162nd CSO Meeting 14-15 June 2005
Proposal for a new COST Action

COST B29
FOR A BETTER UNDERSTANDING OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) EXACERBATIONS

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DRAFT
MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action
designated as
COST B29

“FOR A BETTER UNDERSTANDING OF CHRONIC
OBSTRUCTIVE PULMONARY DISEASE (COPD)
EXACERBATIONS”

The signatories to this ‘Memorandum of Understanding’, declaring their common intention to participate in the concerted Action referred to above and described in the ‘Technical Annex to the Memorandum’, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 400/01 ‘Rules and Procedures for Implementing COST Actions’ the contents of which the Signatories are fully aware of.

2. The main objective of the COST Action B29 is to identify the best definition and characterisation of COPD exacerbations (COPD-Exac) and their role in the natural history of COPD with the key purpose to better understand COPD-related morbidity and mortality.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EURO 15 Million in 2005 prices.

4. The Memorandum of Understanding will take effect on being signed by at least five Signatories.

5. The Memorandum of Understanding will remain in force for a period of four years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter 6 of the document referred to in Point 1 above.
“FOR A BETTER UNDERSTANDING OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) EXACERBATIONS”

ABSTRACT

The main objective of the Action is to identify the best definition and characterisation of COPD-Exacerbations (COPD-Exac) and their role in the natural history of COPD with the key purpose to better understand COPD-related morbidity and mortality. The most important secondary objectives are: a) the definition of clinical, functional and biological outcomes to assess therapeutic strategies in management programmes; b) a more detailed understanding of underlying pathogenic mechanisms and aetiological factors; c) the optimisation and integration of treatment and preventive strategies to reduce the social and personal burden of the abrupt COPD events. The Dissemination Plan consists of: assemble and publish on a specific website a directory of European hospitals devoted to the COPD; develop a common protocol for database collection during clinical follow-ups of COPD patients to prospectively assess a sufficiently large sample of the European COPD patient population; set up a list of reference centres for specific research activities on COPD-Exac; update development of guidelines for diagnosis, management and therapy of COPD-Exac.

A. Background

Over the past 10 years, a major effort has been made to increase awareness of all facets related to chronic obstructive pulmonary disease (COPD). Several international societies, such as the European Respiratory Society (ERS) and the American Thoracic Society (ATS), and national scientific societies, among other international initiatives sponsored by public and scientific institutions have developed major concerted efforts towards this objective. COPD has been identified as a major and growing worldwide health problem associated with long-term exposure to toxic gases and particles, predominantly cigarette smoking, heavily challenging our current millennium. The major goal of all these initiatives is to decrease both mortality and morbidity from COPD by providing to healthcare workers, healthcare authorities and the general public state-of-the-art information concerning COPD.

Major causes related to COPD are: tobacco smoke, occupational dust, outdoor and indoor pollution, socioeconomic status, and genetic factors. Research prospects according to the European Lung White Book should be to: 1) create a stronger foundation for fighting COPD by acquiring accurate data on illness, COPD exacerbations (COPD-Exac), natural history, deaths and cost; 2) perform scientific surveys with spirometric of forced expiratory volumes in population samples in all European countries to improve knowledge of the distribution of COPD; 3) establish higher standards of COPD care through studies on the effectiveness of current prevention, education, medication and rehabilitation; 4) develop new therapeutic modalities that can inhibit the decline in lung function; 5) establish studies of the most
effective smoking cessation intervention, and techniques to prevent individuals from starting to smoke; 6) guide caregivers in the most efficient and effective ways to manage this disease. COPD is the only leading cause of death that is increasing in prevalence worldwide. Awareness of the increased burden of COPD in Europe has to reach governments, industry and the public. Europe should implement strategies for effective prevention, diagnosis and treatment of this disabling and life-threatening disease.

