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ERS TASK FORCE REPORT

Recommendations for epidemiological studies on COPD

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ABSTRACT: The prevalence of chronic obstructive pulmonary disease (COPD) has been extensively studied, especially in Western Europe and North America. Few of these data are directly comparable because of differences between the surveys regarding composition of study populations, diagnostic criteria of the disease and definitions of the risk factors. Few community studies have examined phenotypes of COPD and included other ways of characterising the disease beyond that of spirometry.

The objective of the present Task Force report is to present recommendations for the performance of general population studies in COPD in order to facilitate comparable and valid estimates on COPD prevalence by various risk factors.

Diagnostic criteria in epidemiological settings, and standardised methods to examine the disease and its potential risk factors are discussed. The paper also offers practical advice for planning and performing an epidemiological study on COPD.

The main message of the paper is that thorough planning is worth half the study. It is crucial to stick to standardised methods and good quality control during sampling. We recommend collecting biological markers, depending on the specific objectives of the study. Finally, studies of COPD in the population at large should assess various phenotypes of the disease.

KEYWORDS: Biomarkers, chronic obstructive pulmonary disease, epidemiology, lung function, phenotypes, questionnaires

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Chronic obstructive pulmonary disease (COPD) is currently ranked as the fourth most common cause of death worldwide [1]. In 2020, the disease is expected to rise to number three [2]. The prevalence of COPD has been extensively studied, especially in Western Europe and North America. However, few of the data are directly comparable due to differences between the surveys regarding composition of study populations, diagnostic criteria of the disease and definitions of the risk factors [3]. The Burden of Obstructive Lung Diseases (BOLD) initiative has only recently presented comparable data from a large number of countries [4]. In Eastern Europe, scarce data are available on the prevalence of COPD.

Throughout Europe and the rest of the world, there are limited data on the incidence of COPD and the burden of the disease to society, both in terms of disability-adjusted life years lost and cost of care. The few published studies on COPD incidence as defined by recent guidelines mainly arise from studies performed in Nordic countries [5–8]. These studies all show that COPD is a common disease, and is rapidly increasing, particularly among middle-aged and elderly smokers. Recently, COPD incidence data from the European Community Respiratory Health Survey (ECRHS) have also emphasised the importance of COPD in young adulthood to middle age [9].

A review of COPD epidemiology in the *European Respiratory Monograph* gave a thorough overview

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of COPD epidemiology worldwide, but focused less on Eastern–Western European differences [3]. A chapter on COPD epidemiology in the *European Lung White Book* also mainly focused on data from Western Europe [10].

There are several unmet needs related to COPD epidemiology in Europe. First, it seems imperative to obtain comparable data on prevalence, incidence and burden of disease. Secondly, we have been poor at securing knowledge on change in disease burden as a consequence of social change in Eastern European countries following their inclusion in the European Community. Better understanding of this change could provide valuable insight into the effects of changes in risk factors. Thirdly, male smoking has been declining for two to three decades. This warrants data on the increasing relative importance of other COPD risk factors beyond smoking. Fourthly, although spirometry is a prerequisite in COPD studies, more extensive characterisation than that offered by spirometry is required. Novel imaging techniques and biomarkers offer the potential to specifically study subgroups, or phenotypes, of COPD; there is a need to discuss the introduction of these techniques into the field of epidemiology. Finally, to date there are only limited data on gene–environment interactions available in COPD.

Several guidelines have been published on COPD diagnosis and management [11, 12]. However, no updated guidelines are available for the performance of studies on COPD prevalence and severity in the population at large, including population sampling, collection and quality control, and the standardised tools to use to provide information on potential risk factors for COPD [13]. These risk factors not only include smoking, occupational airborne exposure, and indoor and outdoor air pollution, but also socioeconomic status, family history, nutrition, infections and comorbidities. Standardised methodology for performing epidemiological COPD studies could facilitate comparison between populations in Western and Eastern Europe.

The objective of the present European Respiratory Society (ERS) Task Force report is to present recommendations for the performance of general population studies on COPD in order to facilitate comparable and valid estimates of COPD prevalence in the population at large.

METHODS

The Task Force panel was selected from the experienced scientists of ERS Assembly 6, the Occupation and Epidemiology Assembly. A point was made of having the various geographical areas of Europe represented in the panel. The recommendations in the present report are based partly on systematic searches and partly on the expertise of the panel. The recommendations were reached through consensus among the authors.

The topics covered in this report are outlined in table 1. At the end of each section a table summarising the recommendations is presented.

TABLE 1 Topics covered in the present report

Operational diagnostic criteria of COPD
Data on COPD
Lung function
Respiratory symptoms
Biomarkers
Phenotypes of COPD
What actual and potential risk factors for COPD should be considered and how?
Active smoking
Occupational airborne exposure
Outdoor and indoor air pollution
Socioeconomic status
Diet
Comorbidity
Family history
Practical advice for planning and performing an epidemiological study on COPD
Population sampling and sample size
Ensuring a high response rate
The preparatory phase
The study team
Methods for data collection
The pilot study
Quality control

COPD: chronic obstructive pulmonary disease.

OPERATIONAL DIAGNOSTIC CRITERIA OF COPD

Previous population studies on COPD have used a variety of operational diagnostic criteria, usually based on lung function [14–16], respiratory symptoms [17–19] and/or clinical examination [20]. Any operational criteria should be valid, reproducible and simple to perform in a community study. In the American Thoracic Society (ATS)/ERS Task Force report on interpretative strategies for lung function tests, obstructive abnormality is defined as having a ratio of forced expiratory volume in 1 s (FEV_1) to slow vital capacity (SVC) lower than the 5th percentile of the normal distribution [21]. This definition differs from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criterion of FEV_1/forced vital capacity (FVC) <0.70 [22], and the British Thoracic Society (BTS) criterion of FEV_1/vital capacity (VC) $<70\%$ and FEV_1 $<80\%$ of predicted value [23].

One argument for using SVC rather than FVC is that the FEV_1/VC ratio is more accurate in identifying obstruction patterns than the FEV_1/FVC ratio, since FVC is more dependent on flow than SVC [21]. VC was intended to refer to the highest acceptable VC recorded, whether it is from forced VC manoeuvres or SVC manoeuvres (inspiratory or expiratory). If more than one of these indices is available, the largest should be used to derive the FEV_1/(F)VC. We understand that the FVC is most commonly available. In healthy subjects, there is little difference between FVC, expiratory vital capacity and inspiratory vital capacity (IVC), so the reference equations for FEV_1/FVC can be used as an approximation [24].

In most epidemiological surveys, a COPD diagnosis will be based on spirometry and few clinical characteristics, *e.g.* the absence of self-reported asthma or other respiratory diseases. However, this is fundamentally different from the clinical diagnosis of COPD that is based on a clinician's evaluation of smoking history, other exposures, symptoms and spirometry. A COPD criterion based on the fixed ratio of FEV_1/FVC <0.7 is

simple to apply and is independent of reference values. However, a fixed ratio will lead to overestimation of COPD prevalence in the elderly and underestimation in younger subjects, as compared to the 5th percentile of the FEV_1/FVC ratio, when spirometry is the only tool applied for the diagnosis of COPD [25, 26].

