A Normal Life Expectancy From Alpha-1 Proteinase Inhibitor: Methodological Considerations Related to Research on Augmentation Therapy in Alpha-1 Antitrypsin Deficiency

Position Paper

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Table 1: Clinical Effectiveness and Useful Outcome Indicators
## 1. Acronyms & Initialisms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>α1</td>
<td>Alpha-1</td>
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<tr>
<td>A1AT</td>
<td>Alpha-1 antitrypsin deficiency</td>
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<tr>
<td>AAA</td>
<td>Alpha-1 Association of Australia</td>
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<tr>
<td>AATD</td>
<td>Alpha-1 antitrypsin deficiency / α1-antitrypsin deficiency</td>
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<tr>
<td>ADMAPP</td>
<td>Alpha-1 Disease Management and Prevention Program</td>
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<tr>
<td>AFBP</td>
<td>Adipocyte fatty acid-binding protein</td>
</tr>
<tr>
<td>BODE</td>
<td>Body mass index, airflow obstruction, dyspnea and exercise capacity</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>COPD-X</td>
<td>Chronic obstructive pulmonary disease guidelines</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DES</td>
<td>Desmosine</td>
</tr>
<tr>
<td>DLCO</td>
<td>Decreased diffusing capacity of the lung for carbon monoxide</td>
</tr>
<tr>
<td>EARCO</td>
<td>The European Alpha-1 Research Collaboration</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>EXACTLE</td>
<td>EXAcerbations and computed tomography scan as lung end-points</td>
</tr>
<tr>
<td>FEVI</td>
<td>Forced expiratory volume in one second</td>
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<tr>
<td>GOLD</td>
<td>Global initiative for chronic obstructive lung disease</td>
</tr>
<tr>
<td>HDCT</td>
<td>High density computed tomography</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health Related Quality of Life</td>
</tr>
<tr>
<td>IDES</td>
<td>Isodesmosine</td>
</tr>
<tr>
<td>KCO</td>
<td>Carbon monoxide transfer coefficient</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred reporting items for systematic reviews and meta-analyses</td>
</tr>
<tr>
<td>PROSPERO</td>
<td>International prospective register of systematic reviews</td>
</tr>
<tr>
<td>PA</td>
<td>Plasminogen activator</td>
</tr>
<tr>
<td>RAPID-RCT</td>
<td>Randomised, placebo-controlled trial of augmentation therapy in alpha-1 proteinase inhibitor deviancy</td>
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<tr>
<td>RAPID-OLE</td>
<td>RAPID open label extension</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised control trial</td>
</tr>
<tr>
<td>SGRQ</td>
<td>St George’s respiratory questionnaire</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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</tbody>
</table>
2. **Executive Summary**

2.1. The opportunity of having a normal life expectancy from alpha-1 antitrypsin augmentation therapy\(^1\) is a very important issue for patients with alpha-1 antitrypsin deficiency. Even with standard COPD treatment, the lack of antitrypsin augmentation therapy leads to an early death, as many individuals with alpha-1 antitrypsin deficiency are known to be rapid decliners\(^2\) compared to non-deficient COPD.

2.2. Alpha-1 antitrypsin deficiency longitudinal patient registry studies and randomised clinical trials (RCTs) have shown that augmentation therapy improves survival, slows the development and severity of emphysema\(^,1,2,3\) rebuilds lung density and reduces elastin degradation\(^4\) and that individuals can have a normal life expectancy\(^1\), showing that any scepticism about the benefits of augmentation therapy for alpha-1 antitrypsin deficiency can be abandoned.\(^5\) However, the benefit of augmentation therapy remains a topic of intense debate due to methodological issues related to alpha-1 antitrypsin deficiency research on augmentation therapy and poorly conducted literature reviews. Meanwhile augmentation therapy remains the only standard therapy\(^6\) for lung affected alpha-1 antitrypsin deficient individuals. Doubt about the clinical efficacy of augmentation therapy is linked to the lack of sensitivity of typical research outcome measures\(^,6,7\) and a lack of appreciation of the problem of studying rare diseases\(^7\) using RCTs. RCTs can’t be sufficiently powered due to the logistical challenge of recruiting a large enough sample size when studying rare diseases\(^8\) and the short timescale (length of follow up). Up to 10 years is required\(^7\) to show change with some outcome indicators used in augmentation therapy research. In addition, it has been confirmed that there is a marked variation in individual FEV\(_1\) decline in alpha-1 antitrypsin deficient individuals, that different outcome indicators are required as well as a personalised approach to patient management.\(^6\) Patient variability\(^6\) can also explain why standard outcome indicators used in alpha-1 antitrypsin deficiency RCTs have failed to provide a consistent picture of the benefit of augmentation therapy.