The natural history of COPD is one of a progressive lung function reduction, mainly expressed by an accelerated decline in the Forced Expiratory Volume in one second (FEV1), associated with limited exercise activity and health status (quality of life) deterioration and interspersed with varying frequency of episodes of COPD-Exac of symptoms. The mechanisms by which COPD-Exac could contribute to accelerated deterioration in health status and to progressive compromise of lung function in COPD are insufficiently known and remain elusive, being highly likely that several mechanisms are involved. There has been considerable interest in the identification (definition and characterisation), triggers (aetiology), mechanisms (pathobiology, pathophysiology, pathogenesis), management, therapy, and prevention. Despite that the heterogeneity of COPD is being appreciated increasingly, this is not always taken into consideration in studies of COPD-Exac, which are also heterogeneous into their own right. It has been demonstrated that the frequency of COPD-Exac increase with increased disease severity, mostly in patients with advanced (severe) stages (GOLD-Stage III) of the disease (FEV1<50% predicted), who are often prone to frequent and repeated episodes (named frequent exacerbators).

While understanding of the nature and triggering factors of COPD-Exac has increased greatly in recent years, these advances have been useful to confirm and assess their complexity and their heterogeneous nature, which vary enormously from person to person. This heterogeneity encompassing several different factors causes, such as bronchial infections, air pollutants, and/or climate, represents an additional problem as an increase in the underlying inflammatory response of the lungs may not be commonplace to all COPD-Exac. Furthermore, COPD-Exac represents one of the major battlefronts of the physicians’ clinical burden who have access to a limited therapeutic arsenal. Recent attempts have been made to evaluate the effects of standardising treatment and improving patient’s knowledge as part of a disease management healthcare programme to develop preventive strategies of COPD-Exac. Similarly, new comprehensive home care interventions in non-acidotic episodes of COPD-Exac, in the way of hospital at home (“home hospitalisation”), appear to be cost effective, a key feature of such new approaches being the redefinition of the roles and skills of specialised nurses and other allied professionals.

Among the principal reasons for cooperation are to reach a better definition and characterisation of COPD-Exac and to identify the role of COPD-Exac in the natural history of COPD for a better understanding of disease related morbidity and mortality. Important complementary areas of interest are the definition of biological, functional and clinical outcomes to assess therapeutic strategies in management programmes, a more detailed understanding of underlying pathogenic mechanisms and aetiological factors in COPD-Exac, optimisation and integration of treatment strategies, definition of more optimal preventive strategies and integration of these preventive determinants in integrated management programmes for COPD in general.
Complementary joint benefits are to closely collaborate with the European Respiratory Society (ERS) within the context of its research programmes developed according to its European Lung White Book and also with other major concerted efforts, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD), among others.

The COST Action B29 offers the best framework to foster an interactive platform facilitating synergisms by integrating the potential of one of the most solid networks of European centres of high excellence with the scientific bodies of a vast majority of national teams while having in parallel direct access to the major pharmaceutical industry principally involved in the development of new therapeutics molecules to improve the management and prevention of the major challenges imposed by COPD.

B. Objectives and Benefits

The main objective of the COST Action B29 is to identify the best definition and characterisation of COPD-Exac and their role in the natural history of COPD with the key purpose to better understand COPD-related morbidity and mortality.

Secondary objectives are: a) the definition of clinical, functional and biological outcomes to assess therapeutic strategies in management programmes; b) a more detailed understanding of underlying pathogenic mechanisms and aetiological factors; c) the optimisation and integration of treatment and preventive strategies in order to reduce the social and personal burden of the abrupt events, with integration of these preventive determinants in comprehensive management programmes for COPD; and, d) new models of patient centred health care by implementation of optimal self-management and substitution of care.

The major benefit of this concerted effort is the improvement of patient care, management and treatment of COPD-Exac. Such an ambitious goal can have a major beneficial impact on mortality and morbidity.

C. Scientific Programme

Five areas are identified to facilitate their development within the COST Action B29:

1. More data is needed to better define and classify COPD-Exac by severity. Specifically, one topics will address the development of a practical (operational) definition of an individual patient episode and the relationship of episodes defined in this way to the consensus-based definition of a COPD-Exac. Data about the symptom-based events have been collected using patient diary cards and the measurement properties of these instruments require exploration and standardisation for use in a consistent way in different countries. A practical approach, which will be made by the Action, to assessing the severity of the event require a comparison of systems which grade severity by the change in global symptom intensity with those which use the number of new symptoms reported during the attack as their index of severity. Clinical outcomes related to COPD-Exac, such as duration, frequency, “treatment-failure”, “treatment-resolution”, and also end-of-life (or end-stage) issues will all be
influenced by the choice of definition criteria.

