A Normal Life Expectancy - Augmentation Therapy for Alpha-1 Antitrypsin Deficiency

Position Paper

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1 Acronyms and Initialisms

α1	Alpha-1
A1AT	Alpha-1 antitrypsin deficiency
AAA	Alpha-1 Association of Australia
AAT	Alpha-1 Antitrypsin
AATD	Alpha-1 antitrypsin deficiency / α1-antitrypsin deficiency
ADMAPP	Alpha-1 Disease Management and Prevention Program
AFBP	Adipocyte fatty acid-binding protein
AT	Augmentation therapy (for AATD)
BODE	Body mass index, airflow obstruction, dyspnea and exercise capacity
COPD	Chronic obstructive pulmonary disease
COPD-X	The Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
CT	Computed tomography
DES	Desmosine
D_{LCO}	Decreased diffusing capacity of the lung for carbon monoxide
EARCO	The European Alpha-1 Research Collaboration
ERS	European Respiratory Society
EXACTLE	Exacerbations and computed tomography scan as lung end-points
FEVI	Forced expiratory volume in one second
GOLD	Global initiative for chronic obstructive lung disease
HDCT	High density computed tomography
HRQoL	Health Related Quality of Life
IDES	Isodesmosine
KCO	Carbon monoxide transfer coefficient
MAC	Mycobacterium avium complex
MSAC	Medical Services Advisory Committee (an independent non-statutory committee) established by the Australian Government for Health)
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International prospective register of systematic reviews
PA	Plasminogen activator
RAPID-RCT	Randomised, placebo-controlled trial of augmentation therapy in alpha-1 proteinase inhibitor deviancy randomised controlled trial
RAPID-OLE	RAPID open label extension
RCT	Randomised control trial
SGRQ	St George's respiratory questionnaire
TGA	Therapeutic Goods Administration
USA	United States of America
WHO	World Health Organisation

2 Alterations and Additions to V1.21

The Alpha-1 Association of Australia's (AAA) Position Paper includes important peer reviewed evidence and information supporting government funded augmentation therapy (AT) and establishes that:

a) CT lung density is a clinically meaningful measure associated with lung disease, including alpha-1 antitrypsin deficiency (AATD) and, therefore, Rule of Rescue criteria are met, supporting immediate access to government funded therapy for lung affected AATD patients;

b) AT rebuilds lung density, controls proteases linked to lung destruction in AATD patients and restores the protease / antiprotease balance required for lung health;

c) AT improves survival in severely deficient individuals with D_{LCO} values <60%, independent of FEV_1 levels. Patients with low D_{LCO} values need to be included in AATD therapy guidelines;

d) AT has additional health and life saving benefits for lung affected AATD patients, namely control of devastating mycobacterium avium complex (MAC) and pseudomonas infections which are associated with a high mortality rate (five years following infection) if left untreated and AT is an important adjunct to antibiotics to control MAC in lung compromised patients;

e) Lung affected AATD patients are immunocompromised, disabled, unable to work and many have to live in social isolation to protect themselves from infection which causes further rapid lung destruction leading to an early death. Their impairment limits their involvement in more than one major life activity. They are a vulnerable group left untreated to suffer unjustly when good scientific evidence exists regarding the health benefits of AT. Under the *International Covenant on Economic Social and Cultural Rights* individuals with AATD have the right to health, a right to work, and the right to a family life and participation in cultural life. AATD individuals have a right to the highest attainable standards of health care supported by sound evidence as is presented in this Position Paper;

f) The 2016 AATD Cochrane Review is flawed due to publication bias and its narrow focus on RCTs does not reflect Cochrane's Handbook on mandatory inclusions when undertaking a systematic review. This failure has led the Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease (COPD-X Guidelines) to wrongly not support AT when AT evidence exists;

g) The Australian Government's Medical Services Advisory Committee (MSAC) has overlooked critical evidence, including CT lung densitometry evidence, when making its recommendation not to fund AT.

3 Executive Summary

3.1 The Essential Protein Known as Alpha-1 Antitrypsin

Alpha-1 Antitrypsin (AAT) is an essential anti-inflammatory, anti-infective, immunomodulating protein, required for normal lung health. (1; 2) The rare genetic condition known as AATD predisposes individuals to early onset genetic emphysema, sometimes as early in a person aged in their 20s. (3) If left untreated, affected individuals can expect a reduced life expectancy (4; 5) as their lungs are destroyed from proteases and inflammation due to the lack of inhibitory antiprotease (i.e. AAT) and they are susceptible to bacteria that colonise lungs which are linked to high mortality. (6)

3.2 Treatment for AATD

The only non-surgical disease-specific treatment for AATD is AT, (7) a weekly infusion of the missing protein known as AAT, shown to have biochemical efficacy at a dose of 60 mg/kg which raises serum levels of AAT to a protective threshold. (8) AT is life changing for deficient patients, taking life expectancy from 59 to over 80 years of age. (4; 5) AT has been shown to improve survival in AATD patients with low FEV_1 (< 65% predicted) and independently in patients with low gas exchange (D_{LCO} <60% predicted). AT has been registered for use in Australia by the Therapeutic Goods Administration (TGA) since February 2017 but AT is not funded by the Australian Government. AT remains unaffordable to most patients at over AUD $100,000 per annum for life. Vulnerable lung-affected AATD patients are left to unjustly suffer physically and psychologically, and face an early death if a costly double lung transplant is not available or unsuccessful. Many patients live in social isolation, in fear of catching a virus which typically leads to pneumonia and accelerated lung destruction. (9) AATD transplant patients face a lifetime of immunosuppressant medications to prevent organ rejection, hospitalisations and expensive medical procedures such as plasmapheresis if rejection occurs. AATD patients have a higher rate of organ rejection than non-AATD patients (10).

