0	Patients (n=23) Dyspnoea 3 (13%) Chest tightness 1 (4%)	Death due to an adverse event (bronchopneumonia) 1/23 (4%)
Barros-Tizón et al. 2012	Adverse events Patients Patients (n=127) Pulmonary TE Myeloid leukaemia Acute MI Haemorrhagic infarction Chills Facial redness Sensation of cold Mild oedema Cutaneous exantema	14 11 (8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%)	Patients (n=127) Pulmonary TE 1 (0.8%) Myeloid leukaemia 1 (0.8%) Acute MI 1 (0.8%) Haemorrhagic infarction 1 (0.8%)	Patients (n=127) Chills 1 (0.8%) Facial redness 1 (0.8%) Sensation of cold 1 (0.8%) Mild oedema 1 (0.8%) Cutaneous exantema 1 (0.8%) Fever 1 (0.8%) Anxiety 1 (0.8%)	Discontinuation due to an adverse events 0/27 Death due to an adverse event 0/27

Authors Publication Year Study ID	Adverse events*		Severe adverse events	Treatment-related adverse events Events Patients (%)	Discontinuation/ Hospitalisation / Death due to adverse events
	Fever Anxiety Sleep apnoea UTI Hypertension Pneumonia	1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%)			
Campos et al. 2013**	Adverse events Patients Patients (n=30) COPD exacerbation UTI Contusion Thrombocytopenia Proteinuria Increased blood creatinine Increased blood glucose 	[60] 69 [120] 43 [60] 23 (77%) [120] 18 (60%) [60] 7 (23%) [120] 5 (17%) [60] 3 (10%0 [120] 0 [60] 1 (3%) [120] 0 [60] 2 (7%) [120] 0 [60] 2 (7%) [120] 1 (3%) [60] 0 [120] 2 (3%) [60] 0 [120] 2 (3%)	Patients (n=30) [60] 0 [120] 0	Events [60] 5 [120] 1 Patients (n=30) [60] 3 (10%) [120] 1 (3%)	Discontinuation due to an adverse event 0/30 Death due to an adverse event 0/30
Hubbard & Crystal1988	Patients (n=9) Clinical adverse events Change in body weight Infection from treatment	 0 0 0	NR	NR	NR

Authors Publication Year Study ID	Adverse events*	Severe adverse events	Treatment-related adverse events Events Patients (%)	Discontinuation/ Hospitalisation / Death due to adverse events
Sandhaus et al. 2014 GLASSIA	Adverse events at 3 m 39 Adverse events at 6 m 25 Patients 49 (98%) Patients (n=50) 3 months Cough 9 (18%) Upper respiratory infection 4 (12%) Nasopharyngitis 0 Rash Pharyngeal pain 0 Headache 0 COPD exacerbation 7 (14%) Productive cough 4 (8%) Nausea 3 (6%) Fatigue 3 (6%) Epistaxis 3 (6%) Urticaria 2 (4%) Hypersensitivity 2 (4%) 2 (4%) 6 months (n=21) Cough Upper respiratory infection 0 Nasopharyngitis 10 (47%) Rash 6 (28%) Headache 4 (19%) COPD exacerbation 0 Productive cough 0 Nausea 0 Fatigue 0 Epistaxis 0	Patients (n=33) 3 months Glassia: COPD exacerbation 1 (3%) Endoscopic retrograde cholangiopancreatography 1 (3%) Prolastin: Pulmonary emboli 1 (6%)	Patients 3 months Glassia: Headache 3/33 (9%) Hypertension 1/33 (3%) Prolastin: Headache 1/17 (6%) Hypertension 1/17 (6%) 6 months Glassia: Urticaria 1/21 (5%) Influenza symptoms 1/21 (5%) Lowered platelet count 1/21 (5%) Joint swelling 1/21 (5%) Dizziness 1/21 (5%) Rash 1/21 (5%)	Discontinuation due to an adverse event Patients 3 months Glassia: Pulmonary embolism 1/33 (3%) Prolastin: Urticaria 1/17 (6%)

Authors Publication Year Study ID	Adverse events*		Severe adverse events	Treatment-related adverse events Events Patients (%)	Discontinuation/ Hospitalisation / Death due to adverse events
	Urticaria Hypersensitivity	0 1 (5%) 0			
Schmidt et al. 1988	Adverse events Patients Patients (n=20) Haematoma-like spots Weight loss Infection from treatment	2 2 (10%) 1 (5%) 1 (5%) 0	Events 0	NR	NR
Schwaiblmair et al. 1997	*Adverse events* *Patients* Patients (n=20) Fever and exanthema Infection from treatment	1 1 (5%) 1 (5%) 0	Events 0	Events 0	Hospitalisation due to an adverse event 0/20 Death due to an adverse event 1/20
Stocks et al. 2010**	Adverse events Patients –Intervention 1 Patients –Intervention 2 Patients – open label Events Upper respiratory tract infection UTI Headache Rales Arthralgia Infection from treatment	14 11/12 (46%) 9/12 (37%) 11/12 (46%) 4 3 3 2 2 0	Events 2	Events Pruritus 2 Patients (n=24) Pruritus 1 (4%)	Discontinuation due to an adverse event 0/24 Death due to an adverse event 0/24
Stoller et al. 2003	Adverse events Patients Events	990 174 (20%)	Events Dyspnoea 61 Wheezing 14	NR	Events Discontinuation due to an adverse event 8/720 (1%)

Authors Publication Year Study ID	Adverse events*		Severe adverse events	Treatment-related adverse events Events Patients (%)	Discontinuation/ Hospitalisation / Death due to adverse events
	Headache Dizziness Fever Dyspnoea Flushing Fever Nausea Chills Rash Chest tightness Anxiety Mild pain Muscle cramps Tachycardia Chest pain Wheezing Emesis Hypotension Infection from treatment	339 121 64 61 54 53 53 47 37 37 32 31 27 20 16 14 12 2 0	Hypotension 2		Hospitalisation due to an adverse event 12/720 (2%) Physician visit or new medication due to an adverse event 152/720 (21%)
Wencker et al. 1998	Adverse events Patients Events Nausea/vomiting Increased dyspnoea Uticaria Fever Fatigue Anaphylactic reaction Worsened congestive	124 65 (15%) 21 19 18 17 7 4	Events 5 Patients (n=443) Anaphylactic reaction, 4 (1%) Worsened congestive heart failure with respiratory failure,1 (0.2%)	NR	Patients Hospitalisation due to an adverse event 5/443 (1%) Discontinuation due to an adverse event 3/443 (1%) Death due to an adverse event 0/443

Authors Publication Year Study ID	Adverse events*	Severe adverse events	Treatment-related adverse events Events Patients (%)	Discontinuation/ Hospitalisation / Death due to adverse events
	heart failure with respiratory failure 1 Infection from treatment 0			
Wewers et al. 1987	Adverse events 4 Patients 4 (19%) Patients (n=21) Fever 4 (19%) Infection from treatment 0	Patients (n=21) 0	NR	NR

Abbreviations: **TE** = thromboembolism, **m** = months. *Two single arm studies combined in this column only. **These studies report on the same patients at different time points and intervention products.

APPENDIX E EXCLUDED STUDIES

Studies potentially considered eligible for inclusion based on the PICO criteria, but subsequently excluded (due to containing duplicate information, in another language and not being a higher level of evidence than that available in English, being unable to extract the data etc), are described in the table below.

Trial ID	Grounds for seeking exclusion	Details	Report
Browne et al. 1996	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study	Browne, RJ, Mannino, DM & Khoury, MJ, 1996. Alpha 1-antitrypsin deficiency deaths in the United States from 1979-1991. An analysis using multiple-cause mortality data, *Chest*, 110(1), pp. 78-83.
Campos et al. 2009	Study design/outcomes	No safety data or other relevant outcomes were reported in this single-arm trial, there was some resource utilisation data that turned out to be of no use to the economics	Campos, MA, Alazemi, S, Zhang, G, Wanner, A, Salathe, M, Baier, H & Sandhaus, RA, 2009a. Exacerbations in subjects with alpha-1 antitrypsin deficiency receiving augmentation therapy, *Respir Med*, 103(10), pp. 1532-1539.
Dirksen et al. 1997	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study	Dirksen, A, Friis, M, Olesen, KP, Skovgaard, LT & Sorensen, K, 1997. Progress of emphysema in severe alpha 1-antitrypsin deficiency as assessed by annual CT, *Acta Radiol*, 38(5), pp. 826-832.
Esquinas et al. 2018	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study	Esquinas, C, Serreri, S, Barrecheguren, M, Rodriguez, E, Nunez, A, Casas-Maldonado, F, Blanco, I, Pirina, P, Lara, B & Miravitlles, M, 2018. Long-term evolution of lung function in individuals with alpha-1 antitrypsin deficiency from the Spanish registry (REDAAT), *International Journal of COPD*, 13pp. 1001-1007.
Green et al. 2016	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study	Green, CE, Parr, DG, Edgar, RG, Stockley, RA & Turner, AM, 2016. Lung density associates with survival in alpha 1 antitrypsin deficient patients, *Respir Med*, 112pp. 81-87.
Hutsebaut et al. 2015	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study	Hutsebaut, J, Janssens, W, Louis, R, Willersinn, F, Stephenne, X, Sokal, E & Derom, E, 2015. Activity of the alpha-1 antitrypsin deficiency registry in Belgium, *COPD* 12pp. 10-14.
King et al. 1994	Study design/outcomes	No appropriate outcomes were reported in this biomarker study, which was not patient-	King, MB, Campbell, EJ, Gray, BH & Hertz, MI, 1994. The proteinase-antiproteinase balance in alpha-1-proteinase inhibitor-deficient lung