Another potential consequence of a fixed ratio is the underestimation of the relationship between risk factors and COPD in younger and elderly subjects compared with middle-aged subjects [25, 27]. A recent report from an 11-yr follow-up study of 4,965 subjects aged $\geqslant$65 yrs at baseline, showed that subjects with an FEV_1/FVC ratio <0.7 but above the 5th percentile still had an increased risk of death and COPD-related hospitalisation compared with asymptomatic subjects with normal lung function [28]. However, this does not necessarily affect the diagnostic criteria of the disease [29]. Although there is debate on whether to use the lower limit of normal (LLN) or the fixed ratio in epidemiological studies [25–33], there are advantages of using the LLN above the fixed ratio. Hence, we recommend that the LLN is used in epidemiological studies (table 2). However, we acknowledge that the fixed ratio is widely used.

Most often, reference values are based on values found in asymptomatic never-smokers. In populations in which smoking is not the overwhelming cause of COPD, the prevalence of COPD may be underestimated using LLN. This could particularly be the case in less developed economies, where perinatal and childhood factors play a role alongside non-tobacco exposures, such as biomass fuel burning.

It could be argued that a criterion of FEV_1 below, for instance, 80% pred could be added to the $FEV_1/(F)VC$ <5th percentile [33]. As of today, we think that not enough data are available to recommend a specific criterion on FEV_1 in addition to the ratio.

All criteria suggested thus far advocate using post-bronchodilator values. Several studies have claimed that they have applied the ATS/ERS or GOLD criteria, but have actually used pre-bronchodilator spirometric values. It may make a substantial difference to prevalence estimates of COPD as well as relationships to risk factors if pre- instead of post-bronchodilator values are used [34–36]. In the recent series on the standardisation of lung function testing, the ATS and ERS recommended the use of a short-acting inhaled drug, for instance the β-agonist salbutamol or the anticholinergic agent ipratropium bromide [37, 38]. Based on our own experience, we recommend a 400 μg dose of salbutamol or 80 μg of ipratropium.

TABLE 2 Recommendations for the diagnostic criteria of chronic obstructive pulmonary disease (COPD) in epidemiological studies

1) Spirometric values should be post-bronchodilatory whenever possible
2) Salbutamol or ipratropium bromide should be used as bronchodilators
3) $FEV_1/(F)VC$ <5th percentile of predicted (LLN) should be used to define COPD[#]

FEV_1: forced expiratory volume in 1 s; (F)VC: (forced) vital capacity; LLN: lower limit of normal. [#]: we acknowledge that the fixed ratio is widely used.

DATA ON COPD

Lung function

Lung function measurements should be performed according to current ATS/ERS recommendations [37]. The staging of COPD is based on airflow limitations in terms of FEV_1 % pred. The classifications of severity of airflow limitations according to the clinical guidelines by ATS/ERS and GOLD are presented in table 3. The number of categories and the exact cut-off points are arbitrary [21].

The staging of COPD depends on the applied reference values of FEV_1. Detailed statements on the selection of reference values and interpretation of lung function tests have previously been published [39–41], and new recommendations have recently been created [21].

When selecting appropriate reference values, it is important to choose a source that uses similar equipment and has a test population that includes the age range, sex, height and ethnic group of the individuals being tested [42, 43]. An ongoing ERS Task Force (TF-2009-03) aims to establish improved lung function reference values (www.lungfunction.org).

Another variable that may be measured with spirometry is inspiratory capacity (IC). IC is the maximum volume of gas that can be inspired from end-tidal expiration, which is the difference between total lung capacity (TLC) and functional residual capacity (FRC). In COPD patients, IC is more closely related to level of dyspnoea and exercise intolerance than FEV_1 [44]. IC is an indicator of dynamic hyperinflation [45]. There

TABLE 3 Classification of severity of airflow obstruction according to American Thoracic Society (ATS)/ European Respiratory Society (ERS) and Global Initiative of Chronic Obstructive Lung Disease (GOLD) criteria

ATS/ERS criteria	
Mild	FEV_1/VC <5th percentile of predicted and FEV_1 $\geqslant$70% pred
Moderate	FEV_1/VC <5th percentile of predicted and FEV_1 60–69% pred
Moderately severe	FEV_1/VC <5th percentile of predicted and FEV_1 50–59% pred
Severe	FEV_1/VC <5th percentile of predicted and FEV_1 35–49% pred
Very severe	FEV_1/VC <5th percentile of predicted and FEV_1 <35% pred
GOLD criteria	
Mild	FEV_1/FVC <0.70 and FEV_1 >80% pred
Moderate	FEV_1/FVC <0.70 and 50%$\leqslant$FEV<80% pred
Severe	FEV_1/FVC <0.70 and 30%$\leqslant$$FEV_1$<50% pred
Very severe	FEV_1/FVC <0.70 and FEV_1 <30% pred or FEV_1/FVC <0.70 and FEV_1 <50% pred and chronic respiratory failure

FEV_1: forced expiratory volume in 1 s; VC: vital capacity; % pred: % predicted; FVC: forced vital capacity.

are currently no established predictive values for IC, and this is an important task for future studies.

Although spirometry is the key lung function measurement in epidemiological studies of COPD, it does not provide information on static lung volumes. Measurements of FRC and residual volume require a plethysmograph, which costs much more than a spirometer. Plethysmography is also technically more demanding and requires more training than spirometry. Diffusing capacity of the lung for carbon monoxide may also be used to characterise COPD in epidemiological studies [21, 46].

Thus, FEV_1 and VC (FVC) should always be measured in epidemiological studies on COPD (table 4). As hyperinflation of the lungs is not reflected in these variables, IC measurement should also be considered as this is an easy way of obtaining an indirect proxy variable for the level of hyperinflation. However, the interpretation of IC longitudinally should be cautious as TLC may change. Hence, the best method of measuring hyperinflation is still *via* plethysmography, particularly in longitudinal studies [47].

Respiratory symptoms

Data on respiratory symptoms should be obtained for several reasons. First, spirometric data in terms of FEV_1, VC (FVC), and the ratio between them, only characterise part of the disease status. Given the same spirometric level, cough and sputum production may dominate the clinical picture in some patients while dyspnoea may dominate in others. These pictures may represent different phenotypes of COPD. Secondly, respiratory symptoms such as cough and sputum production may precede the development of spirometric airflow limitation [15, 48]. Thirdly, data on respiratory symptoms may help to clarify whether the subject suffers from asthma. Fourthly, recent data have suggested that subjects with COPD GOLD Stage 1, with and without respiratory symptoms, differ in prognosis [32, 49]. Hence, combining spirometry and symptoms may enhance the phenotyping of COPD. Finally, in a two-phased sampling strategy, knowledge of respiratory symptoms may be used to sample the participants into the second phase.

Data on respiratory symptoms should be collected using standardised questionnaires. Several questionnaires are available; the most commonly used are listed in table 5. Their similarities and differences have previously been elegantly reviewed [50, 51].

TABLE 4 Recommendations for lung function measurements in epidemiological studies on chronic obstructive pulmonary disease

1) Spirometry should always be carried out
2) Performance of other lung function measurements should be dependent on the specific aim of the study
3) Lung function measurements should be performed according to current ATS/ERS guidelines
4) Predicted values should be obtained from studies of normal or healthy subjects of the same sex, age height and ethnic characteristics as the subjects being studied

ATS: American Thoracic Society; ERS: European Respiratory Society.