2.3. An examination of such complexity is required when policy makers review the evidence associated with clinical efficacy and mortality linked to augmentation therapy. In addition, proper consideration needs to be given as to why some RCTs and narrow literature reviews have not presented the expected disease modifying effects of augmentation therapy when using traditional indicators such as FEV\(_1\), exacerbations, health related quality of life (HRQoL) and mortality. A proper comprehensive systematic review is required to identify issues associated with studies using traditional and new endpoints and to include the significant evidence typically excluded ie. evidence gathered using non-RCT designs. Different data sources, including pooled analyses and patient registry data (providing longitudinal comparative data) are particularly important to provide large scale data to answer questions that clinical trials alone cannot provide.\(^7,8,9,10,11\) Pooled data, subgroup analysis and longitudinal comparative studies using patient registry data have all identified statistically significant benefits from augmentation therapy in deficient Alphas (Table 1). Data collection on the natural history of the disease\(^7\) and looking at differences between phenotypes via registries will eventually allow all questions about treatment to be answered. To gather the same compelling evidence using RCTs, they would have to run for up to 10 years which is unacceptable regarding radiation risks associated with repeat high density CTs (HDCTs)\(^7,12\) which is compounded by the fact that CTs are used routinely in standard alpha-1 antitrypsin deficient patient management. The time that a control group would be on placebo
and denied treatment is also unacceptable. It is already known from existing studies (including registry studies and subgroup analysis within other studies) that augmentation therapy maintains lung density, slows emphysema decline, reduces the severity and frequency of exacerbations and can lead to a normal life expectancy. In short, clinical research in rare diseases, including alpha-1 antitrypsin deficiency, faces challenges not shared by common diseases. Standard RCTs are not a viable option in rare disease research, therefore, adaptive designs should be the norm including cross over designs and natural history studies using patient registers along with databases of rare disease.

2.4. Assumptions that the gold standard RCT is the only design that can provide insight into whether augmentation therapy is clinically effective is problematic. Short term clinical trials using outcome indicators (eg. FEV₁, exacerbations, HRQoL), that lack the sensitivity to identify change have been used in the past, presenting a picture that augmentation therapy does not have the desired therapeutic impact. Relying on classic RCT designs or calling for more of the same will unfortunately not clearly reveal the positive impact of augmentation therapy due to methodological design issues associated with traditional RCTs, including the number of years required to identify change.

2.5. There is no debate that the biochemical evidence supports augmentation therapy as serum antitrypsin levels are raised to a protective level and there is evidence from RCTs, patient registries and from other study designs that augmentation therapy extends life. Augmentation therapy has also been shown to reduce severity and length of exacerbations, however, HDCT is the most sensitive measure followed by diffusing capacity of the lungs for carbon monoxide (D_{LCO}). Furthermore, there is evidence of savings from reduced hospitalisations associated with augmentation therapy in alpha-1 antitrypsin deficient patients (Table 1).

2.6. Patients are their carers are main stakeholders of this orphan disease. A patient-centred management approach needs to be adopted. All patients who could potentially benefit from augmentation therapy need to be provided with it as soon as possible to prevent physiological and radiological deterioration as the weight of evidence shows that a safe treatment is available which slows lung emphysema decline and reduces mortality.

2.7. Narrow reviews that overlook more useful study designs and ignore the grey literature will result in the wrong conclusion being reached which leads to the unacceptable denial of augmentation therapy when other rare and life shortening genetic diseases are publicly funded. This paper raises issues associated with narrow reviews and questions how the findings presented by many alpha-1 antitrypsin deficiency experts who have published on the life prolonging effect of augmentation therapy and the importance of early intervention to slow disease progression can be overlooked. This paper also shows why different methodological considerations are required in the study of augmentation therapy so important information is never excluded from the alpha-1 antitrypsin deficiency policy agenda.
3. Systematic Reviews in Rare Diseases

3.1. Narrow Literature Reviews
While systematic reviews and RCTs are held in high esteem and are of immense value to medical professionals, narrow literature reviews examining augmentation therapy and poor systematic reviews that don’t meet review standards diminish their value to policy makers, clinicians and patients. Policy makers should ensure that reviews have addressed the methodological issues listed in this paper and need to appreciate that RCTs are not going to provide all of the answers called for by traditionalists and why alpha-1 antitrypsin deficiency longitudinal studies from patient registries must be considered. Therefore, reviewers must be prepared to consider different levels of evidence especially in rare diseases and go beyond Level 1 and GRADE A evidence when undertaking literature reviews.

3.2. Systematic Review Expectations
A systematic review uses systematic methods to collect medical evidence on a topic and critically appraises the studies and synthesises findings qualitatively and quantitatively and ideally follows a framework and a preferred checklist such as PRISMA. The PRISMA approach for reporting systematic reviews uses the internationally accepted statement covering 27 items. Following PRISMA ensures that important review elements are not overlooked, including sub-group analysis, that show benefit from augmentation therapy within RCTs and cohort studies (Table 1).

A systematic review is meant to be complete, unbiased and exhaustive, should include the grey literature and be relevant to the research question. Use of a broad range of related search terms is vital, so that important considerations and clinical evidence are not overlooked e.g. if looking at mortality, related terms would be included such as “survival”, “death”, “morbidity”, “rate of decline” associated with “augmentation therapy”, “plasma-purified A1AT”, “replacement therapy”, “fluid therapy”, “AAT therapy”, “intravenous augmentation”, “α1-proteinase”, “A1-PI” and “COPD”, “genetic emphysema”, “antitrypsin deficiency”, “α1-antitrypsin deficiency”, “Alpha-1”, “α-1” “AATD”, “alpha-1 antitrypsin deficiency” and all published variations of these terms.

3.3. There needs to be an end to narrowly focused so-called systematic reviews that exclude important evidence when it isn’t level 1 evidence. The following points are made in regard to normal systematic review expectations and should apply to alpha-1 antitrypsin deficiency augmentation systematic reviews considered by policy makers and organisations formulating positions associated with COPD:

- a) Inclusion of a clearly formulated answerable research question that uses systematic and explicit methods;
- b) Broad cut-off dates and the choice of a research study methodology that is not too restrictive to understand best treatment options that can assist survival in individuals with alpha-1 antitrypsin deficiency;
- c) To reduce bias, at least two independent reviewers agree on the same inclusion and exclusion criteria using the same criteria;
- d) The registration of systematic review protocols, to support accountability, research integrity and transparency of the review (eg. registration with PROSPERO or the Cochrane Database of Systematic Reviews);
If previous systematic reviews and meta-analyses are used it is important that a broad range of other publications before and after these publication dates are included to ensure that relevant historical data and recent publications are not overlooked; and

To answer questions related to alpha-1 antitrypsin deficiency treatment impact and survival, and due to the known methodological shortcomings related to the use of RCTs in rare diseases, all clinical trials, cohort studies, registry database study reports and subgroup analysis should be included.