2. The contribution of chronic lower airway colonisation/infection to COPD-Exac which is far from clear will be approached. Patients reporting chronic cough and sputum production are more likely to develop lower respiratory tract colonisation but the importance of other factors, i.e. co-existing bronchiectasis, COPD-Exac history, and severity of airway inflammation remains unsettled. More specifically, the role of lower airway infection (bacterial versus viral) against other potential mechanisms (i.e. climatic conditions, inflammation per se, ambient temperature, air pollution, etc) and their own interaction will be considered. Methods to identify lower respiratory tract colonisation without resort to complex and potentially invasive approaches, such as fiberoptic bronchoscopy, need exploration. The use of induced sputum specimens with quantitative microbiology and viral polymerase chain reaction (PCR) analysis may provide a robust methodology that can be applied in patients who appear clinically stable.

3. A better understanding of the mechanism of action and the optimal use of the existing pharmacological treatment approaches constitute one of the major goals of the Action. The effectiveness of antibiotic therapy on inflammatory markers and subsequent recovery from COPD-Exac has only recently been addressed and more work is needed to define the role of anti-infectious therapy in hospitalised as opposed to ambulatory patients. Although systemic corticosteroids are known to shorten COPD-Exac duration, their use in ambulatory outpatients is less clear while the optimum duration of treatment in patients admitted to hospital who normally have more advanced disease has not been defined. The importance of changes in dynamically regulated end-expiratory lung volume during the resolution of COPD-Exac is only now being appreciated; data about the effect of bronchodilators and other therapy on these processes, the degree to which change in lung volume predicts symptom improvement and the relationship of lung volume change to subsequent relapse will be studied.

4. The economic consequences of hospitalisation and the hazards to the patient of exposure to hospital-acquired infection have led many countries to develop an early-discharge ‘hospital-at-home’ (HaH) approach to the management of those COPD-Exac without accompanying acidosis in patients with serious co-morbidities. A particular focus of this issue will be put by the Action on the early prevention of relapse either by therapy plans or use of an individual case-managed approach following established protocols. The expectation is that those patients receiving these interventions after their initial COPD-Exac, will develop better coping strategies and increased self-efficacy that will reduce their subsequent medical care contact and will be associated with better health status. The interaction of the patient with other non-pulmonary (systemic) co-morbidities is necessary and needs to be explored to optimise management and treatment. Likewise the barriers to successful self-management in this programme will be identified by the Action.

5. The development of hypercapnic respiratory failure with its accompanying worsened hypoxaemia and acidosis is a critical point in the natural history of the COPD patient and commonly occurs for first time, often temporarily during a COPD-Exac. The relationship of the gas exchange disturbances to the underlying lung mechanics is not
well characterised and more data are needed using modern techniques to evaluate lung volumes and the presence of tidal flow limitation during expiration at rest if the existing therapy is to be applied in a more rational fashion. A second important area here is the systemic consequence of these episodes specifically the change in weight that commonly accompanies a severe COPD-Exac. How this relates to changes in body composition specifically in fat-free mass, to the structure and function of the skeletal muscle and the presence of circulating markers of inflammation that are increased in these episodes all require clarification.

D. Organisation

The Management Committee (MC) will be responsible for proposal of annual activities, distribution of funds according to the scientific needs of the Action (meetings, short term scientific missions, etc.) and will prepare the Annual Reports/Final Report. The Management Committee will meet at least two times per year during the planned scientific meetings. Their members will be also actively working for the Action during inter-Meeting periods.

The MC Chair will put together all the necessary information provided by the members of the MC and will assemble the directory of the European centres and scientists involved in research on COPD-Exac. The directory will appear on a website page dedicated to the COST Action B29 aimed at disseminating all the necessary information. The MC Chair will also be in charge of updating the directory, communicating the workshops which will be organised and disseminating the documents/guidelines produced by the COST Action B29.

