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# Protocol for the EARCO Registry: a pan-European observational study in patients with $\alpha_1$ -antitrypsin deficiency

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## ABSTRACT

**Rationale and objectives:** Alpha-1 antitrypsin deficiency (AATD) is a genetic condition that leads to an increased risk of emphysema and liver disease. Despite extensive investigation, there remain unanswered questions concerning the natural history, pathophysiology, genetics and the prognosis of the lung disease in association with AATD. The European Alpha-1 Clinical Research Collaboration (EARCO) is designed to bring together researchers from European countries and to create a standardised database for the follow-up of patients with AATD.

**Study design and population:** The EARCO Registry is a non-interventional, multicentre, pan-European, longitudinal observational cohort study enrolling patients with AATD. Data will be collected prospectively without interference/modification of patient's management by the study team. The major inclusion criterion is diagnosed severe AATD, defined by an AAT serum level  $<11 \mu\text{M}$  ( $50 \text{ mg}\cdot\text{dL}^{-1}$ ) and/or a proteinase inhibitor genotype ZZ, SZ or compound heterozygotes or homozygotes of other rare deficient variants. Assessments at baseline and during the yearly follow-up visits include lung function testing (spirometry, body plethysmography and diffusing capacity of the lung), exercise capacity, blood tests and questionnaires (symptoms, quality of life and physical activity). To ensure correct data collection, there will be designated investigator staff to document the data in the case report form. All data will be reviewed by the EARCO database manager.

**Summary:** The EARCO Registry aims to understand the natural history and prognosis of AATD better with the goal to create and validate prognostic tools to support medical decision-making.



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The EARCO Registry is a non-interventional, multicentre, pan-European, longitudinal observational cohort study enrolling patients with AATD to elucidate the natural history, pathophysiology, genetics and prognosis of this condition <http://bit.ly/369ScCc>

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## Introduction

Alpha-1 antitrypsin deficiency (AATD) is a common, but under-recognised genetic condition that affects approximately 1 in 2000 to 1 in 5000 individuals in European countries, and predisposes to early-onset emphysema and liver disease [1, 2]. AAT is mainly produced in the liver, and its function is to protect tissues, especially the lung, against proteolytic damage from serine proteinases including neutrophil elastase [3]. To date, >100 variant alleles of the AAT gene have been described, but the Z allele (p.E366 K, c.1096G>A, rs28929474) is the most prevalent severe deficiency gene leading to lung and liver disease. The Z protein forms polymers that remain trapped within the rough endoplasmic reticulum of hepatocytes leading to reduced levels of AAT in the bloodstream [4]. The liver disease arises secondary to accumulation of the protein in hepatocytes, whereas the imbalance between low blood and hence tissue levels of AAT and neutrophil elastase in the lung increases the risk of emphysema [1]. Although tremendous improvements have been made in the understanding of the pathophysiology of the disease in recent years, many questions remain unanswered.

The natural history of AATD patients is not well known, and there is a lack of prognostic tools to support medical decision-making, such as early referral for lung transplantation [5]. Although the vast majority of patients with severe deficiency share the same genetic disorder (PI\*ZZ genotype; PI standing for proteinase inhibitor), the prevalence and severity of liver and respiratory disease vary markedly. Genetic and environmental cofactors have been suspected, but few have yet been identified [6, 7].

Augmentation therapy, when assessed using computed tomography (CT) lung densitometry, has been shown to slow the progression of emphysema significantly [8–10]. However, its impact on forced expiratory volume in 1 s (FEV<sub>1</sub>) decline, quality of life and mortality has not been definitively established. Consequently, the efficacy of augmentation therapy is still debated [11], and the cost of therapy is not reimbursed in all European countries [12, 13]. Furthermore, most studies on AATD have focused on the ZZ population, and the impact of other rarer variants on outcomes is largely unknown [14].

The answer to these questions requires the access to large cohorts of patients and cannot be addressed solely at individual country level. This was the main reason to initiate a European Alpha-1 Clinical

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Research Collaboration (EARCO) [15]. EARCO is an initiative under the umbrella of the European Respiratory Society (ERS) and its clinical research collaborations, pan-European, multicentre research networks of different fields of respiratory diseases [16]. The initiative brings together multiple stakeholders including researchers, healthcare providers, patients and industry with the aim of advancing understanding through clinical and scientific research and improving the quality of life of patients with the deficiency.