3.3 Evidence Supporting AT

Research synthesis supports AT but Australian regulators tend to focus on level 1 evidence, at the expense of other compelling synthesised evidence, leading to AT funding denial. The 2019 COPD-X Guidelines (11) reflect the flawed 2016 AATD Cochrane Review (12), overlooking relevant non-RCT evidence. When making recommendations to the Minister for Health, expert advisors and MSAC need to consider all statistically significant evidence identified via a broad systematic review. When results are assessed, AT is found to improve AATD patient survival, reduce the severity of exacerbations, reduce hospital costs associated with exacerbations, build lung density, maintain pulmonary health and improve quality of life.

3.4 Evidence Requiring Immediate Consideration

MSAC's Public Summary document, released in response to Application No. 1530 for funded AT for AATD, (13) indicates that MSAC overlooked pooled evidence that shows the clinical efficacy of CT densitometry, its superiority to FEV1, and that it is a better predictor of survival (14) in AATD.

This position paper presents statistically significant results that need to be considered by MSAC. Peer reviewed research shows that CT lung densitometry is a proven method to determine AT impact and lung decline, and that it is clinically relevant. Results also indicate that AT:

a) results in fewer and less severe exacerbations;
b) results in fewer hospital admission-derived costs related to exacerbations;
c) improves respiratory function;
d) improves quality of life;
e) improves survival.

3.5 Just Health and the Rule of Rescue

Australia is party to international law and supports the right to health i.e. the right to the enjoyment of the highest attainable standard of physical and mental health. Australian AATD patients are a vulnerable group requiring "essential" therapy. (15) Based on the strength of evidence, the Rule of Rescue (16) should be applied to lung affected AATD patients as a moral, socially just and scientific response, giving patients every opportunity to be treated and extend their lives.

3.6 Purpose

The AAA believes that it is unethical to leave patients to physically and mentally suffer, with no access to government funded AT, when AT has been saving lives internationally and AT was registered with the TGA since early 2017. (17) AT funding denial has unfairly arisen due to the narrow examination of evidence by the MSAC, with important evidence (including survival and the clinical role of CT densitometry) being overlooked. This paper examines the range of issues associated with AATD funded treatment denial and presents evidence that needs to be considered which supports government funded life-saving treatment.

4 Background

4.1 The Essential Protein Known as AAT

AAT is an essential immunomodulating, anti-infective and anti-inflammatory protein that keeps lungs healthy. (2) (8) The presence of AAT creates the necessary protease / antiprotease balance for lung health, while supporting the resolution of inflammation via neutrophil apoptosis. (18; 19) This interplay explains why standard inhaled treatment for chronic obstructive pulmonary disease (COPD) does not save the lungs or lives of AATD patients as regular inhalers do not contain the essential protein that protects lungs. Many lung-affected AATD patients are rapid decliners, (20) with early onset emphysema and accelerated destruction of lung elastin due to the imbalance of protease and antiprotease and lung inflammation, required for normal lung function.

Being severely deficient in AAT typically leads to rapid decline in lung function. (20) Without AAT, patients have weak immune systems and the majority of deficient patients will suffer with life-threatening bacterial lung infections e.g. mycobacterium avium complex (MAC) and pseudomonas (6) as these organisms are found everywhere. (21)

There is no debate that the biochemical evidence supports AT as serum AAT levels are raised to a protective level. (22) AT is required to reduce inflammation, to restore the lung protease / antiprotease balance to a protective level (22) and it is the only non-surgical treatment for lung affected AATD patients.

Following lung transplant, AATD patients face a higher rate of acute rejection and require AT to assist healing. (10) In the first-year post-transplant, AATD patients have a higher reduced early survival compared to COPD patients. (10)

4.2 Emphysema Protection from AT

Emphysema is a result of a proteinase / anti-proteinase imbalance leading to the breakdown of elastin in the parenchyma of the lung. (18) AT has been shown to reduce elastin degradation which saves lives. (23) AT is required to limit widespread destruction of lung parenchyma (14) and to prevent lung transplant.

Lung affected AATD patients may be fast decliners with early onset emphysema compared to non-deficient COPD individuals but AATD is a slow progressive disease (8) making change hard to detect in short-term randomised control trials (RCTs). Clinical trials and international patient registry studies show AT to be disease modifying with sustained change following therapeutic intervention. (4) This is why AT should be funded by government as it treats the deficiency and permits patients to lead normal lives. AT reduces the frequency of health care use and social services utilisation, allows individuals to be actively involved in society and in many cases, being able to contribute to employment and productivity.

4.3 Comorbidities

In addition to emphysema, systemic vasculitis, necrotising panniculitis, and a variety of different inflammatory and neoplastic diseases have also been associated with low AAT levels. (2; 24) Choate et al. (2016) suggest that improved survival of AATD patients from a mean age of 68.9 to 80.4 years results from the positive impact of AT on lung health and from the positive treatment effect on comorbidities. (4)

4.4 Protection from Serious Lung Infections

AATD is a chronic progressive disease and it is not sufficient to treat symptoms and infections resulting from impaired immunity instead of the underlying deficiency. Patients with AATD are vulnerable to repeat episodes of pneumonia and life-threatening respiratory tract infections enriched with serine protease causing proteolytic lung tissue damage, inflammation and invasion of respiratory organisms including MAC and pseudomonas. MAC is a ubiquitous organism and has been found in approximately 63% of patients with AATD. (25) MAC disease leads to a poor prognosis with five-year mortality seen in approximately 27% of patients. (6) MAC is difficult to treat due to antibiotic resistance and biofilm growth state. Due to the ubiquitous nature of MAC, AATD patients are often reinfected requiring further treatment (with treatment comprised of three antibiotics taken concurrently for at least 18 months). In severely deficient AATD patients, AT can prevent the development of emphysema and associated bronchiectasis (25) which are aggressive and progressive diseases that reduce pulmonary function. AT can control MAC and other bacteria that colonise patients' lungs and other organs. AT can stop the cycle of lung destruction, minimize the number of annual lung transplants and save lives. (26)