4. Alpha-1 Antitrypsin Deficiency and Augmentation Therapy Evidence

4.1. The Role of Antitrypsin and the Need for Augmentation Therapy
Consideration should be given to the broader clinical benefits of augmentation therapy in alpha-1 antitrypsin deficiency. It was reported more than 15 years ago that alpha-1 antitrypsin deficiency has a variety of associated illnesses and diseases. Based on the evidence from augmentation therapy, Sandhaus suggests that damage to organs can be halted and may possibly reverse some organ injury. While alpha-1 antitrypsin deficiency most commonly manifests as genetic emphysema, antitrypsin plays an important systemic anti-infective and anti-inflammatory role and is a tissue repair molecule. In addition, genetic deficiency of alpha-1 antitrypsin results in a proteinase/anti-proteinase imbalance leading to the breakdown of elastin in tissues mainly in the parenchyma of the lung. However, augmentation therapy has been shown to reduce elastin degradation including pulmonary elastin.

4.2. In addition to genetic emphysema, some of the diseases associated with alpha-1 antitrypsin deficiency includes abdominal and intracranial aneurysms, asthma, bronchiectasis, colon diverticulitis, connective tissue disorders, genetic emphysema, fibromyalgia, heart failure, lung cancer, osteoporosis, necrotising panniculitis, pancreatitis, proliferative glomerulonephritis, pulmonary embolism, stroke, systemic vasculitis including Wegener’s granulomatosis with polyangiitis and urticaria.

4.3. Patients with genetic emphysema often have hyperinflated lungs. As alpha-1 antitrypsin deficiency is a chronic progressive disease it is not sufficient to treat symptoms alone.

4.4. Lung affected alpha-1 antitrypsin deficient individuals may be fast decliners with early onset emphysema compared to non-deficient COPD individuals but alpha-1 antitrypsin deficiency it is still a slow progressive disease, making change hard to detect in short-term RCTs. Typical COPD treatment in Australia focuses on the resultant disease state rather than dealing with the alpha-1 antitrypsin deficiency. In alpha-1 antitrypsin deficiency related emphysema, treatment with bronchodilators or corticosteroids do not stop the progressive destruction of lung tissue. Therefore, early intervention with augmentation therapy is required to limit widespread destruction of lung parenchyma. Clinical trials and international registry studies show augmentation therapy to be disease modifying with sustained change following therapeutic intervention. This is why augmentation therapy remains an attractive option for alpha-1 antitrypsin deficient patients. Treatment provides an extended life and fewer comorbidities for patients who otherwise face a poor prognosis, for example, use of augmentation therapy has shown...
spectacular results in alpha-1 antitrypsin deficiency-related vasculitis and panniculitis. Augmentation therapy treats the deficiency (illness) and permits patients to lead normal lives, reducing the frequency of health care resources and social services utilisation, allows individuals to be actively involved in society and in many cases, being able to contribute to employment and productivity. Many patients are familiar with the scientific publications associated with the disease-modifying and life-extending possibilities offered by augmentation therapy, and are puzzled as to why it has not been routinely publicly funded, based on the compelling evidence, and are desperate to receive this critical medical treatment to improve health and save their lives.

4.5. Improved Survival from Augmentation Therapy
Augmentation therapy has been available and used for decades in the USA and more recently in parts of Canada and Europe. Therapy is aimed at correcting the underlying genetic abnormality rather than dealing with the impact of alpha-1 antitrypsin deficiency as is the case with standard COPD treatment in Australia. Augmentation therapy can significantly delay time to death, avoid deaths while waiting for lung transplant and lung transplantation costs, crippling respiratory complaints and comorbidities associated with alpha-1 antitrypsin deficiency. Augmentation therapy extends life. The USA’s long-standing patient registry has had registry studies published showing a normal life expectancy for alpha-1 antitrypsin deficient patients when treated with augmentation therapy. Life-years gained have been raised from 54.5 years (individuals not on augmentation therapy) to a median survival of 80.4 years (ie. normal life expectancy) when receiving augmentation therapy. The reasons offered for such good survival include the positive effect augmentation therapy has on lungs and comorbidities and improved disease management.

4.6. The challenge related to appreciating the life-saving impact of augmentation therapy on alpha-1 antitrypsin deficient patients is the interplay of biological (including phenotype), environmental and social factors. These factors affect individual responses to treatment causing results not to be consistent across patients in short duration RCTs. Such challenges have made CT lung density an attractive option in RCTs as it measures destruction of alveolar walls and loss of tissues in emphysema. The HDCT is an appropriate meaningful validated endpoint approved in the USA and elsewhere. Studies show that CT lung density correlates with FEV1 decline and that CT is the most specific and sensitive outcome measure for assessing the progression of emphysema.