TABLE 5 Questionnaires on respiratory symptoms and lung diagnoses

American Thoracic Society and Division of Lung Disease of the National Institute of Health questionnaire (ATS-DLD-78-adult)
International Union Against Tuberculosis and Lung Disease questionnaire (IUATLD-84)
British Medical Research Council questionnaire (BMRC-86)
European Coal and Steel Community questionnaire (ECSC-87)
European Community Respiratory Health Survey questionnaire (ECRHS-94)

The number after the abbreviation in brackets refers to the year of publication of that specific version of the questionnaire.

A Compendium of Respiratory Standard Questionnaires (CORSQ) for adults was developed within the ERS and the European BIOMED-1 Concerted Action entitled ''Epidemiological surveys on chronic obstructive pulmonary disease in different European Countries: prevalence rates and relationship to host and environmental risk factors'' [52–54]. CORSQ covers 18 topics, from general information and early life events, through to environmental risk factors and respiratory symptoms and diseases. It is intended as a reference guide to existing validated questions, from the most widely used European and American epidemiological questionnaires, and as an example for designing new questionnaires on COPD. Further discussion regarding the use of questionnaires in epidemiological studies is given in the online supplementary material. Table 6 summarises the recommendations on the use of questionnaires in epidemiological COPD studies.

Biomarkers

A biomarker is defined as a biological marker that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes or pharmacological responses to a therapeutic intervention [55].

The inflammatory process in the different segments of the airways in COPD patients is still incompletely understood. Although noxious particles or gases clearly are the cause of the disease in most cases, the inflammatory events leading to

TABLE 6 Recommendations for the use of questionnaires in epidemiological studies on chronic obstructive pulmonary disease

1) A respiratory symptom questionnaire should always be used
2) Use of other questionnaires depends on the specific aims of the study, but regardless of aims, a standardised questionnaire should be used if available
3) A Compendium of Respiratory Standard Questionnaires is available and should be consulted in order to find validated questionnaires [52–54]
4) If a questionnaire is not available in the language of the study participants, it should be translated. A validation including a backward translation should then be performed
5) Self-administered questionnaires are preferable to interview-based questionnaires if the questions are not too complex and the study participants are able to complete them
6) A questionnaire to capture the complete working history is an example of a questionnaire that should be interview-based rather than self-completed

obstructive bronchiolitis and destruction of the alveoli have not been clarified [56].

Not everyone exposed to noxious agents develops COPD, and the clinical picture varies greatly between individual patients. Thus, the individual genetic susceptibility probably varies, as does the mechanism by which inflammation causes small airways disease and destruction of the parenchyma. Systemic inflammation may also be a part of the clinical picture in COPD.

The biomarkers for use in COPD may potentially be examined in exhaled breath, sputum, bronchoalveolar lavage (BAL), bronchial biopsies, plasma or serum [57, 58]. In epidemiological studies, biomarkers should be easy to obtain, not too costly, and of a relatively noninvasive character. Consequently, BAL and bronchial biopsies will not be considered here.

Exhaled gases and mediators in exhaled breath condensate

Exhaled gases and mediators in exhaled breath condensate (EBC) are easy to obtain. The procedure is also completely noninvasive. As a result, the method is attractive in epidemiological studies. However, at present there are several problems related to the reproducibility of the measurements. The concentration of many agents is very low, often below the lower detection limit of the assay. Contamination by nasal air or saliva may affect the results [59–62]. In addition, handling and storage of samples is quite important for reliable results, and in larger studies, will require a reasonably large freezer space unless immediately analysed.

Hence, EBC represents a promising research tool. However, more sensitive and standardised procedures are required before it can be recommended as a general tool in epidemiological COPD studies.

Sputum

The first report on sputum induction by inhalation of hypertonic saline was published in 1992 [63]. Whereas the main previous focus was to explore the dominating types of immune cells in sputum samples from patients, new diagnostic tools offered the opportunity to measure cytokines and other proteins indicative of the underlying immune response. Another major improvement in the last decade has been the standardisation of sputum sampling and processing.

Whether induced or spontaneous sputum sampling should be used depends on the research question. Induced sputum sampling is more standardised and is therefore to be considered the gold standard when sampling for inflammatory markers. When the main focus is cell count or detection of microbial agents, spontaneous sampling may be adequate, with a stringent system for quality assessment of sputum processing. The online supplementary material provides a more thorough discussion of this area.

Blood samples

Processing inflammatory products in blood requires a high degree of laboratory expertise; sampling and storing is much less complicated. Blood samples do not provide a direct measure of airway inflammation. However, it is now well established that there are differences in the levels of several inflammatory markers in patients with COPD compared with healthy controls [64, 65]. Thus, at least part of the inflammatory process in the lungs affects the immune system in a manner that can be measured outside the lungs. Novel technology will enable measurements of minute traces of proteins, such as cytokines, and samples from patients with well-defined airway obstruction could provide insight into both the immune response in the lungs and the systemic effects particularly seen in patients with advanced disease [66].

The blood cells will strongly affect the inflammatory marker level in the samples, so the samples need to be centrifuged thoroughly, and stored at low temperatures, preferably -70°C.

Current medication could affect the levels of cytokines measured both in sputum and blood, and should be recorded.

Thus, in epidemiological studies of COPD, sputum and blood represent the most appropriate means of biomarker collection (table 7). At present, little is known about the prognostic values of various biomarkers or their ability to discriminate between various phenotypes in COPD. We would therefore recommend that, where possible, epidemiological studies on COPD collect and store sputum or blood samples. Even if they cannot be analysed immediately, they may be of great value in future analyses, when further knowledge about biomarkers is available. Proper handling and storage of the samples is vital.

Phenotypes of COPD

The term ''phenotype'' is defined as the outward physical manifestation of patients with COPD; anything that is part of their observable structure, function or behaviour. This provides a framework that can be used to document the particular characteristics of patients with COPD [67, 68].

Although spirometry is the cornerstone of diagnosis and staging of COPD in community studies, it has long been realised that FEV_1 provides far from the complete picture of the disease. JONES [69] previously showed that FEV_1 correlated only weakly with quality of life, measured using the St George's Respiratory Questionnaire. Quantitative morphometric analyses *post mortem* and surgical lung specimens, as well as radiographic studies, have shown that FEV_1 is insensitive to anatomic disease severity in COPD [70]. In addition, some patients with COPD develop extra pulmonary manifestations, most of which are poorly related to the degree of airflow limitation [71]. Hence, there is a need for better phenotyping of COPD than that offered by spirometry [68].

TABLE 7 Recommendations for collection of biomarkers in epidemiological studies on chronic obstructive pulmonary disease

1) The collection of biomarker and type depends on the aim of the study
2) One should always consider collecting a blood sample or sputum sample from the study participants
3) Proper handling and processing of the sputum samples is vital
4) If not analysed at once, the blood samples should be stored properly, preferably at -70°C
5) Storage should be planned, with proper procedures before freezing. The storage of samples in several aliquots should also be considered so that they can later be analysed without melting all of the samples
6) There is now no basis for the recommendation of routine sampling of other biomarkers, such as exhaled gases or mediators in exhaled breath condensate

There are currently no recommendations regarding the way in which phenotyping of COPD should be performed in community studies of the disease. Requirements for such phenotyping should be that they have a therapeutic and prognostic consequence [67]. Furthermore, it should be possible to perform phenotyping in a large-scale setting, and it should be reproducible.

