ANNUAL REPORT 2016

Alpha One Foundation

MISSION STATEMENT

The Alpha One Foundation is a charity dedicated to raising awareness, increasing diagnosis, promoting research, and improving the treatment of Alpha-1 Antitrypsin Deficiency (Alpha-1).

CORE ACTIVITIES OF THE ALPHA ONE FOUNDATION

STAFF OF THE ALPHA ONE FOUNDATION:

Ms Kitty O'Connor, CEO
Dr Tomás Carroll, Chief Scientist
Ms Laura Fee, Clinical Research Associate
Ms Margaret Molloy, Research Nurse and Registry Coordinator
Professor Gerry McElvaney, Chairman

PATRON: Uachtarán Michael D. Higgins

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Alpha One Foundation (Ireland) Charity Code: CHY14812

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1 Executive Summary

It has been a very busy 12 months for the Alpha One Foundation. We were delighted to be successfully designated as the National Centre of Expertise for Alpha-1 by the Department of Health in early 2016. This allows us to link up with other similar centres at a European level. We are also pleased to announce that President Michael D. Higgins has agreed to become our patron. This is a great honour and we hope to develop this relationship in the forthcoming years.

While our main activity is the National Alpha-1 Screening Programme which has tested over 16,000 Irish people, this year we have also focused on three main issues. Firstly the reimbursement of augmentation therapy (Respreeza) to treat the severe form of Alpha-1, secondly preparing for the new Alpha-1 research and clinical services in the Mater Misericordiae Hospital site in early 2017, and thirdly the re-development of the National Alpha-1 Registry.

Presently, we are awaiting a decision from the National Centre for Pharmacoeconomics (NCPE) in relation to the reimbursement of Respreeza (augmentation therapy). In July 2015, findings from CSL Behring's RAPID study showed conclusively that Respreeza slows down emphysema caused by Alpha-1. In August 2015 CSL received approval for Respreeza in the European Union. 21 Irish patients took part in this study and are currently receiving this therapy on a compassionate use basis. We are hopeful that this therapy will be reimbursed by the government and that a further 40 Alpha-1 patients could benefit from the therapy. Thank you to those who contributed to our patient group submission to the government which showed Respreeza benefits people with Alpha-1 by improving their quality of life, reducing chest infections and reducing hospitalisations.

In early 2017 the Alpha One Foundation and the National Alpha-1 Clinic will move to the Mater Misericordiae Hospital, Eccles St, Dublin 7. This is a very positive development and will see increased resources for Alpha-1 clinical services. All Alpha-1 outpatients' clinics and diagnostic testing will be carried out in the new site from early 2017. We hope the move will be amenable for everyone attending clinics and we look forward to seeing you there.

The National Alpha-1 Registry and clinical encounter based IT system is currently being redesigned and upgraded. This will be accessible by clinicians in the Alpha-1 clinic and will allow for easier access to medical data and treatment outcomes. We are delighted to welcome Margaret Molloy to the Foundation. Margaret is the new administrator of the National Alpha-1 Registry and her principal role is its redevelopment.

Our awareness activities this year included presentations at the Irish Thoracic Society (ITS) conference in Cork, ANÁIL's respiratory nurse conference in Dublin, UCD School of Medicine, COPD Support Groups in Nenagh and Drogheda, as well as presentations to respiratory, liver and laboratory staff in Crumlin, Tallaght, Letterkenny, Beaumont, and Peamount hospitals. Our annual Alpha-1 conference was held in October 2015 in Marino Institute of Education. This was the best attended conference to date; this provided an excellent opportunity for Alpha-1 patients and family members to meet other Alphas in a relaxed and informal environment. We were delighted to welcome Tommie Gorman, RTE journalist and patient advocate to open the conference. Speakers included Dr. Karen Redmond, Cardiothoracic Surgeon, Lung Transplant Unit, Mater University Hospital, Annemarie Broderick, Consultant Paediatric Gastroenterologist, Our Lady's Children Hospital, Crumlin and Eoin Durkan, PhD researcher, Dublin City University.

The Alpha One Foundation has continued to work with the Medical Research Charities Group (MRCG), the Irish Donor Network, Irish Platform for Patient Organisations, Science and Industry (IPPOSI), the Irish Lung Health Alliance, the Rare Disease Taskforce, the European Organisation for Rare Diseases (EURORDIS) and COPD Support Ireland.

We are very thankful to everyone involved in fundraising in the last 12 months. The efforts have been amazing and varied, mini-marathons, full marathons, fashion shows, coffee mornings and Christmas cards. The money raised has been put to good use in our Alpha-1 screening programme. We would also like to congratulate Stephen Smith who won 3 bronze medals for Team Ireland at the European Transplant Games in Finland this year.

Hopefully this brief synopsis will give an idea of the progress made by the Alpha One Foundation over the past 12 months. This work is a team effort and I wish to thank all my colleagues for their hard work and dedication throughout the year, particularly Dr. Tomás Carroll, Laura Fee and Margaret Molloy.

Kitty O'Connor,
CEO, Alpha One Foundation

2 An Update from the National Alpha-1 Antitrypsin Deficiency Targeted Detection Programme

Alpha-1 antitrypsin deficiency (or Alpha-1 for short) can be diagnosed by a simple blood test but unfortunately remains hugely under-diagnosed. A diagnosis of Alpha-1 gives the doctor a unique opportunity for early medical intervention and in some cases the prevention of lung disease in both the affected individual and first-degree relatives. In May 2004, a national targeted detection programme for Alpha-1 was launched by the Alpha One Foundation.

WHO SHOULD BE TESTED FOR ALPHA-1?

World Health Organisation (WHO), American Thoracic Society (ATS), and European Respiratory Society (ERS) guidelines advocate targeted detection programmes for Alpha-1. These guidelines recommend targeted testing of patients with chronic obstructive pulmonary disease (COPD), severe non-responsive asthma, cryptogenic (unexplained) liver disease and first-degree relatives of individuals with Alpha-1 (Table 2.1).

TABLE 2.1. *ATS/ERS recommendations for diagnostic testing for Alpha-1 (type A recommendations).*

Who Should Be Tested?
Adults with symptomatic emphysema or COPD (regardless of age or smoking history)
Adults with asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators
Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g. cigarette smoking, occupational exposure)
Adults with necrotising panniculitis
Siblings of individuals with Alpha-1
Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly

HOW DO WE TEST FOR ALPHA-1?

There are two tests needed to correctly diagnose Alpha-1. The first test measures how much alpha-1 antitrypsin (or AAT) is in the blood. If this result is low, the second test looks at what type of alpha-1 antitrypsin protein is present. To look at the type of alpha-1 antitrypsin, we use a technique called isoelectric focusing. This method identifies variants of alpha-1 antitrypsin circulating in human blood, and is known as phenotyping (Figure 2.1). It is the most accurate method of testing for Alpha-1 and identifies not only the most common but also rare AAT variants. From a quality point of view, we have been participating in the UKNEQAS quality assurance scheme for AAT phenotyping since 2007, achieving 100% compliance to date.