4.7. As shown in Table 1, augmentation therapy has been demonstrated to work via longitudinal studies, in sub-group analyses and in other study designs. Results reveal that moderate to severely affected patients have slower decline and reduced mortality compared to baseline FEV1. These positive results have led many international alpha-1 antitrypsin deficiency medical and methodological experts to call for a broader understanding of the benefits of augmentation therapy as results are unequivocal and statistically significant.
5. **Methodological Issues in Rare Diseases and AATD**

5.1. **Lack of Sensitivity in Outcome Measures**

Early studies used the gold standard FEV₁ as a marker for monitoring disease progression, however, changes in FEV₁ occur slowly and FEV₁ lacks sensitivity. This means that a placebo-controlled trial would need to run for at least five years with a minimum of 1000 subjects to see the benefits of augmentation therapy. Clearly there are limitations to the use of FEV₁ in short term trials, including its failure to identify all patients with decline in lung density. As Stolk et al. (2007) and Stockley et al. (2016, 2010) note, FEV₁ and gas exchange are not nearly as sensitive as CT lung densitometry to effectively chart disease progression in Alpha-1 antitrypsin deficiency emphysemic patients as it is a slow progressive disease and uneven over time. The problem with FEV₁ as an outcome indicator in trials has been raised for many years. It has been reported that 550 patients would be required to show a 50% reduction in annual lung decline while the use of CT lung densitometry would only require 130 patients in a similar trial. Unfortunately this information appears to have been overlooked by many in the field.

5.2. **There is evidence to support funded access to augmentation therapy.** The Rapid Study and the Rapid Extension study have demonstrated that lung density decline can be measured with CT and that augmentation therapy slows decline. Edgar’s 2017 systematic review concluded with the same finding, that intravenous augmentation in alpha-1 antitrypsin deficiency slows emphysema determined by CT density. Other studies have reported significant results showing that certain groups do better on augmentation therapy. McElvaney et al. (2016) for example report that the relative proportions of fast and slow decliners is different in augmentation therapy and placebo groups. These positive findings may have been dismissed due to assumptions that short duration RCTs will show desired results using traditional outcome indicators. A limitation of some literature reviews, therefore, relates to the fact that registry data and other trial studies, with statistically significant results are overlooked as RCTs using FEV₁, HRQoL, exacerbations and mortality as endpoints are thought to be more valuable. This oversight continues despite publications showing that lung density is a better short term measure and that registry data studies are invaluable to show improved survival related to augmentation and alpha-1 antitrypsin deficiency.

5.3. **FEV₁ is not a good trial outcome measure.** This issue was suggested by Rennard in 2006 when it was noted that health status in COPD is more closely related to functional capacity than to changes in FEV₁. Green et al. 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, another reason why registry data is attractive. The BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) index has been validated and used in alpha-1 antitrypsin deficiency and has been found to be better in discriminating and predicting survival than FEV₁. As CT densitometry provides information regarding overall lung destruction, location of lung destruction and is a specific and sensitive outcome measure for assessing progression of emphysema and is linear and more consistent than traditional endpoints, the BODE index could be used in addition to CT densitometry.
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. These requirements are due to the fact that traditional RCTs are not considered a viable option in alpha-1 antitrypsin deficiency. As early as 1983, Burrows noted challenges associated with alpha-1 antitrypsin deficiency clinical trials. He reported that the variability in rate of functional loss in alpha-1 antitrypsin deficiency lung disease is high and patients often present in the late stage of the disease making it even harder to test the survival impact of alpha-1 antitrypsin deficiency.

5.4. It has been suggested that a clinical trial duration would have to be least 5 years and involve 684 individuals if mortality is the primary endpoint, using a 40% reduction in mortality with baseline FEV1 35-49% predicted. Such recruitment numbers are challenging in rare diseases and delays access to augmentation therapy which has been shown to stabilise lung density, slow emphysema and provide a normal life span. Brantly et al (2019) suggest even a longer trial duration if mortality is the preferred outcome as trials have not been sufficiently powered to detect the effect of augmentation therapy. However, it would actually require a 10 year RCT to see the effect on mortality, which would be dangerous due to high radiation exposure and is unethical. Any suggestion for long term RCTs using CT lung density to repeat what is already known would also be alarming due to the high risk of cancer from repeat HDCTs.

5.5. It is likely that the best RCT data has already been provided in the RAPID-RCT and the RAPID-OLE studies. The importance of the RAPID study and the RAPID extension study has been echoed by other authors as augmentation therapy slows disease progression highlighting the importance of early intervention with A1P1 as lung density is never recovered. A significantly higher proportion of patients receiving augmentation therapy were slow decliners (72% vs 50%), a benefit which was maintained in the Extension study.

5.6. Further evidence comes from a meta-analysis of five trials observing a 23% slower decline in FEV1 among trial participants receiving augmentation therapy. Slower decline was found in patients with baseline FEV1 percent predicted <20%, <30% and 30-65%. Such evidence appears to have been denied due to the misguided belief that single RCTs are essential in the study of rare disease.

5.7. In their 2019 paper on the current state of evidence associated with augmentation therapy, Brantly et al. present the positive impact of augmentation therapy including survival improvement. Brantly raises the important role that registry data plays in questions related to augmentation therapy and survival, noting the need for longitudinal studies and that the majority of alpha-1 antitrypsin deficiency 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 augmentation therapy compared to non-treated individuals. This finding was predominantly observed in patients with FEV1 < 50% predicted. An important more recent finding is that survival improvement was also found in patients with low baseline FEV1 < 20% and < 30% predicted. Brantly claims that there is enough evidence to show that augmentation therapy is useful for early and late stage disease.