Examples of potential phenotypes are rapid FEV1 decliners, frequent exacerbators, cachectic patients and the classical dichotomy of emphysematic *versus* airway disease. These phenotypes may not be distinct entities [72].

As we begin to understand these different aspects of the COPD disease spectrum [73–75], knowledge of their distribution and risk factors in the population at large will be important to healthcare providers, patient organisations and the pharmaceutical industry. Hence, when planning a community study on COPD, we recommend describing the COPD cases using more than just spirometry (table 8). The possibility of using chest radiography to phenotype COPD cases in epidemiological studies has recently been revitalised [76].

Rapid decliners

Assessment of subjects with an accelerated loss of FEV1 (rapid decliners) requires a longitudinal study design with at least two points of time at which the participants are examined. Most longitudinal studies use only two examinations. However, use of only two data points may mean the results are subject to bias due to regression towards the mean [77]. In addition, given the same length of follow-up and inter- and intra-variability of the variable being studied, increasing the number of examinations above two will exponentially reduce the confidence intervals of the estimates [78]. Hence, when planning longitudinal studies to assess the natural history of COPD, we recommend using at least three points of time at which the participants are examined. The minimum time of follow-up for FEV1 assessment should be 3 yrs. A computer modelling has suggested an interval of 6 yrs to achieve a highly statistical exposure effect [79].

TABLE 8 Measurements that can be used in epidemiological studies to characterise chronic obstructive pulmonary disease cases beyond spirometry

Respiratory symptoms
Exacerbation frequency
Comorbidity assessment
Lung function tests
Inspiratory capacity
TLC
$D_{L,CO}$
BMI and FFMI
Biological markers
EBC
Sputum
Serum
Chest radiography
CT of the thorax

TLC: total lung capacity; $D_{L,CO}$: diffusion capacity of the lung for carbon monoxide; BMI: body mass index; FFMI: fat-free mass index; EBC: exhaled breath condensate; CT: computed tomography. Data from [67].

A rapid decliner has somewhat arbitraryly been defined as a subject who loses FEV1 at a rate >60 mL·yr^{-1} [80, 81]. An alternative approach is to follow the participants prospectively and determine the quartiles of change in FEV1 from baseline. Those in the most negative category are defined as rapid decliners; the other three categories are reference groups [82].

Frequent exacerbators

There is no consensus of an operative criterion for the start or end of a COPD exacerbation in the clinic, and much less for use in epidemiological studies. In a recent ATS/ERS Task Force on outcomes in pharmacological COPD studies [83], four different criteria were presented: 1) those of ANTHONISEN *et al*. [84], who used a combination of three cardinal symptoms (increased dyspnoea, sputum volume and sputum purulence); 2) a definition based on two of the cardinal symptoms above, or one of them and at least one minor symptom experienced for $\geqslant 2$ consecutive days; 3) a definition based on a complex of respiratory events (*i.e.* cough, wheezing, dyspnoea or sputum) for $\geqslant 3$ days in a row; 4) a definition based on a change in regular medication.

The advantage of criteria 2 and 3 is that they require worsening of symptoms for $\geqslant 2$ consecutive days to distinguish the increase from day-to-day variation in symptom score. Criterion 4 does not cover exacerbations that do not require extra medications. The severity of an exacerbation may be characterised as: mild, which involves an increase in symptoms that can be controlled without additional treatment; moderate, which requires treatment with systemic steroids and/or antibiotics; and severe, which requires hospital admittance. None of the above criteria define the end of an exacerbation. However, previous studies have used 5 days free of all symptoms of the exacerbation as the definition [85].

Data on COPD exacerbations in community studies may be obtained through self-completed diary cards, regular retrospective questionnaires, telephone interviews, or tele-monitoring (where subjects are monitored continuously and the data recorded are sent to a computer by means of a telephone/mobile telephone call). Methods involving diary cards may be expensive to organise in large-scale studies and could be subject to noncompliance. Questionnaires are cheaper to apply but may be subject to recall bias. Data obtained by telephone interview may suffer from observer bias. Tele-monitoring offers the possibility of constant surveillance but is expensive in large-scale studies. Limited information is available on the validity of the data obtained [86].

Emphysematic versus *airway disease phenotype*

Quantitative high-resolution computed tomography (HRCT) provides a means of accurately measuring parenchymal changes in COPD [87, 88]. HRCT is more sensitive than normal radiography in assessing emphysema [89]. There is increasing evidence that airway dimensions can be accurately measured using HRCT [90]. HRCT measurements are sensitive to changes in emphysema and airway dimension by sex, age and smoking status in both COPD cases and in subjects without COPD [91]. HRCT has recently been used to distinguish between patients with predominately emphysema and predominately airway

wall thickening, which may prove to constitute different phenotypes [92]. There is a strong relationship between HRCT-assessed emphysema and the level of FEV_1 and FEV_1/FVC, while the association of airway wall thickness and FEV_1 is weak [92].

There are still limitations to the use of HRCT for measurement of the airways. The main limitation is that the small airways responsible for airflow limitation cannot be measured using HRCT [93]. Secondly, there is no definitive consensus regarding the best algorithm to measure the airway wall [89]. Computed tomography represents exposure to ionising radiation, and safety is an important consideration. The lifetime mortality risk for cancer in subjects aged 50–70 yrs after exposure to a low-dose chest HRCT is sufficiently low to justify the use of HRCT in research protocols [94]. However, dosage varies according to equipment and protocol; this therefore needs to be actively assessed in the planning of the study.

Pulmonary cachexia

There is growing evidence that COPD is a disease with systemic consequences. The best understood systemic effect is loss of lean body mass and muscular dysfunction [95]; this feature defines a subgroup with impairments in exercise capacity. The term ''cachexia'' highlights the preferential loss of muscle over fat, with evidence of increased protein degradation [96]. Loss of skeletal muscle is the main cause of weight loss in COPD [97]. Hence, both body mass index (BMI) and fat-free mass index (FFMI) should be considered. BMI is defined as body weight corrected for body height squared, whereas FFMI is fat-free mass corrected for body height squared. Fat-free mass includes all compartments of the body except fat mass. It consists of muscle tissue, bone tissue and body fluids. The gold standard for measurement of fat-free mass is a DEXA scan. However, this can be costly and is of limited availability. The bioelectrical impedance measurement is a cheap and quick alternative. The process takes 5 min and involves minimum training and modest cost.

We recommend that assessment of phenotypes should be considered in epidemiological studies of COPD (table 9). The extent of phenotype characterisation obviously depends on the resources available as well as the specific objective of the survey. A general requirement for any measurement is that it is reproducible, valid, safe and feasible to perform on a large-scale basis.

WHAT ACTUAL AND POTENTIAL RISK FACTORS FOR COPD SHOULD BE CONSIDERED AND HOW?

