Phenotypic Characterization and Course of Chronic Obstructive Pulmonary Disease in the PAC-COPD Study: Design and Methods

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ARTICLE INFO

Article history:
Received December 15, 2007
Accepted March 25, 2008

Keywords:
Epidemiology
Phenotype
COPD

ABSTRACT

Background and Objectives: The Phenotype and Course of Chronic Obstructive Pulmonary Disease (PAC-COPD) study aims to improve our understanding of the phenotypic heterogeneity of this disease and the extent to which this heterogeneity is related to clinical course. The main objectives are a) to characterize the phenotypic variability in first-time hospitalizations for exacerbation of COPD and to propose a classification into subtypes, and b) to ascertain the association between the defined subtypes and the clinical and functional course of COPD.

Patients and Methods: This is a cross-sectional and cohort study of 342 patients with COPD from 9 tertiary hospitals in 3 autonomous communities. The minimum follow-up period is 5 years. The main variables of interest are respiratory symptoms, smoking, alcohol use, physical activity, use of health care services, medical care, treatment received, activities of daily living, comorbid conditions, sleepiness, anxiety and depression, quality of life, forced spirometry and bronchodilator tests, lung volume and inspiratory capacity measured by body plethysmography, carbon monoxide diffusing capacity, baseline arterial blood gas values, respiratory and peripheral muscle function, electrocardiogram, body weight and composition measured by bioelectric impedance, chest radiograph, skin prick test, capacity for exercise measured in the 6-minute walk test and cardiopulmonary exercise test, induced sputum (for quantitative microbiological culture and determination of inflammatory markers), nighttime pulse oximetry, chest computed tomography scan, and echocardiography. Levels of markers of inflammation and oxidative stress are measured in serum and plasma; these samples are also used for genetic analysis and will be stored for other possible measurements that might be required in the future. The statistical analysis combines factor analysis and survival models such as Cox regression analysis. This project will enable us to reconsider the definition and classification of COPD and to better understand the factors associated with its natural history.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in the world. In 2002, it was calculated to be the 11th cause of lost disability-adjusted life-years and the trend is toward an increase, to the extent that in 2030 it could be seventh. On average, 10% of adults worldwide have COPD and the most important causative factor is smoking. Despite the importance of this disease, research during the last few decades has been undeniably insufficient. The Global Initiative for Chronic Obstructive Lung Disease (GOLD), which has created wide international consensus on COPD, drew up a series of recommendations on research priorities. The most important of these was the need for greater knowledge of the phenotypic characteristics of COPD and its clinical course.

The position paper on COPD of the American Thoracic Society and the European Respiratory Society defines the condition as “a preventable and treatable disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.” Thus, in clinical practice and in research COPD is defined by airflow limitation, mainly measured as the forced expiratory volume in 1 second (FEV₁) and the ratio of FEV₁ to forced vital capacity (FVC). However, in recent years we have observed a growing tendency to consider that, in addition to the problem of respiratory function, COPD includes a wide range of other manifestations on cellular, organic, functional, clinical, and social levels that are related to its clinical course. In fact, the guidelines cited above state that “although COPD affects the lungs, it also produces significant systemic consequences.” Nevertheless, research aimed at placing this trend within a new theoretical framework for the disease has been scant. Noteworthy is the COPD staging system proposed by Celli et al., which, in addition to FEV₁, includes dyspnea, distance walked in 6 minutes, and the body mass index.

Evidence in the literature suggests that the phenotypic characterization of COPD that takes into account a wide range of features would enable us to classify the disease into clinically and epidemiologically relevant subtypes. In order to evaluate this possibility, it is necessary to investigate in detail the interrelationship between different phenotypic features and the extent to which the associations (groups) observed are related to clinical course. Under the name of Phenotypic Characterization and Course of COPD (PAC-COPD), this project proposes to apply this approach to a large cohort of patients with incipient COPD. Patients are selected at their first admission to hospital, when the disease still has a considerable course to run and is susceptible to intervention. The groups participating in the project have carried out several studies on COPD that have generated relevant findings on different aspects of its clinical expression and course. Therefore, the hypotheses that guided these studies can now be considered in a more integrated and novel way.