Trial ID	Grounds for seeking exclusion	Details	Report
		specific	transplant recipients, *Am J Respir Crit Care Med*, 149(4), pp. 966-971.
Lara et al. 2015	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study (registry)	Lara, B & Miravitlles, M, 2015. Spanish Registry of Patients With Alpha-1 Antitrypsin Deficiency; Comparison of the Characteristics of PISZ and PIZZ Individuals, *Copd*, 12pp. 27-31.
Lara et al. 2017	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study (registry)	Lara, B, Blanco, I, Martinez, MT, Rodriguez, E, Bustamante, A, Casas, F, Cadenas, S, Hernandez, JM, Lazaro, L, Torres, M, Curi, S, Esquinas, C, Dasi, F, Escribano, A, Herrero, I, Martinez-Delgado, B, Michel, FJ, Rodriguez-Frias, F & Miravitlles, M, 2017. Spanish Registry of Patients With Alpha-1 Antitrypsin Deficiency: Database Evaluation and Population Analysis, *Arch Bronconeumol*, 53(1), pp. 13-18.
Lara et al. 2007	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study (registry)	Lara, B, de la Roza, C, Vila, S, Vidal, R & Miravitlles, M, 2007. Development and results of the Spanish registry of patients with alpha-1-antitrypsin deficiency, *Int J Chron Obstruct Pulmon Dis*, 2(3), pp. 393-398.
Ma et al. 2017	Study design/outcomes	No safety data or other relevant outcomes were reported in this post-hoc analysis of biomarkers	Ma, S, Lin, YY, Cantor, JO, Chapman, KR, Sandhaus, RA, Fries, M, Edelman, JM, McElvaney, G & Turino, GM, 2017. The Effect of Alpha-1 Proteinase Inhibitor on Biomarkers of Elastin Degradation in Alpha-1 Antitrypsin Deficiency: An Analysis of the RAPID/RAPID Extension Trials, *Chronic Obstructive Pulmonary Diseases*, 4(1), pp. 34-44.
Miravitlles et al. 1997	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study (registry)	Miravitlles, M, Vidal, R, Barros-Tizon, JC, Bustamante, A, Espana, PP, Casas, F, Martinez, MT, Escudero, C & Jardi, R, 1998. Usefulness of a national registry of alpha-1-antitrypsin deficiency. The Spanish experience, *Respir Med*, 92(10), pp. 1181-1187.
Piitulainen et al. 2003	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study	Piitulainen, E, Bernspang, E, Bjorkman, S & Berntorp, E, 2003. Tailored pharmacokinetic dosing allows self-administration and reduces the cost of IV augmentation therapy with human alpha(1)-antitrypsin, *Eur J Clin Pharmacol*, 59(2), pp. 151-156.
Schluchter	Study	No safety data or other relevant outcomes were	Schluchter, MD, Stoller, JK, Barker, AF, Buist, AS, Crystal, RG, Donohue, JF, Fallat, RJ, Turino, GM,

Trial ID	Grounds for seeking exclusion	Details	Report
et al. 2000	design/outcomes	reported in this observational study	Vreim, CE & Wu, MC, 2000. Feasibility of a clinical trial of augmentation therapy for alpha(1)-antitrypsin deficiency. The Alpha 1-Antitrypsin Deficiency Registry Study Group, *Am J Respir Crit Care Med*, 161(3), pp. 796-801.
Schmid et al. 2012	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study of biomarkers	Schmid, ST, Koepke, J, Dresel, M, Hattesohl, A, Frenzel, E, Perez, J, Lomas, DA, Miranda, E, Greulich, T, Noeske, S, Wencker, M, Teschler, H, Vogelmeier, C, Janciauskiene, S & Koczulla, AR, 2012. The effects of weekly augmentation therapy in patients with PiZZ alpha1-antitrypsin deficiency, *Int J Chron Obstruct Pulmon Dis*, 7pp. 687-696
Stockley et al. 2010	Study design/outcomes	This review combined the results of EXACTLE and DIRKSEN99, no novel outcomes were presented	Stockley, RA, Parr, DG, Piitulainen, E, Stolk, J, Stoel, BC & Dirksen, A, 2010. Therapeutic efficacy of alpha-1 antitrypsin augmentation therapy on the loss of lung tissue: an integrated analysis of two randomised clinical trials using computed tomography densitometry, *Respir Res*, 11pp. 136.
Stockley et al. 2002	Study design/outcomes	No safety data,or other relevant outcomes were reported in this observational study of biomarkers	Stockley, RA, Bayley, DL, Unsal, I & Dowson, LJ, 2002. The effect of augmentation therapy on bronchial inflammation in alpha1-antitrypsin deficiency, *Am J Respir Crit Care Med*, 165(11), pp. 1494-1498.
Stoller et al. 2000	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study (registry)	Stoller, JK, Brantly, M, Fleming, LE, Bean, JA & Walsh, J, 2000. Formation and current results of a patient-organized registry for alpha(1)-antitrypsin deficiency, *Chest*, 118(3), pp. 843-848.
Ulmer et al. 1990	Study design/outcomes	No safety data or other relevant outcomes were reported in this observational study	Ulmer, WT, Schmidt, EW & Rasche, B, 1990. Long term effect on lung function of alpha 1-protease inhibitor substitution therapy in COPD patients with Pi ZZ phenotype, *Eur Respir J Suppl*, 9pp. 21s-22s.
Zamora et al. 2008	Study design/outcomes	No safety data were reported in this observational study	Zamora, NP, Pla, RV, Del Rio, PG, Margaleff, RJ, Frias, FR & Ronsano, JBM, 2008. Intravenous human plasma-derived augmentation therapy in alpha1-antitrypsin deficiency: From pharmacokinetic analysis to individualizing therapy, *Annals of Pharmacotherapy*, 42(5), pp. 640-646.

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Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1530 – Purified human alpha1-proteinase inhibitor for the treatment of alpha1-proteinase inhibitor deficiency, leading to chronic obstructive pulmonary disease

Applicant: **National Blood Authority (NBA)**

Date of MSAC consideration: **MSAC 74th Meeting, 23-24 November 2018**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting National Product List (NPL) blood product listing of purified human alpha1-proteinase inhibitor (A1-PI) for the treatment of A1-PI deficiency, leading to chronic obstructive pulmonary disease (COPD), was received from the National Blood Authority (NBA) by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support A1-PI for the treatment of A1-PI deficiency. MSAC recognised the large unmet clinical need and the evidence of a radiologically detectable treatment effect, but was concerned with the weak evidentiary basis provided to suggest that changes in CT density predicts clinically meaningful health outcomes. MSAC also advised that, even with favourable assumptions regarding estimates of possible health outcomes of A1-PI treatment, the economic evaluation generated unacceptably large incremental cost-effectiveness ratios at the prices proposed by the sponsors.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted the impact that severe A1-PI deficiency (serum A1≤11μM) with emphysema (FEV_1<80%) has on patients and their carers, resulting in strong consumer support for the proposed treatment both in Australia and overseas.

The proposed treatment is lifelong intravenous blood augmentation therapy via weekly infusions of purified human A1-PI for ex- or never-smoking patients. MSAC noted that the two alternative products are considered to be essentially bioequivalent. MSAC noted that the recommended dosing is 60mg/kg per week, but that there are ongoing clinical trials investigating optimal dosing regimens, with dosing up to 120mg/kg per week. MSAC noted

that if the required dose is higher, then the overall cost would increase if the current price per mg is maintained.

MSAC noted that augmentation therapy with A1-PI is not currently funded or reimbursed in private or public settings in Australia for this or any other clinical indication.

MSAC noted the estimated prevalence of carriers of alleles related to A1-PI deficiency in the Australian population is 1 in 8.9 individuals. The PiZZ allele (with a prevalence of 1 in 5584), contributes to the greatest burden; however, not all people with PiZZ A1-PI deficiency will go on to develop severe emphysema. MSAC noted that the estimated number of people meeting the criteria for treatment with A1-PI in Australia in 2018 was s47(1)(b) Treatment is lifelong and not curative; therefore, the number of patients being treated is expected to moderately cumulative increase over time.

MSAC noted that the comparator intervention for patients with severe A1-PIdeficiency and emphysema is best supportive care (BSC).

MSAC noted that, overall, it appears that A1-PI is safe, with most adverse events being related to the underlying disease.

MSAC noted that there are no statistically significant differences between A1-PI and placebo in relation to mortality, exacerbation of COPD, hospitalisation due to COPD exacerbation, quality of life (St. George's Respiratory Questionnaire), respiratory function (FEV_1), exercise capacity (incremental shuttle walk test) or carbon monoxide diffusion capacity (D_{LCO}).

MSAC noted that the only statistically significant difference observed in clinical trials was for CT-measured lung density, which favoured A1-PI therapy compared with placebo. MSAC noted that recommending public funding of A1-PI products requires accepting that effects on CT-measured lung density have been demonstrated to be a surrogate for effects on outcomes known to be clinically meaningful, including respiratory function, quality of life, overall survival, or quality-adjusted life-years (QALYs). However, even the clinical significance of the observed difference in CT-measured lung density is uncertain, as minimal clinically important differences (MCIDs) for changes in this surrogate have not been established in the peer-reviewed literature.

MSAC noted the claim that A1-PI therapy meets three of the four criteria warranting Rule of Rescue. However, it is unclear whether CT-measured lung density is a sufficiently informative surrogate for the Rule of Rescue criterion of 'worthwhile clinical improvement'.

MSAC noted that CT lung density calculations are not routinely performed in Australia, although it is likely all modern scanners could be equipped to do so with access to necessary software (noting that the cost of software is unknown).

A1-PI is known to be ineffective in smokers. Strict requirements would therefore be needed to ensure use is limited to non-smokers (of tobacco and/or cannabis).