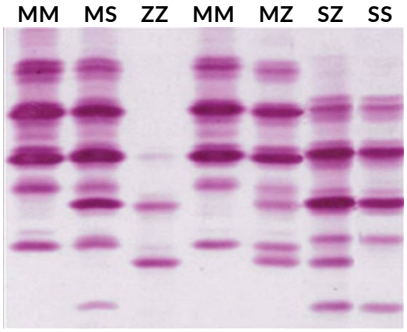


FIGURE 2.1*. Typical isoelectric focusing gel for AAT phenotype identification with the most common phenotypes included.*

WHAT HAVE WE FOUND IN IRELAND?

Since 2004 over 16,000 individuals with COPD, asthma, and liver disease, as well as first-degree relatives of known Alpha-1 individuals have been tested in the National Targeted Detection Programme. We currently receive blood samples from over 30 hospitals in Ireland as well as directly from GPs.

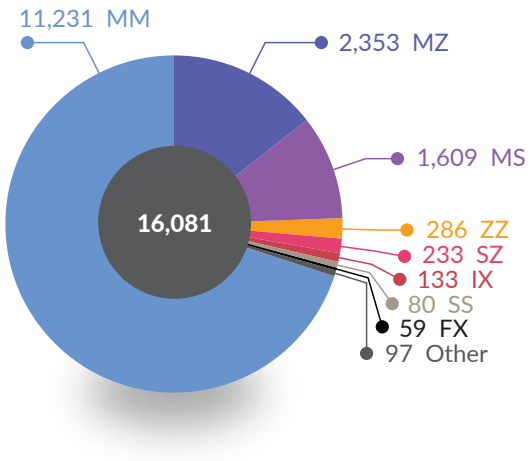


FIGURE 2.2. *Alpha-1 antitrypsin phenotypes identified in National Targeted Detection Programme.*

A total of 286 ZZ (severe Alpha-1) individuals have been identified, as well as 233 SZ (moderate Alpha-1) individuals, who are also at risk of developing lung and liver disease (Figure 2.2). In addition, a large number of other clinically

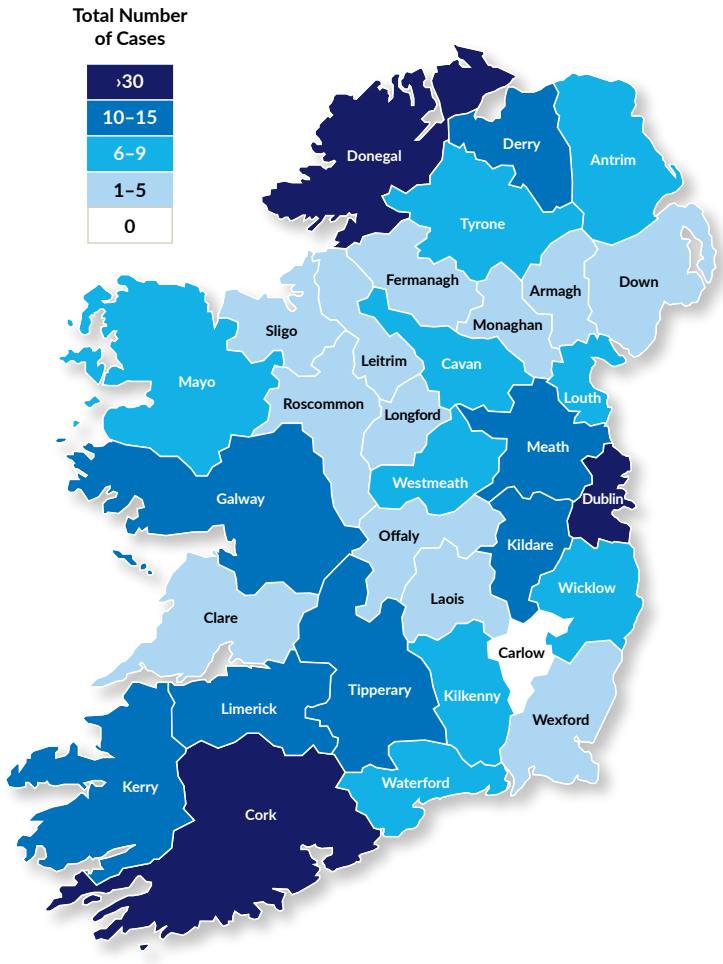


FIGURE 2.3. *Total number of severe AATD cases detected per county to date.*

Mid Western Regional Hospital — BIOCHEMISTRY REPORT — Tel.: 061-482877/482879/482257

SURNAME	FORENAMES	I.D. NUMBER

	DATE & TIME OF COLLECTION	DATE & TIME RECEIVED	LAB NO.
Serum	23/04/2013 u/k	23/04/2013 17:18	

SPECIMEN COMMENT

Clinical Details:

Total Protein	73	g/L	(61 - 79)
Albumin	41	g/L	(35 - 48)
Immunoglobulin-G	9.31	g/L	(5.4 - 16.1)
Immunoglobulin-A	2.32	g/L	(0.9 - 3.4)
Immunoglobulin-M	2.04 *	g/L	(0.5 - 2.0)
Protein electrophoresis:	See comment.		
Alpha-1-antitrypsin	0.80 *	g/L	(0.88 - 1.74)

(a) SPE: Decreased alpha-1 globulins.

Serum alpha-1 antitrypsin of less than 1.00 g/L may be suggestive of alpha-1 antitrypsin deficiency and additional laboratory investigations may be undertaken in this regard.
Further information on alpha-1 antitrypsin deficiency is available from the Alpha One Foundation, Beaumont Hospital, Tel 01 8093871 or www.alpha1.ie. NOTE: revised cut-off value effective January 2013.

Alpha-1 antitrypsin is an acute phase reactant and its serum concentration will increase within days of trauma, acute infection or tissue necrosis.

FIGURE 2.4. *Example of an electronic "red flag" on a laboratory AAT report.*

significant phenotypes have been detected including 2,353 MZ, 80 SS, 20 IZ, and 11 IS phenotypes. The percentage of deficiency alleles (30%) detected has been quite high, even allowing for the targeted nature of screening. A number of rare AAT mutations have also been identified, including I, F, $M_{wurzburg}$, $Z_{bristol}$, M_{malton} and four different Null mutations ($Null_{bolton}$, $Null_{cork}$, $Null_{dublin}$ and $Null_{porto}$).

The goal of the screening programme is to ensure people with Alpha-1 get correctly diagnosed and are given the opportunity to receive expert medical care. Newly diagnosed individuals can be referred to our dedicated Alpha-1 clinic in Beaumont Hospital under the care of Professor Gerry McElvaney. In addition, family screening allows the identification of younger relatives with Alpha-1. These individuals benefit from lifestyle changes such as smoking cessation and closer medical observation which can help prevent or postpone the development of lung disease.

In the past 12 months we have given seminars about Alpha-1 to a mixture of respiratory, liver and biochemistry departments in Crumlin, Tallaght, Letterkenny and Peamount hospitals, to COPD patient support groups in Nenagh and Drogheda, and to 3rd year medical students in UCD. The main aim of these presentations is to increase awareness of Alpha-1 and to encourage testing. While the respiratory (and liver) teams are dealing with patient populations most at risk due to Alpha-1, many hospital Immunology, Biochemistry, and Clinical Chemistry Departments measure alpha-1 antitrypsin levels as a routine test during normal blood investigations.