Here, we present the short-term and long-term objectives of the study and describe in detail the method used to select the participants and evaluate their phenotypic characteristics. We also present the plan for data analysis and other organizational aspects. Given the growing interest in understanding the phenotypic heterogeneity of COPD and other diseases such as asthma or bronchogenic cancer, and in the possible implications of this heterogeneity, we feel that our approach could prove useful for other, similar initiatives.

Thus, the primary objectives of the PAC-COPD study are as follows:

1. To characterize the phenotypic variability of patients who are admitted to hospital for the first time with an exacerbation of COPD and to propose a classification into subtypes.
2. To gauge the relationship between the subtypes defined and a) the clinical and functional course of COPD (eg, deterioration of lung function, hypoxemia, need for continuous home oxygen therapy, and decrease in quality of life); b) the use of health-care resources (eg, treatment received, as well as home visits and visits to the primary care center, specialist, emergency room, and admissions); and c) mortality.
3. To identify the risk factors for readmission for exacerbation—after reducing indication bias from selecting patients during the first admission—and determine whether there is an interaction between the subtypes defined and the risk factors.

The secondary objectives are as follows: a) to select and carry out long-term follow-up of a cohort of patients with incipient COPD who have been exhaustively characterized according to phenotype, and b) create a bank of biological and DNA samples from a COPD population that has been exhaustively characterized according to phenotype.

Patients and Methods

Design

This cross-sectional study has been designed to follow a cohort of COPD patients selected at the time of their first admission for exacerbation in 9 tertiary hospitals in 3 Spanish autonomous communities. Appendix 1 shows how the study is organized and Appendix 2 shows the participating sites and investigators.

Study Population

Patient Selection

Any patient admitted for the first time for an exacerbation of COPD to any of the 9 participating hospitals between January 2004 and March 2006 (27 months) is considered eligible. Admission is defined as in-patient care in any department of the hospital or as a stay longer than 18 hours in the emergency room, with a clinical diagnosis of exacerbation of COPD according to the pulmonologist responsible for the study at each hospital. First admission is established by administering questionnaires, reviewing the medical history, and checking the hospital records. The diagnosis of COPD is confirmed using spirometric criteria (a postbronchodilation FEV1/FVC ratio of 70%) at least 3 months after admission and with the patient in stable condition.

The exclusion criteria are as follows: a) age under 45 years; b) severe comorbidity, such as terminal or advanced cancer; pulmonary tuberculosis with involvement of more than one-third of the total lung parenchyma, pneumectomy, or pneumoconiosis; c) old age or general fragility (eg, difficulty walking, lack of autonomy) that can make it substantially difficult for the patient to participate in the study, regardless of the patient's desire to participate; d) mental disability diagnosed by the attending physician or determined using the Folstein Mini-Mental State Exam; e) not being a resident of the province where the hospital is located; and f) not being able to understand Spanish.

The process for patient selection has been adapted to the procedures used by our group in previous studies to reduce selection bias as much as possible. Information is collected on subjects who refuse to participate in the study in order to analyze the degree of nonresponse bias. The project has been approved by the ethics committees of the participating sites. All the patients receive written information on the objectives of the study and sign to indicate their informed consent. A separate signature is required for the genetic analyses.

Follow-up

The intended follow-up period will be at least 5 years. Patients are only followed for purposes of the study. All will be referred to other physicians for care and treated according to the criteria of each site. This period includes active follow-up interviews and visits—a complete evaluation every 18 to 24 months (visits 1, 3, 5, etc) and short telephone interviews (visits 2, 4, 6, etc) in the intervals between the evaluations—as well as information obtained by passive follow-up (checking hospital records and death records). Additional measures are proposed to maximize the response rate during follow-up (addresses and telephone numbers of relatives or reference contacts).