4.5 MSAC Rejected the Application for Funded AT

On the 22 and 23 November 2018, MSAC considered "Application No. 1530 - Purified human alpha1-proteinase inhibitor for the treatment of alpha1-proteinase inhibitor deficiency, leading to chronic obstructive pulmonary disease". The application was for government funding to support patient access to the only available non-surgical treatment for AATD. (13) Following the meeting, MSAC released a Public Summary Document and advised the Minister for Health that it did not support the application. MSAC's rationale was based on cost and perception of the strength of evidence, claiming that no statistically significant differences were found between AT and placebo in relation to mortality, exacerbations, hospitalisation due to exacerbations, quality of life, respiratory function (FEV1), exercise capacity or carbon monoxide diffusion capacity (D_{LCO}). MSAC also claimed that there was weak evidence to suggest that changes in CT density predicts clinically meaningful health outcomes. (13)

MSAC's decision appears focused on a narrow selection of evidence and ignores the weight of evidence that shows that a safe treatment (i.e. AT) is used internationally to slow disease progression, improve survival and leads to a normal life expectancy. (4; 14; 27) This paper presents evidence that shows that treatment:

a) slows lung emphysema decline
b) builds lung elastin

c) reduces lung infections (exacerbations)
d) improves survival
e) rebuilds lung density
f) reduces lung elastin degradation
g) slows disease progression
h) reduces the severity and frequency of exacerbations
i) improves quality of life
j) provides hospital savings from reduced patient admissions, and that
k) CT density predicts clinically meaningful health outcomes in AATD patients.

MSAC observed that the "only statistically significant difference observed in clinical trials was for CT-measured lung density". MSAC also reported "concerns related to CT density evidence, considering it weak in regard to predicting clinically meaningful health outcomes" and that recommending public funding of AT 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. (13)

The AAA finds MSAC's comments surprising as statistically significant evidence, showing the positive impact of AT on survival, exacerbations, hospital savings, respiratory function, D_{LCO} and CT density is available in the peer reviewed medical literature, most of which was provided to government in the original April 2019 version of this Position Paper.

5 Discussion

This paper focuses on statistically significant research findings published in peer-reviewed studies that have been overlooked by MSAC, resulting in patients being denied access to publicly funded AT. It presents evidence of the life-prolonging effect of AT and the importance of early intervention to slow AATD disease progression, identified in a range of studies including non-RCTs and by CT densitometry.

The importance of acknowledging a range of methodological considerations and different levels of evidence when assessing AATD research findings is presented, ensuring that important information is never excluded from AATD government funded treatment considerations.

This paper demonstrates that an update of the 2016 AATD Cochrane Review is urgently required as it wrongly ignores non-RCT evidence, against the core mandatory standards outlined in the Cochrane Handbook for Systematic Reviews of Interventions. This in turn has led to key lung disease treatment guidelines (see section P12 of the COPDX Guidelines) favoring the narrow and flawed Cochrane Review at the expense of other evidence, resulting in the unjust denial of funded AT. Taken together, the evidence indicates that the Rule of Rescue needs to be immediately applied to save the lives of severely AATD patients and patients facing lung transplant need to be given AT to limit acute rejection.

5.1 AATD Patients are Denied Funded AT

Evidence is presented immediately below against the nominated domains in the MSAC Public Summary Document showing that evidence does exist where the Committee claims there is no evidence:

5.1.1 Exacerbations

a) Barros-Tizon et al.'s 2012 paper examines the **reduction of severe exacerbations and hospitalisation-derived costs** in AATD patients treated with AT reported positive results from a multi-center, observational, retrospective study spanning three years examining impact of AT on exacerbations before and after treatment. (28)

b) Lieberman's 2000 study found that AT was associated with a marked **reduction** in the frequency and severity of lung infections. (29)

c) Dirksen et al. (2009) found that patients treated with AT had **less severe exacerbations**. (30)

d) Kohnlein et al.'s 2010 study demonstrated patients receiving AT had a **significantly lower exacerbation frequency and lower exacerbation severity**. (31)

5.1.2 Hospital COSTS due to COPD Exacerbations

a) Barros-Tizon et al.'s 2012 study confirmed the effectiveness of AT in the reduction of the incidence and severity of exacerbations, with the consequence of **lower hospitalisation and associated expenditure, fewer hospital admission-derived costs and less administration of concomitant medications**. (28)

b) Kohnlein et al.'s 2010 study demonstrated patients receiving AT had a significantly lower severity of exacerbations and **less need for hospital treatment compared to patients on placebo**. (31)

5.1.3 Respiratory Function (FEV1)

a) Barros-Tizon et al. (2012) looked at respiratory function and found that the rate of decline was more marked prior to AT compared to control subjects, indicating the **AT assisted respiratory function (FEV_1)**. They concluded that AT is able to sustain lung function of AATD patients in a profile equivalent to that of normal population. (28)

b) Seerholm et al. (1997) identified a **significant difference in annual FEV1 decline** in patients receiving AT. (32)

c) Wencker et al. (2001) identified the **FEV1 declined more slowly** in the AT group. (33)

d) Tonelli (2009) found that AATD patients receiving AT had **better FEV1**. (34)

5.1.4 AT and Survival

a) The Alpha-1 Antitrypsin Deficiency Registry Study Group (1998) identified that **survival was higher in the AT group** of patients and significantly lower for those not treated. (35)

b) Sclar et al. (2012) found that AT was associated with a significant **increase in years of life** gained (more than 10 years gained in non-smokers). (36)