MSAC noted that the treatment cost with A1-PI is high (approximately s47(1)(b) per patient per year) for the patient's lifetime and the base case modelled incremental cost-effectiveness ratio (ICER) is s47(1)(b) per QALY gained using a weighted average price for the two available A1-PI therapies. MSAC advised that this ICER/QALY was unacceptably large and based on assumptions of long-term clinical effect that favoured the intervention, and substantial price reductions would be required to bring it within an acceptable range.

MSAC noted that the assessment group attempted to improve the modelled cost-effectiveness of the A1-PI products by applying an evidence-based stopping rule for patients who demonstrate limited treatment response to A1-PI therapy. In the model, 113/1,000 individuals in the cohort progress from no decline or slow decline to rapid decline, despite being on A1-PI therapy for four years – the A1-PI therapy costs for these individuals beyond four years was then removed from the model. However, this was only associated with a modest improvement in cost-effectiveness and the ICER remained unacceptably large (s47(1)(b) /QALY compared with s47(1)(b) /QALY for the base case).

MSAC also noted that an additional univariate sensitivity analysis (performed by the assessment group by changing specific transitions from FEV_1 >50 to FEV_1<50 to remove a modelled treatment effect on FEV_1 which contradicted the results of the randomised trials) did not have a major impact on the ICER. If both A1-PI therapy and BSC arms had FEV_1 annual probability declines of s47(1)(b) then the ICER would increase from s47(1)(b) /QALY to s47(1)(b) /QALY.

MSAC noted that there is significant uncertainty regarding the number of patients who will be diagnosed with A1-PI deficiency if the A1-PI products are available on the NPL. The NBA would need to be able to negotiate an overall risk sharing arrangement with suppliers to mitigate this financial risk.

MSAC concluded that there is a clear physiological effect on lung density which is detectable radiologically; however, there is no basis on which to draw a large clinical effect, and thus no evidence of patient-relevant outcomes.

MSAC again acknowledged the high priority the public consultation feedback gave to meeting the clinical need that the applicant claims will be helped by this intervention, but considered that the evidence was inadequate to justify the therapeutic claims made in the application.

4. Background

Augmentation therapy with any A1-PI therapy is not currently funded or reimbursed in private or public settings in Australia (for this or any other clinical indication).

5. Prerequisites to implementation of any funding advice

PROLASTIN-C and Zemaira (marketed as Respreeza in Europe), are two augmentation therapy products registered on the Australian Register of Therapeutic Goods (ARTG) in Australia. The two therapies consist of the same components with slightly different eligibility criteria (Table 1).

Table 1 Approved augmentation therapies and their indications

Product	ARTG ID and details
PROLASTIN-C	ARTG ID 234553: indicated to increase serum A1-PI levels in adults with congenital deficiency of alpha-1 anti-trypsin and with clinically significant emphysema (FEV_1 less than 80%). The data for clinical efficacy of PROLASTIN-C is derived from changes in the biomarkers alpha-1 anti-protease level and CT lung density. Efficacy on FEV_1 or patient relevant endpoints such as quality of life or pulmonary exacerbations has not been established in randomised clinical trials. Clinical trials have only included patients who were not smoking.
Zemaira	ARTG ID 273182: indicated for maintenance treatment, to slow the progression of emphysema in adults with documented severe A1-PI deficiency (A1-PI less than 11 µM) and progressive lung disease. Patients are to be under optimal pharmacologic and non-pharmacologic treatment.

Abbreviations: **ARTG** = Australian Register of Therapeutic Goods, **FEV_1** = forced expiratory volume in 1 second, **µM** = micromolar.

6. Proposal for public funding

Augmentation therapy with A1-PI is proposed for reimbursement on the NPL, managed by the NBA. As such, no Medicare Benefits Schedule item descriptor is required.

7. Summary of public consultation feedback/consumer issues

Six associations provided targeted feedback, and one individual provided non-targeted feedback on this consultation. All respondents using the feedback form 'strongly agreed' with the clinical claim made by the applicant and argued the urgent priority to address the unmet clinical need.

8. Proposed intervention's place in clinical management

The population to be considered in this assessment is ex- or never-smoking patients with emphysema (defined as FEV_1 <80%) and severe A1-PI deficiency (defined as serum A1 levels ≤11 μM (approximately 59 mg/dL); Hatipoglu and Stoller 2016).

Patients with A1-PI deficiency are currently managed with best supportive care (BSC). BSC includes pharmacological strategies (e.g. inhaled medications) and non-pharmacological strategies (e.g. pulmonary rehabilitation and physical activity) aimed at providing symptomatic relief. The current (Figure 1) and proposed (Figure 2) clinical management algorithms are presented below.

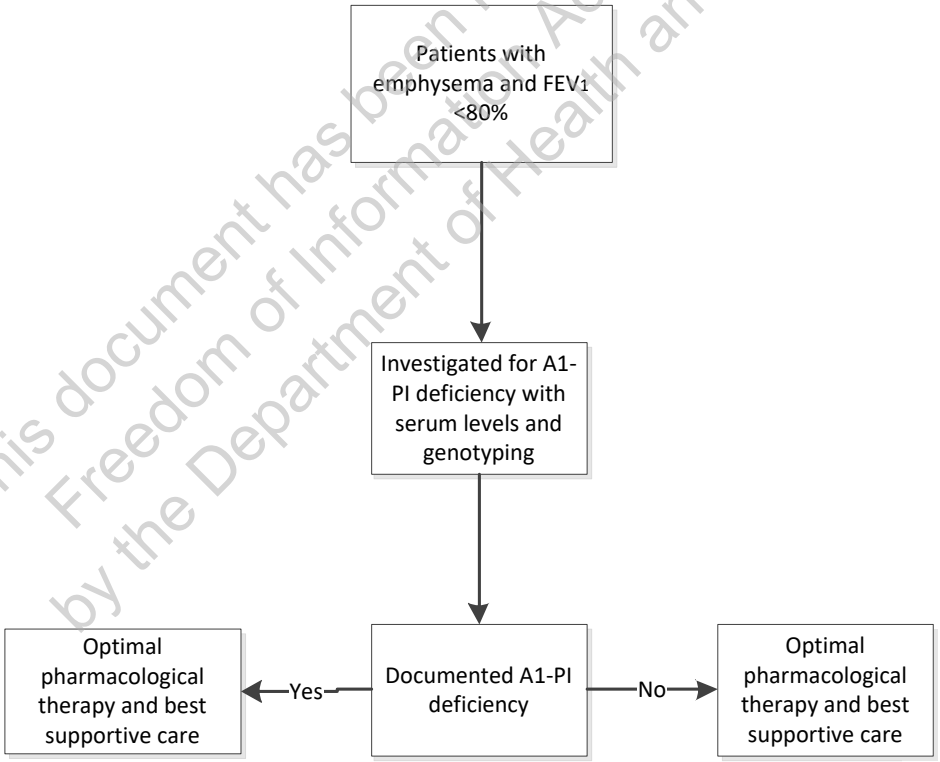

Figure 1 Current clinical management algorithm for patients with emphysema and FEV1 <80%

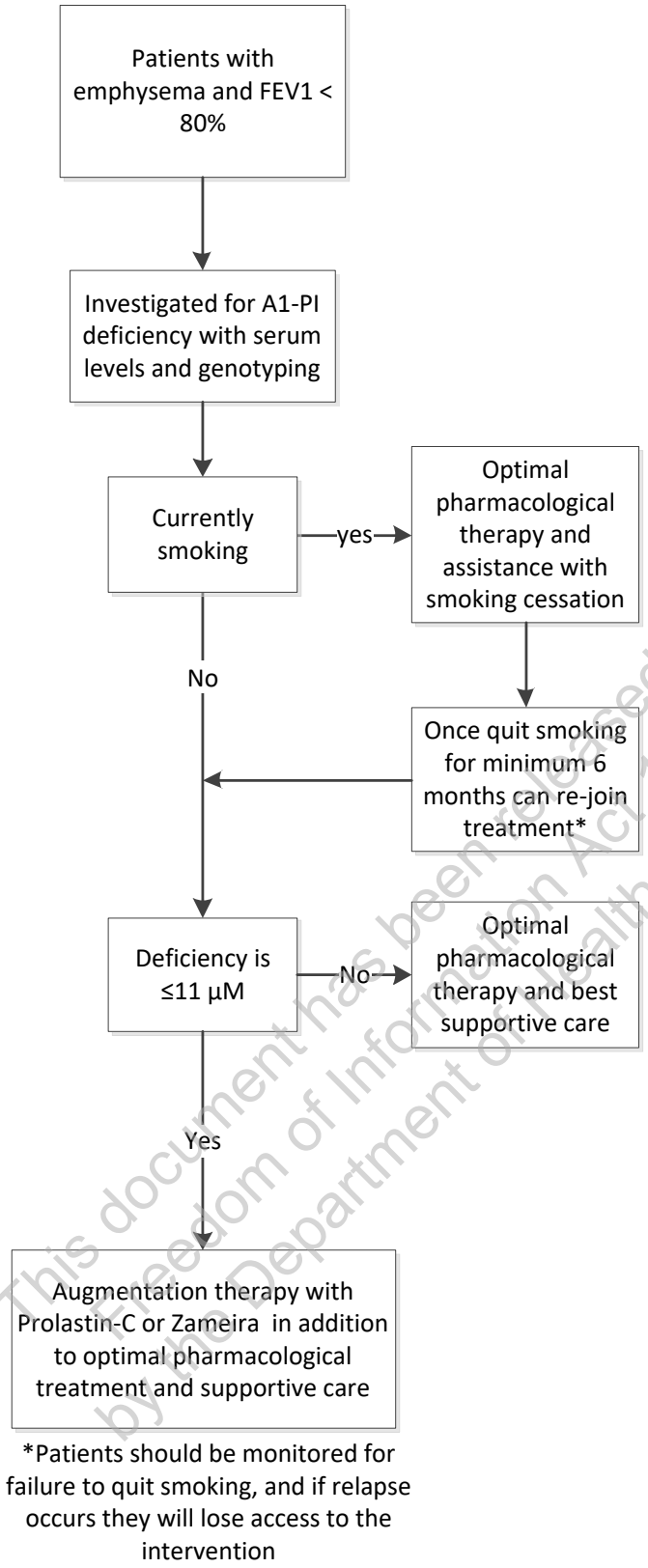

Figure 2 Proposed clinical management algorithm for patients with emphysema and FEV1 <80%

9. Comparator

The application stated that there are currently no active comparators for augmentation therapy that modify the progression of emphysema or COPD in patients with A1-PI deficiency. The comparator for patients with COPD is BSC.