Sample Size

A previous study of 346 patients with COPD in several hospitals in Barcelona revealed that 19% of admissions for COPD are first admissions. This percentage is equivalent to a mean of 30 first admissions per year for COPD at each of the participating hospitals and a total number of candidates exceeding 500. If we assume a 30% lack of response (greater than in previous studies, given that these patients are not severely ill), the study would allow us to analyze between 300 and 400 patients with COPD. As there are no standardized sample size calculations for the study of phenotypic classification by factor analysis, the criterion applied is that the number of observations must exceed the number of variables; this requirement would be amply fulfilled in our case. Using the data from the study cited above to analyze clinical course, we assume that 15% and 20% of the patients selected at the first admission for COPD would die after 1 and 2 years, respectively, whereas 50% and 60% would be readmitted during the first and second years of follow-up. These rates mean that, if patients are classified into 2 groups (phenotypes) of equal numbers, a relative risk of death of 1.8 or more (and a relative risk of readmission of 1.5 or more) could be calculated using a log-rank test and Cox regression model and given an α error of .05 and a β error of less than .20 in a 2-tailed comparison with loss to follow-up estimated to be 15%.

Outcome Measures and Measurement Tools

The information necessary to characterize phenotypes is obtained from questionnaires or tests carried out during visits to the hospital. Personal information, sociodemographic and lifestyle data, as well as some clinical and functional data are obtained during the first hospital stay. The interim telephone interviews between the yearly visits are used to obtain information on changes in any of the previous data and on use of health-care resources. Below, we provide a detailed description of the tests used and the information recorded during each phase.

Patient Selection

Patients answer a computerized epidemiologic questionnaire. All the questions from pre-existing scales or questionnaires are validated for use in Spain and the investigators have used them in previous studies. Other questions are from the EFRAM study, carried out in Barcelona. Some questions have been adapted for this study after previous validation in a sample of 20 patients with COPD at the Hospital del Mar. The questionnaire includes items on personal details, use of health-care services and medical care (questions from the EFRAM study), pharmacologic treatment (any the patient has taken during the study period), smoking (using questions from the EFRAM study), the European Community Health Survey, and the study on bladder cancer in Spain), physical activity (the Yale questionnaire in the validated version for Spanish adults), home oxygen therapy and pulmonary rehabilitation (according to questions from the EFRAM study), and sociodemographic data (previously itemized in the EFRAM study).
Complete Evaluations

All the complete evaluations are carried out during a period when the patient is clinically stable. This period is defined using the following criteria: 3 months with no admissions for a respiratory condition, 3 months with no oral corticosteroids or antibiotics, 2 weeks with no substantial changes in symptoms, and 2 weeks with no changes in treatment. All complete evaluations are organized over a minimum of 3 sessions in order not to tire the patients and prevent interference in the tests. These evaluations involve the following questionnaires and tests:

- A computerized epidemiologic questionnaire. The questionnaire covers respiratory symptoms (using the European Community Respiratory Health Survey), as well as usual dyspnea using questions from the mMRC dyspnea scale and a visual analog scale, the validated Spanish language version of the St George's Respiratory Questionnaire, activities of daily living (Barthel index), validated Spanish language version of the Epworth Sleepiness Scale, the anxiety and depression scale from the validated Spanish language version of the Hospital Anxiety and Depression Scale (HAD), environmental exposure to atmospheric pollutants, and exposure to smoke from coal or wood fires in the home. The questionnaire also asks about changes in the data recorded at previous interviews: personal details, pharmacologic treatment, use of health-care services and medical care, smoking, pulmonary rehabilitation, and home oxygen therapy.

- Physical examination by the pulmonologist responsible for the study.

- Complete lung function testing: forced spirometry and a bronchodilator test, body plethysmography with lung volumes and inspiratory capacity (before and after administration of a bronchodilator), carbon monoxide diffusing capacity, and resting arterial blood gas analysis. All the procedures were standardized according to the manual of procedures for the evaluation of lung function of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). The bronchodilator test involved the administration of 400 µg of salbutamol through a holding chamber, according to the GOLD recommendations.

- Respiratory muscle function tests measured using the maximum mouth pressure generated during forced inspiration close to the residual volume and forced expiration close to total lung capacity. Reference values were used.

- Peripheral muscle function tests using a hand dynamometer.

- 12-lead electrocardiogram set up by trained staff (with at least 3-5 beats per lead and a long 15-30-beat reading in lead 2).

- Determination of body fluid compartments using bioelectric impedance analysis, which allows for easy measurement of body composition and weight, as validated elsewhere for patients with COPD. In order to reduce variability, almost all sites use the same device (Bioelectrical Body Composition Analyser, Quantum X, RSL Systems, Clinton Township, Michigan, USA).