In epidemiological studies of COPD, one should always consider collecting data on its potential risk factors. Although tobacco smoking is established beyond any doubt as the cause of the majority of cases of COPD, other factors may also cause COPD or contribute in conjunction with tobacco smoking. Much remains unknown about some occupational exposures, smoking of drugs other than tobacco, hereditary factors, the role of nutrition, comorbidities, and respiratory infections, to name a few potential factors. It is crucial to realise that one can only assess the effect of factors that are measured. If only smoking habits are considered, smoking will appear to be the only risk factor for COPD.

The simplest way to obtain information about most risk factors is through questionnaires. Questionnaires should generally contain simple questions that are easy to understand.

TABLE 9 Recommendations for chronic obstructive pulmonary disease (COPD) phenotype characterisation in epidemiological studies

1) Although spirometry is important for diagnosis and staging of COPD, FEV_1 is unable to explain the whole picture of the disease. Hence, other phenotypes than those deduced using spirometry should be measured in epidemiological studies
2) The extent of phenotype characterisation depends on the aim of the study and the available resources
3) A general requirement for any phenotype characterisation is that the measurement should be safe, reproducible, valid and feasible to perform in epidemiological studies
4) The planning of the phenotypes used in the subsequent data analysis should be considered before estimating the sample size of the study, in order to ensure that the study is large enough to allow the COPD cases to be divided into phenotypes

FEV_1: forced expiratory volume in 1 s.

Active smoking

All standardised respiratory symptom questionnaires include questions on active smoking [50]. A disadvantage of most questionnaires is the lack of information on cumulative smoking load, such as pack-yrs and age of starting smoking; this is information that should be collected. A variety of biomarkers are available for verifying smoking status, but none of them constitutes a gold standard [98]. Some biochemical misclassification of smoking status will occur [99]. Nevertheless, the biochemical measurement error may be randomly distributed, while self-reported error is usually biased towards nonsmoking [100]. However, this bias is limited and in surveys, self-reported smoking status generally provides accurate data [98]. Consequently, in large population studies on COPD, biochemical validation of active smoking is not necessary. However, in case of any intervention being incorporated into the study, validation of smoking status should be performed [100] (table 10).

Occupational airborne exposure

There is little consensus regarding how information about occupational airborne exposure in community studies of COPD should be obtained. As COPD is a chronic disease with no clear onset, any occupational exposure related to COPD may have occurred many years prior to the study. The assessment of occupational exposure through use of a questionnaire may therefore be the most useful approach. A simple question

TABLE 10 Recommendations for assessment of active smoking in epidemiological studies

1) Active smoking should be measured using standardised questionnaires
2) The characterisation of active smoking is based on current smoking status, number of pack-yrs and age of onset of smoking
3) It is not necessary to validate the information on current smoking status in epidemiological studies. The exception is if the study includes a smoking-cessation intervention
4) Number of pack-yrs is defined as: daily cigarette consumption × number of yrs smoked/20

addressing past or present occupational exposure to dust, gases or fumes has been proven to measure exposure as effectively as more detailed questions on specific exposures [101]. This is an inexpensive method, which has been used by an *ad hoc* ATS committee to estimate the occupational contribution to the burden of asthma and COPD [102]. However, it may be subject to recall bias, particularly in diseased rather than non-diseased subjects [103].

A job exposure matrix (JEM) is an alternative to simple questions on post and current exposures. A JEM has a two-dimensional structure, with jobs or work tasks on one axis and exposures on the other axis [104]. The JEM allows the researcher to translate specific jobs into different exposures and degrees of exposure. A JEM designed specifically for COPD is available [105]. To obtain the right information about the exposures from a JEM, the study participants must state all jobs they have had since leaving school or at least the longest job held and the current job, as well as the year of entering and leaving the job(s) [106]. A disadvantage of the JEM is that the work tasks and exposures in one occupation may vary from job to job, over time and between countries. Not all farmers are substantially exposed to dust, nor are all painters exposed to fumes, whereas some clerical employees may be exposed to toxic inhalants. These disadvantages may be partly adjusted for if the JEM uses survey responses on exposures to modify risk assessment [107].

Finally, when estimating the degree of exposure, it is necessary to include a substantial number of subjects in the study sample to be able to show an association between exposure and outcome. Thus, a JEM is best suited to dealing with very large study samples. A third alternative for obtaining exposure data is structured interviews performed by occupational hygienists; however, this is a very expensive and time-consuming method.

The decision of whether to use a general question on dust, fume or gas exposure, a JEM, or an occupational hygienist depends primarily on the main objective of the study (table 11). A few simple questions regarding previous and current occupational exposures should always be included. If the study aims primarily to focus on occupational exposures and COPD, a JEM is probably more appropriate. In this setting we urge the planners to carefully consider sample size prior to the study.

TABLE 11 Recommendations for occupational exposure characterisation in epidemiological studies on chronic obstructive pulmonary disease (COPD)

1) The degree of the occupational exposure characterisation depends on the aims of the study
2) In most cases, the occupational exposure of importance took place in the past
3) Occupational exposure characterisation should be based on standardised questionnaires
4) If occupational airborne exposure is only planned to be a covariate in subsequent analyses, the following two questions are enough [108]:
   Have you ever been exposed to dust or gas at work?
   If yes, for how many years have you been exposed?
5) If the study aims to examine airborne exposure in relation to COPD, a job exposure matrix should be applied and/or structured interviews performed by occupational hygienists should be considered, depending on the specific aim and available resources

Outdoor and indoor air pollution

Exposure assessment of both outdoor and indoor air pollution should ideally be based on personal monitoring of each study participant. However, performing such a measurement in a community setting is expensive, and can only cover a limited time and one or few pollutants. Any effect of pollutants may be caused by previous exposure.

Hence, when it comes to assessment of exposure to indoor risk factors for airway disease in community studies, one is often left with questionnaire data [109, 110] (table 12). The validity of such data is hard to assess as the gold standard is difficult to obtain [111, 112]. The repeatability of questionnaire data on indoor air pollution has only been examined to a limited extent [113].

Exposure to environmental tobacco smoke (ETS) is a specific example of indoor air pollution. Questionnaires should include data about ETS, allowing quantification of exposure in the work place, at home and in locations other than the work place or home. Collecting such information is important, as increasing exposure to ETS is associated with an increasing prevalence of respiratory symptoms that are common in COPD [114, 115]. ETS exposure in fetal life and childhood should also be considered.

If data on outdoor air pollution are to be taken into account in population studies on COPD, data from central measuring stations closest to the participant's home are usually obtained [116]. Alternatively, a system of samples of the agent(s) under study may be used to assess each participant's exposure based on their home address [117]. Such data are clearly only proxies of each individual's true exposure. It could be argued that outdoor air quality is of limited value, as most people in the Western world spend >90% of their time indoors [118]. However, most outdoor pollutants penetrate indoors, and indoor air quality is largely determined by outdoor pollutant concentration [116, 119].

Socio-economic status

Socio-economic status is an independent risk factor for COPD and is also related to several other causes of COPD. It should always be taken into account when examining potential risk

TABLE 12 Recommendations for the assessment of indoor and outdoor air pollution in epidemiological studies on chronic obstructive pulmonary disease (COPD)

1) The degree of exposure characterisation depends on the aim of the study
2) If indoor or outdoor air pollution is not the main objective of the study, the exposure characterisation should be based on self-reported questionnaires
3) Data on exposure to ETS should always be collected in epidemiological studies of COPD
4) ETS should be divided into exposure at work, at home and in other places
5) ETS in early life may also be of importance in adult life. Such data should be collected and divided into fetal exposure and childhood exposure

ETS: environmental tobacco smoke.