5.1.5 CT Lung Density and Survival

a) Dirksen et al. (2009) reported that in patients treated with AT that **CT was a more sensitive outcome measure** than physiology and health status. (30)

b) Green et al.'s (2016) study of CT densitometry reveals that it is **linked to survival** with CT density shown to be the most sensitive measure and can predict CT density decline. (37)

c) **Annual deterioration in lung density is less for those receiving AT** (EXACTLE study). (7)

5.1.6 CT Lung Density and Respiratory Function & HRQol

a) Dirksen et al. (2009) found that **CT densitometry was more sensitive than other measures (e.g. FEV_1)** in measuring emphysema progress but noted that CT density and FEV_1 are correlated. (30)

b) Dowson et al. (2001) found that CT density is related to lung function and health status. (38)

c) CT density in the assessment of emphysema has been validated against pathology, lung function and health status and is **useful in the clinical management of patients to see the effect of therapeutic interventions including survival**. Many papers have, therefore, validated the use of CT density and clinically meaningful outcomes. (7; 39)

5.1.7 HRQoL

a) Dowson et al. (2001) found that **CT scans are well correlated with the HRQoL and pulmonary physiology**. (38)

b) Gelmont et al. (2009) reported **significant improvements in HRQoL mental functioning** over two years while on augmentation therapy. (40)

5.2 CT Densitometry Evidence Supports AT

5.2.1 The Value of CT Densitometry

Green's evidence and evidence from systematic reviews of the clinical utility of CT densitometry in pulmonary disease has been overlooked by MSAC. (7; 37; 41) CT densitometry is an accurate and reliable method for detecting lung disease, showing the progression of emphysema and treatment effect and a link to survival. (37) CT density is the most sensitive measure, followed by diffusing capacity of the lungs for carbon monoxide (D_{LCO} and decline in D_{LCO} has a higher sensitivity than FEV_1 to predict CT density decline.) (37)

CT lung density is an attractive option in AATD management as it measures destruction of alveolar walls, lung damage and loss of tissues caused by emphysema.

Government advisors looking for AT effect tend to focus on FEV_1 while overlooking the fact that CT density is superior. Any doubts about the clinical utility of CT density can be dismissed.

5.2.2 FEV1 versus CT Densitometry in Research

Early studies used the gold standard FEV_1 as a marker for monitoring disease progression, however, changes in FEV_1 occur slowly and FEV_1 lacks sensitivity. This means that a placebo-controlled trial would need to run for at least five years with a minimum of 1,000 subjects to see the benefits of AT. (14) The problem with FEV_1 as an outcome indicator in RCTs is shown in the numbers of patients required e.g. 550 would be required to show a 50% reduction in annual lung decline while the use of CT lung densitometry only requires 130 patients.

Mascalchi et al. raise five reasons why CT lung densitometry should be the main tool to monitor lung disease: (I) improved reproducibility; (II) complete *vs.* discrete assessment of the lung tissue; (III) shorter computation times; (IV) better correlation with pathology quantification of pulmonary emphysema; (V) better or equal correlation with pulmonary function tests (PFT). (42)

5.2.3 CT Density in Emphysema

FEV_1 is a measure of both airway wall thickening and collapse of the small airways while lung density measures airspace enlargement such as in alveolar destruction found in emphysema. While FEV_1 is a valued traditional indicator of pulmonary function it is not a good trial outcome measure and it doesn't discriminate between emphysema and airway disease. CT density is better at identifying emphysema, a point continually overlooked by traditionalists working in the respiratory field. CT densitometry is a statistically robust tool with reproducible results and has been proven to be a valid, reliable indicator in lung disease identification, emphysema and treatment impact. (7; 37; 41; 43)

5.2.4 Multiple AT Benefits

The synthesis of AATD research results e.g. longitudinal patient registry studies, sub-study analyses and RCTs demonstrate that AT improves patient survival, slows the development and severity of emphysema, rebuilds lung density and reduces elastin degradation. (4; 36) Treatment also reduces the severity and frequency of exacerbations, improves quality of life and provides hospital savings from reduced patient admissions (see Table 1).

AT leads to a normal life expectancy. (4) Rahaghi et al. (2014) conclude that severely deficient individuals with low lung function have improved survival when treated with AT including patients with low FEV_1 (< 65% predicted) and independently in patients with low D_{LCO} (<60% predicted) and air trapping (residual volume >120% predicted). (27)

5.2.5 Improved Survival

AT has been used for decades in North America (since 1988) and more recently in Europe. Therapy is aimed at providing essential AAT and protecting lungs. AT can significantly delay time to death, (4) avoid deaths while waiting for lung transplant and lung transplantation costs. AT also reduces crippling respiratory complaints and comorbidities. The USA's long-standing Alpha-1 Research Registry has had registry studies published showing a normal life expectancy for AATD patients when treated with AT. Life-years gained have been raised from 54.5 years (individuals not on AT) to a median survival of 80.4 years (i.e. normal life expectancy) when receiving AT. (4)

The life-saving impact of AT for patients is the interplay of biological and environmental factors. These factors affect individual treatment responses in short duration RCTs. As shown in Table 1, various study designs show statistically significant treatment effects from AT. These results have led many international AATD medical and methodological experts to call for a broader understanding of the benefits of AT as results are unequivocal and statistically significant.

Any doubt about the clinical efficacy of AT is linked to the lack of sensitivity of research outcome measures used in AATD research – such as FEV_1 (8) and a lack of appreciation of issues associated with the use of RCTs in the study of rare diseases. (44) Doubt appears to also stem from a failure to undertake a proper systematic review of the literature, and to look beyond the

RAPID studies. (45; 46) The need for systematic reviews and an appreciation of issues associated with outcome indicators is presented below.