- Chest radiographs, according to the protocol the radiologists at the participating sites agreed on: left lateral and posteroanterior projections with the patient standing and the distance between the X-ray tube and the image plate set at 150 cm. The radiograph was taken at 120 kV or higher and the number of milliamperes varied with the characteristics of each patient.

- Skin prick tests for the following allergens: Dermatophagoides pteronyssinus, cat, Alternaria alternata, Cladosporium herbarum, timothy grass, birch, Parietaria judaica, olive, and ambrosia, with a positive control (histamine) and a negative control. These tests are only performed at the first complete evaluation.

- Blood sample extraction for the standard laboratory workup (total proteins, triglycerides, cholesterol, albumin, the albumin-globulin ratio, prothrombin time, white blood cell count, fibrinogen, C-reactive protein, erythrocyte sedimentation rate, hemoglobin, hematocrit, total immunoglobulin E, α1-antitrypsin values) and serum and plasma samples for freezing at –80°C. Serum is used for centralized measurement of inflammatory markers at the Hospital Son Dureta (tumor necrosis factor, interleukin IL-8, human growth factor, IL-10, interleukin-6, C-reactive protein) and oxidative stress at the Institut Municipal d'Investigació Mèdica (carbonyl, nitrotyrosine, malondialdehyde, hepatocyte growth factor). DNA is extracted from plasma and stored at –80°C until required for future measurements. Specific informed consent is requested for the genetic analyses and additional confidentiality measures are applied.

- 6-minute walk test to determine exercise capacity. All sites strictly follow the same protocol, which is adapted from published guidelines. This consists of 2 attempts (with at least a 30-min rest between them) in 30-m corridors. Encouragement is given every 1 minute and the test is interrupted if symptoms of exhaustion appear. Two attempts are made at the first evaluation only. From the second evaluation onward, only 1 test is carried out.

- Cardiopulmonary exercise test to determine exercise capacity. This is adapted from the SEPAR guidelines and those of the American Thoracic Society. The test is carried out on an electromagnetic cycle ergometer and consists of the following: a) a rest phase before exercise (3 min), b) exercise without load (3 min), and c) progressive increases in load (10-20 W/min) until the tolerance limit is reached (approximately 10 min). The test is supervised by trained staff who encourage patients so that they can reach the limit of tolerance determined by their symptoms. The symptoms (dyspnea, muscle fatigue) are evaluated at the end of the exercise test using the Borg scale and blood samples are taken 1 minute after the load is removed to determine the lactate concentration. The equipment is calibrated before each test. Analysis of the results is based on the average of recordings taken every 15 seconds for the following variables: a) the fractions of oxygen and carbon dioxide in exhaled breath, b) workload, c) minute ventilation and its components (respiratory rate and tidal volume), d) heart rate, and e) pulse oximetry. Results are shown graphically according to the 8 basic graphs set out in the guidelines and the reference values of Neder et al are used. This is only performed at the first complete evaluation.

- Induced sputum test, carried out by trained personnel according to a protocol adapted from previous studies for the following purposes: a) quantitative microbiological culture at each site; b) storage of frozen strains at –80°C for subsequent centralized analysis at Hospital Germans Trias i Pujol; c) freezing of the supernatant at –80°C for centralized analysis of inflammatory markers (tumor necrosis factor, IL-10, IL-6, IL-12p70, IL-1b, and IL-8) at Son Dureta; and d) smears for centralized cytology (viable cells, differential cell count) at Hospital de la Santa Creu i Sant Pau.

- Nighttime pulse oximetry with a portable pulse oximeter using the same device at almost all the sites (Pulsox 3i, Minolta, Osaka, Japan). This is only performed at the first complete evaluation.

- Computed tomography, based on 2 series of images: a) spiral computed tomography during inspiratory apnea with caudocranial projections of consecutive 7- to 8-mm slices for quantitative evaluation of lung densities and volumes, as well as the emphysema index, and b) high-resolution computed tomography during inspiratory apnea from the aortic arch to the highest point of the diaphragmatic dome, with 1- to 2-mm slices every 15 mm for the visual evaluation of emphysema and the airway. The computerized images are sent to the coordinating site, from
which they are sent for a quantitative evaluation (centralized at Hospital del Mar) using PulmoCT (Siemens, Munich, Germany), and for the visual evaluation by 4 trained radiologists (from Hospital Vall d’Hebron, Hospital de la Santa Creu i Sant Pau, and Hospital del Mar). This is only performed at the first complete evaluation.