10. Comparative safety

The application stated that three randomised controlled trials (RCT)s were identified that evaluated the effectiveness of A1-PI compared to placebo (n=313). Included patients were relatively homogenous across the included studies, representing ex- or never-smokers with severe A1-PI deficiency (serum A1 ≤11 µM) and emphysema (forced expiratory volume in 1 second (FEV_1) 25% to 80%). The included RCTs were generally well conducted; however, the method of allocation concealment was poorly reported across all trials. Seventeen single-arm studies were identified that provided evidence on the safety of A1-PI. Key safety outcomes were: death due to adverse events, severe adverse events, and discontinuation or hospitalisation due to adverse events.

The application stated that six deaths occurred in the eligible studies, which included a total of 899 patients. None of these deaths was reported to be treatment-related. Severe adverse events were also uncommon, with a median occurrence of 2% in the patient population (range 0%-38%). Discontinuation due to adverse events had a median occurrence of 0.5% in the patient population (range 0%-12%) across nine studies. Hospitalisation had a median occurrence of 1.5% in the patient population (range 0%-14%) across four studies.
The application stated that three studies reported safety in patients treated with one of the two therapies under assessment, Zemaira and PROLASTIN-C. All of these studies found that rates of severe adverse events were unchanged across intervention groups (Figure 3).

Figure 3 Forest plot indicating the pooled rate of severe adverse events for A1-PI compared to placebo

The application stated that fifteen studies reported any adverse event, with a rate ranging from 0% to 100% and a median of 37%. Differences between the RCTs and observational studies in the rates of any adverse event may indicate under-reporting in the observational studies. Dyspnoea and treatment-related adverse events were also reported. Dyspnoea occurred after augmentation therapy in 12.5% of the patient population (range 0%-35%). Events reported by the authors to be treatment-related had a median occurrence of 11% in the patient population (range 0%-38%).

The application stated that overall, it appears that the intervention is safe, with most events being related to the underlying disease.

11. Comparative effectiveness

CT-measured lung density was the primary outcome in two RCTs, and FEV_1 was the primary outcome in one RCT.

No significant differences between A1-PI and placebo were identified in relation to mortality, exacerbation of COPD, hospitalisation due to COPD exacerbation, quality of life (St. George's Respiratory Questionnaire), respiratory function (FEV_1), exercise capacity (incremental shuttle walk test) or carbon monoxide diffusion capacity (D_{LCO}). No relevant data were identified for dyspnoea.

The only statistically significant difference observed was for CT-measured lung density (Figure 4), which favoured A1-PI.However, the clinical significance of this difference is uncertain, as MCIDs for changes in CT-measured lung density have not been established in the peer-reviewed literature.

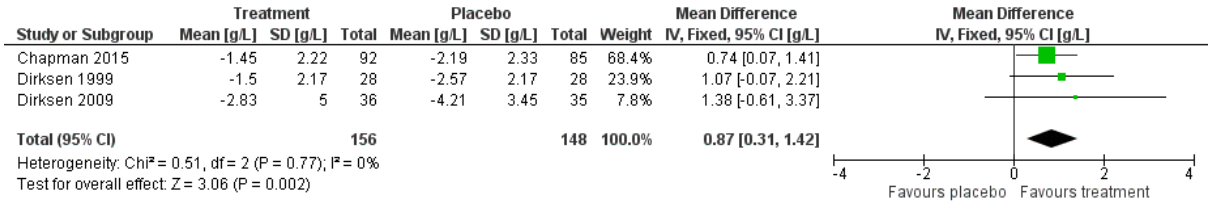

Figure 4 Forest plot indicating changes in CT-measured lung density (g/mL) in A1-PI compared to placebo measured at 24 to 30 months follow-up. (Chapman 2015 and Dirksen 1999 reported an annualised rate, whereas Dirksen 2009 reported the change from baseline at 24 months.)

The summary of findings (incorporating both benefits and harms) is shown in Table 2.

Table 2 Balance of clinical benefits and harms of A1-PI relative to placebo as measured by the critical patient-relevant outcomes in the key studies

Outcomes (units) Follow-up	Risk with placebo	Risk with A1-PI (95% CI)	Relative effect (95% CI)	Participants (studies)	Quality of evidence (GRADE)	Comments
Mortality F/U 24 months	34 per 1,000	12 per 1,000 (2 to 78)	RR 0.35 (0.05 to 2.27)	180 (1 RCT)	⨁⨁⨁⊙ MODERATE	Uncertain due to low event rate, RR subject to error
Quality of life (SGRQ) F/U 24 to 30 months	-	MD 0.83 points lower (3.49 points lower to 1.82 points higher)	-	248 (2 RCT)	⨁⨁⊙⊙ LOW	Direction favours placebo; not statistically significant
Annual exacerbation rate F/U 24 to 30 months	-	-	Higher reported RR (1.26, 95% CI 0.92 to 1.74), MD (0.36, 95% CI -0.44 to 1.16) in A1-PI group	257 (2 RCT)	⨁⨁⨁⊙ MODERATE	Direction favours placebo; not statistically significant
CT-measured lung density F/U 24 to 30 months	-	SMD 0.87 g/L higher (0.31 higher to 1.42 higher)	-	304 (3 RCT)	⨁⨁⨁⨁ HIGH	Direction favours A1-PI; statistically significant
Mortality due to treatment-related adverse events F/U 24 months	No treatment-related deaths reported			180 (1 RCT)	⨁⨁⨁⊙ MODERATE	No reported deaths due to treatment-related adverse events
Severe adverse events F/U 24 to 30 months	341 per 1,000	283 per 1,000 (195 to 406)	RR 0.83 (0.57 to 1.19)	257 (2 RCT)	⨁⨁⨁⨁ HIGH	Direction favours A1-PI; not statistically significant
Discontinuation due to adverse events F/U 24 to 30 months	48 per 1,000	10 per 1,000 (2 to 62)	RR 0.22 (0.04 to 1.30)	248 (2 RCT)	⨁⨁⨁⊙ MODERATE	Direction favours A1-PI; not statistically significant
Hospitalisation due to adverse events F/U 3 to 6 years	Median rate 1.4% (range 0.0% to 14.3%)			497 (4 observational studies)	⨁⨁⊙⊙ LOW	-

Abbreviations: **F/U** = follow-up, **MD** = mean difference, **RR** = relative risk, **SGRQ** = St George's Respiratory Questionnaire, **SMD** = standardised mean difference.
GRADE Working Group grades of evidence (Guyatt et al., 2013)
⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Clinical claim

The clinical claim is that, relative to best supportive care, A1-PI (with either product) slows disease progression in patients with severe A1-PI deficiency and emphysema. On the basis of the evidence presented, the contracted assessment stated that A1-PI therapy has uncertain effectiveness relative to best supportive care, and that relative to placebo, there appear to be no important differences in safety outcomes associated with A1-PI therapy.

12. Economic evaluation

A cost-utility analysis was undertaken to determine the value of A1-PI in addition to optimal pharmacological treatment and supportive care (best supportive care).

Table 3 Summary of the economic evaluation

Perspective	This economic evaluation was conducted from the perspective of the Australian health system. It includes resource use supported by government and patients, along with health outcomes applicable to the treatment of patients with emphysema due to A1-PI deficiency.
Intervention	Augmentation therapy in addition to optimal pharmacological treatment and supportive care.
Comparator	Best supportive care: optimal pharmacological treatment and supportive care
Type of economic evaluation	Cost-utility analysis
Sources of evidence	RAPID study, RAPID-OLE study, UK Registry data
Time horizon	30-year time horizon in the base case Sensitivity analyses include a time horizon of 20 years and 40 years
Outcomes	Quality-adjusted life years (QALYs) gained and life-years gained
Methods used to generate results	Cohort expected value analysis
Health states	1. $FEV_1 \geq 50\%$ predicted, no lung density decline 2. $FEV_1 \geq 50\%$ predicted, slow lung density decline 3. $FEV_1 \geq 50\%$ predicted, rapid lung density decline 4. $FEV_1 < 50\%$ predicted, no lung density decline 5. $FEV_1 < 50\%$ predicted, slow lung density decline 6. $FEV_1 < 50\%$ predicted, rapid lung density decline 7. Lung transplant 8. Dead
Cycle length	1 year
Discount rate	5% used for base and 3.5% and 7% sensitivity analyses
Software packages used	Microsoft Excel 2010

Using a weighted average price for the two A1-PI products, the modelled incremental cost-effectiveness ratio (ICER) of A1-PI in addition to BSC (relative to BSC alone) was found to be s47(1)(b) per QALY over a time horizon of 30 years. Adopting a modelled time horizon equivalent to the trial duration (four years) yielded an ICER of s47(1)(b) per QALY (Table 4).