Furthermore, we have helped to introduce a "red flag" system for AAT testing. This system means that if AAT concentrations are measured by a hospital laboratory and found to be lower than normal (<1.0 g/L) an automatic "red flag" is included on the laboratory report which recommends further testing for Alpha-1 (Figure 2.4). It is hoped that the electronic prompt system will lead to earlier diagnosis of Alpha-1. The ultimate goal would be the adoption of this red flag system on AAT lab reports in every hospital in Ireland.

3 The National Alpha-1 Antitrypsin Deficiency Registry

WHAT IS THE REGISTRY?

The registry is a confidential database of individuals with alpha-1 antitrypsin deficiency (Alpha-1). The registry stores relevant medical, family and social history of individuals diagnosed with Alpha-1. Data from investigations such as pulmonary function tests, CT scans of the chest, ultrasounds of the liver and certain blood tests are obtained from the medical chart, entered in the registry and updated at regular intervals. Once data is entered in the registry it is analysed and compared to individuals with various types of Alpha-1. This information is essential in improving our knowledge of the condition which will lead to better treatments and improved outcomes for those diagnosed with Alpha-1.

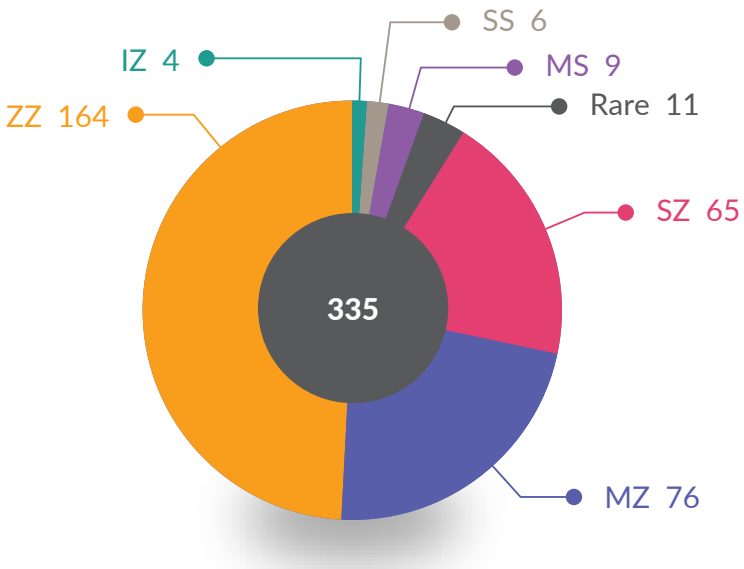


FIGURE 3.1. *Phenotype analysis of people enrolled on the National AATD Registry*

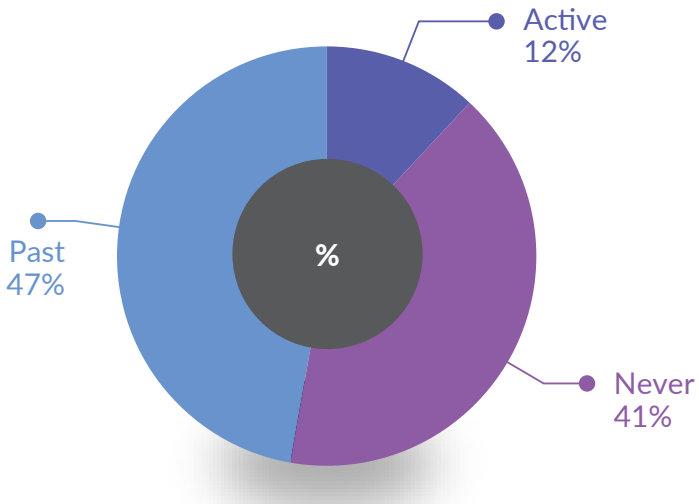


FIGURE 3.2. *Smoking history of people enrolled on the National AATD Registry*

A registry is also an important tool to identify people who might be suitable for a new experimental drug as part of a clinical trial. Registries can be used to monitor the safety and effectiveness of new medications and to monitor outcomes of a clinical trial over a certain length of time.

WHO CAN ENROL IN THE REGISTRY?

Individuals diagnosed with various forms of Alpha-1 are eligible to enrol in the registry. Enrolment is completely voluntary and an individual must provide their written informed consent prior to enrolment. A member of the Alpha One Foundation team will provide individuals with an information leaflet and answer any questions at the time of enrolment. An individual has the right to withdraw from the registry at any time by contacting the Alpha One Foundation. Withdrawal from the registry will not affect an individual's care in any way.

REGISTRY DATA

Currently there are over 300 individuals from 31 counties in Ireland enrolled in the registry. The majority of enrolees are ZZ followed by MZ, SZ, MS, SS and other rare mutations.

The average age of individuals enrolled on the registry is 54 years with a range of 16 - 91 years of age. The majority of individuals are past smokers, followed by never smokers and only a small percentage of individuals are active smokers.

Common tests for individuals diagnosed with Alpha-1, which are captured by the registry, include pulmonary function tests, CT scans of the chest, liver function tests and ultrasounds of the abdomen. Just over half of all enrolled individuals showed evidence of obstruction on pulmonary function tests with the majority presenting with moderate or severe lung disease. One quarter (25.3%) of the available CT scans of the chest were normal and the most common abnormality detected was emphysema (23.7%) followed by bronchiectasis (22.4%). Of the available liver

function tests, 32.8% of individuals had abnormal results. Ultrasounds of the abdomen revealed no abnormality of the liver in 55% of individuals while the most common abnormality detected was fatty liver (15.9%) with only a small percentage of individuals displaying evidence of severe liver disease or cirrhosis (1.6%).

The data presented below gives an overview of the most common findings in those with Alpha-1. There is much to be learned about the various phenotypes of Alpha-1 and risk factors for developing lung, liver and skin disease. The Alpha One Foundation is in the process of redeveloping the registry to better capture information and improve the use of this information once collected. A company specialising in the use of technology in healthcare, OpenApp, is helping us develop a new registry which will potentially be used as a clinical tool to collect the most up to date and accurate information.

FIGURE 3.3. *Results of common investigations recorded on the National AATD Registry*

COMMON FINDINGS OF REGISTRY ENROLEES		
Test	**Result**	**Percent (%)**
Pulmonary function tests	Mild obstruction	18.5
	Moderate obstruction	29.6
	Severe obstruction	29.6
	Very severe obstruction	22.2
CT chest	Normal	25.3
	Emphysema	23.7
	Bronchiectasis	22.4
	Bronchiectasis & emphysema	21.6
	Other	7.0
Liver function tests	Abnormal	32.8
Ultrasound of the abdomen	Normal	55.0
	Fatty liver	15.9
	Liver cysts	4.2
	Cirrhosis	1.6
	Other liver findings	15.9
	Extrahepatic/incidental findings	7.4

4 Liver Disease in Alpha-1 Antitrypsin Deficiency (AATD)

AATD LIVER DISEASE IN CHILDREN

Annemarie Broderick, Consultant Paediatric Gastroenterologist, Our Lady's Children's Hospital, Crumlin and UCD Associate Clinical Professor, School of Medicine and Medical Science, University College Dublin.