EARCO takes advantage of existing AATD registries that have been developed at the national and international level. Several countries have established registries in which AATD patients are included and followed-up with clinical and biological data collected [14, 17–23]. However, these registries differ in terms of inclusion criteria, data collected and frequency and extent of follow-up. Within EARCO, we will harmonise the data collection process and assess the quality of the data entered into the database. This article describes the EARCO registry protocol: a pan-European multicentre observational study in patients with alpha-1 antitrypsin deficiency.

### Study objectives

The study objectives are

- to develop a pan-European, multicentre AATD registry incorporating baseline data from  $\geq 3000$  individuals during the first 3 years of the registry;
- to harmonise the data collection process between existing national registries and to ascertain high quality of the data by monitoring entered data closely;
- to generate longitudinal long-term, high-quality clinical data covering a pan-European population of AATD individuals of all age groups and all stages of disease severity;
- to understand the natural history and prognosis of AATD better with the goal to create and validate prognostic tools to support medical decision-making;
- to investigate the effect of AAT augmentation and other therapies on the progression of emphysema and to examine their potential impact on clinical and functional outcomes, such as FEV<sub>1</sub>, quality of life and mortality in a “real-life” population;
- to learn more about the course of the disease in patients suffering from severe AATD with genotypes other than PI\*ZZ.

### Study design

The EARCO Registry is a non-interventional, multicentre, pan-European, prospective, observational cohort study enrolling patients with AATD, as confirmed by biochemical and genetic data. Study centres are distributed in >20 European countries (figure 1) and include centres in primary, secondary and tertiary care, according to national arrangements. Current countries have been selected by personal contacts and invitations of all steering committee members. We will step up efforts in recruiting more countries through presentations on congresses, meetings and through the webpage ([www.earco.eu](http://www.earco.eu)). The registry is open to every clinician who manages AATD patients. Patients will be managed according to their local procedures and policies and without any clinical intervention from the study team. All patients will provide written informed consent to participate, and participating investigators will collect data prospectively. The following domains are covered: demographics, proteinase inhibitor genotype and other laboratory analyses, comorbidities, lung function, respiratory symptoms, ultrasound-based elastography of the liver, exacerbations of respiratory disease, quality of life, physical activity, chest CT (as applicable) and treatment.

The study protocol has received central ethics approval by the research ethics committee of the Vall d’Hebron University Hospital of Barcelona, Spain (PR(AG)480/2018), and the study database will be hosted in the Vall d’Hebron Research Institute (Barcelona). The study website is located at [www.EARCO.eu](http://www.EARCO.eu). The registry was developed according to recommendations on the design, implementation, governance and long-term sustainability of disease registries in the European Union (EU) [24, 25]. We expect to collect detailed information from  $\sim 1000$  patients from  $\geq 10$  countries during the first year after creation of the registry, expanding to 3000 from >20 countries over the following 2 years.

### Population

The study population will consist of individuals with diagnosed severe AATD regardless of the clinical features and severity. The inclusion criteria are a diagnosis of AATD, defined as AAT serum level  $< 11 \mu\text{M}$  ( $50 \text{ mg}\cdot\text{dL}^{-1}$ ) and/or proteinase inhibitor genotypes ZZ, SZ and compound heterozygotes or homozygotes of other rare deficient variants. The only exclusion criterion is lack of patient consent. Patients will be discontinued from the study if the informed consent is withdrawn by the patient or his/her legal custodian. If a patient withdraws from the study, the investigator will undertake every possible effort to determine the primary reason for a patient’s withdrawal and record this information on the case report form (CRF).



FIGURE 1 European countries in which study centres are located.