5.3 Systematic Reviews in Rare Diseases

5.3.1 Narrow Literature Reviews

The benefit of AT remains a topic of intense debate due to methodological issues related to AATD research and narrow literature reviews that favour level 1 evidence and FEV_1. Systematic reviews and RCTs are of immense value to medical professionals, but narrow literature reviews that don't meet review standards diminish their value. Reviewers need to embrace the methodological issues raised in this paper and realise that RCTs in rare disease research have limitations requiring consideration of other levels of evidence (44) as the weight of evidence shows that a safe effective treatment exists that reduces mortality.

5.3.2 Systematic Review Expectations

A systematic review critically appraises studies and combines results qualitatively and quantitatively. Ideally a framework such as PRISMA is used which ensures that important review elements are not overlooked, such as sub-group analysis. A systematic review is meant to be exhaustive and include the grey literature. (47) Use of a broad range of related search terms is vital so clinical evidence is not overlooked. Systematic reviews require the inclusion of all relevant publications including clinical trials, cohort studies, patient registry studies and subgroup analysis, so questions related to treatment impact is really understood.

5.4 Methodological Issues in Rare Diseases

5.4.1 Rare Disease Research Requirements

Rare disease research faces challenges not shared with common diseases. (48) In rare disease research various study designs and pooled analysis is required with patient registry data being valuable to provide large scale data to answer questions that clinical trials alone cannot provide. (48) Pooled analysis has indicated a significant reduction in lung density decline following treatment with AT. (49)

Flexibility is required with the inclusion of non-RCT designs. The need for adaptive designs including natural history studies, crossover designs, the use of patient registry data, enhanced clinical trials and continuous outcomes are some of the designs required for the study of AATD.

(48) This requirement has led to scientists meeting with regulators to explain RCT limitations and evidence and design options. (48)

5.4.2 Methodological Flexibility

The RCT has traditionally been accepted as the gold standard. However, in the case of rare diseases methodological flexibility in clinical trials has been called for along with an acceptance by reviewers to use the best evidence available. (44) Standard short term RCTs lack the sensitivity to identify change (e.g. FEV_1, exacerbations, HRQoL) are not a viable option in rare disease research, therefore, adaptive designs should be the norm and government advisors need to fully embrace results from a range of research designs to save patients where no affordable treatment options exist.

Green et al. (2016) note that it is not surprising that mortality difference has not been observed in clinical trials as Kaplan Meir plots show that deaths occur in the longer term, (37) another reason why registry data is attractive. CT densitometry provides clear information regarding location and overall lung destruction. It is a specific and sensitive outcome measure for assessing disease progression, is linear and more consistent than traditional endpoints and evidence shows that it should be used by regulators to support funding.

5.4.3 Study Duration and Power Issues

As early as 1983 challenges associated with AATD clinical trials were reported including the variability in the rate of functional loss in lung disease and that patients often present in the late stage of the disease, making it hard to test AT and survival impact. (50)

RCT use in rare diseases can't be sufficiently powered due to the logistical challenge of recruiting a large enough sample size and the typical short timescale. (44; 51) Clinical trial duration would have to be at least 5 years and involve 684 individuals if mortality is the primary endpoint, using a 40% reduction in mortality with baseline FEV_1 35-49% predicted. (14) Such recruitment numbers are challenging in rare diseases and delays access to AT. Brantly et al. suggest even a longer trial duration if mortality is the preferred outcome as trials have not been sufficiently powered to detect the effect of AT. (8) However, it would be unethical as it would require a 10-year RCT to see the effect on mortality, which would be unacceptable due to high radiation exposure. (8; 52)

5.4.4 The Need for Other Research Methods

Many studies have identified statistically significant AT benefits (Table 1). As RCTs lack the sensitivity to identify change (e.g. FEV_1, exacerbations, HRQoL) they are not a viable option in rare disease research. (48) Pooled data and adaptive designs need to be supported by government advisors when assessing treatment options associated with treatment urgency.

The choice of traditional outcome measures in RCTs is problematic. Patient variability can explain why standard outcome indicators used in AATD RCTs have failed to provide a consistent picture of the benefit of AT. (53) To overcome the challenge of underpowered studies, pooled analysis has shed light on the efficacy of AT with results showing a decline in lung density destruction derived from AT.

5.4.5 The RAPID and RAPID-OLE Studies

There is good evidence to support government funded AT. The Rapid Study and the Rapid Extension study have demonstrated that lung density decline can be measured with CT and that AT slows decline. (54; 55) Edgar's 2017 systematic review came to the same conclusion, that intravenous AT slows emphysema determined by CT density. (7)

The importance of the RAPID study and the RAPID Extension study has been echoed by authors as AT slows disease progression, highlighting the importance of early intervention with AT. (46)

5.4.6 Meta-analysis

Evidence from a meta-analysis of five trials observing that the rate of FEV_1 decline is reduced by AT. (56) Slower decline was found in patients with baseline FEV_1 percent predicted <20%, <30% and 30-65%. (14; 54) Such evidence appears to have been overlooked.

