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Summary

Alpha-1 Antitrypsin Deficiency (AAT Deficiency or Alpha-1) is one of the most common serious hereditary disorders in the world and can result in life-threatening liver disease in children and adults or in lung disease in adults.

Alpha-1 has been identified in virtually all populations. An estimated 1,000 Irish citizens have the deficiency.

An estimated 200,000 people in Ireland carry a single deficient gene that causes Alpha-1 and may pass the gene on to their children.

Recent research suggests that some Alpha-1 carriers may be at risk for lung and/or liver disease.

Alpha-1 is widely under-diagnosed and misdiagnosed.

Less than 10% of those predicted to have Alpha-1 have been diagnosed.

It often takes an average of five doctors and seven years from the time the symptoms first appear before proper diagnosis is made.

Alpha-1 can be detected by a simple blood test.

The World Health Organisation (WHO) recommends that all individuals with Chronic Obstructive Pulmonary Disease (COPD), as well as adults and adolescents with asthma (an estimated 300,000 in Ireland) be tested for Alpha-1.

Early in 2004, the Minster of Health and Children approved funding for a project for Targeted Detection Programme for Alpha-1 Antitrypsin Deficiency. Ireland was the first European country to be awarded government funding for such a proposal, a significant foresight. Ireland is also the first country to use the most up to date technology available on the internet to house data.

Objectives

During the initial year a nurse and a scientist have been employed to formulate, implement and analysis the Programme. This report focuses on the first year of operation from May 2004 to May 2005.

1. To identify, collect, classify, record, store and analyse information relating to the prevalence, incidence and treatment of Alpha-1 Antitrypsin Deficiency.

2. To collect, classify record and store information in relation to existing and newly diagnosed Alpha-1 Antitrypsin deficient patients.

3. To promote and facilitate the use of the data collected in approved research projects and in the planning and management of services.

4. To furnish advice, information and assistance in relation to any aspect of Alpha-1 Antitrypsin to the Department of Health, H.S.E. and other service providers and persons with Alpha-1 Antitrypsin.

5. To provide data on long term prognosis for Alpha-1 Antitrypsin patients in the Republic of Ireland- including treatment outcomes, quality of care, international best practise.

6. To provide data on long term prognosis for Alpha-1 Antitrypsin patients in the republic of Ireland and to compare this same information with international data.

7. To publish an annual report based on the activities of the Alpha-1 Foundation and Targeted Detection Programme.

Aims

1. To routinely check for Alpha-1 in COPD patients.
2. To enlist the assistance of paediatric liver specialists and asthma specialists.
3. To screen all children presenting with severe liver conditions for Alpha-1.
4. Adolescents and adults presenting with non responsive asthma will be routinely checked for Alpha-1.
5. All samples will be referred to the Alpha-1 Speciality Centre for analysis and confirmation.
6. To provide Alpha-1 Antitrypsin information service for the Department of Health and Children, HSE, hospitals and Clinicians.
7. To provide annual reports on the incidence, prevalence and treatment of patients registered, at a sufficient level of morbidity and geographical detail to make them available to those involved in planning and delivering Alpha- 1 Antitrypsin diagnosis and treatment services, and to disseminate these to all parties.
8. To register all Alpha-1 patients whose usual residence is in the Republic of Ireland and to record phenotype of all Alpha-1 patients treated in the Republic of Ireland.
9. To ensure that this registration is complete, accurate, timely and confidential; to effectively use the data collected.
10. To be an active contributor to the National Anti Smoking Campaign.
11. To compare and contrast Alpha-1 management and treatment with best practice internationally.

Description

Alpha-1 Antitrypsin deficiency is a hereditary disorder, resulting from a variety of mutations in the AAT gene, and classically presents with emphysema in young to middle-aged adults and liver disease in childhood. Recent recommendations of the World Health Organisation advocate screening programme among patients with Chronic Obstructive Pulmonary Disease (COPD) and Asthma.

A total of 500 individuals to date have been screened, all attending Respiratory Outpatients, Beaumont Hospital. A collective history of smoking, lung disease, liver disease, medication, family history lung disease and pulmonary function values were obtained at time of screening. This screening information is currently entered in the Alpha-1 Database.

All individuals screened at the Respiratory Outpatients in Beaumont are firstly identified as COPD or asthmatic. They are individually approached by the clinical research nurse. Explanations are given regarding Alpha-1 Antitrypsin deficiency, also why and how to be screened. Patient information booklets explaining the potential benefits and drawbacks, contact numbers for the Alpha-1 Foundation were also provided to all who are screened.

A venous sample of 2.7mls was taken in the phlebotomy department, and then collected for analysis. These samples are then analysed by scientist in the Alpha-1 Foundation to determine the amount of AAT in the blood and whether or not you have the normal genes, are a carrier or have a severe deficiency of AAT.

AAT Serum Levels

All patients detected are offered appropriate therapies.
Medical intervention includes, influenza vaccination, pneumonia vaccination, aggressive therapy of respiratory tract infections, bronchodilator therapy/inhaled steroids as applicable, home oxygen/nebulizer as applicable and the opportunity to participate in studies evaluating efficacy of A1AT augmentation therapy.