Alpha-1 antitrypsin (AAT) is a protein made in the liver and in AATD the protein is not produced correctly and can build up within the liver causing liver disease**.** This can present in children from shortly after birth usually in the form of cholestatic jaundice to adolescence when raised transaminases may be detected on a routine blood test in an apparently well teenager. Most infants who present early with jaundice will improve. In a study from Sweden where 200,000 new-born infants were screened for AATD between 1972-1974; 171 were found to have severe AATD, of whom 120 were ZZ. By the age of 18 years, 85% of these children had no evidence of liver disease clinically or in lab tests. To date, we know a very small number can develop serious liver disease, almost all with the ZZ phenotype, and a few will require liver transplantation. The reasons for such variable outcomes are not understood.

Treatment for children with AATD liver disease in Ireland is provided at Our Lady's Children's Hospital, Crumlin (OLCHC) by a multi-professional team liaising with King's College London if liver transplantation is required. Treatment is mainly supportive with an emphasis on education, nutrition, immunisation, family support and promotion of normal development with access to specialist services as required. All children learn from a very early age the need for life long avoidance of tobacco smoking. Currently there is no specific medical treatment for AATD liver disease but drugs which stimulate autophagy, the mechanism by which the liver clears the abnormally folded AAT protein, or drugs which block the production of the abnormal AAT protein in the liver, may prove useful.

Families receive genetic counselling for AATD at the National Centre for Medical Genetics at OLCHC or from the Alpha One Foundation. Young adults with severe liver disease are referred to adult services at St. Vincent's University Hospital (SVUH), Dublin, and those with AATD but no liver disease are referred to the National Centre of Expertise for AATD at Beaumont Hospital. Family members identified through screening are referred appropriately depending on age. In future, we at OLCHC hope to participate in a study to identify infants with cholestatic jaundice, the type of jaundice associated with AATD earlier than currently happens. We hope that earlier identification of affected infants will improve nutrition and health outcomes and allow more children to benefit from any new treatments.

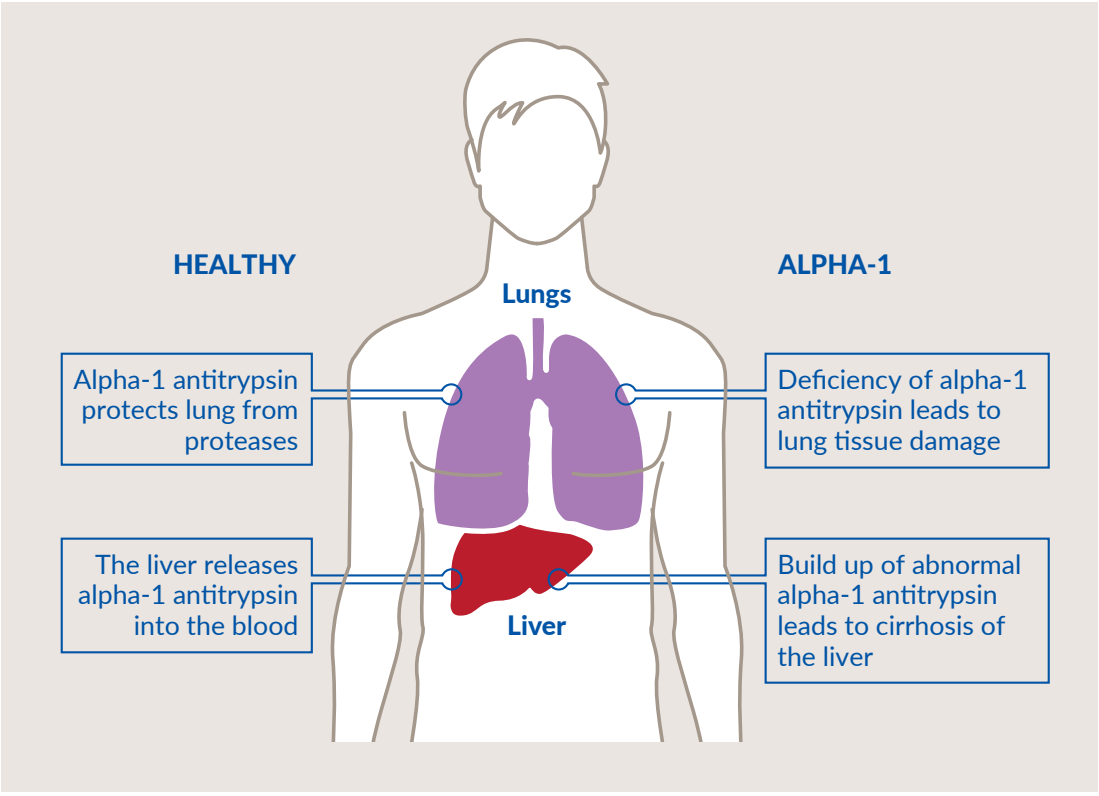


FIGURE 4.1: *The alpha-1 antitrypsin protein in health and disease.*

TABLE 4.1: *Examining Liver Disease using the National AATD Registry*

Phenotype	ZZ	SZ
Total	188	67
Gender (M/F)	58% / 42%	48% / 52%
Average age (years)	52.9 (15–85)	52.5 (19–81)
Average BMI	26.2 (13–47)	26.9 (16–41)
Abnormal Liver Enzymes	30%	28%
Abnormal Ultrasound	28%	26%
– Fatty Liver	15%	19%
– Cirrhosis	8%	4%
Liver transplant	6 (0.03%)	1 (0.015%)

AATD LIVER DISEASE IN ADULTS

Dr. Tomás Carroll, Chief Scientist, Alpha One Foundation, and Abdulaziz Alghamdi, RCSI Medical Student.

Liver disease in AATD can occur at different times and give rise to different manifestations. The famous Swedish study of the 1970s which continues to follow 120 ZZ newborns into adulthood found that at the age of 30 only 3-5% of the original cohort had elevated liver enzymes. However, it is thought the risk of liver disease increases with age. Adults may develop chronic hepatitis with or without cirrhosis. There is also an increased risk for development of hepatocellular carcinoma in ZZ adults although the magnitude of the risk remains unclear. Five to ten percent of ZZ adults over the age of 50 develop cirrhosis but one of the conundrums associated with AATD liver disease is the finding of histologically significant but clinically silent liver disease in 40-50% of older ZZ individuals. This was highlighted in a more recent 2015 study, where 35% of asymptomatic ZZ individuals in an adult natural history study were found to have clinically significant liver disease on biopsy.

Other factors predisposing to liver disease in AATD include male gender and obesity. The role of viral infection (hepatitis) is less clear but a 1992 study in Austria showed that in AATD patients with cirrhosis 62% were hepatitis C positive, 33% were hepatitis B positive and 41% had a history of chronic alcohol abuse. This led to the so called "second hit' hypothesis which is similar to the situation in the lung where lung disease is precipitated and exaggerated by cigarette smoking. In the liver the second hit may be alcohol, viral infections or prematurity.