TABLE 13 Recommendations for the assessment of socioeconomic status and diet in epidemiological studies of chronic obstructive pulmonary disease

1) The degree to which socioeconomic status and diet are measured depends on the study aims
2) Educational level and one other measurement of socioeconomic status should always be used
3) If diet is not a specific aim of the study, we do not recommend that such data is routinely collected

factors for the disease (table 13) [111, 120, 121]. The most common methods of assessing socio-economic status are educational level, income and occupational status, of which educational level is the most frequently used [122]. Information on educational level is easy to obtain and is often more accurate than information regarding income [122]. In most subjects, the completion of education predates the onset of the disease. This may not be the case for income and occupational status. Consequently, by using educational level, one may reduce the problem of whether socio-economic status is a cause or a consequence of the disease. A disadvantage of assessing socio-economic status in terms of educational level is that it is stable over the lifetime of most subjects. Hence, changes in socio-economic status will not be noticed when educational level is used, but are better reflected by income and occupational status. Furthermore, educational level is often measured by the number of school years completed. This may vary between birth cohorts and may tend to reduce the specificity of educational level as a measure of socio-economic status. We therefore recommend measuring at least two different indices of socio-economic status in community studies of COPD.

Diet

Two methods of dietary assessment in epidemiology are commonly used: questionnaires and blood samples. Questionnaires obtain information on the frequency of consumption of the main types of food in a specific period of time, usually a year (table 13). Using computerised programs, it is also possible to translate the questionnaire data into assessment of consumption of nutrients [123]. Such data are obviously dependent on the subject's recollection and the validity of the computerised programs. These programs should be tailored specifically to the target population in question. Measurement of dietary constituents in the blood is particularly used for vitamins, lipids and trace metals [124]. Such measurements usually give an indication of recent intake.

Comorbidity

Subjects with COPD are often also affected with other diseases and conditions [12]. These conditions may arise partly as a direct effect of COPD and partly as a result of common risk factors, such as tobacco smoke. Pulmonary hypertension and cor pulmonale are common among subjects with severe COPD [125]. Cardiovascular diseases in general are also common in subjects with COPD [96]. In questionnaire studies, it is not possible to achieve detailed and valid information regarding the differentiation of heart diseases. However, questions about heart disease in general, particularly ischaemic heart disease, cardiac failure, hypertension, and medication for heart disease and hypertension, can be included. For detailed information, clinical tests must be incorporated.

Other frequent comorbidities in COPD are osteoporosis [126], depression [127, 128] and anaemia [129]. Depending on the specific aim of the study, one should consider obtaining data on these conditions [130, 131].

Markers of systemic inflammation, such as increased C-reactive protein and fibrinogen, may reflect involvement of several organ systems. Markers of inflammation are often elevated in moderate and severe COPD. Epidemiological studies of COPD in which blood samples will be taken may thus include screening of markers of inflammation.

From a clinical point of view, malnutrition appears to be a problem in severe COPD, and low BMI is related to an increased risk of death among subjects with COPD [96, 132]. Questions about length and weight allow estimations of BMI, providing some information about malnutrition. To achieve valid data, the subjects should be measured at the time of the survey.

Studies on cancer, particularly lung cancer, as a comorbidity of COPD may be relevant to studies able to register a link between the study database and cancer registers, as the survival time among subjects with several types of cancer is low.

Family history

Several studies have shown that a family history of COPD is related to an increased risk of COPD, although the risk ratios are considerably lower than in asthma, with relative risks or odds ratios below 2 [133, 134]. In contrast to asthma, COPD is still not well known amongst the general population. Thus, questions about a family history of COPD will often include chronic bronchitis, emphysema or COPD [135], and are likely to be imprecise. An alternative is genetic studies, an increasing field of research for COPD. However, such studies are costly and outside the scope of this report.

In general, most information about potential risk factors for COPD may be obtained through questionnaires when the population at large is to be studied. It is important to use standardised questionnaires that are already available (table 14). For many questionnaires, there is limited information on the precision (repeatability) and the accuracy (validity) of the data offered by the questionnaire. If no data on precision and accuracy of a given questionnaire is available, the researcher

TABLE 14 Recommendations for the assessment of comorbidities and family history in epidemiological studies of chronic obstructive pulmonary disease

1) The degree to which comorbidities and family history are assessed depends on the aims of the study
2) Data on heart disease should always be collected
3) Data on height and weight should always be collected in order to assess body mass index

should seek to obtain this information from their own study where possible.

PRACTICAL ADVICE WHEN PLANNING AND PERFORMING AN EPIDEMIOLOGICAL STUDY ON COPD

Population sampling

Most epidemiological studies require sampling. It is simply too costly and time-consuming to examine the entire population. A sample of the population in question, often called the target population, may be obtained in several ways. The purpose of sampling is to obtain a representative sample of the target population. A simple random sample may be drawn. Each member of the population will then have the same probability of being included in the sample. Random sampling has the advantages of being simple to carry out and allowing for easy calculation of means and variances. A random sample also reflects and represents the population studied, as long as the size of the sample is not too small. However, it requires knowledge of the entire target population in advance, which is often not the case. Furthermore, estimates of COPD in certain subgroups may be imprecise, as the subgroups may be small.

Stratified sampling is an alternative. With this method, certain subgroups have a higher probability of being included in the sample. If, for instance, the objective of the study is to examine the prevalence of COPD in the elderly, one may stratify by age, giving subjects in the oldest age groups a higher chance of being sampled. This will ensure a more precise prevalence estimate in these age groups than simple random sampling would have allowed. A disadvantage of stratified sampling is that data analysis is more complicated. As the subjects in the various strata have a different probability of being included in the sample, they have a different weight in the analysis. This has to be taken into account.

Stratified sampling still requires advanced knowledge of the target population. If this is not available, cluster sampling is an alternative. This implies that certain clusters, for example cities or households, are sampled rather than individuals. Within each cluster, all of the subjects of the age group of interest may be included in the sample. The advantage of cluster sampling is that no precise data for the target population is necessary beforehand. It may also enable the researcher to make more economical use of resources than random sampling. It is worth noting that for the same number of subjects, the variance is greater for cluster sampling than for simple random sampling.

Two-phased sampling has been used in several community studies of COPD [7, 114]. In the first phase, the group sampled from the target population is screened using a questionnaire containing respiratory symptoms. Subjects fulfilling certain criteria in their responses to the questionnaire are then sampled into the second phase, which often includes respiratory physiological or clinical examinations. This is a way of increasing the cost-effectiveness of the study, *i.e.* the amount of information obtained relative to the expenditure in time and money. In two-phased sampling, the various sampling procedures mentioned above may be combined. It is important to realise that since many subjects with COPD deny any respiratory symptom, a two-phased sampling as described above may underestimate COPD prevalence. In order to avoid such bias, a random sample could also be invited [17].