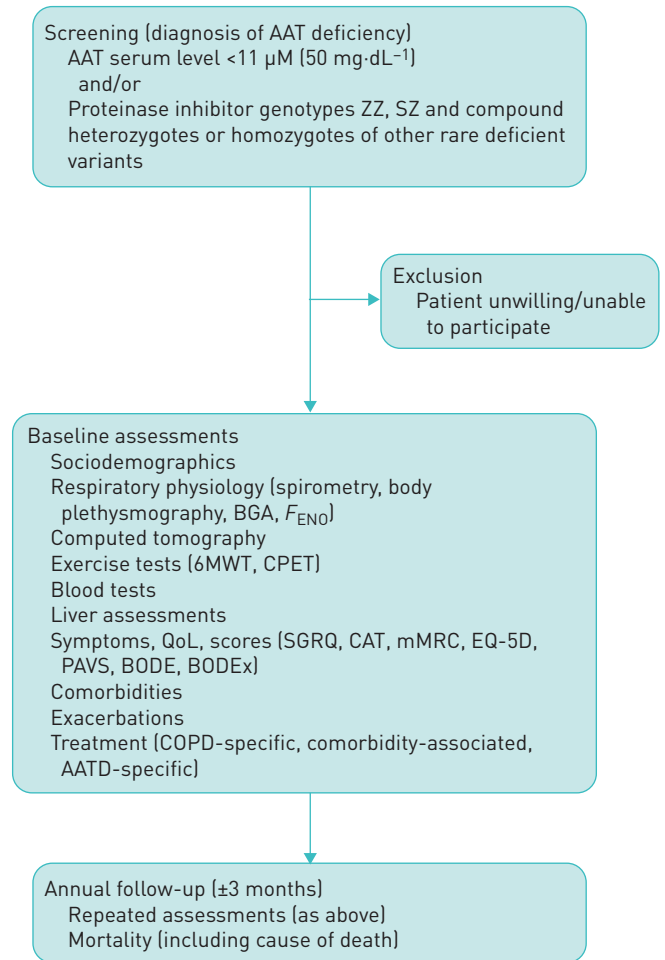
For patients who are lost to follow-up (*i.e.* those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show “due diligence” (if allowed by national ethics committee standards) by documenting in the source documents steps taken to contact the patient, *e.g.* dates of telephone calls, registered letters, *etc.*

### Visit schedule and assessments

Written informed consent form will be obtained at the baseline visit. All available information will be collected according to the CRF. Follow-up visits will be scheduled on a yearly basis ( $\pm 3$  months) and assessments, as described in the following sections, will be performed and recorded in the CRF ((b) represents baseline only) (figure 2). Because the registry reflects standard assessments in many different countries and healthy individuals (fulfilling the inclusion criteria) will be included, only the participant’s sociodemographics and basic information about the presence/type of lung or liver disease will be absolutely mandatory. All other assessments are not mandatory, but the data manager will request a minimal set of clinical data through queries to the investigators.

### Patient sociodemographics

The following data will be collected from the patient’s medical history: date of birth (b), sex (b), race and ethnicity (b), height, weight, smoking history, alcohol consumption, working status (including relevant occupational exposures and type of agent), year of diagnosis of AATD (b), information about family



**FIGURE 2** Baseline and follow-up assessments. Only demographics and information about lung and liver disease are mandatory. AAT: alpha-1 antitrypsin; BGA: blood gas analysis;  $F_{\text{ENO}}$ : exhaled nitric oxide fraction; MWT: 6-min walk test; CPET: cardiopulmonary exercise testing; QoL: quality of life; SGRQ: St George's Respiratory Questionnaire; CAT: COPD Assessment Test; mMRC: modified Medical Research Council dyspnoea scale; EQ-5D: EuroQoL 5-dimension quality of life questionnaire; PAVS: physical activity vital signs questionnaire; BODE: body mass index, obstruction, dyspnoea and exercise; BODEx: body mass index, obstruction, dyspnoea and exacerbations.

history (*i.e.* index case *versus* non-index case), AAT level, phenotype/genotype (b), information about AATD-related diseases (lung disease, liver disease, vasculitis and other AATD-related diseases).

### **Respiratory physiology**

Spirometry equipment and performance of spirometric testing must conform to American Thoracic Society (ATS)/ERS standards [26]. Pre- and/or post-bronchodilator spirometry values will be collected at baseline, but post-bronchodilator values alone will be recorded at follow-up visits. Absolute values will be recorded, to enable the use of different reference equations to calculate the severity of impairment. In order to reduce the variability of observations, the same equipment must be used and the same staff member should evaluate and coach a given patient at each visit throughout the study, where possible.

For body plethysmography and diffusing capacity of the lung for carbon monoxide, international recommendations will be followed [27]. Arterial blood gas analysis will be measured using a quality controlled analyser. Measurements from the arterialisated ear lobe are also acceptable [28]. The procedure for measurement of the fraction of exhaled nitric oxide will follow the ERS recommendations [29]

### **Exercise tests**

The 6-min walk test will be performed according to the ATS guideline [30]. The patient's assessment of dyspnoea and fatigue will be captured using the Borg CR10 scale both before and after the test. Cardiopulmonary exercise testing will be performed according to the current recommendations [31].



**Blood tests**

Levels of liver enzymes, haematology values including red blood cells, platelets, leukocytes and white blood cells distribution, fibrinogen, C-reactive protein and hepatic virus titres will be measured and recorded in the database.