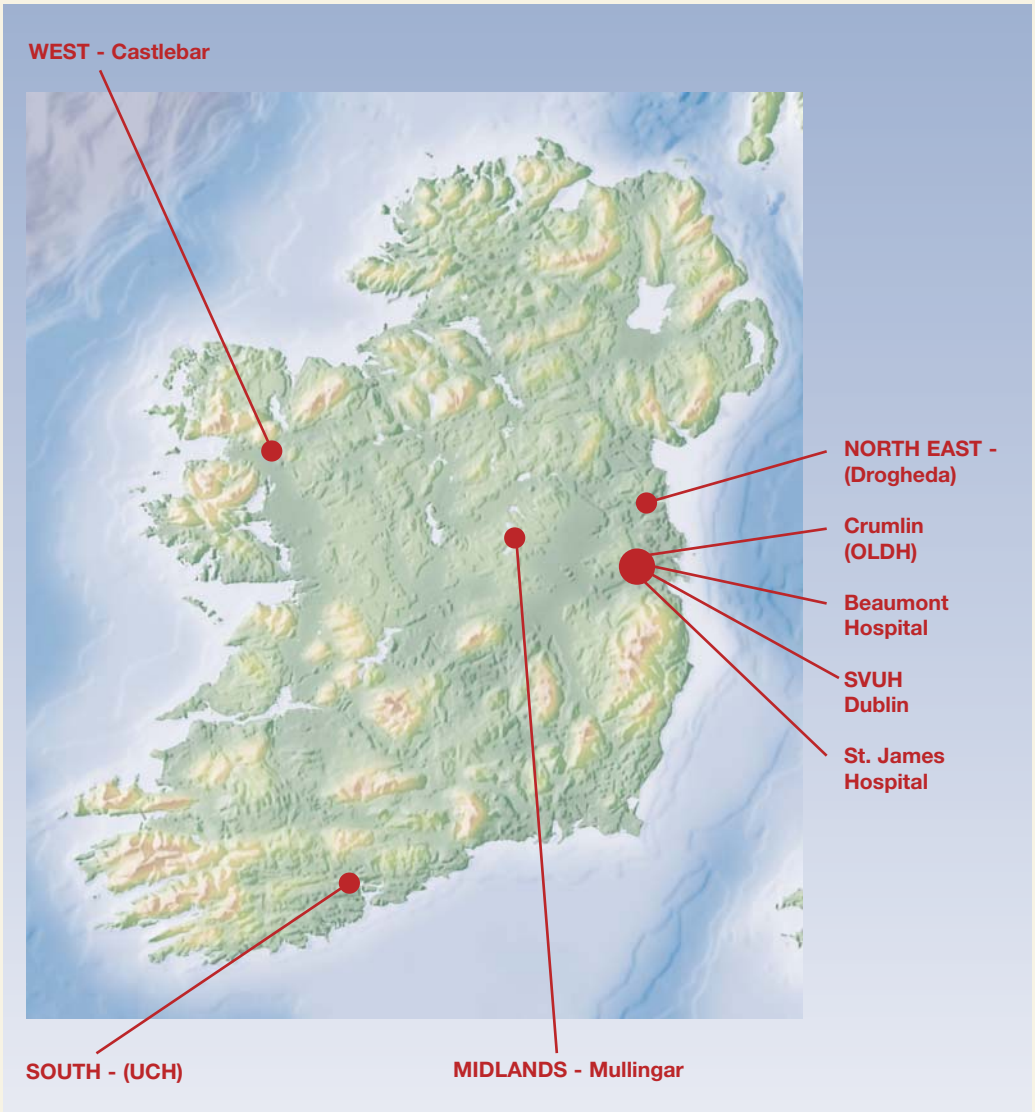
Patient's families are advised to be tested. All patients are made aware of the dangers of smoking. International evidence indicates that the overwhelming majority of detected Alpha-1 patients quit or don't start smoking. Patients are linked to the smoking cessation officer in Beaumont or the nearest community officer.

Patient's with A1AT are more susceptible to permanent and irrevocable lung changes during and after pulmonary infections. This is because the protective effects of A1AT are limited in these patients.

Aggressive treatments include antibiotic therapy at the earliest onset of respiratory symptoms, e.g. increased cough, increased sputum, change in colour of sputum. This treatment to be supplemented by inhaled bronchodilators /steroids and occasionally oral steroids.

Although lethal, Alpha1 is a relatively simple condition easily understood, as are its therapies. Complex counselling, in our opinion, is not necessary and could generally be handled by the respiratory staff and specialist nurses. The Foundation provides peer counselling as well as individual, group and family support.

The programme nationwide is represented in the map, showing current screening centres in Beaumont, Drogheda, Mullingar and St. Vincent's hospitals. Those hospitals who have agreed to commence screening in the near future are St. James's, Cork, Crumlin and Castlbar. Potential centres that will be approached to screen are Galway, Letterkenny, Waterford, Limerick, Tralee, Tullamore and Ballinasloe.



Dear Dr,

It was a pleasure talking to you about out National Targeted Detection Programme, which we are beginning to roll out at the moment. Thank you for your very positive interest in becoming part of this programme.

I enclose some literature, as promised, which outlines the programme and also a test kit of the type we use. We are happy to offer a full service free of charge to you and your patients. We have both a dedicated research nurse counsellor and laboratory scientist to deal with patients and to perform diagnostic assays.

