ERS EUROPEAN RESPIRATORY SOCIETY

Operational procedure EARCO Registry

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1.Introduction:

The EARCO registry is a non-interventional, multi-centre, international, longitudinal observational cohort study enrolling patients with AATD. EARCO is an initiative under the umbrella of the European Respiratory Society (ERS) and its Clinical Research Collaborations (CRCs), multicentre research networks of different fields of respiratory diseases. Data will be collected prospectively without interference/modification of patient's management by the study team.

The study objectives are:

- To develop an international, multicentre AATD registry incorporating baseline data from at least 3000 individuals during the first three years of the registry.
- To harmonize the data collection process between existing national registries and to ascertain high quality of the data.
- To generate longitudinal long-term, high-quality clinical data covering an international population of AATD individuals in 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 augmentation therapy on the progression of emphysema and to examine its impact on clinical and functional outcomes, such as FEV1, 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 different from Pi*ZZ.

2. Methodology:

Each participating country may have a designated national coordinator, which name and contact details will be available at www.earco.eu.

2.1 Inclusion criteria:

The inclusion criterion is diagnosed AATD, defined as AAT serum level < 11 µM (50 mg/dl) and/or proteinase inhibitor genotypes ZZ, SZ, and compound heterozygotes or homozygotes of other rare deficient variants.

2.2 Exclusion criteria:

1. Having one or two normal M alleles.
2. Patients are unwilling or unable to participate in the study.

Patients must be discontinued from the study if the informed consent is withdrawn by the patient or his/her legal custodian.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 must undertake every possible effort to determine the primary reason for a patient's withdrawal and record this information on the case report form (CRF).

2.3 Identification of the individual registered:

EARCO will not hold any identifiable data. Each case registered will have an individual identifier generated automatically by EARCO system linked to the registering investigator.

Individual data will be accessible only by the registering centre's team as well as EARCO data manager.

Patients already included and previously followed in national registries should include their national identificatory number in order to link the historic data with the newly collected prospective data in EARCO.

2.4 Data collection:

No data will be accepted to be submitted to EARCO database prior to obtain patient's informed consent. Date of consent will be recorded in https://earco.vhir.org/login/ prior to enrol the patient and uploading any clinical data.

Data collection will be performed based on patient's medical notes and uploaded by the local team through https://earco.vhir.org/login/ using their personal username and password.

Paper CRF or pdf CRF are not available. Post or e-mail submissions won't be accepted.

Uploading anonymised reports in PDF format from pulmonary function test and CT scan is recommended but it remains the responsibility of the registering researcher to make sure that personal data as name, hospital number etc are removed from the document before being submitted.

Data collection will be recorded in the following forms within https://earco.vhir.org/login/

1. Enrollment form: minimal patient's information, EARCO patient ID and date of consent.
2. Baseline form: data from first encounter with the patient after signing EARCO informed consent as well as clinical data regarding AATD diagnosis whenever it happened
3. Follow up: data from last 12 months following baseline registration or previous follow up
4. End of collection: this form can be completed at any time if one of the following situations occurred: consent withdrawal, death, or lost to follow up for a significant period of time.

2.5 Source of information and flow of information:

Clinical information and investigations will be collected by the researcher from medical notes and/or during clinical visits.

Quality of life questionnaires are strongly recommended as part of EARCO data collection so arrangements to perform these tests during clinical consultation will need to be considered by the registering team.

Approval for EARCO use of CAT, SGRQ and EQ-5D questionnaires has been obtained.

EARCO database provides automatically a basic report about recruitment and a minimal dataset summary per centre, accessible only to this centre's researchers

More detailed reports about EARCO registered cohort will be produced periodically and disseminated at medical journals and scientific conferences. EARCO has a policy about authorship of scientific communications that can be obtained at https://www.earco.eu/
EARCO cohort data can be downloaded from EARCO only by EARCO data manager.
Each centre cohort data can be downloaded from EARCO database only by that centre principal investigator.
The national coordinator will have access to the data generated in each specific country.

2.6 Inclusion, modification, exclusion, validation, mortality:
Inclusion and modification of data will be performed by each investigator.
Submission won't be available until all mandatory data are completed but it is allowed if non mandatory data are missing. A colour code will indicate the researcher his/her progression with completion (red=mandatory data pending, amber=non mandatory data pending, green= all data completed).

EARCO database manager has the 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 listed on the investigator database view and answered directly there. Designated investigator site staff are required to respond to the queries and make any necessary changes to the data.
Validation will be completed by EARCO database manager once data submitted by each site is considered complete.
Notification of deceased cases is strongly recommended and can be recorded any time in the 'end of collection' section.

2.7 Technical aspects: server, database characteristics, confidentiality issues:

EARCO database server is hosted by Vall d' Hebron Research Institute (VHIR) Barcelona, Spain and fullfills all the high security requirements to store sensitive health-related information.

EARCO database is anonymised; no identifiable data will be stored.

Some countries will use EARCO platform to develop their national AATD registries or they may consider merging new data collected at EARCO with their historical national database. In those cases, patient may require consenting specifically for their data to be transferred to the national registry. Each national coordinator is responsible of checking their national regulations about this topic.

Storage, submission and handling of data will be performed following European Law about Data protection and contract between hosting institution and each participating centre, assuring that national confidentiality legislation is respected.

EARCO database has a track of access record for audit proposes.