Table 4 Incremental cost-effectiveness ratio (1,000-patient cohort)

	Cost (AU$)	Incremental cost (AU$)	Effectiveness (QALYs)	Incremental effectiveness	ICER (AU$)
Trial period					
A1PI augmentation therapy	s47(1)(b)		2,985.3	162.7	s47(1)(b)
Best supportive care	18,531,803		2,822.6		
Lifetime					
A1PI augmentation therapy	s47(1)(b)		5,826.6	1,301.1	s47(1)(b)
Best supportive care	37,389,939		4,525.4		

Abbreviations: **A1PI** = Aplha-1 proteinase inhibitor; **ICER** = incremental cost-effectiveness ratio; **QALY** = quality-adjusted life year.

The assessment noted that the price paid for the augmentation therapy product is the key driver of model results (Table 5).

Table 5 Drivers of the economic model

Description	Method/Value	Impact
Cost of the AT product	The average dosing for augmentation therapy is taken from the RAPID trial and applied to an average weight of 75.9 kg. The number of vials (rounded to a whole number) is multiplied by average, high and low AT product prices.	The base cost of augmentation therapy assumes a price per 1,000 ml s47(1)(b) This varies from s47(1)(b) per 1,000ml vial. The estimated ICER varies considerably between s47(1)(b) and s47(1)(b) per QALY.
Transition between FEV_1 and CT density decline during RAPID drives clinical benefit	There were considerable differences in transition between health states for the augmentation therapy and BSC arms in the RAPID trials. The economic model assumes movement to no, slow and rapid decline tracks during the trial period is sustained for a lifetime.	A higher number of patients move to the FEV_1<50 decline states on the BSC arm in RAPID. Movement during the trial period drives economic results. Allowing transition between no, slow and rapid tracks after 4 years has limited impact on the estimated ICER.
Selection of extrapolation model for the FEV_1<50 rapid-decline group survival	In most cases the Gompertz model is the best fit model to extrapolate survival and this model is used across all non-transplant states. The model is varied as part of sensitivity analyses that included use of the Log-logistic, Lognormal, Weibull, Exponential and Generalised Gamma specifications. Large numbers of patients transition to this state during the trial period, particularly on the BSC arm.	The specification of the FEV<50 rapid-decline model had the largest impact on the estimated ICER. The use of Lognormal, Generalised Gamma and Weibull models resulted in the ICER being 10% more cost effective, while use of the Exponential model resulted in a 10% decrease in cost effectiveness.
Disease management costs for COPD	Disease management costs in many reviewed COPD economic models were an aggregate of maintenance and acute care costs during flare ups. The frequency of flare ups was not explicitly modelled in this assessment. The Thomas et al. 2014 analysis included acute care proportions for each state. They are varied by 20% for each COPD state.	This variation has limited impact as economic results are governed by AT product costs. The proportion of severe COPD patients who are very severe, assumed to be 74% in the base cases, also varied. Similarly, this scenario had limited impact on the estimated ICER.

Abbreviations: **BSC** = best supportive care, **COPD** = chronic obstructive pulmonary disease, **CT** = computed tomography, **FEV_1** = forced expiratory volume in 1 second, **ICER** = incremental cost effectiveness ratio.

13. Financial/budgetary impacts

The financial impact of the potential listing of A1-PI augmentation therapy is calculated using an epidemiological approach over a five-year period, based on an estimate of the number of patients eligible for treatment.

Table 6 Estimated financial impact to government from augmentation therapy listing

	2019	2020	2021	2022	2023
Total government costs					
AT patients	s47(1)(b)				
NBA-supported AT product costs					
MBS-supported infusion service delivery	277,422	328,838	381,828	436,429	443,412
Total net costs to governments	s47(1)(b)				

Abbreviations: **AT** = augmentation therapy, **MBS** = Medical Benefit Schedule, **NBA** = National Blood Authority.

A key uncertainty is the price of augmentation therapy. Variations in price have a large impact on both financial and economic attractiveness because of the large contribution of the augmentation therapy itself to overall resource in the economic model. The proposed price of PROLASTIN-C is s47(1)(b) per 1,000ml vial and ZEMAIRA s47(1)(b). An average price of s47(1)(b) is

included, with s47(1)(b) and s47(1)(b) used as high and low bounds in sensitivity analyses. Varying the prevalence proportions by 10% has a lesser financial impact. Uptake rate also has an impact. A decrease in year 2022 uptake from 90% to 80% results in a s47(1)(b) budget requirement in that year. MSAC noted that the financial estimates were sensitive to assumptions regarding rates of diagnosis of A1-PI deficiency and non-smoking rates. MSAC noted advice from the product manufacturers in their pre-MSAC responses that patients receiving A1-PI are highly motivated to maintain their non-smoking status.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Rarity or under-diagnosis of condition in Australia	Alpha1-proteinase inhibitor (A1-PI) deficiency appears to be underdiagnosed in the USA, which means it could also be the case in Australia. The population may therefore be much larger than the estimated s47(1)(b) patients.
Safety	Overall, it appears that the intervention is relatively safe compared to placebo, in addition to best supported care.
Effectiveness	The only statistically significant difference observed was for CT-measured lung density, which favoured A1-PI therapy compared to placebo; however, the clinical significance of this difference is uncertain, as MCIDs for changes in CT-measured lung density have not been established in the peer-reviewed literature. No significant differences between A1-PI and placebo were identified in relation to mortality, exacerbation of COPD, hospitalisation due to COPD exacerbation, quality of life (SGRQ), respiratory function (FEV_1), exercise capacity (incremental shuttle walk test) or carbon monoxide diffusion capacity (DLCO).
Costs	Not all relevant costs were captured (e.g. additional A1-PI serum tests, additional IgA tests, IV device, additional consultations).
Population	Trials included patients with a wide range of lung function.
Rule of Rescue	It is claimed that A1-PI deficiency meets three of the four criteria warranting the Rule of Rescue. It is unclear whether CT-measured lung density is a sufficiently informative surrogate for judging the Rule of Rescue criterion of 'worthwhile clinical improvement'.
Potential bias	The small pool of researchers and the low frequency of investigator-initiated trials mean there is potential for selection and/or reporting bias.

ESC discussion

The request is for lifelong intravenous blood augmentation therapy via weekly infusions of purified human A1-PI (60 mg/kg per week) for the treatment of A1-PI deficiency, also known as alpha-1 antitrypsin deficiency (AATD). ESC noted that ongoing trials are investigating optimal dosing regimens (including higher doses). ESC noted the manufacturers' claim that successful listing of the blood product in the target population and setting will lead to slower disease progression compared to best supportive care.

ESC noted that A1-PI deficiency is an inherited genetic condition that results in decreased circulating, and/or abnormally functioning, A1-PI protein. Severe A1-PI deficiency (defined as serum levels of A1-PI ≤11 μM) most commonly manifests as emphysema or liver disease.

Prevalence data in Australia are limited. The prevalence of the PiZZ (protease inhibitor, homozygote Z) allele in Australia, which is identified in the most severely affected patients (with greatly increased risk of emphysema), is estimated at 1 in 5,584. The prevalence of PiSZ, which is identified in individuals who produce less A1-PI than normal (and have an increased risk of emphysema), is estimated at 1 in 841. ESC noted that it is the PiZZ allelle that contributes to the greatest burden of lung disease in the A1-PI deficient population, but not all people with PiZZ A1-PI deficiency go on to develop severe emphysema.

ESC noted that the intended population comprises ex-smokers or patients who have never smoked, who have emphysema and severe A1-PI deficiency (serum A1-PI ≤11 μM). ESC noted that the contracted assessment estimated that the number of people meeting the criteria for treatment with A1-PI in Australia in 2018 was likely to be s47(1)(b) Considering treatment is lifelong and not curative, the number of patients being treated is expected to have a moderate cumulative increase over time. However, ESC noted that A1-PI appears to be under-diagnosed in the USA, which means it could also be the case in Australia. ESC noted that there are estimated 80,000–100,000 patients with severe A1-PI deficiency in the USA (Stoller et al.; *UpToDate*).

A1-PI augmentation therapy is an intervention that can be added to BSC for patients with emphysema. ESC noted clinical advice received during the assessment that emphasised the necessity for patients to maintain a non-smoking status for this augmentation therapy to be effective.

ESC noted that 17 single-arm studies were included for the evaluation of safety outcomes. Overall, it appears that the intervention is safe, with most observed events judged as being related to the underlying disease. ESC noted that patients with an IgA deficiency are at risk of an anaphylactic reaction.

ESC noted that no studies comparing A1-PI augmentation therapy to optimal pharmacological treatment and supportive care were identified. ESC noted that, because of the rarity of A1-PI deficiency, clinical trials are often underpowered to detect statistical differences in outcomes (such as quality of life and mortality). The key studies of A1-PI therapy have used CT-measured lung density (PD15; 15th percentile lung density) as a primary outcome. It is claimed that CT-measured lung density correlates to markers of lung health and mortality, and this correlation has been used to infer clinical efficacy. PD15 has been validated as a consistent measure of lung density, specifically in A1-PI deficient patients, in order to overcome the challenges of adequately powering a study to detect significant differences in functional outcomes (such as FEV_1) (Parr et al. 2006; Schluchter et al. 2000). However, ESC noted that minimum clinically important differences (MCID) in CT-measured lung density for predicting changes in disease progression have not yet been defined in the peer-reviewed literature.

ESC noted that three randomised controlled trials (RCTs) were identified (RAPID, EXACTLE and DIRKSEN99) that evaluated the effectiveness of A1-PI therapy compared to placebo in 313 patients. The studies included ex-smokers or patients who have never smoked, with severe A1-PI deficiency (serum A1-PI ≤11 μM) and a range of emphysema severity (FEV_1 [forced expiratory volume in 1 second] 25% to 80%). ESC noted that different

primary outcome measures were defined by the investigators: the RAPID and EXACTLE trials used CT-measured lung density, while the DIRKSEN99 trial used FEV_1.