Our method of detection is as follows:

- Blood is collected and serum isolated
- Serum is used in two assays - measurement of circulating AAT levels and phenotyping of AAT present
- Levels are determined by radial immunodiffusion (RID)
- Phenotyping is performed by isoelectric focussing (IEF)

However, in the next few months we will be validating a new finger prick test kit. This will involve the collection of a dried blood spot (DBS) from patients. The finger prick kit is more convenient and less invasive than venous blood sample collection and should increase patient numbers being tested. Once collected, the DBS sample can be stored at room temperature and sent more easily via conventional post to us (We will provide a pre-paid envelope). DNA is then isolated from the blood spot and genotyping performed on the sample. Levels of circulating AAT can also be measured from this blood spot. We hope to have this DBS system in operation in the coming weeks.

We would be very happy to meet with you discuss whatever methodologies would most suit you and your patients in pursuing the programme and sharing with you the information we obtain on a national basis.

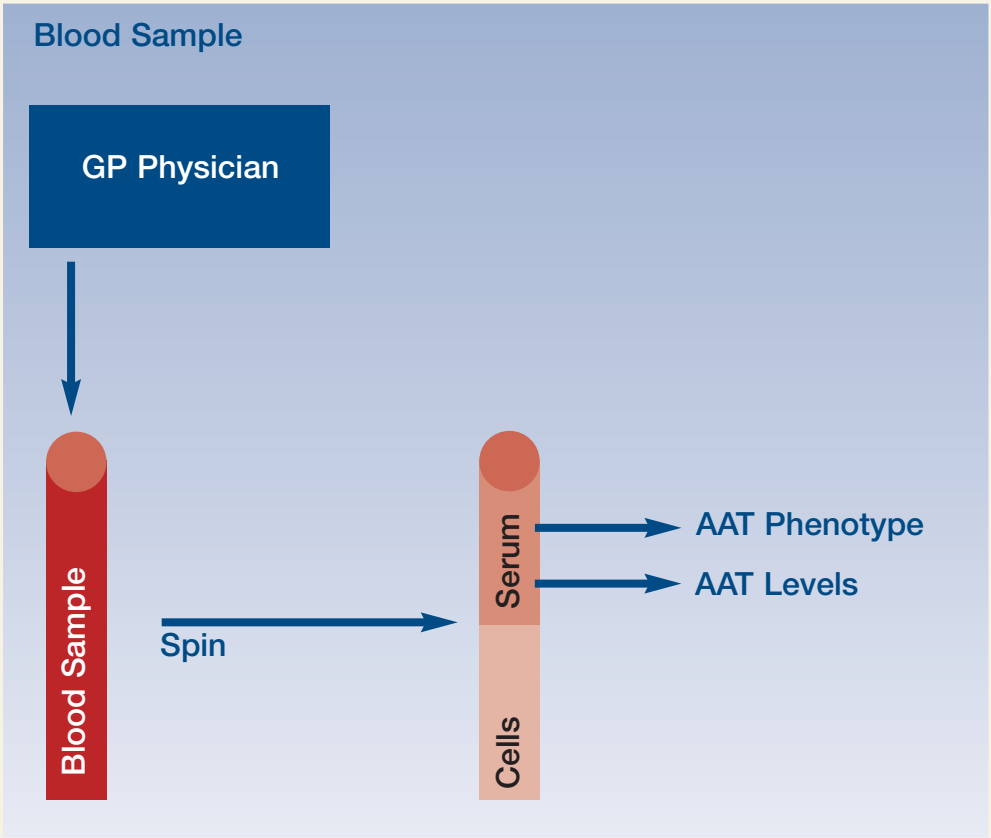
As we are building a national AAT registry we thought that you may also be interested in participating in that also.

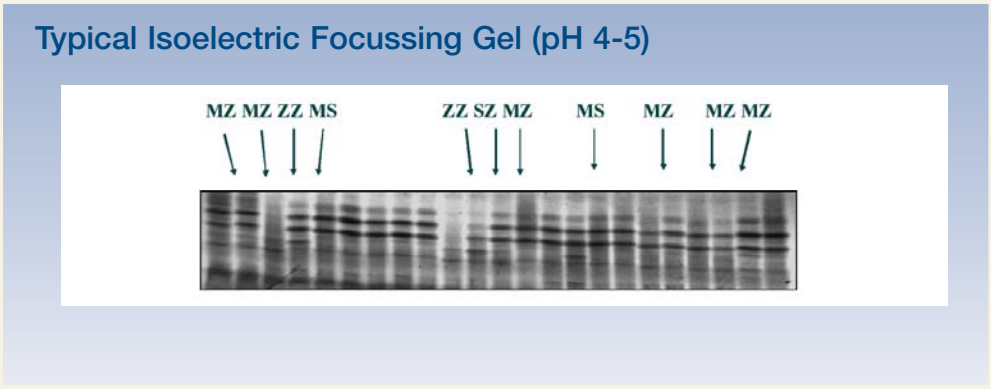
You may contact out research Nurse, Kitty O'Connor at 01 8093871 or myself at the numbers attached.

Many thanks for your kind consideration.