3. Description of database variables:

3.1 Definitions:

- Mandatory field: variables identified with *. Missing mandatory variables will cause a failure to submit the case for registration. See colour code description above
- Optional field: expected but not necessary to submit the case.

3.2 Enrollment data and baseline data:

a) Individual data:

- EARCO Identification number (idearcopac):

Mandatory field generated by EARCO system automatically, composed by: country code, centre code, number (example: 440101)

-National registry identification number (idnatpac):

Optional field recommended for those patients previously registered at national level.

- Pseudonym (idpseupac): Optional field to facilitate local identification of the case

-Initials: non mandatory but advisable

- ZIP code (exclusive for French centres)

- Date of birth: mandatory field despite depending on national data protection regulations only year will be mandatory, day and month will be optional.

- Date of enrolment (date of consent)

b) Sociodemographic data:

- Education and employment status
- Risk factors: information about smoking status, alcohol intake and occupational exposures are required

c) Disease manifestation: this section includes information about AATD related diseases and their date of diagnoses

d) AATD related symptoms: this section includes two parts: symptoms at presentation (when the patient was diagnosed) and current symptoms. If the patient has recently been diagnosed information will be the same in both. Age of symptoms onset is also required. (If the patient has never had symptoms write "0")

e) Diagnoses: information required in this section is related with the diagnoses of AAT deficiency and includes serum AAT levels, phenotype and genotype. Cases without confirmation of AATD diagnoses not confirm by phenotype or genotype won't be accepted but both can be recorded if available.

f) Clinical history: this section requires brief information about number of exacerbations and admissions in the 12 months prior to the registration (antibiotics and steroids use, NIV, ITU admission and length of stay). Each exacerbation will be recorded separately. Comorbidities (a list of most relevant diseases is displayed).

g) Physical examination: height and weight (cm and kg) are required (mandatory), BMI will be calculated automatically. Basic vital signs are also required (heart and respiratory rate and saturation of oxygen.

h) Medical assessment: this section has different subsections to record the following investigations: liver elastography (if available), pulmonary function test (PFT) (spirometry, lung volumes and gas transfer), arterial gases, CT scan, 6MWT, CPET, FeNO, basic blood test, hepatitis virus screening and microbiology (sputum culture).

Please check the units of each laboratory parameter. NOTE: C-reactive protein should be reported in mg/L

Pulmonary function tests are one of the most important tests to record in EARCO and investigators are encouraged to make sure this information is available by the time of registration. However, some patients may not be fit to perform the test or some techniques may not be available at the registering centre and theses issues can also be reported to EARCO using the form.

PFT report can be uploaded to EARCO once the case has been submitted. Identifiable data have to be removed form the document on site before being submitted to EARCO.

CT scan details are recorded according to the following definitions:

1.Emphysema:

- Centrilobular emphysema: Focal lucencies in the lung, classified as trace, mild centrilobular, moderate centrilobular, confluent, and advanced destructive
- Panlobular emphysema: Diffuse decrease in density in the lung, often lower lung predominant
- Paraseptal emphysema: Subpleural lucencies, classified as mild or substantial

2. Bronchiectasis:

- Cylindrical (or tubular) bronchiectasis, the most commonly identified morphologic type, is a smooth uniform enlargement of bronchi without focal outpouchings or tortuosity
- Varicose is characterized by irregular bronchial contours with alternating segments of bronchial dilatation and relative bronchial narrowing.
- Saccular, or cystic bron-chiectasis, involved bronchi show focal pouch-like areas of enlargement.

3. Airway Wall thickening:

- Bronchial wall thickening: Subjective thickening of the walls of bronchi, classified as probable or definite

5. Interstitial changes: Nondependent abnormalities affecting 5% of any lung zone, including reticular, ground-glass changes, centrilobular nodularity, nonemphysematous cysts, honeycombing, and traction bronchiectasis

Definitions' references:

Lynch DA, Austin JH, Hogg JC, Grenier PA, Kauczor HU, Bankier AA, et al. CT-definable subtypes of chronic obstructive pulmonary disease: a statement of the Fleischner Society. Radiology 2015;277:192–205

Surya P. Bhatt,et al. Imaging Advances in Chronic Obstructive Pulmonary Disease Insights from the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) Study. Am J Respir Crit Care Med Vol 199, Iss 3, pp 286–301, Feb 1, 2019

Milliron B, Henry TS, Veeraraghavan S, Little BP. Bronchiectasis: Mechanisms and Imaging Clues of Associated Common and Uncommon Diseases. (2015) Radiographics : a review publication of the Radiological Society of North America, Inc. 35 (4): 1011-30

CT scan report can be typed on the free test provided and it can also be uploaded if anonymised previously.

i) Treatment: this section is composed by several sub-sections: pharmacological (bronchodilators named by family of drugs instead of by individual drug or brand names and other treatments for AATD related COPD and augmentation therapy), non-pharmacological including surgical and other interventional treatment).

j) Questionnaires: physical activity, CAT, SGRQ (Germany only) and EQ-5D. We strongly recommend completing these questionnaires. A copy of each of them in the language of the investigator will be provided by the data manager once the new user application will be approved and the user receives his/her username and password to access EARCO platform.

3.3 Follow up data:

Clinical information and investigations collected from medical notes from 12 months after baseline or last follow up data. This form is very similar to the baseline form but diagnoses and symptoms at presentation are not required. Physical activity and quality of life questionnaires are recommended as at baseline.