- Doppler echocardiography to measure right ventricular dimensions and function, the pulmonary artery systolic pressure, and other indirect signs of pulmonary hypertension. The cardiac dimensions are calculated in M-mode, with the exception of right ventricular diameter, which is evaluated in 2 dimensions. The left ventricular ejection fraction is calculated using the Simpson rule. Cardiac valves are evaluated using continuous wave and color flow Doppler ultrasound. To assess tricuspid insufficiency, the maximum regurgitant velocity is calculated. This enables the transthrucspid pressure gradient to be calculated. If recordings are suboptimal, echo contrast agents are used to enhance the Doppler signal. Diastolic function is analyzed using mitral-tricuspid pulsed Doppler and tissue Doppler recording of the mitral and tricuspid rings. Finally, the diameters of the vena cava are measured in 2 dimensions in M-mode. The protocol agreed on by the echocardiographers of the participating hospitals, in accordance with the recommendations of the American Society of Echocardiography, is followed at all participating sites.30 Quality control and readings are centralized at the Hospital Clinic. Two readings of a random sample of the echocardiograms are performed, only at the first complete evaluation.

### Telephone Interviews

Every 12 to 18 months, during the interval between the periodic evaluations, patients reply to a computerized telephone survey administered in all cases by the same interviewer from the coordinating site (Institut Municipal d’Investigació Mèdica). The questionnaire is adapted from that used during the complete evaluations and covers the following areas: use of health-care services, respiratory symptoms, changes in treatment or risk factors (oxygen therapy, pulmonary rehabilitation, physical activity, weight) and changes in the patient’s data (or other information necessary for follow-up).

### Passive Follow-up

The personal identification number on the patient’s medical card will be used to link up with the Minimum Basic Data Set of Hospital Discharges for each autonomous community in order to obtain information on hospital admissions (number, place, date of admission and discharge, primary and secondary diagnoses), after obtaining the authorization of the ethics committees and corresponding bodies, in fulfillment of Spanish law on statistical secrecy (Law 14/1987, dated July 9).

The name, surname, sex, and date of birth will also be used to cross-reference with the death records of each autonomous community to obtain information on mortality (date and causes of death), after obtaining authorization from the relevant bodies and in fulfillment of Spanish law on statistical secrecy (Law 14/1987, dated July 9).

### Quality Assurance

Data quality is essential for the study results to be valid30 and to reduce variability. To ensure that quality remains high, it is closely monitored during the different phases of the study, both in hospitals where patients are selected and evaluated and at the coordinating site. Quality assurance involves the following:

1. During preparation of the protocol and before collecting data from each phase

- Ensuring consistency in the test protocols (including the radiology and echocardiography protocols) within the investigating group in accordance with local and international consensus guidelines. All these protocols envisage aspects such as the need for daily calibration of measuring tools, control of environmental conditions, and the repetition of tests until an acceptable, minimal variability is obtained as appropriate for each test (eg, <150 mL in FEV₁, and FVC in 2 of 3 acceptable maneuvers, or <5% of thoracic gas volume).

- Training by qualified staff of those responsible for data collection before each phase of the study (eg, patient selection, first complete visit, first telephone interview, second complete visit).

- Automation of filter variables and definition of intervals in the design of the questionnaires and forms. The software Questionnaire Development System (NOVA Research Company, Bethesda, Maryland, USA) is used to administer all the questionnaires by computer (in order to reduce possible transcription errors) and generate the corresponding databases.

2. During data collection

- Periodic telephone conversations with the data collection manager at each site to comment on doubts and problems, after a preliminary analysis of the data collected to determine whether there are differences between sites or interviewers as to data collected.

- Weekly dispatch of follow-up forms for patient selection and performance of tests to draw up summary tables and detect delays or errors.

- Monthly dispatch of the results of tests carried out to detect and resolve errors or protocol deviations.

- Taping of interviews for later evaluation at the coordinating site (a standard form is used).