5.8. Flawed Cochrane Reviews
The methodological limitations used in alpha-1 antitrypsin deficiency literature
reviews are now discussed in more detail. The recent flawed and poorly designed 2016 Cochrane review by Gotzsche and Johansen\(^3^8\) (2016) ignores patient registry data and other studies showing a survival benefit from augmentation therapy and downplays the importance of subgroup analysis with statistically significant results. The review states that “studies should be large enough to detect a possible effect on mortality”. The good news is that in 2016 commanding registry study results were published on the positive impact on mortality from augmentation therapy, involving over 1000 extremely deficient Alphas who now expect a normal life expectancy.\(^1\)

5.9. The Gotzsche and Johansen Cochrane findings have been brought into question by the Alpha-1 Foundation in an open letter\(^3^9\) as the reviews overlook the problems raised above and evidence that lung density is a better (faster) indicator than FEV\(_1\), and that augmentation therapy is linked to survival.\(^1^4\) This oversight by the Cochrane reviewers appears to have resulted in patients with alpha-1 antitrypsin deficiency being denied augmentation treatment, the only treatment shown in trials and by longitudinal studies to be life extending. Treatment denial is unethical and is an international inequity. Alpha-1 antitrypsin deficient patients are living with extreme distress knowing that augmentation therapy can save their lives. Patients are aware of the thousands of publications on alpha-1 antitrypsin deficiency, the huge pool of funding gone into alpha-1 antitrypsin deficiency research, the existing evidence and the lack of translational research\(^6\) to assist alpha-1 antitrypsin deficient individuals. Patients are very keen to access augmentation therapy as it is clearly lifesaving.

5.10. Surrogate endpoints

Noting the methodological issues raised above, CT lung density is an acceptable biomarker\(^1^2\) and the BODE index has the capacity to predict survival.\(^3^4\) Furthermore surrogate endpoints can be considered in the study of alpha-1 antitrypsin deficiency research. For example, 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.

5.11. Health Related Quality of Life

Consideration of HRQoL as an outcome indicator in alpha-1 antitrypsin deficiency studies is important, however, the complexity associated with alpha-1 antitrypsin deficiency raises a question around the suitability of commonly used HRQoL instruments in alpha-1 antitrypsin deficiency and explains why there has been a call to develop a specific tool with better sensitivity as the St George’s Respiratory Questionnaire (SGRQ) has a low sensitivity index in alpha-1 antitrypsin deficiency.\(^4\) Treatment denial in many jurisdictions stems from the limitations of commonly used outcome measures including HRQoL and FEV\(_1\) in alpha-1 antitrypsin deficiency short term studies and lack of appreciation of the design needs associated with the study of rare diseases. Ideally policy makers would embrace the positive findings from sub-group analyses within studies and from prospective patient registry studies. Narrow literature reviews continue to unfairly deny access to augmentation treatment which extends the lives of individuals with alpha-1 antitrypsin deficiency. Augmentation therapy can reduce alpha-1 antitrypsin deficiency comorbidities and save individuals from an early death from genetic emphysema. A patient centred and ethical approach would be to use the current evidence to save lives while new prospective studies are undertaken to confirm what is already known.
5.12. An Industry Perspective
In addition to the above issues, an industry perspective on conducting a traditional clinical efficacy augmentation therapy trial with a placebo-controlled group raises many obstacles including recruitment in rare diseases, commercially available augmentation therapy making the population even smaller, logistics with international sites, keeping a placebo group blinded as alpha-1 antitrypsin deficiency blood levels are taken through commercial laboratories, health risks for the placebo group (from treatment denial), ethical issues for the participating investigators and the sponsor, endpoint selection with cheaper measures having low sensitivity eg FEV\textsubscript{1}, and the expense.\textsuperscript{40}

5.13. Use of Patient Registry Data
Published results indicate how important it is to consider various study designs including patient registry studies and the importance of research collaboration using patient registry data. The European Alpha-1 Research Collaboration (EARCO) is one example of data availability based on collaboration and international sharing. The EARCO approach will provide the sample sizes required to test current augmentation therapy knowledge. EARCO can explore the natural history of the disease and treatment response.\textsuperscript{41} Policy makers are encouraged to consider alpha-1 antitrypsin deficiency national registry data from the USA and elsewhere which is providing an insight into disease modification and the life saving effects of augmentation therapy. The Alpha-1 Association of Australia (AAA) believes that registry data analyses should be incorporated into policy considerations and policy makers should be able to explain treatment denial when significant evidence exists to support funded augmentation therapy. The limitations of clinical trials in rare diseases have been raised by many international senior Alpha-1 researchers and the call for the use of combined patient registries to enhance prospective long-term follow up, facilitate research and quality improvements in health and translational priorities in accordance with patients’ concerns. Researchers can gain important insight through partnership focusing on registry data studies. For example, the Alpha One International Registry, established in 1997, has facilitated collaborations between clinicians from many countries.\textsuperscript{42}

6. The Broader Context of Augmentation Therapy

6.1. United States of America
The USA is a leader in augmentation therapy, founding Alpha-Net in 1995 which coordinates treatment and management of alpha-1 antitrypsin deficiency. Its patient registry holds many records allowing cohort analysis. Their 2016 study on survival of alpha-1 antitrypsin deficient patients comparing three cohorts in five year intervals [1) 1999-2004; 2) 2005-2009; 3) 2010-2015] shows the median survival age increases in each cohort from 68.9 yrs to 78.8 years to 80.4 years with an overall average survival age of 75.65 (95% CI 73.85-76.79), showing the profound impact of augmentation therapy leading to normal life expectancy.\textsuperscript{1}

6.2. European Respiratory Society (ERS)
It is noteworthy that augmentation therapy is supported in the updated 2017 European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha-1 antitrypsin deficiency. Fifteen expert panel members representing 16 institutions from many countries developed the statement.\textsuperscript{43}
To minimise bias in its systematic review of augmentation therapy, ERS takes a suitably broad approach and includes eight RCTs on intravenous augmentation, three against placebo and five against another active comparator, six observational studies reporting a control group (largely from alpha-1 antitrypsin deficiency registry data). They also looked at 11 uncontrolled observational studies and note two registered ongoing clinical trials. The review identified enough evidence to support augmentation therapy. The ERS statement for treatment of alpha-1 antitrypsin deficiency supports the use of augmentation therapy as part of an integrated management program for alpha-1 antitrypsin deficiency. By doing so, alpha-1 antitrypsin deficient individuals can expect reduced mortality.