ESC noted that, at 24–30 months, no significant differences between A1-PI augmentation therapy and placebo were identified across these RCTs in relation to mortality, exacerbation of chronic obstructive pulmonary disease (COPD), hospitalisation due to COPD exacerbation, quality of life (St George's Respiratory Questionnaire; SGRQ), respiratory function (FEV_1), exercise capacity (incremental shuttle walk test) or carbon monoxide diffusion capacity (DLCO). No relevant data were identified for dyspnoea as a measure of respiratory function, or the BODE index (BMI, obstruction, dyspnoea, exercise capacity).

The only statistically significant difference observed was for CT-measured lung density, which favoured A1-PI therapy. However, ESC noted that the clinical significance of this difference is uncertain, as MCIDs for changes in CT-measured lung density have not been established in the peer-reviewed literature. However, ESC noted a recent American Thoracic Society conference abstract that has proposed an MCID threshold of –2.89 g/L (95% CI: -2.59, -3.25; Crossley et al 2018). In this context, one of the product manufacturers stated that "based on the annual preservation of lung tissue (0.74 g/L/year) demonstrated in the RAPID trial in favour of A1-PI therapy, the proposed MCID would be achieved within 3.9 years as compared to an untreated patient."

ESC noted that the EXACTLE trial reported four methods for measuring CT-measured lung density. The assessment report used the 24-month data from the physiological adjustment method for comparability with the DIRKSEN99 and RAPID trials. ESC noted that a Cochrane review (Gotzsche and Johansen 2016), that included an average of the four methods, yielded almost identical results as the assessment meta-analysis, indicating concordance of the different methods.

ESC noted that the comparative effectiveness measured by FEV_1 (showing no statistically significant difference between A1-PI therapy and placebo) was also similar across the assessment meta-analysis and the Cochrane review.

ESC noted that 12 studies reported on the correlation between CT-measured lung density, and lung function measures (FEV_1, KCO gas transfer) and patient-relevant outcomes (mortality and quality of life). However, ESC noted confounding variables, such as differences in assessing lung density and lung zones, and that the reported correlations were largely cross-sectional rather than comparing changes in CT-measured lung density with changes in lung function measures over time. ESC noted a meta-analysis (Crossley et al.) reported a correlation between CT-measured lung density and FEV_1 and KCO gas transfer, although there was a high degree of heterogeneity across included studies.

ESC noted the conclusions of the Assessment Report that, overall, CT-measured lung density correlates with lung function measures (FEV_1 and K_{CO}) and mortality, but findings were inconsistent regarding correlations between CT-measured lung density and quality of life.

ESC noted the claim that A1-PI therapy meets three of the four criteria warranting Rule of Rescue. However, it is unclear whether CT-measured lung density is a sufficiently informative surrogate for the Rule of Rescue criterion of 'worthwhile clinical improvement'.

ESC noted there is the potential for selection and/or reporting bias in this area of research, given the small pool of researchers and the low frequency of investigator-initiated trials.

ESC also noted an earlier meta-analysis (COPD 2009; 6(3):177-84) showed A1-PI augmentation therapy was associated with a 26% reduction in rate of FEV_1 decline (absolute difference 17.9 mL/year; 95% CI 9.6 to 26.1 mL/year) in a subset of patients with baseline FEV_1 of 30–65%. Similar trends were seen in patients with baseline FEV_1 of <30% or >65%, but they were not statistically significant. This 26% treatment effect was used to drive differences across the A1-PI therapy and BSC arms of the modelled economic evaluation.

ESC provided the following responses to key clinical policy issues:

- Regarding whether there is clinical evidence to support a recommendation for public funding of A1-PI products – ESC noted that this requires accepting that CT-measured lung density has been demonstrated to be a surrogate for outcomes known to be clinically meaningful.
- Regarding potential management criteria – ESC queried whether FEV_1 should be added to the proposed initial eligibility criteria as a more objective measure of emphysema severity. ESC noted that FEV_1 25% to 80% reflected the eligibility criteria across the three identified RCTs, and queried whether this could form the basis for stipulating a suitable threshold.
- Regarding whether there is any material distinction between alpha-1 products currently registered in Australia (Prolastin-C and Zemaira), affecting clinical utility or price level – ESC noted evidence in the contracted assessment that demonstrated the two agents are bioequivalent, with 60 mg/kg once weekly regimens yielding equivalent changes in trough serum antigenic A1-PI levels. Neither product was found to be cost-effective at the prices currently proposed by the respective manufacturers.

ESC noted that the results of the modelled economic evaluation were presented in two steps. The first step outlined cost-effectiveness results for the trial period of four years. This length of follow-up reflects the maximum follow-up of the RAPID trial (Chapman et al. 2015) and the open-label extension study (RAPID-OLE) (McElvaney et al. 2017). An average hypothetical cohort of 1,000 patients progresses between FEV_1% and CT-measured lung density decline states based on results of the trial within a cohort-based semi-Markov model. Numerical differences in mortality across the A1-PI therapy and BSC arms were taken from the RAPID-OLE and RAPID studies for the first two and four years, respectively (McElvaney et al. 2017); (Chapman et al. 2015).

The efficacy benefit associated with treatment that leads to improvements in patient morbidity were captured in the model using RAPID trial data, with the primary analysis being expressed as the incremental cost per additional QALY gained. Resource use was attached to each state using proposed A1-PI maintenance therapy product costs and MBS item costs. Australian Refined Diagnosis Related Groups (AR-DRG) costs were applied to the frequency of GP and hospital presentations for UK COPD patients of differing severity (Thomas et al. 2014) to estimate disease management costs of A1-PI deficiency.

The second step involved extrapolating RAPID transition data over an additional 26 years (lifetime). It was assumed that transitions between health states with varying rates of CT-measured lung density decline occurred during the follow-up of the RAPID and RAPID-OLE studies and that patients stayed on no, slow or rapid decline tracks for the remaining 26 years. The patient-level data on which the post hoc linear regression analyses were based were provided to the Assessment Group by the manufacturer that sponsored the RAPID and RAPID OLE studies.

Mortality data for the remainder of the model's lifelong time-horizon were based on observations from 10 years of followed-up patients in the UK AATD registry. A number of parametric models were fitted to the UK registry data by the Assessment Group to extrapolate observational data for the lifetime projections.

ESC noted that a range of sensitivity analyses were undertaken to test the robustness of the results of the modelled economic evaluation. This included changes in baseline distributions of individuals with emphysema or COPD stratified according to extent of airflow obstruction, and being mild, moderate, or severe.

ESC noted that most models for COPD health states are stratified by FEV_1. However, given that CT-measured lung density was the primary outcome in the RAPID trial, the model also incorporated FEV_1 to define the health states in the model as well as three levels pf predicted decline in CT-measured lung density (none, slow or rapid decline) as a driver for mortality. Patients could move from FEV_1>50% to FEV_1<50% health states, but not the other way around.

ESC noted clinical advice provided to the Assessment Group that, for the extrapolation after 4 years, the rate of CT-measured lung density decline in A1-PI patients stabilises. Accordingly, the model assumed that, after the first 4 years of the modelling timeframe, patients would remain in the no, slow or rapid decline pathways for the remainder of the modelled timeframe.

In the pre-modelling studies undertaken by the Assessment Group to extrapolate overall survival from UK registry with follow-up to 10 years, the Gompertz function was found to have the best fit (lowest AIC statistic) across most subpopulations and, for consistency, was used in the base case for all subpopulations. ESC noted that, whilst this choice was reasonable, other extrapolation functions of this overall survival curve were more favourable for the intervention.

ESC noted that the model was driven by the larger number of patients who are retained in the FEV_1<50% slow decline state, as a result of augmentation therapy. Most incremental life years saved (LYS) and quality-adjusted life years (QALYs) accrue to the FEV_1<50% slow decline state from the FEV_1<50% rapid decline state.

ESC noted the economic model yielded base case results well above the threshold usually considered by MSAC to be acceptably cost-effective: with an ICER of s47(1)(b) per QALY for the trial period of 4 years, and an ICER of s47(1)(b) per QALY for the lifetime (30 year) model.

ESC noted that the incremental clinical benefit in the model accrues between 5 and 15 years (i.e. is driven by extrapolation of effects beyond the 4-year trial period). Sensitivity analyses showed that the cost of A1-PI product is the key driver of the economic model (accounting for s47(1)(b) of the cost). It is therefore uncertain what price would be acceptably cost-effective.

ESC noted that, even at the lowest proposed price of s47(1)(b) per 1,000 mL of A1-PI therapy, the lifetime modelled ICER is s47(1)(b) per QALY. Unit prices that would generate ICERs within the range usually considered to be acceptable by MSAC are unlikely to be acceptable to the manufacturers. Consequently, ESC suggested the assessment group be asked to explore different 'continuation rule' scenarios, using the existing model structure, that are evidence-based and clinically feasible.

For example, what would the ICER impact be if A1-PI therapy was ceased after 4 years (the trial period), in patients who exhibit a rapid CT-measured lung density decline rate (for example >2.0 g/L) while on treatment? ESC noted this would require inclusion of CT-measured lung density scans (at a frequency that would need to be justified) to monitor response, and therefore need to be added to treatment costs in the model, while being removed from disease management costs (to avoid double-counting).

When looking at the financial/budgetary impacts, ESC noted that there is no direct estimate available for the number of Australian patients with COPD with A1-PI deficiency. Estimates were derived from the prevalence of COPD patients in Australia, the estimated prevalence of ZZ phenotypes in the USA (adjusted to reflect Australian ethnicities), and the rate of A1-PI diagnosis using US data. ESC noted that if A1-PI augmentation therapy is funded on the NPL, current testing rates are likely to increase due to the availability of a treatment option.