5.4.7 Patient Registry Data

In their 2019 paper on the current state of evidence associated with AT, Brantly et al. present the positive impact of AT including survival improvement. (8) They raise the important role that registry data plays in questions related to AT and survival, noting the need for longitudinal studies and that the majority of AATD deaths occur after 4 to 9 years follow up. Registry data show a beneficial effect on survival with a statistically lower mortality rate in patients receiving AT compared to non-treated individuals. This finding was predominantly observed in patients with FEV_1 < 50% predicted. An important more recent finding is that survival improvement was also found in patients with low baseline FEV_1 < 20% and < 30% predicted. Brantly et al. claim that there is enough evidence to show that AT is useful for early and late stage disease. (8)

5.4.8 Flawed Cochrane Reviews

The *Cochrane Handbook for Systematic Reviews of Interventions* includes a section called "Methodological Expectations for Cochrane Intervention Reviews (MECIR)" which includes mandatory activities including consideration of different types of evidence including non-randomized studies. The flawed, poorly designed 2016 Cochrane review (12) ignores patient registry data and other studies showing a survival benefit from AT and downplays the importance of subgroup analysis with statistically significant results. The Cochrane review states that "studies should be large enough to detect a possible effect on mortality". Such data exists, i.e. pooled analysis shows improved survival from AT.

The Gotzsche and Johansen Cochrane findings have been brought into question by the North American Alpha-1 Foundation in an open letter (57) and results have been widely criticised by specialists (7) as the Cochrane reviews overlook the important methodological issues raised in this Position Paper. Evidence that lung density is a better (faster) indicator than FEV_1 and that AT and CT density linked to survival has also been ignored.

This oversight and restricted analysis by the Cochrane reviewers have resulted in patients with AATD being denied the only non-surgical treatment available. AT funding denial is unethical and is an international inequity. AATD deficient patients are living with anxiety and depression from a debilitating disease knowing that AT could save vulnerable lives. (58)

5.5 Surrogate Endpoints

CT lung density is a proven and acceptable biomarker and the BODE index has the capacity to predict survival. Surrogate endpoints should be considered in the study of AATD research. Beike et al. (2017) note that C-reactive protein (CRP), adipocyte fatty acid-binding protein (AFBP) and plasminogen activator (PA) are all associated with baseline genetic emphysema and with emphysema progression and are useful biomarkers in future research / evaluation and are promising compared to traditional biomarkers of COPD lung decline. (59)

5.6 Patient Registry Data

The compelling life-years gained argument from AT is supported by historical survival improvement observations based on longitudinal patient registry data. (4; 14) These findings are supported by Green et al., who showed that the improvement in the rate of lung-density decline is greater than the difference between the whole-lung densities of those who died and those who survived. (37)

The AAA believes that registry data should be incorporated into AT funding considerations and government advisors and regulators need to be able to explain AT funding denial when evidence exists to support government funded AT. The call is for the use of combined patient registries to enhance prospective long-term follow up, to facilitate translational research and quality improvements in health.

5.7 The Broader Context of AT

5.7.1 Guideline Requirements

While low FEV_1 is typically included in international treatment guidelines, low D_{LCO} and air trapping have been overlooked due to regulators' familiarity with FEV_1, leaving these groups of patients to die prematurely. Therefore, three groups of patients need to be reflected in AT guidelines.

Individuals with AATD may present with lower than predicted FEV_1 or poor gas exchange (D_{LCO}) and both D_{LCO} and FEV_1 need to be independently considered for AT as there is no correlation between them. Individuals with AATD require a personalised approach to AT as there are differing individual types and rates of lung function decline in AATD patients. (53) This is an important point as traditionally FEV_1 has been privileged over gas exchange, despite gas exchange being a better indicator of emphysema. There is an opportunity to address this oversight as guidelines for AT are developed for Australia.

5.7.2 AT in Northern America and Europe

The USA and Canada support AT as do many countries in Europe. A cohort analysis from the USA's Alpha-Net patient registry database shows the **median survival age of 80.4 years** (95% CI: 78.1 – 82.7), showing the profound impact of AT i.e. a normal life expectancy. (4)

The European Respiratory Society notes that CT lung density decline relates well to AATD clinical outcomes, such as mortality and HRQoL. The ERS statement supports the use of AT as part of an integrated management program for AATD.

The ERS discusses the 1972 Swedish patient birth cohort as it highlights the diversity of pulmonary disease and a lack of concordance between siblings raised in the same environment. Their analysis shows that FEV_1 is a poor surrogate measure for emphysema. The ERS notes that FEV_1 decline reflects a late physiological change in the disease process whereas gas transfer is reduced much earlier indicating that gas exchange may be a more sensitive and specific test of emphysema development. (20) This suggests that the earliest change is a decline in gas transfer, independent of and faster than FEV_1 decline.

5.7.3 The COPD-X Guidelines

Within Australia, AATD is bundled with COPD despite AATD being a very different treatable disease with AT. The COPD-X Guidelines include scant information on AATD and acknowledge that AT isn't funded in Australia. The Guidelines should be updated with the broader evidence

showing that AT treatment works, reflecting acknowledgement of the flawed 2016 AATD Cochrane Review and the existence of broader evidence supporting AT treatment.

5.8 Compelling Evidence

Table 1 presents a range of significant findings showing the positive effect of AT and that CT lung density and registry data are important sources of information. Possible reasons for Government overlooking compelling evidence include:

a) Acceptance of the methodologically flawed AATD Cochrane Reviews.

b) Using narrow literature reviews and overlooking non-RCT data.

c) Assumption that mortality is a good RCT outcome indicator when it is difficult to measure in short-term trials.

d) Reliance on advisors who have not considered all evidence.

e) A lack of understanding of the need to use the best available evidence when studying rare diseases as RCTs will always be underpowered.

f) Not appreciating that many traditional outcomes e.g. FEV_1 are not sensitive to change in the short term.