The ERS has accepted that CT lung density decline has been shown in cross-sectional and longitudinal studies to relate well to clinical outcomes, such as mortality and HRQoL. Furthermore, the RCT results related to CT lung density decline are consistent with the longer observational work showing a mortality benefit. They note that survival was reported in the most recent RCT but the low mortality rate prevented any conclusion.

The ERS notes that more recently, the establishment of alpha-1 antitrypsin deficiency registries and follow-up data from the 1972 Swedish birth cohort have highlighted the diversity of impact and type of lung disease, and that there is a lack of concordance found between siblings raised with the same environmental background. Their analysis highlighted several issues with common indicators including that FEV₁ is a poor surrogate measure for emphysema in these patients, and that other unknown environmental or genetic influences may play a role in determining the outcome. This point is echoed by Brantly (2019) who states that several studies show FEV₁ is not a sensitive endpoint for determining the effects of augmentation therapy on emphysema progression.⁷

The ERS also notes that FEV₁ decline reflects a late physiological change in the disease process whereas gas transfer is reduced much earlier indicating that it may be a more sensitive and specific test of emphysema development. Their hypothesis is supported by the observational monitoring of the Swedish birth cohort, where abnormal gas transfer was present in some patients in their fourth decade while FEV₁ remained within normal ranges. Also physiological assessment confirms a discordance of lung function with some patients retaining normal gas transfer even with reduced FEV₁ and vice versa. This finding suggests that the earliest change is a decline in gas transfer, which may be independent of and faster than FEV₁ decline. These insights support longitudinal studies in alpha-1 antitrypsin deficiency rather than more RCTs.

6.3. Canada
The Canadian Thoracic Society supports augmentation therapy as per its 2012 clinical practice guideline, while recognising gaps in data and suggesting further study opportunity to address some clinical questions. Its analysis includes a patient registry data report showing improved mortality for patients with alpha-1 antitrypsin deficiency.⁸

6.4. Australia
While augmentation therapy has been approved for use in Australia by Australia’s Therapeutic Goods Administration (TGA), the associated expense makes it out of reach for the majority of alpha-1 antitrypsin deficient patients so patients are suffering and dying prematurely.
The Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease (COPD-X Guidelines) include reference to the RAPID study findings and the associated post hoc findings including the following positive results:

a) That the annual rate of lung density loss measured by CT at total lung capacity TLC was significantly less in patients receiving augmentation therapy compared to placebo;

b) A reduced rate of lung density loss and higher serum antitrypsin levels in patients receiving augmentation therapy was found;

c) The decrease in lung density loss was maintained in patients receiving augmentation therapy after a further 24 months of treatment; and

d) Evidence to date demonstrates that augmentation therapy modifies the development of emphysema.

The COPD-X Guidelines state that optimal dosing information has not been determined. However, the protective threshold has been widely established and 60 mg/kg/wk is commonly used in treating countries to achieve the 11 μM threshold. The Guidelines also state that “it is unclear if (augmentation therapy) improves clinical outcomes” and appear to call for evidence related to FEV₁ improvements from augmentation therapy, but FEV₁ is known to have poor sensitivity and the Guidelines acknowledge this when they quote Stockely. The Guideline’s narrow literature focus appears to have led to the incorrect conclusion that no evidence exists on the clinical efficacy of augmentation therapy, a surprising conclusion when the Guidelines note that emphysema progression is modified from augmentation therapy. If the authors of the COPD-X Guidelines looked at the published mortality data (Table 1) they would find that normal life expectancy can be the norm when patients are treated with augmentation therapy.

6.5. World Health Organisation (WHO)

The WHO expert committee endorses the use of augmentation therapy for alpha-1 antitrypsin deficiency and has endorsed an international standard (WHO/BS/08.2092). In 1997 the WHO accepted that investigations of whether augmentation therapy retards emphysema progression had been hampered by the long intervals needed to study outcomes and the large numbers of patients needed and the expense of such trials. Regardless of issues associated with RCTs in rare disease, the WHO endorsed augmentation therapy as a potentially life saving intervention. The WHO also recommended that COPD patients should be screened to identify alpha-1 antitrypsin deficient individuals.
6.6. **GOLD**

The 2019 *Global Initiative for Chronic Obstructive Lung Disease: Pocket Guide to COPD Diagnosis, Management and Prevention* (GOLD) notes the importance of screening of all patients with COPD for alpha-1 antitrypsin deficiency and that deficient individuals may be candidates for augmentation therapy. Australian alpha-1 antitrypsin deficient patients are missing out on receiving the best care from clinicians. The over-reliance on insensitive traditional research outcome measures in alpha-1 antitrypsin deficiency research and the blind alignment with RCTs, combined with the challenge of studying rare diseases, appear to have led to the flawed section on alpha-1 antitrypsin deficiency in the current COPD-X guidelines which indirectly denies Australian alpha-1 antitrypsin deficient patients life saving treatment. Regrettably Australian alpha-1 antitrypsin deficient individuals continue to suffer and die early when international alpha-1 antitrypsin deficient patients are benefitting from augmentation therapy.