In a recent analysis of the National AATD Registry, 30% of ZZ individuals and 28% of SZ individuals had abnormal liver enzymes (see Table 4.1). However, a more accurate method to investigate possible liver disease is abdominal ultrasound. 28% of ZZ and 26% of SZ individuals showed liver abnormalities on ultrasound. The most common finding was fatty liver followed by cirrhosis, a more severe condition which can require liver transplantation. The risk factors gender and obesity were examined. In the ZZ group with cirrhosis, the overwhelming majority (92%) of individuals were male. This suggests that adult ZZ males are at increased risk of developing serious liver disease, an observation supported by other studies. The gender balance in the SZ cirrhosis group was equal. When we looked at obesity as a risk factor, there was a significant difference in body mass index (BMI) between the normal and fatty liver groups, but no difference between the normal and cirrhosis groups. Future analysis will examine alcohol consumption and viral infection as risk factors. In addition, Professor McElvaney is working with liver specialist colleagues to develop better ways of detecting liver disease using a new technique called transient elastography (Fibroscan).

While the data concerning liver disease risk in ZZ AATD is unclear the understanding of liver disease in SZ and MZ individuals is even less clear. The risk of liver disease in SZ is thought to be lower than in ZZ but this is not proven. A recent report from the large US National Institutes of Health CHiLDREN study reported 8% of AATD children with liver disease are SZ. The risk of liver disease in MZ individuals is also unclear. Data from retrospective studies show a 3 - 5 fold increased number of MZ individuals in groups with chronic liver disease but this may reflect referral bias. It may be that MZ remains a risk which is hidden until a second hit such as hepatitis or excess alcohol. In the years ahead, new techniques for detecting early liver damage and the emergence of specific treatments for liver disease will improve the prognosis for individuals with AATD liver disease.

5 Augmentation Therapy and Living with Alpha-1

In June 2015 the European Medicines Agency approved RESPREEZA (formerly known as Zemaira) for use in Europe. RESPREEZA is the name of the augmentation therapy produced by the pharmaceutical company CSL Behring. It is a treatment for emphysema caused by severe Alpha-1 (for example those who are ZZ, Z/Null, Z/Mmalton, Null/Null, Mmalton/Mmalton).

Approval was given on the basis of results from an international clinical trial called the RAPID study. Over 20 Irish people took part in this study which showed that RESPREEZA slows down the progression of emphysema. Like all augmentation therapy products, RESPREEZA is highly purified alpha-1 antitrypsin which is isolated from human blood and given as a weekly intravenous infusion. Following European approval, the company then applied to the Irish Government for reimbursement. If successful, this means RESPREEZA would become available for people with severe Alpha-1 who have progressive lung disease and meet certain eligibility criteria. The National Centre for Pharmacoeconomics (NCPE) is currently assessing RESPREEZA both in terms of clinical effectiveness and, importantly given the high price, cost effectiveness.

The Alpha One Foundation is committed to ensuring people with Alpha-1 have access to new therapies. Importantly, when the pharmaceutical company applied for reimbursement to the government, the Alpha One Foundation was given the opportunity to make a separate patient group application in support of RESPREEZA. The aim of our application was to highlight how Alpha-1 can affect people's health and day to day life but also to showcase how RESPREEZA can improve health and wellbeing. This is possible because a small group of people who took part in the original RAPID study have been receiving the drug on a compassionate basis since the trial finished. The majority of the information in our application was collected using questionnaires and focus group discussions.

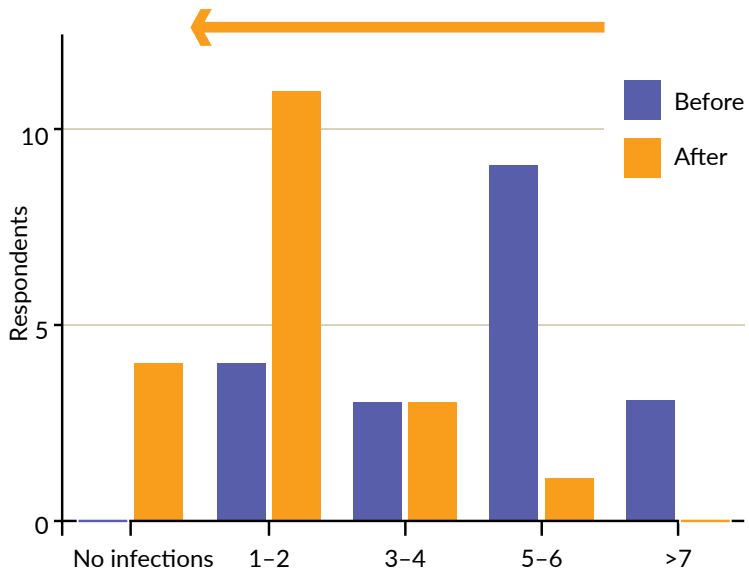


FIGURE 5.1. *Effect of RESPREEZA on annual number of chest infections (green arrow shows reduction).*

A total of 160 questionnaires were posted out to people with severe Alpha-1 in early May. 86 questionnaires were returned giving an overall response rate of 54%. Respondents were divided into two broad groups, those already receiving RESPREEZA and a much larger group made up of those diagnosed with severe Alpha-1 but not receiving RESPREEZA.

1. AUGMENTATION THERAPY (RESPREEZA)

The vast majority of this group was made up of people who took part in the RAPID study. The RAPID study was a multicentre, double-blind, randomised, parallel-group, placebo-controlled trial of RESPREEZA treatment in patients with severe alpha-1 antitrypsin deficiency. Eligible non-smokers (aged 18–65 years) were recruited in 28 centres in 13 countries if they had proven lung disease, specifically a forced expiratory volume in 1 second (FEV1) of 35–70% (predicted). Patients were excluded if they had undergone, or were on the waiting list to undergo, lung transplantation, lobectomy, or lung volume-reduction surgery, or had selective IgA deficiency.

Hospitalisations caused by chest infections per year dropped by 69%.

In our survey we found that people receiving RESPREEZA strongly felt that the drug had stabilised their condition, with 84% reporting an improvement in general symptoms. This was supported by a reduction in the frequency and severity of chest infections and associated hospital admissions. Chest infections per year dropped by 68% while hospitalisations caused by chest infections per year dropped by 69%. Figure 5.1 shows that the annual number of chest infections people experienced was greatly reduced when compared to the period before they began receiving the drug. Many reported being significantly less reliant on the health service. People also reported improvements in their ability to work and to lead an active and fulfilled family and social life.

Chest infections per year dropped by 68%.

Some respondents stated they simply would not be alive without augmentation therapy and strongly believe the treatment has stabilised lung function and improved their overall health and quality of life. This real life patient-reported data supports the clinical trial data which convincingly showed RESPREEZA slows down the rate of emphysema progression.

Q. What is it like to live with Alpha-1? And what has Alpha-1 augmentation therapy meant to you?

From a 49 year old woman who took part in the RAPID study:

Through the receipt of RESPREEZA during the last few years I have been able to raise my children with ease. I believe without my weekly infusions my children would have to grow up quickly in the role of carers, thus neglecting their education and putting their own future ambitions on hold. There is a history of Alpha-1 in my family. My older sister was diagnosed in 1991 and unfortunately received no effective treatment and died in 1997 aged only 39. My older brother was diagnosed in 1995 and again received no effective medication which resulted in years of pain struggling to breathe and unable to do basic tasks without oxygen and finally a double lung transplant in 2014. This was the life I thought I had in store for me until I was lucky enough to be selected for a clinical trial for RESPREEZA in Beaumont Hospital, which I completed and am now in receipt of weekly infusions at my home. I no longer have chest infections and my quality of life has not deteriorated over the last few years my lung function has stayed the same and I believe my medication has been instrumental in maintaining my good health. I strongly believe that without my weekly infusions my short term future would be a continual deterioration of lung function struggling for breath and quickly needing a transplant.