Table 1: Clinical Effectiveness of AT

AUTHOR	YEAR	EXAMPLES OF AUGMENTATION THERAPY EVIDENCE
		MORTALITY / SURVIVAL from AT
NHLBI AATD Registry Study Group (35)	1998	Decreased mortality in patients receiving AT – Pooled data of 198 treated German patients and 97 untreated Danish patients). (Observational cohort, concurrent controls)
Rahaghi et al. (27)	2014	AT improves survival at baseline FEV_1 values < 20%, < 30% and 30-65% predicted; and in DLC values 60% predicted and RV 120% predicted and in individuals with air trapping from hyperinflated lungs.
Choate et al. (4)	2016	Normal life expectancy from AT (median survival 80.4 years) in severely deficient AATD. (Large observational cohort from patient registry)
		CLINICAL EFFICACY – LUNGS
Seerholm et al. (32)	1997	Prospective multi-centre, controlled non-randomised study involving 295 individuals showed an increase in FEV_1 over 2 years from 59 to 74.5 for the AT arm compared to comparator group. Slower decline in FEV_1 in treated vs untreated group. Slower FEV_1 predicted decline in patients with FEV_1% predicted 31–65%. (Observational cohort, concurrent controls)
Wencher et al. (60)	1998	The rate of decline in FEV_1 in AT treated patients (~57 ml/yr) was approximately half that reported (historical data) for untreated controls. (Observational study 7 yrs)
Dirksen et al. (30)	1999	CT densitometry is correlated to FEV_1. Reduced decline of lung tissue and beneficial effect of AT assessed by CT. (Prospective, randomised, parallel double-blind, placebo-controlled trial)
Wencher (33)	2001	Rates of FEV_1 decline pre and post AT were 49.2 vs 34.2 ml/yr respectively.
NHLBI AATD Registry Study Group (35)	1998	The group receiving AT survived longer than the non-AT group. The group with slow decline shown by FEV_1 was 35-49% predicted. The results buttress the rationale for AT. (Observational cohort)
Dirksen et al. (30)	2009	CT is more sensitive a measure of emphysema-modifying AT than physiology and health status, and demonstrates a trend of AT benefit. (Prospective randomised, double-blind, placebo controlled, parallel group. Alpha-1-Antitrypsin (AAT) To Treat Emphysema in AATD Patients (EXACTLE)
Tonelli (34)	2009	In patients receiving AT their rate of FEV_1 was significantly better than the non-AT group. (Observational study of data registry)
Chapman et al. (54)	2009	AT slows lung function decline in FEV_1 in the moderate sub-group 30-65% FEV_1% predicted. (Prospective, meta-analysis)

Stockley et al. (49)	2010	Significant change in lung density in AT group over 2.5 years. 60 treated /59 non treated. (Clinical trial data from 5 centres)
McElvaney et. al (46)	2015	Annual CT lung density decline rate in the first 2 years was less by 0.75 g/L/yr in the first cohort. Lung density decline was reduced to -1.26 after 4 years. 34% reduction in lung density decline in patients receiving alpha1-PI 60 mg/kg IV compared to placebo. (RAPID Extension trial. 4 yrs.)
Chapman et al. (45)	2015	Slower lung density decline in AT individuals, compared to placebo. (RAPID Clinical trial - RCT from 28 international centres)
Green et al. (37)	2016	Improvements in the rate of lung-density decline from AT is greater than the difference between the whole lung densities of those who died and those who survived. Rate of change in lung densitometry predicts survival in AT group. Decline in KCO and DL_{CO} had a higher sensitivity than FEV_1 decline to predict CT density decline in non-AT patients. Changes in the lower zone lung CT densitometry in non-AT participants relates to survival in AATD and FEV_1 and gas transfer alone do not identify all patients with declining lung density. (Observational cohort).
		FEWER EXACERBATIONS and LOWER SEVERITY
Lieberman (29)	2000	AT reduces frequency of lung infections in AATD. The number of lung infections per year decreased from 3-5 pre-AT to 0-1 post-AT. (Observational study)
Gildea et al. (61)	2003	AT is cost effective for patients with severe AATD. (Markov-based decision analytical model)
Dirksen et al. (30)	2009	Post hoc analysis from the EXACTLE study found a reduction in exacerbation severity in the AT group compared with placebo ($P < 0.05$). (Randomised Control Trial)
Barros-Tizon et al. (28)	2012	Reduction in the incidence and severity of exacerbations in AATD which results in lower hospital expenses. (Retrospective multicentre observational cohort)
Campos et al. (39)	2018	Reports the positive effect of AT in reducing exacerbations by 36.1% in a cohort analysis and in overall savings due to fewer and shorter hospitalisations. (ADMAPP observational cohort)
Kohnlein et al. (31)	2010	Patients receiving AT had a significantly lower severity of exacerbations and less need for emergency room visits compared with patients treated with placebo.
		BIOMARKERS
Ma et al. (23)	2017	DES/IDES were significantly reduced versus baseline in patients receiving AT. AT reduces elastin degradation, including pulmonary elastin in patients with AATD. Results show a correlation between biomarkers of elastin degradation and a clinical marker of emphysema progression (CT lung density) in patients with AATD.

5.9 A Right to Health

While AT has been approved for use in Australia by the TGA, it is not government funded making it out of reach for the majority of AATD patients.

MSAC's recommendation not to fund AT is scientifically, morally and socially unjust as the evidence synthesis shows that AT is related to survival, less severe exacerbations, improved quality of life, hospital savings and that CT lung density is relevant in lung disease identification and patient management.