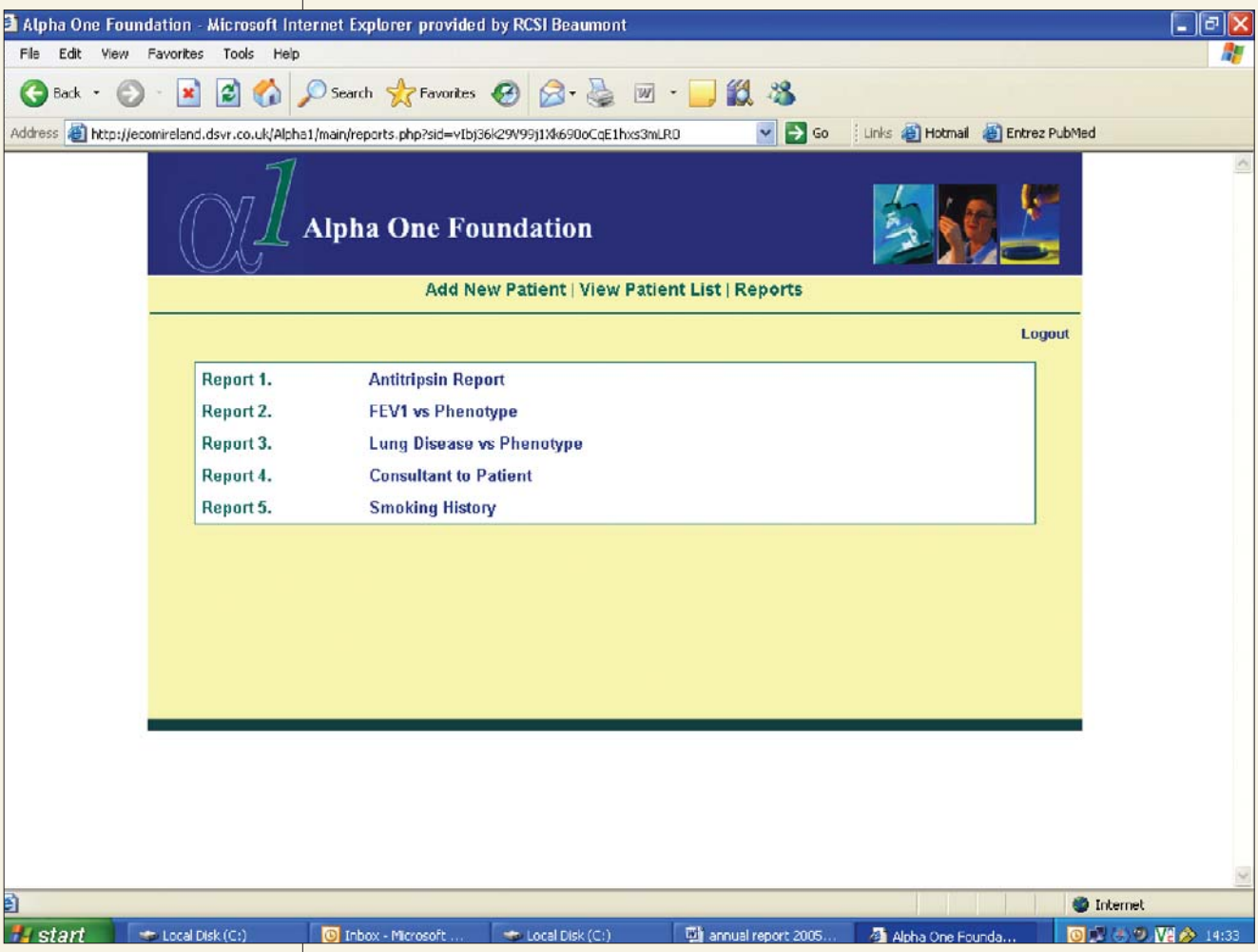
Yours sincerely,
Larry Warren, Chief Executive

The data collection process takes place in the Respiratory Outpatients department. Personal details, nationality, smoking history, lung disease history, liver disease history, medication, family lung history and pulmonary function values are obtained. These are then entered into the Alpha-1 database for analysis for comparisons between phenotypes and this collective history.

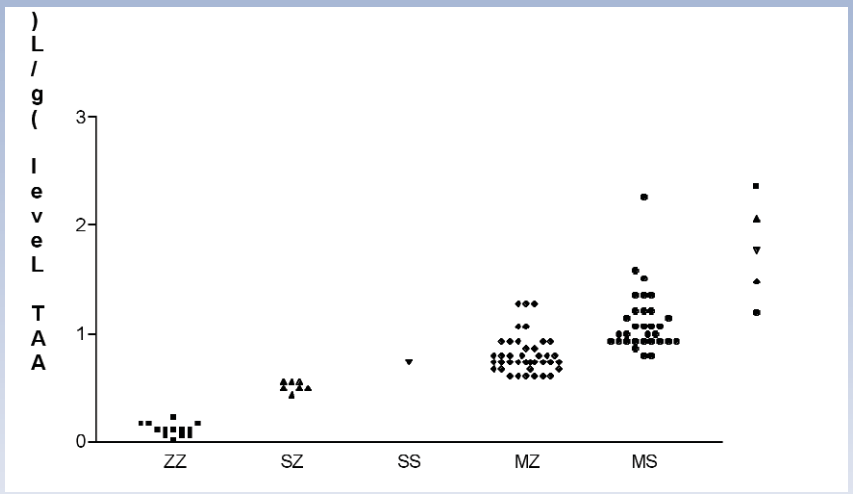




To date we are in the process of analysis of the complied data. Our database for our targeted detected screening programme can generate reports from our collected data to compare lung function and lung disease in relation to phenotype of the individual. We also can provide individual consultant reports to differentiate patient genotype, smoking history, lung function and respiratory symptoms.