- Annual visit to sites to observe the interview and test process and to detect possible errors or protocol deviations (a standard form is used).

3. After data collection

- Double entry of all the data from the tests and detailed review of inconsistencies, with the calculation of the number and percentage of inconsistent data entries per test, per site, and per data input clerk.

- Checking: verification of improbable data and limits, search for inconsistencies, and verification of lost data.

- Analysis: distribution of data and of lost data as follows: a) by trend over time, to identify whether there is a learning or tiredness effect in the application of protocols; b) by hospital, to detect possible systematic differences in the results of the tests owing to differences in the equipment at each site; and c) by interviewer, to detect possible systematic differences due to differences in the application of protocols. In all cases, the results of this analysis will be used in the analyses corresponding to the project objectives and in the interpretation of results, including whether the period, site, or interviewer should be considered an adjustment variable.

### Plan for Data Analysis

Phenotypic variability and COPD subtypes will be studied using a descriptive and stratified analysis of all the baseline variables (objective 1). Descriptive factor analysis will be used to establish groups of phenotypic variables (factors). The possibility of applying a confirmatory factor analysis to possible groups of phenotypic features based on mechanistic hypotheses (eg, separating variables related to inflammation and variables related to emphysema) will be considered.

The association between the different phenotypic factors and outcome measures (loss of FEV₁, medical visits, hospitalizations,
mortality; objectives 2 and 3) will be studied by estimating the
independent association between these factors (as the exposure
variable) and the outcome measures obtained during follow-up. For
this purpose, the odds ratio will be calculated in the logistic
regression models or the hazard ratio in the Cox models. Analysis
with outcome measures with repeated observations will be by
Poisson regression with the total number of events (eg, hospital
admissions) as the outcome measure and the logarithm of person-
days at risk included as an offset. The independent association
between the different phenotypic characteristics and outcome
events will be studied.

Planned Timing and Progress Made as of December 2007

The Figure 1 shows the study calendar from the start to the third
complete evaluation (approximately 4 years of active follow-up per
patient).

Patient selection and the first complete evaluation finished in
December 2007. A total of 1111 potential candidates were identified.
Of these, 324 were excluded because of severe comorbid conditions,
75 because of mental disability, 33 because of fragility, 17 because
they did not live in the province where the hospital was located, 9
because they died before the evaluation, and 49 because of an FEV
/FVC ratio greater than 70% after bronchodilation. The remaining 604
patients were eligible. Of these, 342 (57%) agreed to participate in
the first complete evaluation. The first telephone follow-up interview
was completed with a total of 301 participants (88%), 196 of whom
have already participated in the second complete evaluation.

The project has made it possible to put together a second level of
investigation in which some groups interested in specific research
lines can participate. To date, 4 projects within the general project
have been prepared and funded: Systemic Inflammation and
Autoimmunity in the Phenotypic Characterization of COPD (Principal
Investigator, Jaume Sauleda), Effects of Physical Activity on the
Course of COPD (Principal Investigator, Judith Garcia-Aymerich),
Characterization and Effects of Bronchial Inflammation and
Colonization (Principal Investigator, Eduard Monsó), and Measurement
of the Effect of Diet on COPD (Principal Investigator, Josep M. Antó).

Conclusions and discussion

COPD is one of the main causes of morbidity and mortality in the
world, yet research to date is insufficient for developing satisfactory
diagnostic and therapeutic strategies. Diagnosis is based mainly on
airflow limitation, although, given that deterioration of lung function
is a long-term process, the disease is usually diagnosed in advanced
phases with the result that underdiagnosis is a serious problem.3
Furthermore, the distinction between COPD and asthma has not yet
been resolved. After diagnosis, few treatments are really effective,
except for smoking cessation and, in the advanced phase, continuous
home oxygen therapy.6