**Additional liver assessments**

One of two available ultrasound-based methods, either transient elastography or acoustic radiation force impulse [32] is recommended to assess early fibrosis of the liver. According to the methodology, the result will be recorded in kPa or  $\text{m}\cdot\text{s}^{-1}$ .

**Patient-reported outcomes: symptoms, quality of life, scores**

The commonest relevant respiratory symptoms of dyspnoea, cough and sputum production will be assessed. When the results of sputum culture are available, the bacterial strains isolated will be recorded. The CRF will also include fields dedicated to elevated liver enzymes and jaundice.

Several standardised questionnaires related to quality of life, symptoms and physical activity, available in multiple languages, will be used to collect information on patient-reported outcomes. These questionnaires will include the COPD assessment test [33], the modified Medical Research Council (mMRC) dyspnoea scale [34], the EuroQoL 5-dimension (EQ-5D) generic quality-of-life questionnaire [35] and the physical activity vital sign (PAVS) [36]. In some countries, the St George's Respiratory Questionnaire will be collected [37]. Patients will complete the questionnaires when rested and in a quiet area, and will be allowed to ask questions to obtain the truest or best response. The questionnaires will be collected and checked for completeness before the patient leaves the centre. Instrument scoring and handling of missing item data will be conducted in accordance with the user guidelines.

The body mass index, obstruction, dyspnoea and exercise (BODE) and the Body mass index, Obstruction, Dyspnoea and Exacerbations (BODEx) indices will be calculated automatically from entered and quality-controlled data [38, 39].

**Comorbidities**

Information on comorbidities (ischaemic heart disease, heart failure, pulmonary hypertension, peripheral artery disease, diabetes, arterial hypertension, osteoporosis, lung cancer and others) will be collected according to available information from the medical records. In some countries, an additional set of comorbidities will be recorded.

**Exacerbations of COPD**

An exacerbation is defined as an acute worsening of pre-existing respiratory symptoms that results in additional therapy [40]. COPD exacerbations are classified as mild or treated with increased use of short-acting bronchodilators only; moderate or treated with antibiotics and/or systemic corticosteroids; and severe requiring hospitalisation or visits the emergency room.

The following items will be collected: ambulatory and hospital-based exacerbations during the previous 12 months (total number, requiring systemic steroids, requiring antibiotics requiring new-onset non-invasive ventilation or intensive care unit admission, and main respiratory symptoms).

**Information on treatment**

The information collected will include the following items: bronchodilators, inhaled corticosteroids, oral corticosteroids, theophylline, phosphodiesterase-4 inhibitors, long-term oxygen therapy, long-term antibiotic treatment, noninvasive ventilation, pulmonary rehabilitation, vaccination, lung volume reduction and transplantation (lung, liver).

**Augmentation therapy**

The status of augmentation therapy (start, stop, dose, frequency, name of medication) will be assessed at baseline and at each follow-up visit.

**Discontinuation of follow-up**

If a patient is lost to follow-up, the reason for this will be assessed whenever possible. Patients who undergo lung or liver transplantation will be followed-up further. If a patient dies during follow-up, the cause of death, according to the treating physician, will be recorded.

## Data review and database management

### *Data collection*

It is the investigator's responsibility to ensure adequate source documentation for all collected data. Designated investigator staff will enter the data required by the protocol into the CRFs. Spirometry reports (including the flow-volume curve) and CT reports may be uploaded after appropriate anonymisation. The investigator must certify that the data are complete and accurate by entering a password. After review for completeness, plausibility and correctness (flow-volume curve, assessed in uploaded curves) by the EARCO database monitor, the data will be locked.

### *Database management and quality control*

It is the EARCO database manager's responsibility to review the CRF data entered by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries will be sent to the investigational site. Designated investigator site staff are required to respond to the query and make any necessary changes to the data.

## Discussion

In the last official statement about AATD from the ERS, the development of a European, follow-up registry (a longitudinal cohort) was identified by healthcare providers and patients as a research priority [12]. Registries have the potential to provide important insights into the natural history of rare diseases where epidemiological data cannot be derived from small-scale prospective cohort studies [41]. In developing the EARCO registry, we have followed guidance proposed in the EU and the extensive experience from other registries in the field of respiratory disease [24, 25, 41, 42]. According to these recommendations, it is essential to define a minimum required dataset that allows the collection of relevant information and limits the burden on investigators entering the data. Furthermore, the definitions across participating sites have to be harmonised to ensure that data are consistent and reliable. We will provide a shared data collection platform, and standardised definitions will be made available on the website ([www.earco.eu](http://www.earco.eu)) and upon request to all study sites.