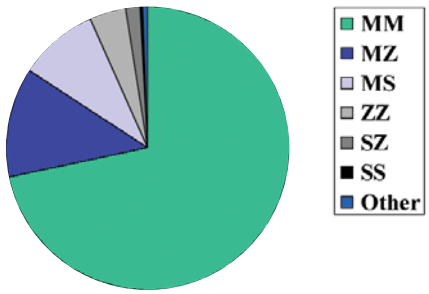
Levels v Phenotype in Ireland



Screening to date

Of 358 screened since beginning of programme in May 2004

– 13 ZZ
– 41 MZ
– 7 SZ
– 32 MS
– 1 SS



26.8% of tested population posses a mutant AAT allele

Our first year of the targeted detection screening programme has seen us accomplish many of our original objectives. For the forthcoming year we have reviewed our projected figures of potential individuals to be screened. Not having reached predicted figures in the first year we have identified unforeseen obstacles and problems facing our programme. These include a poor response from medical staff, obstacles in testing methods, equipment problems, delays in getting primers and protocols, some patient's unwillingness to participate in giving a venous blood sample, lack of awareness among allied health professions, low screening figures throughout hospitals nationwide. We accomplished figures within the first year in keeping with Germany, U.K., Spain, Italy and the U.S. In our second year our projected figures are 2,500 individuals to be screened, we feel these are realistic targets, having rectified many of the initial problems encountered.

Objectives

- Roll out to other centres
- Mullingar, Drogheda, SVUH Dublin ongoing screening
- Cork (Mercy, CUH),Castlebar, Galway (Merlin,GUH), Crumlin (Our Ladys), St. James, Castlebar have agreed to commence screening
- Galway(Merlin, GUH), Letterkenny, Limerick, Waterford, Ballinasloe, Tralee, Derry,Cavan are all potential centres
- Distribute information packs to General Practice clinics
- Improve levels of awareness among Nurses, Dieticians, Physiotherapists and Smoking Cessation officers
- Ensure AATD a central plank in GOLD annual COPD days
- Close association with Asthma Society of Ireland
- Attend Respiratory meetings
- Patient friendly testing method
- Easy delivery of samples
- Quicker results time span
- Find new methods of advertising - Ploughing Championships 2005, Over 50's Show, Cork 2005, Dublin 2005, Articles in Journals
- Attend and participate in ITS
- Encourage patients to attend Marino Institute Education patient meeting
- Cooperate with Practice Nurse and Anail Meetings

Alpha-One Foundation Registry

It has become obvious in recent years that quality information regarding Alpha-1 Antitrypsin Deficiency (Alpha-1) in Ireland was not readily available to The Alpha-1 One Foundation, the Dept. of Health & Children, HSE or health professionals. This situation does not help the diagnosis, treatment and maintenance of Alpha-1 patients.

This also puts us at a disadvantage when we need to make comparisons with EU and other countries and promote accurate research programmes or develop consensus diagnosis and treatment. It also creates problems developing a system of quality assurance for Alpha-1 care.

In order to rectify this situation and assist planning health programmes for people with Alpha-1 and to speed the availability of data for research, the Foundation has set up an Alpha-1 Registry.

Description

A registry administrator has been appointed to oversee the setting up and implementation of the Registry. All possible sources of information will be made available for entry into this database. These sources of information include hospital patient charts, doctors, nurses, physiotherapists, dieticians and patients themselves.

Information will be tabulated on a HSE/regional basis in order to support planning for local and regional services for the betterment of Alpha-1 patients country-wide.

The Registry will be accessible to permitted users only through the internet. Information that is stored in the database will be taken from hospital medical charts. Every hospital that contributes patient data to the Registry must approve the Registry through an Ethics Committee, where they decide whether to release hospital chart information to the Registry.

Description

All relevant data is transcribed from the medical chart onto the Registry database. Copies of the signed consent form will be kept in the patient's chart and at the Registry Office, located in the Alpha-1 Suite, Beaumont Hospital. Participation in the Registry will be treated as confidential and disclosure of any personal records or results relating to the Registry will be limited to the patients doctor and/or Registry administrator.

Security of Registry

The Alpha-1 Registry is housed on a server in a secure building.
To gain access to the database via the internet, one requires both a user name and password which are issued and confined to the Alpha-1 Foundation.

The data held on the database is encrypted. Only an authorised user will have a "key" to unlock the code and view the data.

Every person who is enrolled in the Registry may have a copy of the records kept on the Registry. This is guaranteed by the Data Protection Commission of Ireland and the Data Protection Act, 1988.

The process of data collection for the first phase of operation is shown below.

Step 1

Information Booklets
Discussion with Consultant/Team
Consent Form
Patient Signs Consent Form = One copy to chart
One copy to investigator
One copy to patient

Step 2

One copy of Consent Form to Registry to be kept on file.

Step 3

Administrator visits hospital to review patient chart.

Step 4

Initial Data Entry
A. Registration and Diagnosis Form
B. Annual Assessment Form

Alpha-One Foundation Registry - Data Collection

Primary categories of data collection are Registration, Diagnosis and Annual Assessment.