2. LIVING WITH ALPHA-1

The findings among this group relate to those with severe Alpha-1 not currently receiving augmentation therapy. This was an attempt to capture the real life experiences of adults with Alpha-1 of all ages. Some respondents are well and have no health problems, others are affected by lung, liver or skin problems. Those with lung disease may be eligible to receive RESPREEZA in future if the reimbursement application is successful. The total eligible number in this group was 132 and we received 63 responses, yielding a 47.7% response rate. In terms of age, the mean age of respondents was 55.6 years of age with the youngest 23 and the oldest 77. It is worth pointing out that the response rate was highest in those with severe lung disease.

Health Problems

The major health problem is shortness of breath (79%), with other lung symptoms of sputum production (51%), cough (49%) and wheeze (41%) common. Our focus group discussions revealed a broad array of symptoms (Table 5.1).

When asked specifically when or where people felt breathless, 75% said climbing stairs and 67% said while walking and talking. Others were breathless when doing simple tasks like dressing themselves in the morning and housework, and some were even breathless while at rest or lying down. Almost one third (30%) have been prescribed oxygen. However, many reported being embarrassed or ashamed to use it.

TABLE 5.1. *Detailed symptom responses.*

Symptom	Total (n)	Total (%)
Shortness of breath	50	79.4
Cough	31	49.2
Sinus	23	36.5
Wheeze	26	41.3
Sputum	32	50.8
Chest pain	7	11.1
Coughing up blood	2	3.2
Fever	6	9.5
Unwell	15	23.8
Stress/Anxiety	19	30.2
Loss of appetite	9	14.3
Weak/Fatigued	32	50.8
Liver problems	1	1.6
Skin Problems	13	20.6
Joint Problems	18	28.6
Other	4	6.3

Regarding chest infection data;

- 84% have experienced 1 or more chest infections in the past 12 months
- 54% have had 3 or more chest infections in the past 12 months
- An average of 3 chest infections were reported in the last 12 months

People were also asked about antibiotic use and hospital admissions due to Alpha-1. The group reported;

- An average of 2.8 oral antibiotics in the last 12 months
- 56% reported using 3 or more oral antibiotics in the last 12 months
- 25% of the group were admitted to hospital for intravenous antibiotics in the last 12 months
- 17% of the group reported being hospital at least twice for intravenous antibiotics in the last 12 months

Importantly, 8% have been referred for lung transplant assessment. This self-reported data highlighting the impact of Alpha-1 on lung health is supported by patient testimonials, in particular shortness of breath and the frequent and severe chest infections. More general symptoms of weakness and fatigue were reported by almost 51%, approximately 30% said they were stressed and anxious, and focus group discussions revealed depression was also a feature.

Of interest, 37% reported sinus problems, 21% said they had skin problems, and 29% reported joint problems. There is a rare skin manifestation of AATD called panniculitis which if uncontrolled by steroid treatment, responds successfully to intravenous augmentation therapy. The success of this approach is shown in several published case reports, including one Irish case report from Beaumont Hospital (Franciosi AN et al., Chest, 2015).

General Health, Wellbeing and Daily Living

When people were asked to rate their health currently, 68% responded to say their health was excellent, very good or good. A significant 32% said their health was poor or very poor. More than half of respondents (56%) said daily activities were affected by Alpha-1. Planning ahead was an issue for 38%. Major daily concerns and issues highlighted in our focus groups were;

- Avoiding activities that make shortness of breath worse
- Using lifts instead of stairs
- Avoiding smoke at all costs
- Trying to avoid infections by avoiding certain situations (e.g. large crowds, hospital visits, mass)
- Using oxygen in public

Impact on Personal and Family Relationships

Living with Alpha-1 puts a significant strain on personal and family relationships. Family life was affected for 27%, while relationships were affected for 13%. In some instances, spouses or children have become carers. People reported their ability to be a parent to their children was affected because of the inability to do simple tasks. Many felt a burden on loved ones and on young children, and stated this role reversal was unnatural.

Financial Impact and Ability to Work

Over half (51%) of respondents said that Alpha-1 has affected them financially in a number of ways, including;

- Cost of regular GP visits
- Cost of medications
- Cost of oxygen
- Home insurance when you use oxygen at home
- Travel insurance difficulties
- Difficulties getting money back from HSE

Regarding employment status, 40% are working full-time or self-employed, with 3% working part-time. 24% of respondents said their work or education had been affected by Alpha-1 in the past 12 months. Of those respondents eligible to

answer the specific question about days absent from work or education due to Alpha-1, 45% had to take time off work in the last 12 months.

A considerable 25.4% reported being unable to work due to illness and 28.6% stated they were retired. For the 25.4% unable to work, the average age was 54 years of age [range 52 – 64]. Unfortunately, respondents were not asked at what age they were forced to leave the workforce. This would have collected valuable data on the true economic impact of Alpha-1. As a result the average age of 54 is certainly an underestimate. Several participants did reveal leaving the workforce many years earlier due to illness caused by Alpha-1.

It is clear there is a huge and largely hidden economic cost associated with Alpha-1. Our data shows that the ability to work and contribute to society can be greatly impaired. Many with Alpha-1 are forced to leave the workforce early due to health problems which can manifest as early as their 30s, and this loss of earning power is made worse by the significant medical costs.

Social Life

Over 35% of respondents said their social life had been directly affected by Alpha-1. People reported being unable or afraid to attend dances, GAA matches, and simple pleasures such as visiting a friend's house. The fear of infection means many people avoid certain situations. Places with large crowds, hospital visits to see friends or relatives, and sometimes family occasions are avoided, particularly in winter time.

Of note, 36% of respondents said holidays were affected. Travel is very difficult for those on oxygen. For those able to travel sometimes getting to an airport is difficult due to breathlessness and the crowds involved often exacerbate anxiety and breathlessness. Other issues reported during group discussions included the need to see a physiotherapist to be assessed for oxygen requirements while away from home, paying for oxygen, the many documents to be completed by medical staff, and the wheelchair assistance often required at airports.

Unmet Needs

The consensus among respondents with lung disease was that none of the current treatments address the underlying cause of Alpha-1. The group identified three key treatment priorities;

1. **A treatment to prevent ongoing and repeated infections**
2. **A treatment to maintain lung function and alleviate breathlessness.**
3. **A treatment to slow down the progress of the lung disease.**

Q. What it is like to live with Alpha-1 and what difference do you think Alpha-1 augmentation therapy could make?

From a 52 year old mother:

Alpha-1 is a very frightening condition. You can get out of breath very quickly sometimes you can take panic attacks after doing something stressful, but simple. For instance I was vacuuming one day. I thought I was ok but suddenly I could not get my breath. I felt weak and started to sweat hot and cold. I sat down and tried to get my breath. It took me 15 minutes to come back to normal. I thought I was going to die. I have a young child who is always wanting me to play with her and I feel terrible because I just can't do it. When you have alpha-1 you have to plan everything you do before you go. Such as have you far to walk? Is there stairs? Even to go shopping. I would not be able to try on clothes in a changing room unless there was a seat to sit on. I cannot talk to anyone when I am walking. I can get out of breath when talking on the phone. It can be very embarrassing with people who don't understand the illness. I was asked to join in at my daughter's sports day at school and when I said I couldn't they thought I was just being awkward. If I had this therapy it could make such a difference to my life. If the augmentation therapy could help just a little it would be wonderful. Even if it could slow down the illness and let you live a little longer. I would like to see my daughter's wedding day.