ESC noted that the base case estimate of total costs to government was s47(1)(b) million (2019–2023). ESC noted that these estimates are highly sensitive to the price of the products and were based on the weighted average of the price proposed by each of the two manufacturers.

ESC noted that the financial estimates were also sensitive to assumptions around diagnosis rates and assumptions regarding the proportion of non-smokers in otherwise potentially eligible patients, and that higher rates for both of these assumptions are plausible and could reasonably be expected to yield financial estimates 2–3 times higher than those presented as the base case.

ESC noted that the financial estimates are highly sensitive to:

- the price of A1-PI therapy;
- assumptions around the proportion of patients with COPD who are diagnosed as A1-PI-deficient; and
- the proportion of potentially eligible patients who are assumed to be non-smokers.

ESC suggested the assessment group also undertake additional sensitivity analyses of the financial estimates around the price of A1-PI therapy, that correspond directly to the 'continuation rule' scenarios explored in the economic model, noting that, for the scenario suggested above, this might require extending the timeframe of the financial analysis to 10 years so that the impact of therapy cessation after 4 years can be captured. If a 'continuation rule' is proposed, any additional MBS costs associated with implementing the rule (e.g. for CT-measured lung density scans, smoking status tests) would need to be captured in the revised financial estimates.

ESC noted that an issue was raised at PASC about whether Indigenous Australians might be discriminated against if treatment was stopped when a patient continues smoking. However, ESC noted that PASC had received clinical expert advice that this is a disease mainly affecting non-Indigenous Australians. It was noted that objective criteria would be needed for all patients receiving therapy, and that there is a significant opportunity cost for continuing A1-PI therapy in patients who smoke (as the treatment is rendered entirely ineffective by smoking).

ESC noted the following key economic and financial policy issues for MSAC:

- The prices proposed by manufacturers do not yield ICERs within the range that is typically considered to be acceptably cost-effective.

- There is uncertainty surrounding both the primary outcome measure (CT-measured lung density), and also its correlation with survival, which suggests post-listing data collection would be warranted – the Australian Patient Registry proposed by one of the companies, could facilitate this.
- The treatment is high cost (s47(1)(b) per patient per year) for their lifetime, and known to be ineffective in smokers. Strict requirements would be needed to ensure use is limited to non-smokers.
- The potential role for other continuation rules for A1-PI therapy could be explored, e.g. in patients who are not or no longer responding to treatment (after an agreed duration of treatment, and according to pre-specified, objective criteria) – again, the proposed Australian Patient Registry could assist with this.
- The potential role for a Risk Sharing Agreement between the NBA and the manufacturers could be explored to manage the real potential of under-estimation of diagnosis and treatment rates in the potentially eligible population.
- Public funding of A1-PI therapy may result in changes in management; for example, increased use of prior tests (i.e. capturing test-negative individuals as well as diagnosed individuals), use of tests to monitor compliance with smoking cessation, and use of tests to monitor response to A1-PI therapy. If MBS-funded, these impacts are not currently captured in the financial estimates.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

CSL Behring is disappointed MSAC did not support A1-PI replacement therapy for the treatment of A1-PI deficiency with COPD. A1-PI deficiency with COPD is a life-threatening and very rare condition with no currently funded disease-modifying treatment alternatives. CSL Behring agrees with MSAC that there is a high unmet medical need for patients with A1-PI deficiency and strong consumer support for funded access, and is pleased that MSAC acknowledged the clear physiological effect of A1-PI therapy on lung density. CSL Behring maintains that the evidence supporting the benefit of A1-PI therapy is strong in the context of this rare and slowly progressive disease, noting that it is not feasible to collect survival outcome data in a clinical trial setting likely to be sufficient to satisfy MSAC's requirements in a timely manner. CSL Behring believes there is a strong basis for applying a broader decision-making framework in this context, beyond the conventional evaluation approach used in MSAC's consideration. CSL Behring remains committed to working with the National Blood Authority and the Jurisdictional Blood Committee to continue to progress the application for timely funded treatment for Australian patients suffering from this devastating disease.

Grifols is disappointed with the decision by the Medical Services Advisory Committee (MSAC) not to support purified human alpha1-proteinase inhibitor (A1-PI) for the treatment of patients with A1-PI deficiency, but is committed to work with the National Blood Authority (NBA) and other relevant stakeholders, including clinicians and patient organisations, to ensure that this effective medicine, with a positive impact on survival, will be made available to those in need and who have the greatest capacity to benefit using appropriate mechanisms (e.g. Grifols latest generation genetic tools, initiation and continuation criteria). Grifols welcomes the acknowledgement by the Evaluation Sub-committee (ESC) that A1-P1 deficiency is a rare disease and that clinical trials for rare

diseases are often underpowered to detect clinically significant outcomes. Furthermore, the company is keen to work through the cost-effectiveness, albeit acknowledging the current conventional framework is not well suited to treatments for rare diseases like A1-PI. Indeed, other factors such as the current lack of clinically effective treatments, clinical need, seriousness of the disease, the rule of rescue, as well as access and affordability from the patient perspective and the comparatively small financial implications to the government, should also be considered when assessing the social value of medicines to treat A1-PI.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website

Purified human alpha1-proteinase inhibitor for the treatment of alpha1-proteinase inhibitor deficiency, leading to chronic obstructive pulmonary disease

November 2018

MSAC application no. 1530

Assessment report

Annex to Section D

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LIST OF TERMS

A1PI	Alpha-1 proteinase inhibitor
AT	Augmentation therapy
BSC	Best supportive care
CT	Computed tomography
ESC	Evaluation Sub-Committee
FEV_1	Forced expiratory volume in 1 second
ICER	Incremental cost-effectiveness ratio
QALY	Quality-adjusted life year

SECTION D ANNEX ADDITIONAL SENSITIVITY ANALYSIS

BACKGROUND

Following review of the Contracted Assessment report for MSAC Application 1530, the Evaluation Sub Committee (ESC) suggested different 'continuation rule' scenarios be explored, using the existing model structure, that are evidence-based and clinically feasible. Two patient scenarios were suggested for investigation:

1. Patients who demonstrate limited treatment response to augmentation therapy (AT), measured with computed tomography (CT) lung density scans.

2. Patients that recommence smoking after starting treatment with AT.

This document reports the results of additional economic sensitivity analysis for the first stoppage rule only (limited treatment response). The second scenario has not be investigated based on clinical feedback suggesting patients treated with AT in Australian practice do not recommence smoking (J Burdon & P Wark 2018, personal communication, 10 November).

The financial impact of the continuation rules was not investigated because there is no impact to the MBS. There are no existing MBS items for urinalysis or CT lung density scanning, and clinical feedback suggests that software needed for CT lung density scanning is not routinely available in Australian clinical practice (J Burdon & P Wark 2018, personal communication, 1 November).

Questions were also asked about the use of a non-significant 26% reduction in FEV_1 decline for the AT arm which was not supported by randomised trials outlined in Section B of the assessment. The rationale for the inclusion of 26% based on the meta-analysis of Chapman et al (2009) is provided, along with an additional sensitivity analysis if both arms are assumed to have the same FEV_1 decline, or reversed.

SENSITIVITY ANALYSIS A – STOPPING RULE

Transition probabilities for the economic model are derived from RAPID individual patient data, outlined by s47G Patients move between FEV_1<50 and FEV_1>50 CT-scan lung density decline states according to what was observed in the four years of RAPID and RAPID OLE for AT (Chapman et al. 2015, McElvaney et al. 2017). The annual probabilities are provided in Table 1, which are taken from s47G

Lung density decline is a progressive disease, therefore it could be expected that decline would continue under AT, albeit at a slower pace compared to best supportive care (BSC). The stoppage rule would most likely be applied to patients who move from no decline or slow decline to rapid

decline tracks for both FEV_1 greater or less than 50 (i.e. not no decline to slow decline given the disease is progressive) even though they are availing AT. The transition from no or slow decline to rapid decline represents a clinically significant progression of symptoms, suggesting that AT is ineffective. The annual probabilities for these transitions are outlined in Table 1 and are highlighted in yellow. None are higher than s47(1)(b) and most between s47(1)(b).

Table 1 Base transition matrix, augmentation therapy Years 1-4

	FEV_1>50 no decline	FEV_1>50 slow decline	FEV_1>50 rapid decline	FEV_1<50 no decline	FEV_1<50 slow decline	FEV_1<50 rapid decline
FEV_1>50 no decline	s47(1)(b)					
FEV_1>50 slow decline						
FEV_1>50 rapid decline						
FEV_1<50 no decline						
FEV_1<50 slow decline						
FEV_1<50 rapid decline						

Source: s47G

Abbreviations: **FEV_1** = forced expiratory volume in one second

The numbers of patients in a 1000 hypothetical starting cohort from 0 to 4 years on the AT arm are presented in Table 2. It is evident that most are on the FEV_1>50 slow decline and FEV_1<50, slow decline tracks as the annual probabilities from the key trial reported by CSL direct most patients this way. Of the 1000, around s47(1)(b) are in rapid CT decline FEV_1>50 and s47(1)(b) n rapid CT lung decline FEV_1<50 tracks by Year 4. The progressing patients who would cease using AT based on a stopping rule are among these two patient groups.

Table 2 Augmentation therapy patient numbers, Years 1-4 (hypothetical cohort of 1000)

Years	FEV_1>50 no decline	FEV_1>50 slow decline	FEV_1>50 rapid decline	FEV_1<50, no decline	FEV_1<50, slow decline	FEV_1<50, rapid decline	Lung t-plant	Cumulative Death
s47(1)(b)								

Abbreviations: **FEV_1** = forced expiratory volume in one second

Annual probabilities for no and slow decline transition to rapid decline tracks are set to zero to gauge how many of the rapid decline patients progressed from no decline and slow decline tracks. The adjusted annual probabilities are presented in Table 3.