Registration Details

Personal details including name and address

Date of Birth

Health Board

Ethnicity

Name of consultant and Family doctor

Diagnostic Details

Diagnostic tests e.g. Alpha-1 level

Phenotype

Symptoms/Method of Diagnosis

Age of diagnosis

Number of hospitalizations between annual assessments

Complications

Pulmonary Function Tests

Chest X-ray reports

Computerized Tomography (CT) scan

Clinical Chemistry

Long term Therapies

Vaccinations/Immunizations

Physiotherapy regimes

Nutritional regimes

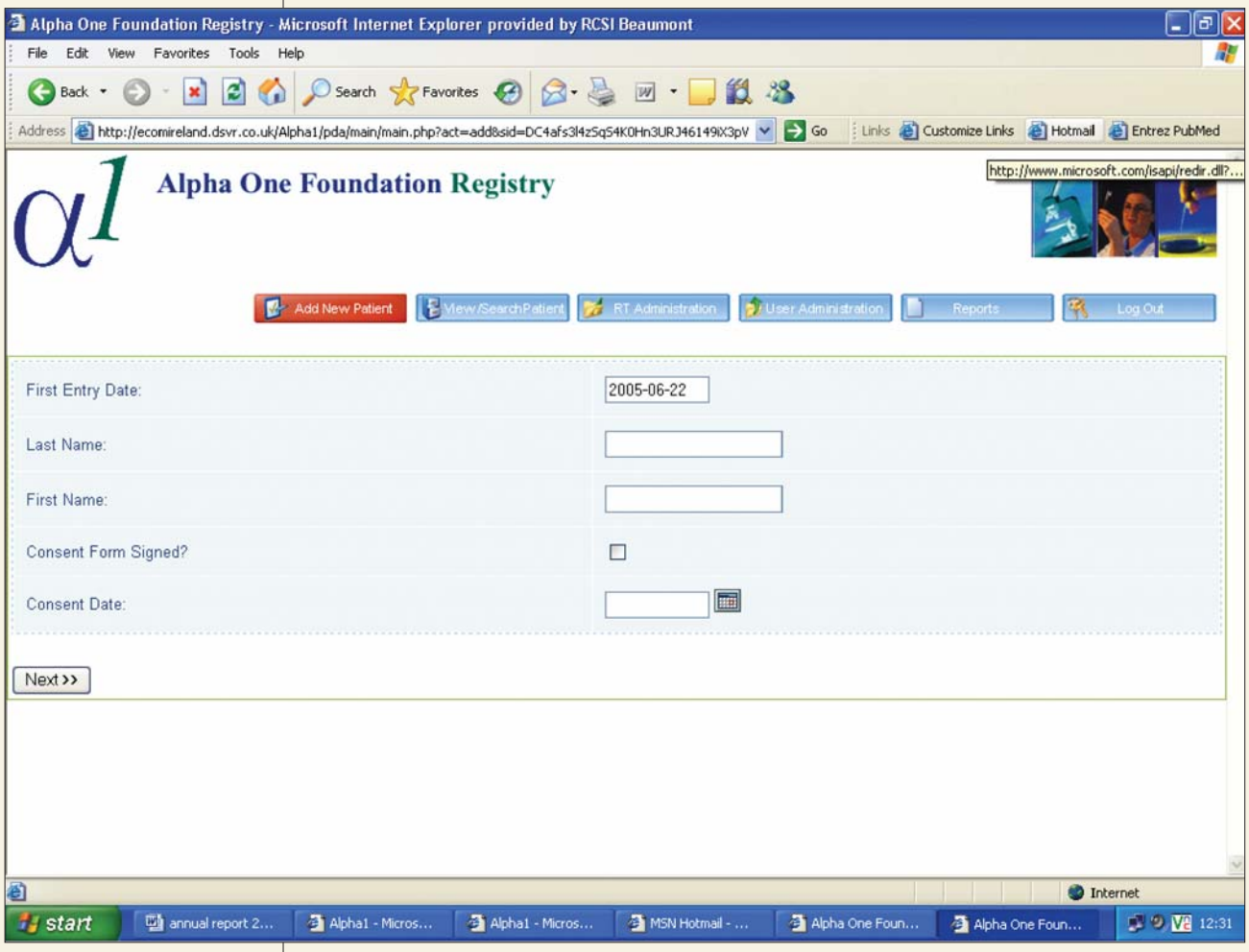
Transplant Status

Social Details

Data Analysis and Reports

Standard reports will be available on the website from live data after the initial Data Entry of at least 50% of patients. The report section of the registry is in ongoing discussion.

There is a wealth of information that can be obtained from the Registry. Much of this information will be summarized and included in each Annual Report.
Further analysis of the data will be done through various research projects and expert epidemiology advice will be sought.