6 Recent Events

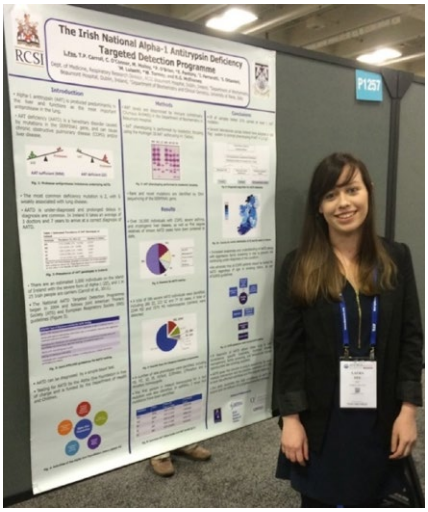
Big congratulations to Stephen Smith who won three bronze medals for Team Ireland at the European Transplant Games in Finland from 10–17 July 2016.

Stephen, who has Alpha-1, had a successful double lung transplant in the Mater Hospital in November 2013. He has become a passionate advocate for organ donation since his transplant.

Stephen won bronze in singles badminton, doubles badminton, table tennis and came 4th in the bowling competition. Congratulations Stephen!

The US Alpha-1 Foundation announced its 2016 grant awardees on May 16, 2016 during a reception at the American Thoracic Society (ATS) International Conference in San Francisco.

Among the award recipients were two Irish Alpha-1 researchers, Professor Gerry McElvaney and Dr. Emer Reeves, who are both based at the RCSI Smurfit Building in Beaumont Hospital.



Laura Fee from the Alpha One Foundation was invited to present data from the Irish National Alpha-1 Screening Programme at the American Thoracic Society Scientific Conference in San Francisco, May 2016.

Congratulations to Declan Moore for completing the Limerick Marathon in May 2016 on behalf of his mother who has been diagnosed with Alpha-1. A huge thank you to Declan & Lisa for their fundraising in aid of Alpha-1.

Congratulations to Colette and Audrey Stears for completing the VHI Womens Mini-Marathon in May 2016. Thanks to Colette & Audrey for flying the flag for Alpha-1 and their generous donation.

A huge thank you to everyone who participated in a charity coffee morning with a fashion flair in the Glenroyal Hotel in Maynooth in June 2016. All monies raised went toward the Alpha One Foundation and the Irish Sarcoidosis Support Network (iSARC). A special thanks to Orla Keane, Maura May and their merry band of helpers.

The respiratory research department led by Professor McElvaney was awarded 'Research Paper of the Year' at the Irish Healthcare Awards for their paper, 'The circulating proteinase inhibitor α-1 antitrypsin regulates neutrophil degranulation and autoimmunity.' Congratulations to Professor McElvaney and to all involved in this research particularly lead co-authors of the study, Dr. Emer Reeves and Dr. David Bergin.

Members of the Irish Lung Health Alliance, a group of 17 Irish charities who promote healthy lungs with the winners of the 'Lovin Our Lungs' Movie Awards. The purpose of the awards was to increase awareness of lung health by highlighting the importance of exercising for 30 minutes most days, eating a healthy diet and not smoking. The winning movie was created by a group of five teenagers from the House of Swag Dance School in Swords, Co. Dublin.

A book of poems called 'Window to My World' was highlighted at the 2015 annual Alpha-1 patient conference in the Marino Institute of Education in Dublin. The book was written by John O'Donnell from Donegal who unfortunately passed away at a young age due to Alpha-1. The family generously donated proceeds from the book to the Alpha One Foundation.

The conference ended with everyone out of their seats for an exercise demonstration led by Dr. Noel McCaffrey and Eoin Durkan from DCU.

Many thanks to Josephine McGuirk for coordinating the sale of Christmas cards at the patient conference last year. The cards will be available again this year, please contact the Alpha One Foundation or visit our website at *www.alpha1.ie* for more information.

In coordination with World COPD Day on November 18, 2015, COPD Support Ireland conducted a nationwide 'Save Your Breath' campaign which provided health checks to those with breathing difficulties. Individuals were offered pulmonary function testing, nutritional advice and information about Alpha-1. Margaret Molloy of the Alpha One Foundation is shown here carrying out testing on a member of the public.

7 Current Research Developments in Alpha-1

Awards for Alpha-1 research

In the past 12 months researchers from the Royal College of Surgeons in Ireland (RCSI) and Beaumont Hospital have had a major success as their paper, "The Circulating Proteinase Inhibitor Alpha-1 Antitrypsin Regulates Neutrophil Degranulation and Autoimmunity", was awarded Research Paper of the Year at the Irish Healthcare Awards. The research findings showed how the alpha-1 antitrypsin protein plays an important role in controlling inflammation caused by white blood cells that circulate throughout the body in the blood stream. The paper explains how a lack of the Alpha-1 protein can increase the release of proteins from white blood cells and how this can lead to autoimmunity and production of oxidants harmful to the body.

RCSI researchers aim to build upon this success, and in May of this year funding was provided by the US Alpha-1 Foundation to investigate additional beneficial effects of alpha-1 antitrypsin augmentation therapy. In this new study researchers will explore the effect of the alpha-1 antitrypsin protein on platelets, which are tiny cells that help the blood to clot if you cut yourself. However, platelets can also cause white blood cells to travel from the blood to the lungs where neutrophils can cause harmful effects. The beneficial way that the alpha-1 antitrypsin protein attaches to platelets and white blood cells and reduces their travel to the airways will be explored.

This scientific research is being carried out by a dynamic team in the Department of Medicine in RCSI including scientists, doctors and nurses. Researchers working on Alpha-1 projects have presented their research findings at national and international conference meetings and received a number of awards including prizes at the 25th Sheppard Prize Competition in Beaumont Hospital, and the Irish Thoracic Society annual scientific meeting. Two students completed their Alpha-1 research projects in fulfilment of the requirements for the Degree of Doctor of Philosophy and graduated in June, 2016.

Research investigating exercise as a treatment for Alpha-1

Dublin City University Sport (DCU), MedEx Wellness and the Alpha One Foundation are delighted to to provide an update on the progress of our 3 year research project. The aim of which is to develop an exercise programme specifically designed for people living with Alpha-1. To date we have completed two days of testing on 13 participants recruited from the Alpha-1 Clinic at Beaumont Hospital. Of these 13, 10 have started their twelve week pulmonary rehabilitation exercise programme provided by MedEx in DCU.