Many different national registries on AATD exist throughout Europe [14, 17–23], but inclusion criteria, variables collected and level of quality control are different. The EARCO registry will harmonise the collection of prospective data, and its design will allow the new prospectively recorded data to be linked with the historical data collected in the different national registries. In order to do that, the EARCO registry will include the sum of all variables included in all national European registries, but some of them will only be mandatory for patients in a given country where these variables were collected historically. With this design, EARCO will consist of a set of common mandatory fields and a series of variables that will be mandatory at a national level.

The inclusion and exclusion criteria are deliberately broad to allow the inclusion of a large and varied population representative of “real-life” AATD patients and management across Europe.

As an example of variables to be collected, lung function tests are used in the assessment of the severity, progression and prognosis of COPD [40]. Most studies of lung function decline in COPD are based on FEV<sub>1</sub>, because it shows the least variability. However, the main pathological marker of the progression of the lung disease of AATD is an increase in the destruction of the lung parenchyma, as shown most specifically by CT densitometry [8, 43]. However, lung densitometry requires careful standardisation and is not yet ready for use in routine clinical practice [44–46]. EARCO may therefore represent a platform for the development of future multicentre studies using CT densitometry to evaluate the evolution of emphysema in large cohorts of patients with AATD in usual clinical practice [47]. In contrast, other lung function derived markers that have the potential to reflect the magnitude and evolution of emphysema are gas transfer and the hallmarks of hyperinflation [48]. Therefore, diffusing capacity of the lung for carbon monoxide and body plethysmographic measurements are measured routinely in the majority of participating countries, according to the most recent international recommendations [49–51].

We consider a biobank as an important objective for EARCO. However, in the first step we have to overcome the legal and organisational hurdles that are associated with an international database. As these hurdles are even higher for an international biobank we will apply for additional funding in a second step and try to organise/build a biobank in the future.

The participation of patients, coordinated by the European Lung Foundation and Alpha-1 Global has been crucial for the development of a CRF that takes into consideration not only physiological variables, but also the variables that have recognised impact and importance patients. Therefore, the inclusion of patient-reported outcomes was essential. However, although different patient-reported outcomes have been used in patients with AATD [52], there has been little formal validation of them in this population. We



therefore included patient-reported outcomes validated in COPD [53]. The EQ-5D is a simple but effective standardised instrument designed for use as a measure of health outcome. It provides both a compact descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care [35]. The COPD assessment test has been developed as a simpler tool to assess quality of life and symptom burden in COPD patients specifically [33]. The mMRC is an easy-to-use instrument designed for the quantification of dyspnoea [54]. The latter two questionnaires are also part of the multidimensional categories of COPD severity [40]. PAVS is a brief (<30 s) physical activity questionnaire intended to be administered to patients just as vital signs, and height and weight are measured [55]. PAVS is intended to assess how much light, moderate or vigorous physical activity a person performs in a typical week. The assessment facilitates patient counselling about physical activity [56]. Composite scores that combine different physiological measures are used to assess the severity and prognosis of obstructive lung disease and liver disease, but the experience in AATD is very limited [57]. We will use the BODE [38] and BODEx [39] for lung disease and the Fibrosis-4 [57] for liver disease to assess their values in monitoring and determining long-term prognosis in AATD.

The EARCO registry is not the first European registry in AATD. The Alpha One International Registry (AIR) group included representatives from 14 European and some non-European countries [58]. AIR was very successful in collecting baseline data. However, due to limited funding, longitudinal data could not be collected systematically, and the quality of existing data (completeness and accuracy) may be regarded as suboptimal. This can be partially explained by the fact that data were not processed centrally for data clearing and data control [59]. The EARCO registry will collaborate closely with existing national AATD registries and will harmonise the process of data collection and assess the quality of the data included prospectively, thus overcoming the limitations present in AIR.

The target sample size is based on experiences with similar projects. A short-term target of 1000 patients in the first year of the project after database setup has been set. To ascertain representativeness for the European population we aim to include >3000 patients from  $\geq 20$  European countries by the end of the third year.

Acknowledging the imminent limitations of a non-interventional cohort study, the EARCO registry itself will not provide an answer to all the research questions in the field of AATD, but it can be the backbone of different research initiatives, some of which have already been highlighted [15].

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