### Table 1

Table 1 presents a range of significant findings showing conclusively that augmentation therapy works in alpha-1 antitrypsin deficient individuals and that CT lung density and registry data are valid and importance sources of information.

Possible reasons for overlooking compelling evidence include:

i. Acceptance of the methodologically flawed alpha-1 antitrypsin deficiency Cochrane Reviews that overlook important evidence and considerations when studying rare disease.

ii. The lack of recognition that important endpoints (study outcomes) have been published and endorsed by many international experts, showing the efficacy of augmentation therapy.

iii. Ignoring longitudinal patient registry studies that have shown huge survival improvement from augmentation therapy compared to placebo.

iv. Assuming mortality is a good RCT outcome indicator when it is not appropriate in a short term trial making longitudinal studies attractive.

v. Reliance on advisors who have not considered all evidence.

vi. A lack of understanding of the need to use the best available evidence when studying rare diseases as RCTS will always be underpowered due to the small number of patients available for clinical trials.

vii. Not appreciating that while RCTs are important in some contexts they are not always the answer or appropriate and that other research methods including longitudinal studies can provide and have provided information on the treatment effects of augmentation therapy.

viii. Not appreciating that many traditional outcome methods eg FEV₁ are not sensitive to change in the short term.

ix. Using narrow literature reviews not comprehensive systematic reviews.

x. Being influenced by lung guidelines which overlook many statistically significant research results.
### Table 1: Clinical Effectiveness and Valid Outcome Indicators

<table>
<thead>
<tr>
<th>AUTHOR (patient number)</th>
<th>YEAR</th>
<th>EXAMPLES OF AUGMENTATION THERAPY EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seershholm et al.48 (143)</td>
<td>1997</td>
<td>Prospective multi-centre, controlled non-randomised study involving 295 individuals showed an increase in FEV, over 2 years from 59 to 74.5 for the augmentation therapy arm compared to comparator group. Slower decline in FEV, in treated vs untreated group. Slower FEV1% predicted decline in patients with FEV1% predicted 31–65%. (Observational cohort, concurrent controls)</td>
</tr>
<tr>
<td>Wencher et al.49 (443)</td>
<td>1998</td>
<td>The rate of decline in FEV1 in augmentation treated patients (−57 ml/yr) was approximately half that reported (historical data) for untreated controls. (Observational study 7 yrs)</td>
</tr>
<tr>
<td>Dirksen et al.29 (58)</td>
<td>1999</td>
<td>CT densitometry is correlated to FEV1. Reduced decline of lung tissue and beneficial effect of augmentation therapy assessed by CT. (Prospective, randomized, parallel double-blind, placebo-controlled trial)</td>
</tr>
<tr>
<td>Wencher50 (144)</td>
<td>2001</td>
<td>Rates of FEV1 decline pre and post augmentation were 49.2 vs 34.2 ml/yr respectively.</td>
</tr>
<tr>
<td>The Alpha-1-Antitrypsin Deficiency Registry Study Group51 (1,048)</td>
<td>2009</td>
<td>The group receiving treatment survived longer than the non-treatment group. The group with slow decline shown by FEV1, was 35-49% predicted. The results buttress the rationale for augmentation therapy. (Observational cohort)</td>
</tr>
<tr>
<td>Dirksen et al.52 (77)</td>
<td>2009</td>
<td>CT is more sensitive a measure of emphysema-modifying therapy than physiology and health status, and demonstrates a trend of Prolastin-C treatment benefit. (Prospective randomized, double-blind, placebo controlled, parallel group. Alpha-1-Antitrypsin (AAT) To Treat Emphysema in AAT Deficient Patients (EXACTLE))</td>
</tr>
<tr>
<td>Tonelli53 (146)</td>
<td>2009</td>
<td>In patients receiving augmentation therapy their rate of FEV1 was significantly better than the non treatment group. (Observational study of data registry)</td>
</tr>
<tr>
<td>Chapman et al.37</td>
<td>2009</td>
<td>Augmentation slows lung function decline in FEV1 in the moderate sub-group 30-65% FEV1% predicted. (Prospective, meta-analysis)</td>
</tr>
<tr>
<td>Stockley et al.10 (119)</td>
<td>2010</td>
<td>Significant change in lung density in treatment group over 2.5 years. 60 treated /59 non treated. (Clinical trial data from 5 centres)</td>
</tr>
<tr>
<td>McElvaney et al.54 (180)</td>
<td>2015</td>
<td>Annual CT lung density decline rate in the first 2 yrs 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.)</td>
</tr>
<tr>
<td>Chapman et al.3 (180)</td>
<td>2015</td>
<td>Slower lung density decline in augmentation therapy individuals compared to placebo (RAPID Clinical trial - RCT from 28 international centres)</td>
</tr>
</tbody>
</table>
Green et al.\textsuperscript{33} (110) 2016 | Showed that the improvements in the rate of lung-density decline from augmentation therapy 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 augmentation therapy group. Decline in KCO and DLCO had a higher sensitivity than FEV\textsubscript{1} decline to predict CT density decline in non-treated alpha-1 antitrypsin deficient individuals. Changes in the lower zone lung CT densitometry in non treated participants relates to survival in alpha-1 antitrypsin deficiency and FEV\textsubscript{1} and gas transfer alone do not identify all patients with declining lung density. (Observational cohort).