Based upon an inventory of the activities and interests of the participating groups, the initial meeting of the MC will identify the clinical and research areas scheduled in the Scientific Programme and will coordinate how (what by whom) the objectives will be implemented.

A total of five Working Groups will be acting in the COST Action B29 according to the scientific programme provisions.

WG-1: WG on “Definition and characterisation of COPD-Exac”. This WG will develop activities related to the need to understand more about whether events defined by a change in symptom intensity for a specified period are consistent within patients, relate to different clinical outcomes and are similar in patients in different EU member states. This WG will develop a standardised terminology based on their data about the most appropriate approach to the definition of events.

WG-2: WG on “Pathogenetic mechanisms of COPD-Exac” will work based on the need to have more data relating evidence of colonisation/infection to fundamental clinical outcomes, such as heath status and lung function decline. The WG will deal with exploration as a tool to investigate the inflammatory consequences of persistent infection/colonisation and to identify patients where interventions, i.e. extended periods of antimicrobial therapy, may decrease the inflammatory burden and decrease exacerbation numbers and severity.

WG-3: WG on “Management and therapy of COPD-Exac” will deal with the particularly
important issue of pharmacological treatment of COPD-Exac, given the high prevalence of antibiotic-resistant organisms in some European countries, such as Spain or Germany.

WG-4: WG on “Healthcare models to manage and prevent COPD-Exac”. This WG will develop model care protocols and compare these to current standard care to determine whether there are sustained gains for both patient and healthcare payer in adopting newer innovative technologies such as telemedicine in the management of the acute episode. Programmes are needed to explore new models of healthcare to optimise the current “traditional” approaches of outpatient and hospital admission/emergency attendance and their role in preventing new episodes of COPD-Exac.

WG-5: WG on “Respiratory failure of COPD-Exac”. The optimal non-invasive ventilator strategy to maximise patient comfort and improve gas exchange needs to be better defined for different severities of exacerbation and its clinical impact in the post-exacerbation period will be explored.

The Action will held common WG meetings and will approach a permanent and intensive program of STSM to imply in networking activities young scientists and to strengthen the process of transfer of information and techniques between the participating groups.

E. Timetable

The total duration of the Action is four years

Year 1 (6-12 months)

- Joint meeting the of MC and all WGs to develop and implement a general planning of activities.
- First individual meetings of each WG.
- Communication on the website of all the proposals and news from the WGs.
- First release of the directory of centres.
- Approval by the MC of the animal results.

Year 2 (12-24 months)

- Joint meeting of the MC and of all WGs: to report and discuss on the research activities and development of guidelines by each WG. Release of the updated directory of centres. Communication on the website of the agenda of future activities.
- Specific meetings of the MC to scientifically coordinate the network activities.

Year 3 (24-36 months)

- Individual meetings of the five WGs: release of progress reports; coupled with MC meetings, if necessary.
- Integrated meeting of all five WGs and of the MC: discussion on progress reports and planning for release of guidelines.
- Release of updated directory of centres.
- Approval by the MC of the stage 3 results obtained.

**Years 3-4 (36-48 months)**

- Individual meetings and plenary sessions of WGs: Release of guidelines on diagnostic and therapeutic protocols. Statement papers on definition, outcomes and identified biomarkers, pathogenic aspects and future perspectives. Discussion on longitudinal data collected during follow-ups, pathogenic mechanisms, epidemiology and planning of future actions and continuing follow-up of COPD-Exac.
- Elaboration of a concluding document summarising the Action.
- Approval by the MC of the final results of COST Action B29.

The flow-chart of the networking activities is given below:
F. Economic Dimension

The following 13 countries have actively participated in the preparation of the current COST Action: Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Poland, Spain, Sweden and United Kingdom. On the basis of national estimates provided by the representatives of these countries, the economic dimension of the activities to be carried out under the COST Action has been estimated, in 2005 prices, at roughly EURO 15 Million. This estimate is valid under the assumption that all countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

G. Dissemination Plan

To reach the objectives of the COST Action B29, the following programme is planned:

- To assemble and publish a directory of European hospitals devoted to the daily management and care of COPD. Investigators working on similar or complementary clinical and research aspects related to COPD will thus be able to establish cooperation and exchange activities. External experts will also receive the necessary information to communicate and interact synergistically with the identified centres, thus fostering the implementation of a future COPD-Exac European Network.