Alpha-1 Patient Information Evening

Wednesday 20th July 7pm

Alpha-1 Suite
RCSI Building
Beaumont Hospital

Agenda

Introduction: Kitty O'Connor

Larry Warren, Alpha-1

Rachel Mullins, Nutrition

Eleanor Leahy, Physiotherapy

Olive Gibson, Smoking Cessation

Tomas Carroll, Targeted Detection Programme

Prof McElvaney, Clinical Trials

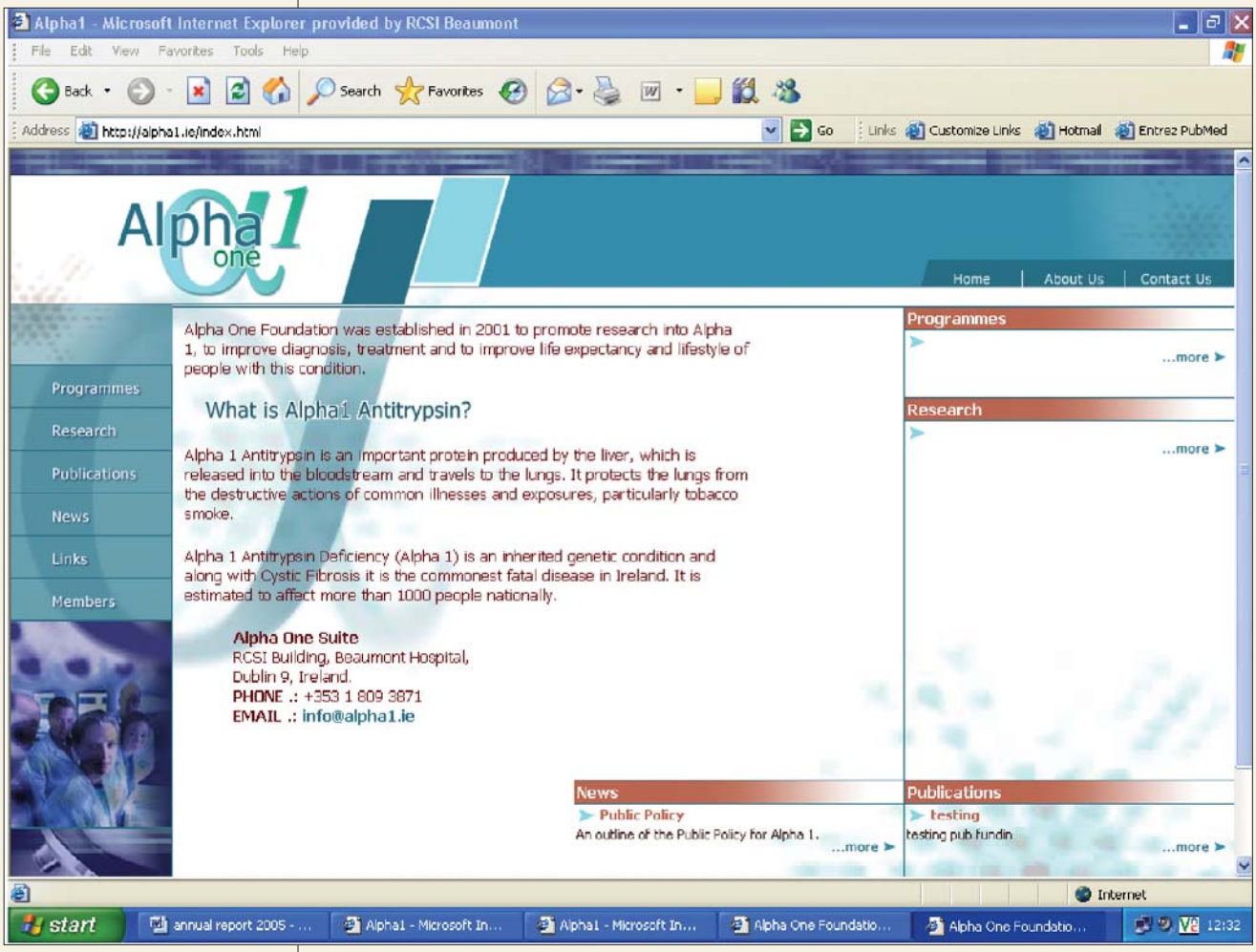
Open Discussion

Patient Meetings

Providing up to date and patient focus information in relation to Alpha-1 Antitrypsin Deficiency is one of our main aims, we organise a patient information evening and one complete day for alpha-1 patients and relatives. These evening sessions are held in Beaumont Hospital and cover aspects of care of alpha-1 from the multidisciplinary team: consultants, scientists, physiotherapist, dietitian, smoking cessation officer, social worker and health promotion staff. A summary and details of the evening are forwarded to patients who are living outside Dublin and unable to attend due to travel or ill health. Newsletters are circulated to patients throughout the year to update them on progress in Alpha-1 Foundation and new clinical trials occurring. Later in the year an opportunity for patients to meet with medical physicians and attend work shops is held in Marino Institute of Education. Different aspects of care are discussed between the patients and medical professionals providing an opportunity to increase and improve communication between these groups. We encourage families to attend and become more closely involved and to participate in patient meetings.