Table 3 **Transition matrix with no and slow decline to rapid progression set to zero, augmentation therapy Years 1-4**

	FEV_1>50 no decline	FEV_1>50 slow decline	FEV_1>50 rapid decline	FEV_1<50 no decline	FEV_1<50 slow decline	FEV_1<50 rapid decline
FEV_1>50 no decline	s47(1)(b)					
FEV_1>50 slow decline						
FEV_1>50 rapid decline						
FEV_1<50 no decline						
FEV_1<50 slow decline						
FEV_1<50 rapid decline						

Abbreviations: FEV_1 = forced expiratory volume in one second

These probabilities are applied to the starting AT cohort of 1000 and patient numbers for the 1000 cohort outlined in Table 4 for Years 0-4. It is evident that there are s47(1)(b) patients in FEV_1>50, rapid decline, and s47(1)(b) in FEV_1<50, rapid CT-measured lung decline, tracks by year 4. This represents a different patient number of around s47(1)(b) between the base and no progression transition matrices for rapid decline tracks in Year 4. Based on this calculation, around s47(1)(b) patients progress from no and slow decline lung decline to rapid decline despite being on AT by Year 4. Given the annual probabilities of transitioning from no and slow to rapid decline when using AT are relatively low (from CSL individual patient data), this number could be expected.

Table 4 **Augmentation therapy patients, under no progression scenario, Years 1-4, (hypothetical cohort of 1000)**

Years	FEV_1>50 no decline	FEV_1>50 slow decline	FEV_1>50 rapid decline	FEV_1<50, no decline	FEV_1<50, slow decline	FEV_1<50, rapid decline	Lung transplant -following	Cumulative Death
0	s47(1)(b)							
1								
2								
3								
4								
s47(1)(b)								

Abbreviations: FEV_1 = forced expiratory volume in one second

The model assumes patients on FEV_1>50 no decline, FEV_1>50 slow decline, FEV_1>50 rapid decline, FEV_1<50 no decline, FEV_1<50 slow decline and FEV_1<50, rapid decline patients follow the same survival curves regardless of whether they are availing AT or BSC treatment. AT treatment results in patients moving to different tracks (mainly slow decline) with the adoption of treatment. Stopping the s47(1)(b) AT patients on the rapid track from using AT results in cost savings from avoided AT product usage and delivery, however, there is no change in the estimate number of QALYs from Year 4 onwards. Patients are assumed to survive the same number of years and have same quality of life once they are on the rapid track regardless of treatment.

The cost saving from avoided AT is significant and presented in Figure 1. Given a year of AT treatment per patient is more than s47(1)(b), stopping s47(1)(b) patients who progressed, results in savings of more than s47(1)(b) per year for the hypothetical cohort. Additional chest CT scans (e.g. MBS Items 56301, 56307) are around $300-400 depending on use of contrast, noting that specialised software is needed to measure lung density that is currently not available in routine clinical practice in Australia (J Burdon & P Wark 2018, personal communication, 1 November). At $300 per scan, the additional cost for all s47(1)(b) patients in Year 4 (those who haven't died or had lung transplant surgery) and all 1000 starting patients is less than $1 million.

The ICERs for the stopping rule and base case scenarios are presented in Table 5. It is estimated that stopping rule ICER is s47(1)(b) compared to s47(1)(b) for the base case, or around 91%. This more cost-effective ratio broadly reflects the decrease in the number (around s47(1)(b), or the starting cohort of 1000) of patients who were deemed to progress from no and slow decline too rapid and stopped AT.

Table 5 ICER over a life time for stopping and base case (hypothetical cohort of 1000)

	Discounted Cost	Incremental discounted cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Stopping rule					
Augmentation therapy	s47(1)(b)		5,826.6	1,301.1	s47(1)(b)
Best Supportive Care	37,389,939		4,525.4		
Base case					
Augmentation therapy	s47(1)(b)		5,826.6	1,301.1	s47(1)(b)
Best Supportive Care	37,389,939		4,525.4		

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

SENSITIVITY ANALYSIS B – RATE OF FEV_1>50 TO FEV_1<50 PROGRESSION

The AT arm has a slower rate of FEV_1>50 to FEV_1<50 progression in the economic model, based on a s47(1)(b) reduction in FEV_1 decline derived from the meta-analysis of Chapman et al. (2009) described by s47G This assumption is evident in Table 6, with BSC FEV_1>50 states having annual probabilities of transition to FEV_1<50 of s47(1)(b) (highlighted in yellow), compared to s47(1)(b) for AT s47(1)(b) less).

Table 6 Augmentation therapy and best supportive care transition matrices (Years 0-4)

	FEV_1>50 no decline	FEV_1>50 slow decline	FEV_1>50 rapid decline	FEV_1<50 no decline	FEV_1<50 slow decline	FEV_1<50 rapid decline
BSC						
FEV_1>50 no decline	s47(1)(b)					
FEV_1>50 slow decline						
FEV_1>50 rapid decline						
FEV_1<50 no decline						
FEV_1<50 slow decline						
FEV_1<50 rapid decline						
AT						
FEV_1>50 no decline						
FEV_1>50 slow decline						
FEV_1>50 rapid decline						
FEV_1<50 no decline						
FEV_1<50 slow decline						
FEV_1<50 rapid decline						

Source: s47G

Abbreviations: AT = augmentation therapy, **BSC** = best supportive care, **FEV_1** = forced expiratory volume in one second

Randomised trials presented in the clinical evidence section of the assessment report (e.g. page 66, Table 35 and Figure 13), indicate however, that a slower rate of FEV_1 overall for the placebo arm than the AT arm, with a non-statistically significant relative reduction favouring placebo in the meta-analysis of 17%. s45

s47G indicated that s45

The difference between these annual probabilities for the AT and BSC arms are presented in Table 7. It is evident that the key differences between the AT and BSC arm annual probabilities are in the no, slow and rapid decline groups within the FEV_1<50 and FEV_1>50 patient groupings (highlighted in yellow), rather than between FEV_1>50 and FEV_1<50 (in red). These probabilities were provided by s47(1)(b) using RAPID study IPD.

Table 7 Differences between AT and BSC annual probabilities of transition (Years 0-4)

	FEV_1>50 no decline	**FEV_1>50 slow decline**	**FEV_1>50 rapid decline**	**FEV_1<50 no decline**	**FEV_1<50 slow decline**	**FEV_1<50 rapid decline**
Diff = AT-BSC	s47(1)(b)					
FEV_1>50 no decline						
FEV_1>50 slow decline						
FEV_1>50 rapid decline						
FEV_1<50 no decline						
FEV_1<50 slow decline						
FEV_1<50 rapid decline						

Abbreviations: AT = augmentation therapy, **BSC** = best supportive care, **FEV_1** = forced expiratory volume in one second

Univariate sensitivity analysis involving changing specific transitions from FEV_1 >50 to FEV_1<50 does not have a major impact on the ICER. If both AT and BSC arms had FEV_1 annual probability declines of s47(1)(b), then the **ICER would increase from** s47(1)(b) **.**

s47(1)(b)

The base ICER s47(1)(b) was generated using a reduction of s47(1)(b) while a s47(1)(b) reduction resulted in an ICER of s47(1)(b). Reversing the FEV_1 decline (i.e. s47(1)(b) for AT and s47(1)(b) for BSC) in the CSL Excel model results in an ICER of s47(1)(b).

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ADDITIONAL SENSITIVITY ANALYSIS (MSAC 1530)

ECONOMIC EVALUATION

Upon request by MSAC, additional sensitivity analysis was conducted around the delivery cost for alpha-1 antitrypsin augmentation therapy (AT). The cost per vial at the requested incremental cost-effectiveness ratio (ICER) thresholds of $60,000, $70,000 and $100,000 are presented in Table 1 (highlighted in yellow), along with the base case (s47(1)(b)) and existing sensitivity analyses evaluating the impact of a 15% increase (s47(1)(b)) or decrease (s47(1)(b)) in cost.

Table 1 Sensitivity analysis (cost per vial) for lifetime analysis

AT delivery cost	Incremental cost	Incremental effect	ICER
s47(1)(b)			

Abbreviations: **AT** = augmentation therapy, **ICER** = incremental cost-effectiveness ratio.

FINANCIAL IMPLICATIONS

The budgetary impact associated with the additional sensitivity analysis on the delivery cost is presented in Table 2. The base case is presented, along with estimated costs at the corresponding ICER thresholds of $60,000 (Scenario 1, vial cost s47(1)(b)), $70,000 (Scenario 2, vial cost s47(1)(b)) and $100,000 (Scenario 3, vial cost s47(1)(b))

Table 2 NET government cost sensitivity analysis (cost per vial)

Projection Year	2019	2020	2021	2022	2023
AT patients	s47(1)(b)				
Base Case					
NBA-supported AT product costs					
MBS-supported infusion service delivery	277,422	328,838	381,828	436,429	443,412
Total costs to government	s47(1)(b)				
Scenario 1: Vial = s47(1)(b)					
NBA-supported AT product costs					
MBS-supported infusion service delivery	$277,422	$328,838	$381,828	$436,429	$443,412

Total costs to government	s47(1)(b)				
Scenario 2: Vial = s47(1)(b)					
NBA-supported AT product costs					
MBS-supported infusion service delivery	$277,422	$328,838	$381,828	$436,429	$443,412
Total costs to government	s47(1)(b)				
Scenario 3: Vial = s47(1)(b)					
NBA-supported AT product costs					
MBS-supported infusion service delivery	$277,422	$328,838	$381,828	$436,429	$443,412
Total costs to government	s47(1)(b)				

Abbreviations: **AT** = augmentation therapy, **MBS** = Medicare Benefits Schedule, **NBA** = National Blood Authority.