- To develop a common protocol for database collection during clinical follow-ups of treated and untreated COPD patients to prospectively assess a sufficiently large patient sample representative of the European patient population.

- The Management Committee will set up a list of reference centres for specific research activities on COPD-Exac. Investigators from these centres will disseminate relevant information on recent vital findings, key publications, and diagnostic applications through the organisation of targeted workshops.

- Specialised centres of researchers will collaborate in the update development of guidelines for diagnosis, management, treatment and prevention of COPD-Exac. This information will be published in the international literature together with related joint studies generated within the network.

These objectives will be achieved through the following activities:

- Elaboration and diffusion (on a specific website) of a directory of European centres involved in the management and research of COPD-Exac. Release on the website of Annual Reports/Final Report.
- Implementation and update of guidelines for diagnosis, management, treatment and prevention of COPD-Exac.
- Release of a list of centres devoted to the research of pathogenic mechanisms of COPD-Exac, including respiratory failure aspects. This will include relevant information on key data, publications and clinical implications through the organisation of targeted scientific workshops.
COST Action B29

“FOR A BETTER UNDERSTANDING OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) EXACERBATIONS”

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2.3 APPENDIX

Chronic Obstructive Pulmonary Disease (COPD): “The Silent Killer”

Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation that is not fully reversible, although it can be preventable and treatable. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Symptoms, functional abnormalities and complications of COPD can partly be explained on the basis of this underlying inflammation and the resulting pathology. These changes may also have systemic consequences.

COPD is a common, costly and preventable disease that has substantial implications for the health of Europeans. However, the interpretation of measurements of the prevalence of disease and mortality in COPD in the population, particularly inter-country comparisons, is extremely problematic. The term COPD is used in a variety of ways when it is judged to be a contributing factor to, but not the main cause of, death, leading to misclassification and omission from medical records and vital statistics. Therefore, mortality data from COPD patients should always be interpreted with caution. In contrast to asthma, the diagnostic term COPD has not been widely used by physicians or other health professionals and is generally not recognised by the public. When questioned about their condition, most patients will say that they have asthma, chronic bronchitis, emphysema or that the disease is unrecognised. A prerequisite for diagnosis is the measurement of airflow limitation by spirometry but, in many areas, primary care physicians rarely use this to detect COPD in smokers or patients with respiratory symptoms. Greater public awareness of COPD is therefore one of the main aims of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (www.goldcopd.com).

Europe has a population of approximately 750 million and the World Health Organization (WHO) includes 51 countries in this region. Within Europe, there are large differences in population structure and great heterogeneity of the environment. Europe should therefore be an ideal region in which to explore the environmental influences on the incidence, prevalence and mortality of COPD. However, accurate estimates of mortality, prevalence and incidence are lacking from many countries.

Mortality

In 1990, the WHO estimated the standardised mortality rate of COPD to be 50 per 100,000 in males and 20 per 100,000 in females in European countries. Thus, approximately
200,000-300,000 people die each year in Europe because of COPD. According to the WHO, in 1997, COPD was the cause of death in 4.1% of males and 2.4% of females in Europe. A recent analysis of mortality trends in the USA from 1979-1993 showed that among 31 million death certificates, 8% had a diagnosis of obstructive lung disease (OLD). However, only 43% of the death certificates listing OLD had defined it as the primary underlying disease. The WHO previously published mortality rates for the combined category of “bronchitis, emphysema and asthma”, International Classification of Diseases (ICD) codes 490-493, which omits the largest category of COPD mortality. ICD code 519.3 in the eighth revision and ICD code 496 in the ninth revision. This results in a considerable underestimation of COPD deaths in France, Germany, Ireland and UK.