The second Alpha-1 International Patient Congress took place in Dublin, Ireland on 8-10 October 2004. The congress brought together more than 100 delegates and featured an impressive panel of speakers who provided clinical and patient perspectives and experiences. PPTA staff was delighted to be in attendance. A reception and a keynote address by Professor Gerry McElvaney, Dublin Beaumont Hospital, formally opened the Congress on the evening of the first day. Day two started with a presentation by Mr. Brian O'Mahony of the World Federation of Hemophilia, on the worldwide implication of international patients' networks. In his presentation, Mr. O'Mahony highlighted the advantages of having global patients' networks to decrease isolation, share information, increase visibility and awareness, receive peer support, establish programs to improve care, and provide training opportunities. Dr. Jan Stolk, Leiden University, The Netherlands and chairman of the Alpha One International Registry (AIR) organization, talked about therapies and how they can be accessed. In his presentation, he reviewed recent progress in therapy research and explained that the inducement of lung growth was being studied by his team. Dr. Stolk's presentation was followed by a series of international reports from various Alpha-1 associations active in different countries worldwide. Prof. David Lomas, University of Cambridge, provided an in-depth clinical background on Alpha-1 and stressed the importance for patients to maintain a healthy lifestyle. Additionally, he discussed the difficulties involved in diagnosing Alpha-1 Antitrypsin Deficiency (AATD). The first diagnosis was made only four decades ago and Prof. Lomas informed delegates that Frédéric Chopin, the famous composer, was very likely one of the first Alpha-1 sufferers, as the postmortem examination carried out at the time described all the signs of AATD and concluded Chopin had died of an unknown disease. Difficulties with diagnosing AATD is still an issue today as patients at the Congress explained. Dr. Billy Bourke, Dublin Children's hospitals, spoke about AAT and liver disease in children. Dr. Neils Seersholm, Respiratory Consultant in Denmark, provided an overview of the Danish AATD national registry and patient alliances, while International Registries and Collaboration was the topic of the presentation given by Dr. Charlie Strange, Medical University of South Carolina, US. Day two closed with presentations from Dr. Kenneth Knight, St. Vincent Hospital, Melbourne who updated delegates on the situation in Australia and Dr. Robert Sandhaus, National Jewish Medical and Research Center, Denver, US, who described ongoing research and developments. The next day was organized into a series of workshops aimed at Alpha-1 patients. The congress was closed by Mr. Larry Warren, Chief Executive, Alpha-1 Foundation and Mr. John Walsh, President, Alpha-1 Foundation US.

Our newly designed and updated website www.alpha 1.ie was introduced in April 2005. This provides up to date information regarding Alpha-1 Antitrypsin Deficiency. How to contact the Foundation, its functions, aims and goals. It also provides information regarding ongoing medical research taking place here in Ireland and worldwide, medical publications and related topics. We have also have a direct e-mail address for information on alpha-1, alpha1@rcsi.ie and useful links.



The Alpha-1 Foundation is closely associated with the following groups:
- AIR
- ALFA Europe (President)
- Medical Research Charities Group
- IPOSSI :Irish Platform for Patients Organisations, Science and Industry
- Irish Donor Network
- Irish Asthma Society
- Member of the Pro Health lobby for the Smoking Ban
- Alpha One International Network (Chair)

These connections provide access for patients and professionals to research and publication links. They also provid access to 'Alpha-1 Disease Management and Prevention Program for Alphas, and their Families, and their Doctors 'by AlphaNet, and 'Standards for Alpha-1 Antitrypsin Deficiency (AAT) 'CD rom, as published in The American Journal of Respiratory and Critical Care Medicine.

Links

http://www.aatregistry.org

http://www.alfaeurope.org

http://www.alpha1.org

http://www.alphanet.org

http://www.alphaone.org

http://www.irishthoracicsociety.com

http://www.asthmasociety.ie

http://www.ncnm.ie/anail

It is vital we understand the mechanisms underlying Alpha-1 antitrypsin deficiency in order to accelerate the development of novel therapies for this condition. Some of the research projects being undertaken in the RCSI Education and Research Centre in Beaumont Hospital at the moment include:

_ ER stress responses activated by Z alpha-1 antitrypsin
_ Caspase activation associated with Z alpha-1 antitrypsin
_ Mucin expression in the lungs of alpha-1 deficient individuals
_ Gene therapy for alpha-1 antitrypsin deficiency using RNA interference

Publications

Z Alpha1-antitrypsin Polymerizes in the Lung and Acts as a Neutrophil Chemoattractant.
Mulgrew AT, Taggart CC, Lawless MW, Greene CM, Brantly ML, O'Neill SJ, McElvaney NG. Department of Medicine, Respiratory Research Division, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland.
Chest, 2004 May;125(5):1952-7.

Activation of Endoplasmic Reticulum-specific Stress Responses Associated with the Conformational Disease Z Alpha 1-antitrypsin Deficiency.
Lawless MW, Greene CM, Mulgrew A, Taggart CC, O'Neill SJ, McElvaney NG. Respiratory Research Division, Royal College of Surgeons in Ireland, Education and Research Center, Beaumont Hospital, Dublin, Ireland.
J Immunology, 2004 May 1;172(9):5722-6.

Alpha1-antitrypsin Deficiency: Biological Answers to Clinical Questions.
Coakley RJ, Taggart C, O'Neill S, McElvaney NG. Pulmonary Division, Beaumont Hospital, Dublin, Ireland.
American Journal of Medical Science, 2001 Jan;321(1):33-41.

Meetings Attended /Contributed to

Irish Thoratic Society: Information booth and poster presentation Targeted Detection Programme
Alpha-1 International Registry: Presentation Prof N. G. McElvaney, Information Presentation Mr. Larry Warren
American Thoratic Society: American Thoracic Society
Plasma and Protein Therapeutics Associations
ALFA Europe: Presentation lecture Mr. Larry Warren
Alpha Deutschland: Presentation lecture Mr. Larry Warren
AIN World Congress: Alpha-1 International Network, Alpha One Foundation organized the World Patient Congress in Dublin.

Acknowledgements

We'd like to thank Alpha-1 Foundations in the U.S.and Italy for Protocols and Primers assistance. Also the Department of Health and Children and Health Service Executive for their continued financial support.