**FEWER EXACERBATIONS and LOWER SEVERITY**

| Lieberman\textsuperscript{55} (165) | 2000 | Augmentation therapy reduces frequency of lung infections in alpha-1 antitrypsin deficiency. The number of lung infections per year decreased from 3-5 pre-augmentation to 0-1 post-augmentation. (Observational study) |
| Gildea et al.\textsuperscript{56} (Hypothetical cohort of 30,000) | 2003 | Augmentation therapy is cost effective for patients with severe alpha-1 antitrypsin deficiency. (Markov-based decision analytical model) |
| Dirksen et al.\textsuperscript{52} (138) | 2009 | Post hoc analysis from the EXACTLE study found a reduction in exacerbation severity in the augmentation therapy group compared with placebo (P < 0.05). (Randomised Control Trial) |
| Barros-Tizon et al.\textsuperscript{57} (127) | 2012 | Reduction in the incidence and severity of exacerbations in alpha-1 antitrypsin deficiency which results in lower hospital expenses. (Retrospective multicentre observational cohort) |
| Campos et al.\textsuperscript{6} (878) | 2018 | Reports the positive effect of augmentation therapy in reducing exacerbations by 36.1% in a cohort analysis and in overall savings due to fewer and shorter hospitalisations (ADMAPP observational cohort) |

**MORTALITY / SURVIVAL**

| NHLBI Alpha-1 Antitrypsin Deficiency Registry Study Group\textsuperscript{51} (134) | 1998 | Decreased mortality in patients receiving therapy - Pooled data of 198 treated German patients and 97 untreated Danish patients). (Observational cohort, concurrent controls) |
| Rahaghi et al.\textsuperscript{58} (983) | 2014 | Augmentation therapy improves survival at baseline FEV\textsubscript{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.\textsuperscript{1} (1541) | 2016 | Normal life expectancy from augmentation therapy (median survival 80.4 years) in severely deficient alpha-1 antitrypsin deficient patients. (Large observational cohort from patient registry) |

**BIOMARKERS**

| Ma et al.\textsuperscript{4} | 2017 | DES/IDES were significantly reduced versus baseline in patients receiving augmentation therapy. Augmentation therapy reduces elastin degradation, including pulmonary elastin in patients with alpha-1 antitrypsin deficiency. Results show a correlation between biomarkers of elastin degradation and a clinical marker of emphysema progression (CT lung density) in patient with alpha-1 antitrypsin deficiency. (RAPID/RAPID Extension RCT data) |
7. Conclusion

7.1. Any decision not to support augmentation appears to stem from a narrow consideration of the literature which allows bias to creep in and results in a conclusion of not to treat which lags behind international best practice for alpha-1 antitrypsin deficiency management. Many international alpha-1 antitrypsin deficiency experts support the available evidence related to appropriate clinical endpoints and the clinical efficacy of augmentation treatment and its disease modifying, life extending capability along with the call for early intervention to preserve lung density, rebuild elastin, assist patients with hyper-inflated lungs and others with a poor prognosis.

7.2. A robust analysis of all of the relevant literature and consideration of study designs beyond the RCT are required to ensure that policy positions are reached that don’t overlook statistically significant analysis from alpha-1 antitrypsin deficiency patient registries, sub-group analysis within various study designs, pooled data, meta-analyses, nor expert opinion from international leaders in alpha-1 antitrypsin deficiency research and the World Health Organisation. A solid review of the literature shows clinical efficacy from augmentation therapy in alpha-1 antitrypsin deficient individuals and augmentation therapy is supported due to the benefits including the slowing of lung emphysema, preserved lung density and rebuilt elastin, reduced exacerbations, hospital savings and a normal life expectancy.

7.3. The purpose of augmentation therapy for lung-affected individuals is to extend life. When using more sensitive endpoints such as lung density and mortality in larger and longer studies, rather than HRQoL, exacerbations and mortality in short RCTs, the research has demonstrated statistically lower mortality in patients receiving augmentation therapy compared to placebo. Furthermore, longitudinal studies show that individuals on augmentation therapy have better survival in all DLCO strata, that augmentation therapy rebuilds elastin throughout the body, maintains lung density and that there are survival benefits for patients with hyperinflated lungs. It has been noted that research efforts related to developing a more sensitive HRQoL tool for use in alpha-1 antitrypsin deficient populations is appropriate and this type of research is endorsed by the AAA.

7.4. This paper includes only some of the available evidence related to the efficacy and disease-modifying effects of augmentation therapy in alpha-1 antitrypsin deficiency and policy makers are encouraged to fully explore the range of available research and evidence. Overlooking evidence allows alpha-1 antitrypsin deficient individuals to die prematurely and unfairly when a treatment option exists for genetic emphysema. An added benefit of augmentation therapy is the systemic benefit for the myriad of alpha-1 antitrypsin deficiency associated comorbidities. In light of the evidence, it is appropriate for governments to fund augmentation therapy for alpha-1 antitrypsin deficiency.

7.5. Alpha-1 antitrypsin deficiency patient registries need to be supported as do alpha-1 antitrypsin deficiency research collaborations using registry data as further RCTS are impractical and unnecessary. Further well designed registry research studies can be carried out while augmentation therapy is provided to patients. Meanwhile easier to administer therapies can be developed. Supporting augmentation therapy, thereby saving lives, is the most appropriate course of action for government.
7.6. In conclusion, lung density is an appropriate endpoint in RCTs, survival shown in sub-studies, pooled and longitudinal studies can’t be ignored. Long-term comparative registry data studies are extremely valuable in the study of rare diseases as demonstrated by the role augmentation therapy plays in survival. Withholding augmentation therapy when good evidence exists about its life saving benefits is not supported by the AAA.

8. References


18. PRISMA. Transparent reporting of systematic reviews and meta-analyses. 2015; accessed 13.3.2018 www.prisma-statement.org