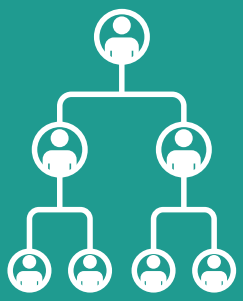
MedEx is a unique partnership between DCU Sport, the School of Health and Human Performance and local health care providers. It offers group exercise classes involving a mixture of aerobic and resistance training in a relaxed and friendly environment. All staff are highly trained and experienced in helping people with various illnesses to exercise safely and become fitter, healthier and better able to enjoy an active lifestyle.

Recruitment to the programme is ongoing. Over the next 12 months we are hoping to recruit up to 60 more participants on a rolling basis. All exercise testing will be taking place in DCU on a weekly basis.

Want to take part?

...If so, please contact:

Eóin Durkan at Tel: 01-700 8470 or Email: eoin.durkan@dcu.ie



What is the risk of lung disease in SZ Alpha-1 Antitrypsin Deficiency?

The purpose of this 2 year research study is to improve our knowledge about individuals who carry both the abnormal S and the abnormal Z types of the alpha-1 antitrypsin (AAT) gene, more commonly referred to as SZ.

We want to clarify whether SZ individuals are at increased risk of developing lung disease when compared to MM, MS and MZ individuals.

Our aim is to enrol 100 SZ individuals with a diagnosis of GOLD Stage II-IV COPD and/or asthma, and by testing their family members we hope to subsequently enrol 400 of their siblings and parents into this study. The strength of this study is in the unique family based design.

Participants will be offered lung function testing, routine blood tests and blood test to confirm alpha-1 status. Each participant will then complete a questionnaire.

We will compare lung function, blood results, smoking history and other environmental exposures between these groups to identify any differences which might suggest a presence or risk of disease. We also hope to further clarify what level of AAT in the blood is protective against lung damage. We believe this level may vary depending on the type AAT each individual produces.

If there are patients that fulfil the above criteria and are interested in partaking in this study...

Want to take part?

...If so, please contact:

Dr Alessandro Franciosi, MB, BCh, BAO, Clinical Researcher, Alpha One Foundation, RCSI Building, Beaumont Hospital, Dublin 9.

Tel: 01-809 3876
Email: alessandrofranciosi@rcsi.ie

Clinical trial for people with liver disease caused by Alpha-1 Antitrypsin Deficiency

This study is being conducted at the Mater Hospital by Professor Gerry McElvaney and his research team. This is an open-label, multi-dose, phase 2 study. The aim is to determine the safety and effect of a new drug ARC-AAT which is produced by a company called Arrowhead.

There is no current treatment for the liver disease caused by AATD, and liver transplantation is the only available cure. The liver disease is caused by the build-up of an abnormal form of AAT in the liver. It is hoped that giving ARC-AAT injections to people with liver problems will decrease abnormal AAT levels in the liver.

The exciting new study is scheduled to start in early 2017. The study is an open-label study, which means that both the researchers and the participants will know what treatment is being administered. There is no placebo in this study and all participants will receive the study drug. It is planned to recruit at least 8 participants, who will be divided into two groups (4 in each) in order to evaluate two different intravenous doses.

Screening for the study will involve a liver biopsy to confirm eligibility prior to receiving the first dose of the study drug. Participants will also require a post-dose liver biopsy at the end of the study.

Participants, who have been screened as suitable and are enrolled on to the study, will receive monthly intravenous doses of ARC-AAT for a period of 7 months. They will be asked to attend the hospital to receive the drug and will be assessed at each visit.

Tests and assessments carried out on participants during the study will include blood tests, a urine cotinine test to detect nicotine, pulmonary function tests, physical examination by a doctor, and fibroscan which is a type of liver scan.

If the study is successful ARC-AAT could be used as a ground-breaking new treatment for patients with liver disease caused by AATD.

For further information, contact the Clinical Research Coordinator on alpha1@rcsi.ie.

8 Acknowledgements

We would like to thank the following:

- Everyone who took part in the Living with Alpha-1 survey which formed the basis of our patient group submission to the National Centre for Pharmacoeconomics (NCPE) in support of RESPREEZA
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- Professor Dermot Kenny and the RCSI Clinical Research Centre (*www.rcsicrc.ie*)
- Anne Gormley, Orla Keane, Eóin Durkan and MedEx DCU for help in the production of the Alpha-1 video
- Abdulaziz Alghamdi, 3rd Year medical student at RCSI, James Lyons, 1st Year medical student at RCSI Perdana University, and Niamh Casserly who carried out research projects with the Alpha One Foundation in 2016
- The Health Research Board (HRB), The Medical Research Charities Group (MRCG), the Irish Platform for Patients' Organisations, Science & Industry (IPPOSI), the Irish Lung Health Alliance, and the Irish Thoracic Society (ITS)
- Dr. Paula Byrne and Dr. Amanda McCann of the UCD School of Medicine
- President Michael D. Higgins for his continued support as patron of the Alpha One Foundation
- A special thank you to everyone who took part in or organised fundraising and awareness events throughout the year

We would also like to thank the Department of Health and Children and the Health Service Executive for their continued financial support.

We would also like to acknowledge the participation of the following hospitals;

- Adelaide and Meath Hospitals, including National Children's Hospital Tallaght
- Beaumont Hospital
- Blackrock Clinic
- Bon Secours Hospital Tralee
- Bon Secours Hospital Dublin
- Cavan General Hospital
- Children's University Hospital, Temple Street, Dublin
- Coombe Women and Infants University Hospital
- Cork University Hospitals
- Galway University Hospitals
- James Connolly Memorial Hospital Blanchardstown
- Kerry General Hospital
- Letterkenny General Hospital
- Mater Misericordiae University Hospital, Dublin
- Mayo General Hospital
- Midland Regional Hospitals: Tullamore, Mullingar, and Portlaoise
- Midwestern Regional Hospital, Limerick
- Naas General Hospital, Co. Kildare
- Our Lady's Children's Hospital, Crumlin
- Our Lady of Lourdes Hospital, Drogheda
- Our Lady's Hospital, Navan
- Peamount Hospital, Dublin
- Roscommon County Hospital
- Rotunda Hospital, Dublin
- Sligo General Hospital
- St. James's Hospital, Dublin
- St. Luke's General Hospital Carlow/Kilkenny
- St. Vincent's University Hospital, Dublin
- South Tipperary General Hospital, Clonmel
- Waterford Regional Hospital
- Wexford General Hospital

84% of those with severe Alpha-1 experienced 1 or more chest infections in the past twelve months with **25% admitted** to hospital for intravenous antibiotics on at least one occasion

84% of those receiving augmentation therapy reported an improvement in general symptoms including shortness of breath, cough and fatigue

Those receiving augmentation therapy reported a **decrease of 69%** in frequency of hospitalisations due to chest infections since beginning treatment

200 blood tests performed by the Alpha One Foundation per month

>30 hospitals in Ireland sending samples for Alpha-1 testing

>16,000 individuals tested for Alpha-1 to date

1 in 25 people in Ireland carry the defective Z Alpha-1 gene

>650 Alpha-1 patients attending National Alpha-1 Centre

Smokers who carry one defective Alpha-1 gene have a **5 times increased risk** of developing lung disease

Alpha One Foundation Email: alpha1@rcsi.ie Web: www.alpha1.ie
Alpha One Foundation (Ireland) Charity Code: CHY14812

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