TABLE 15 Recommendations for sampling and sample size in epidemiological studies of chronic obstructive pulmonary disease (COPD)

1) Sampling should take into account knowledge about the target population, the aims and design of the study, and available resources
2) Sample size estimation is one of the most important parts of study planning and should always be performed
3) Sample size estimation should be based on the main aim and design of the study. It should also take into account nonresponse and loss to follow-up
4) When estimating the sample size, one should also consider the possibility of subsample analyses, and adjust the sample size accordingly. For instance, will males and females or different phenotypes of COPD be analysed separately? If so, the sample size should be planned to enable such analyses

Sample size

The sample size calculation depends on the main objective of the study (table 15). If the main aim is to assess the prevalence of COPD in the population at large, the acceptable precision of the prevalence estimate has to be defined. If the main aim is to assess whether COPD prevalence differs between subgroups of the population, the difference of interest between the groups as well as the significance level and the power of the test have to be defined. When comparing the prevalence of COPD between two groups, it is often necessary to adjust for potential confounders. For instance, if one wishes to examine whether COPD differs between those with occupational airborne exposure and those without, adjusting for smoking and socio-economic status is relevant. Methods that take into account confounding in the calculation of power and sample size when data are analysed in logistic regression can be found elsewhere [136]. As a general rule, the sample should be increased by 5% for every new confounder adjusted for.

When estimating the sample size, it should be taken into account that not all invited subjects will participate. If, for instance, a response rate of 70% is expected and a sample of 500 is required to achieve the desired power for detecting an association, then the number of selected subjects should be $500/0.7=710$.

In longitudinal studies, the sample size should also take into account withdrawal during the study period. The bias related to nonresponse should be assessed by performing a survey of all or a subsample of nonresponders at baseline and at follow-up.

Ensuring a high response rate

One should always aim to achieve a response rate that is as high as possible. This will strengthen the power of the analyses and work to reduce nonresponse bias. When possible, it is useful to sample the nonresponders and obtain at least some information about them, for comparison of the characteristics of responders and nonresponders and for adjustment of estimates and associations [137].

In longitudinal studies, many authors report the response rate only at the second phase (or later). However, the true response rate for any longitudinal study is the number of subjects participating at both baseline and follow-up divided by those invited at baseline. With careful planning, comparing the sex and age distribution of the responders and nonresponders to the initial baseline survey is not difficult. These data will

greatly enhance the evaluation of the validity of the results. To improve the comparison of response rates and results between studies, we recommend that flow charts of the sampling procedures are published.

In studies of respiratory health including COPD, nonresponders tend to be smokers and younger subjects [138, 139]. Although this may affect the estimation of both the exposure and disease variables, there are indications that the exposure–disease relationships are only marginally subject to nonresponse bias [140–142].

A high response rate could be accomplished in several ways. A written invitation to the target population should be used. The invitation letter should state the study's main objective and provide a short description of the study. This information must not be given in such a way that it causes response bias. For instance, if the main objective of the study is to examine the association of occupational airborne exposure with asthma, this should not be mentioned in the invitation letter. If so, it could lead to a higher response of asthmatics that have been occupationally exposed, compared with asthmatics without such exposure; this would result in false-positive associations.

The letter should also state the personal benefits of participating. This could be a free medical examination. Offering money has been shown to increase the response rate, but this may cause a participation bias [143] and may be deemed wrong by ethical committees. The letter should be signed by the principal investigator of the study and may also be signed by other investigators. It may also contain one or several telephone numbers for use if further clarification is needed. The invitation letter should be as short and concise as possible, preferably no longer than one page.

If the subject does not respond to the invitation letter, one or more reminder letters may be sent after 2–3 weeks. Contact by telephone or home visits should also be considered if allowed by the local ethical committee. However, data obtained by telephone or home visit may differ from data obtained through mail questionnaire or personal attendance at an examination.

Where medical or laboratory examination is required, the location should be easily accessible. The opening hours should be flexible, even in the evenings and weekends. Transportation for aged or disabled subjects should be considered. If the participants have medical requirements that are not related to the study, these should be met as far as possible. In follow-up studies or panel studies, each person should be given a telephone number or contact person in case of any problem. Publicity about the study in the local press, on the radio and on television stations should be sought. Recommendations for improving the response rate are summarised in table 16.

Nonresponse bias is particularly a matter of concern in studies of old and very old subjects. One has to decide whether institutionalised subjects will be included in the study. Arguments both in favour and against inclusion may be found [145].

The population's willingness to participate in health studies has declined in recent decades. A way of changing this trend could be making use of new communication tools, such as the internet and mobile telephones, at least in communities where they are widely used. Limited data are available on the effect of these tools in respiratory health surveys [142, 146].

TABLE 16 Recommendations for improving response rate

1) One should always aim to achieve as high a response rate as possible. Solely compensating for low response rate by increasing the sample size is not an alternative
2) An invitation letter of not more than one page should briefly explain the main objective of the study and the benefits of participating. It should be signed by the principal investigator. The letter may contain a telephone number for those seeking additional information
3) In postal studies, the questionnaire should be as short as possible, taking $\leqslant$20–30 min to complete. A pre-stamped return envelope should be included
4) The possibility of responding online or *via* mobile phone should be considered
5) In studies requiring the participant to attend in person, the study site should be easily accessible with good parking facilities.
6) Free transport should be provided for those in need
7) Special planning is needed for certain groups, such as the elderly, homeless and handicapped
8) The participants should always receive a quick response on results from clinical examinations, if available
9) Reminder letters and/or a telephone call to nonresponders should be issued, if allowed by the ethical committee
10) To the extent that it is feasible to do so, a physician should call the nonresponders to invite them to join the study
11) Further advice on improving response rates can be found elsewhere [144]
12) Follow-up of a subsample of the nonresponders should always be performed to assess the representativeness of those examined compared to those eligible

The preparatory phase

When the revised protocol is finalised, permissions from the authorities should be applied for, as well as financial support for the survey. In our experience, the better prepared the protocol, the greater the probability of obtaining the necessary permissions and funding.

This phase also involves the practical preparations of the study. These may include locations used in the study, such as examination rooms, waiting rooms, toilets for the participants, babysitting rooms and car parking areas for the participants. Those conducting the study should also recruit and train the team members, pre-test the forms and equipment to be used, and make plans regarding how to take care of any equipment breakdown during field work. One should also prepare the computer programs for analysis of the data to be collected.

The preparatory phase includes reaching written agreements with cooperating laboratories and research units about analyses of specimen and data, the costs of these analyses and any participation in publications.

Where using register data, the quality of these data should be assessed by examining how they have been collected and the representativeness of the register for the population in question.

The study team

The composition of the study team may vary with the design and objective of the study, and with the resources available. However, in any epidemiological survey, an epidemiologist or

a person with epidemiological training should be the head of the team. A pulmonary physician should also take part in the team, as well as an environmental scientist. In our experience, there has been a tendency to focus on disease in COPD studies examining exposure–disease relationships, with less attention paid to exposure. An environmental scientist should be responsible for collecting, storing and analysing the environmental samples, as well as quality control of these actions.

The study team should also include a statistician. During planning, the main responsibility of the statistician is to assess the number of participants needed to be able to answer the main question of the study. The statistician should assess the quality of the data using various comparisons of the results from different observers and coders, and should assist the team leader in the analysis and interpretation of the data (table 17).

At the time of recruiting the scientific members of the team, agreement should be reached upon participation in the publications resulting from the study.