The PAC-COPD project aims to increase our understanding of the
phenotypic heterogeneity of COPD through several objectives. On
the one hand, it has the potential to help improve how the disease is
defined and diagnosed and provide for better differential diagnosis
with other diseases such as asthma. It should also allow us to propose
new systems for classifying severity that can be applied to new
therapeutic guidelines or to patient referral criteria, thus leading to
better prognostic evaluation and adaptation of clinical follow-up
criteria to prognostic markers. And it should serve as a framework
for the identification of new treatments and the choice of the best
outcome measures in intervention studies. Obviously, each of these
applications will require purpose-designed approaches that follow
suitable methodological principles, such as those indicated by
evidence-based medicine.24 An additional strength of this project is
the fact that it is the fruit of a huge effort by different Spanish research groups with broad experience in different areas of COPD. Therefore, their involvement in this project can only help to increase our knowledge of this disease. The team can profit from the participation of respiratory medicine specialists, epidemiologists, radiologists, and cardiologists. The standardization of techniques is an important added value that has made it easy for several groups to collaborate in studies started after the present project, such as some of those from the Spanish Network of Centers for Biomedical Research on Respiratory Diseases (CibeRes). The ECOS study is an example.

Perhaps the most noteworthy limitation of the present study is the criterion for first admission due to an exacerbation of COPD as the starting point for the selection of participants with incipient COPD. The study excludes patients with COPD who do not go to the hospital for an exacerbation or who come to the emergency room but are not admitted because the exacerbation is mild or for other reasons. Also excluded are patients with COPD who are admitted to private hospitals. In this sense, the decision of the research group was driven by practical considerations (availability of hospitalized patients) and scientific considerations (previous experience with other sources of COPD patients for whom it was difficult to extrapolate results, such as patients selected from hospital outpatient clinics, who usually have more comorbid conditions). In terms of phenotypic heterogeneity, internal validity is not compromised by the criterion of first admission, since the inferences are restricted to the type of patient included in the study. The possibility of a selection bias due to a lack of response will be examined by comparing the sociodemographic, clinical, functional, and lifestyle characteristics of the participants and nonparticipants. The fact of not excluding patients with asthma who also present criteria indicative of COPD is part of the willingness to study and classify the different presentations of COPD. It is conceivable that the study can provide some contribution to the distinction between asthma and COPD, given the wealth of information that will be obtained about phenotypes.

In conclusion, the PAC-COPD project will enable us to reconsider the definition and classification of COPD and increase our understanding of the factors associated with its course. This will undoubtedly generate benefits for patients.

**Appendix 1. Study Organization**

The study is managed by a research group of 30 investigators from 10 sites. These investigators are responsible for the scientific management of the project. Some of the investigators are grouped into 5 working parties focusing on areas where they have proven experience and lead subprojects that have their own funding. The Coordination Committee, which is formed by investigators from the coordinating site and an investigator from each site, is responsible for supervising the study to ensure that it is carried out as set out in the protocol. The persons responsible for data collection have been specially trained for this study. They select patients and carry out tests and interviews according to the protocols (Figure A1).

**Appendix 2. Participating Sites and Investigators**

Institut Municipal d’Investigació Mèdica (IMIM), Barcelona (coordinating site): Josep M. Antó (principal investigator), Judith García-Aymerich (coordinator), Jordi de Batlle, and Marta Benet

Hospital Clínic i Provincial de Barcelona: Joan A. Barberà (site coordinator), Federico P. Gómez, Josep Roca, Robert Rodríguez-Roisin, and Carles Paré

Hospital del Mar, Barcelona: Joaquim Gea (site coordinator), Eva Balcells, Mauricio Orozco-Levi, and Angel Gayete

Hospital de la Santa Creu i Sant Pau, Barcelona: Pere Casan (site coordinator), Rosa Güell, Ana Jiménez, and José Belda (currently at Hospital General Universitari de València)

Hospital General Universitari Vall d’Hebron, Barcelona: Jaume Ferrer (site coordinator), Esther Rodríguez, and Esther Pallisa

Hospital Universitari de Bellvitge, L’Hospitalet de Llobregat: Eva Farrero (site coordinator) and Joan Escarrabill

Hospital Universitari Germans Trias i Pujol, Badalona: Eduard Monsó (site coordinator), Alicia Marín, and Josep Morera

Hospital de Sabadell, Corporació Parc Taulí, Sabadell: Antoni Ferrer (site coordinator)

Hospital Son Dureta, Palma de Mallorca: Jaume Sauleta (site coordinator), and Àlvar Agustí

Hospital de Cruces, Baracaldo, Vizcaya: Batxi Gáldiz (site coordinator) and Lorena López

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