The following issues need to be considered by the Australian Government:

a) Australian AATD patients have the right to enjoy the highest attainable standard of health under *The International Covenant on Economic, Social and Cultural Rights* to which Australia is a party yet AATD (15) patients are being denied life-saving treatment due to the flawed AATD Cochrane Review and narrow COPD-X Guidelines which only focus on RCTs which are known to be methodologically challenging in the study of rare disease, when broader evidence needs to be considered.

b) The annual cost of AATD treatment was considered high by MSAC. However, the real cost to the Australian Government needs to be included in costing studies and the high cost of double lung transplants. Examination of the Public Summary Document indicates that the costing of comorbidities and treatment saving offset effects have been excluded giving a false impression of costs to government.

c) The cost effectiveness ratio of AATD is similar to many currently funded treatments such as hemodialysis. (61)

d) Treatment cost effectiveness should be considered in the context of AT being the only available non-surgical treatment. (61)

e) AT funding denial is associated with a profound economic toll from illness, disability and premature death and includes direct and indirect costs. Costs include for example lost wages plus the physical and mental suffering, disability costs, exacerbations (visits to family physician, antibiotics, corticosteroids), oxygen therapy, comorbidity treatment costs including surgical intervention costs (e.g. lung transplants). Mortality costs of future earnings lost through premature death should also be included. AT should not be denied to AATD patients who are disabled with lung disease when considering that: i) cheaper treatment options (e.g. inhaled, oral therapy) are currently under clinical trial and will replace infused AT; ii) broad and specific evidence supporting AT exists; iii) the number of lung-affected AATD patients requiring immediate AT is small (e.g. 4,126 people in Australia have PiZZ genotype). (62)

f) AATD patients have a significantly longer waiting time to transplant and have a higher likelihood of acute organ rejection compared to COPD patients. (10) Transplant patients face a lifetime of immunosuppressant medications to prevent organ rejection and hospitalisations and expensive medical procedures such as plasmapheresis if rejection occurs.

g) The Australian Disability Discrimination Act 1992 defines disability as a total or partial loss of the person's bodily or mental functions. A person with a disability is defined as a person with a physical or mental impairment that substantially limits one or more major life activities including the ability to carry out normal day-to-day activities. Many severely deficient patients are disabled by their AATD status, unable to work and have to live in social isolation, live on low income and disability pensions, and live in isolation from family and friends as they are immune compromised.

h) Since 1946 international law has supported a right to health and access to treatment as required. Australia is a party to seven core international human rights treaties. The right to health is contained in article 12(1) of the International Covenant on Economic Social and Cultural Rights (ICESCR). As noted on the Australian Government's Attorney-General's Department website, the right to health is the right to the enjoyment of the highest attainable standard of physical and mental health (15) and AATD patients are a "vulnerable" group requiring "essential" therapy.

i) As noted in the Public Summary Document, MSAC identified that the claim for AT met three of the four criteria for warranting Rule of Rescue when in fact it is clear that all four items are met as there is good literature supporting the clinical effectiveness of CT density in the detection of emphysema and other lung diseases and in their clinical management.

j) The Rule of Rescue should be applied to AATD in Australia as: 1) no treatment alternative exists in Australia; 2) AATD is a severe, progressive disease expected to lead to premature death; 3) a small number of patients require AT; 4) the broad evidence shows that AT will provide a clinical improvement with lung density stabilised and a normal life expectancy possible from AT. Based on the supporting CT density evidence and all four Rule of Rescue criteria met, lung affected AATD patients should have access to the means to avoid premature death and preventable morbidity.

k) Patients and their carers are the main stakeholders of this orphan disease and a patient-centred management approach needs to be adopted.

l) AATD has no government funded treatment in Australia while many other diseases have more than one similar treatment funded by government. Savings can be made by Government by limiting how many similar treatments are funded for other diseases, many of which are not life-saving.

m) The World Health Organisation (WHO) supports social justice in health (63) and their expert committee endorses the use of AT and has developed an international standard (WHO/BS/08.2092) supporting AT. (64)

n) The over-reliance on traditional research outcome measures and challenges associated with studying rare diseases, denies Australian AATD patients access to life-saving AT. Australian AATD patients continue to suffer and die early when international AATD patients are benefitting from AT. (4)

6 Conclusion

The purpose of AT for lung-affected AATD patients is to raise serum AAT to levels above the protective threshold, to protect lungs from protease damage, to prevent and slow the progression of emphysema and to extend lives. In addition, the immunomodulatory effects of AAT limit devastating lung infections and associated morbidity and mortality and the need for lung transplant. Patients requiring lung transplant also require AT to heal.

It is scientifically known that AT maintains lung density, slows emphysema decline, reduces the severity and frequency of exacerbations, improves survival, improved quality of life, can lead to a normal life expectancy and saves hospital costs. The literature on CT densitometry in lung disease confirms its clinical effectiveness in lung affected and AATD patients showing that its use can predict clinical improvement and survival and, therefore, lung density is an informative biomarker.

AATD patients are a vulnerable group with a right to health and treatment. AT is essential to stop lung destruction, to control serious pulmonary bacterial infections and it can provide a normal life expectancy. Overlooking evidence allows AATD patients to die prematurely and unfairly when AT exists and can limit genetic emphysema.

MSAC's recommendation to the Minister for Health to not approve funded AT is scientifically, morally and socially unjust based on the breadth of peer review evidence supporting AT. MSAC's questioning of the suitability of CT densitometry indicates that broad evidence on the use and suitability of CT densitometry use in pulmonary disease has been overlooked.

CT lung densitometry is an appropriate, accurate and reliable, clinically meaningful approach, supporting the application of the Rule of Rescue by the Australian Government to vulnerable AATD patients. As all four "rule of rescue" factors are concurrently present, the Australian Government needs to take a moral, socially just and scientific response to the evidence and should immediately apply the Rule of Rescue criteria to save the lives of patients who are severely deficient in AAT.

Patients have been unfairly denied access to funded AT due to the narrow AAT Cochrane Review and COPD-X Guidelines. An ethical approach would be to use the current broad evidence to save lives while new studies are undertaken on alternative solutions.

Withholding funded AT in Australia when good evidence exists and not applying the Rule of Rescue are not supported by the AAA.

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