The team members should also include technicians, who will perform the practical collection of data during field work. Examples of such technicians are interviewers, assistants performing spirometry, laboratory technicians, and occupational or environmental hygienists, as well as secretaries to answer telephones, administer questionnaires, record or file data, *etc.*

When the necessary team members have been recruited, it is important to make all the members feel that they are equally important for a successful study outcome. All the team members should be aware of the main objectives of the survey. In epidemiological studies lasting months or years, regular meetings should be held to inform the team members about study progression. This will help ensure highly motivated collaborators and therefore, a high quality of data.

TABLE 17 Recommendations for the preparation and recruitment of team members

1) All formal permissions for performance of the study should be obtained
2) Proper locations for the study including participants and technicians should be prepared
3) The validity of the equipment should be assessed and plans should be made regarding potential equipment breakdown during data collection
4) Standardised methods for lung function tests and standardised questionnaires should be used
5) Plans for data management should be made, including how the data should be entered into the database and in what form
6) The study team should comprise of experts on the key areas of the study. Most often, this would imply an epidemiologist, pulmonologist, environmental scientist, statistician and technicians
7) The type and number of technicians depends on the objectives and size of the study. Irrespective of this, all technicians should know the aims and outline of the study
8) All the technicians should be trained and tested in the procedures they are to carry out prior to commencing the study
9) Everyone involved, including the technicians, should feel that they are members of a team, meaning the entire team should meet regularly to be updated on study progress

Methods for data collection

The various methods for data collection should be pre-tested on the intended users, *i.e.* the interviewers, the examiners, and the laboratory technicians, and revised and then tested in a pilot study. Finally, their validity and reliability should be examined.

If physical examinations are to be performed, a detailed description of the order and content of the examinations is necessary. Extensive pre-testing of the examiners is also warranted. Regarding clinical examinations of various obstructive lung diseases, the inter- and intra- observer variability still remains a concern. It is crucial that the examiners are blinded to other information about the subjects; exposure data, for example.

The collection of bio-specimens is increasingly used in epidemiological surveys. The technicians performing the sampling and analysis should be properly trained in all parts of the procedures, including storing and transportation of the specimen before analysis. The laboratory should check whether the quality of their work is adequate, also when handling the potentially large number of samples. Plans should be made for specimen storage for later analyses: what analyses are to be performed and what is the proper storage for these analyses, how many glasses per subject, precautions for the potential breakdown of the freezer electricity supply, *etc.*

The technicians collecting any exposure data, either through questionnaires, inspection protocols or by means of objective measurements, should also be extensively trained. It is important that they are blinded to the disease status of the subjects in question.

Pilot study

When all the preparations have been made, a pilot study should be performed. The pilot study should be seen as an effective tool for assessing the overall adequacy and feasibility of the study team members and the equipment. It is important to check the cost and time estimates. The pilot study should be a full-scale operation performed on a similar population to that examined in the survey. Hence, if a general population study on elderly people is to be carried out, one should not only use healthy older subjects but also diseased subjects, including, for example, wheelchair users, the deaf or the blind. Any biospecimen that is planned to be taken should not only be collected but also analysed by the laboratory, and the data should be stored in the computer. An effort should be made to keep the same speed in the pilot study as is planned in the survey. The pilot study may last for 2–3 days. A pilot study should always be performed regardless of the size of the planned survey.

An important part of the pilot study is to test the safety precautions of the study. For instance, if a patient should faint during a spirometric manoeuvre, one should test the necessary equipment and personnel to be involved in taking care of the subject.

A report should be written after the pilot study in which every part of the proposed data collection is assessed. The views of both the team members and the participants in the pilot study should be heard. Based on this report, the protocol of the survey should be finally revised.

TABLE 18 Recommendations for quality control

1) Quality control starts with a well-prepared study, including use of valid, standardised methods, well-trained technicians and a thorough plan for data handling
2) A pilot study should always be performed, testing the study team and all the methods used during the survey
3) The pilot study should be a full-scale operation on a similar population as the one to be examined in the survey
4) During data collection, quality control of each technician, all the instruments and questionnaires, and data handling should be performed regularly
5) Quality control of the technicians implies checking the variability of their observations, and regular training and certification of each technician
6) Quality control of the equipment implies regular calibration
7) Quality control of the questionnaires implies regular control of uncompleted questions
8) Quality control of data entry implies testing for outliers and inconsistent data (*e.g.* a never-smoker cannot report smoking 10 cigarettes per day)
9) The results of quality control should be regularly assessed and discussed within the study team. This is particularly important in long studies to avoid fatigue among the technicians and reduced data quality

Quality control during field work

In epidemiological studies, the results are highly dependent on the quality of the data collected (table 18). Throughout the field work, quality control of data collectors (including interviewers and technicians) and measurement instruments (including questionnaires and spirometers), as well as the entered data, should be performed [147]. When the study has been completed, it is too late to improve the quality of the collected data. Relevant recommendations for quality control during the field survey are summarised here.

Each data collector should have an identification number. These numbers should be recorded on each study subject's form. Collected data may be fed into the computer either by typing, scanning, or online. Immediately after data collection, missing or unclear data should be checked with the study subject by the data collector. If data collection is performed using electronic data entry, range and logic checks should be automatically carried out by the computer. To minimise errors in manual data entry, data should be entered twice and a verification program should be carried out to detect disagreements.

Replication of a small proportion (*e.g.* 5%) of data entry may disclose answers or measurements that are not real, or a systematic bias in the data collection. To detect operator bias, quality control should include analysis of the distribution of the variables of interest among data collectors. The analysis of trends over time may uncover interviewer fatigue or drift in laboratory measurements. Holding periodical study team meetings can be useful for discussion of the problems and to maintain the team's interest in the data quality.

With regard to quality control procedures for lung function measurement, the reader is referred to the recommendations of the joint ATS/ERS Task Force on the standardisation of lung function testing [37]. Calibration of instruments should be evaluated regularly so that immediate action can be taken in case of malfunction. In multicentre epidemiological studies, particularly when using different instruments (*e.g.* spirometers or pneumotachographs), performing inter-laboratory comparisons as a quality control procedure may disclose any systematic instrument bias and validate collected lung function data. A simple quality control protocol may be carried out, such as biological calibration, by comparing data measured in the same subjects (*e.g.* five to 10 subjects) and obtained with both the local instrument and a portable instrument designed as a ''reference instrument'' [148].

Performance of the instruments and the quality of lung function measurements can only be maintained during data collection of a long duration if the variability of the instruments, software and operator is minimised, and regular and strict spirometry quality control programmes are applied [149–151]. Technician training should be performed before the field survey, at least within the pilot study, and only certified technicians should be involved in lung function measurements [152]. Training and certification of technicians should be repeated on a regular basis if the data collection lasts for >3 months.

CONCLUSION

The message of this paper is that thorough planning is worth half the study. It is crucial to stick to standardised methods and good quality control during sampling. This will increase the data quality, enhance comparison with other studies, and improve the possibility of the study results being published. When performing a survey on COPD, one should consider collecting biological markers, depending on the specific objectives of the study. Finally, we strongly recommend measuring as many different characteristics of COPD patients as possible, to help pave the way for an understanding of the disease well beyond spirometric classifications.

STATEMENT OF INTEREST

Statements of interest for P.S. Bakke and J. Vestbo can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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