The mortality rates due to COPD in European countries are two to three times higher in males than in females with no country greatly below or above those ratios. The countries with the highest rates (more than 80 per 100,000) for males are the Ukraine, Kazakhstan, Ireland and Romania while the highest rates for females (more than 30 per 100,000) are in Romania, Ireland, Kazakhstan and Denmark. The lowest rates (less than 20 per 100,000) for males are observed in Greece, Sweden, Iceland and Norway and for females (less than 10 per 100,000) in Greece, Finland, Switzerland and Sweden. When codes other than ICD 490-496 are used for COPD, the distribution of mortality rates for COPD change considerably in these countries.

There were considerable differences in mortality trends from 1980-1990 among European countries. There has been an increase in mortality among females in northern European countries, such as Denmark and the UK, whereas there has been a decrease in the countries of Central and Eastern Europe, such as Bulgaria, Hungary and Romania. The upward trend in mortality is seen in females over 55 years of age and in males over 75 years. It is remarkable that over a short period of time there has been a substantial decline in death rates for the major causes of death in most countries, but not for COPD. In contrast to cardiovascular mortality rates, COPD rates are relatively insensitive to intermittent or short-term smoking cessation.

The WHO has made worldwide estimates of mortality rates for COPD. They estimated that age-specific mortality rates for COPD were considerably higher in China than in countries with established market economies. The death rates for COPD in China were also higher than in six other global health regions being countries with different economies: sub-Saharan Africa, India, Latin America and the Caribbean, the Middle East, and other Asian countries. The Global Burden of Disease Study has projected COPD mortality rates from 1990-2020 and estimates that COPD will account for over 6 million deaths per year in 2020, which will move COPD from the sixth to the third-leading cause of death worldwide over this period. The overall mortality from COPD will probably also increase in Europe due to the increased proportion of females who smoke, as well as the increased age of the population.

I. Prevalence

The frequency of COPD has been distorted by the use of different diagnostic terms and lung function criteria. The Italian general population study showed very large differences in prevalence estimates of COPD when using the 1986 American Thoracic Society criteria, the 1995 European Respiratory Society criteria or “clinical” criteria. The adoption of a simple spirometric definition (forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <70% and FEV1 <80% predicted) with standardised measurements may make it easier in the future to compare COPD estimates with different studies and countries. However, a
meaningful evaluation of the estimates demands knowledge of age distribution and smoking habits in examined populations.

For the last 40 years, the prevalence of COPD has been estimated in community surveys within several Nordic countries. Studies from the last two decades indicate that 4-6% of the adult population suffer from clinically relevant COPD. The prevalence increases greatly with age and recent surveys show only small gender differences. Prevalence studies in the UK have been reviewed and it was found that only one national study of spirometry had been conducted. This study of 5,547 males and females aged 16-65 years of age showed that an FEV₁ of two or more standard deviations below the age- and height-predicted value was present in 10% of males and 11% of females. A Norwegian spirometric survey of the general population aged 18-73 years gave a prevalence of 6% for airflow limitations defined as an FEV₁/FVC ratio below 0.70, while 4.5% has this ratio in addition to an FEV₁ of less than 80% of predicted. Using the stages advocated by the British Thoracic Society (BTS) and Norwegian reference values, only 0.2% of the adult population could be defined as having severe COPD with and FEV₁ less than 40% predicted. Below the age of 45 years severe COPD is a rare disease. A spirometric survey in a random sample of people, aged 25 to 73 years in the Po community in northern Italy, yielded spirometric prevalence estimates similar to those obtained in Nordic countries. Approximately 0.5% of the population could be considered to have severe COPD defined as an FEV₁ less than 50% of predicted. A comparison of community surveys in Sweden, Italy and Norway, using standardised methods showed similar prevalence estimates for bronchitic symptoms and airflow limitation. In a study carried out in random population samples aged 40-69 years in seven different regions of Spain, COPD was defined as an FEV₁/FVC ratio less than 88% of predicted in males and less than 89% of predicted in females with a negative (less than 12% increase in FEV₁) bronchodilator test. This study observed an overall prevalence rate of 10.6% for COPD. In a 1988-1994 population survey of 16,695 inhabitants of the USA, aged 17-89 years, airflow limitation was defined (as in the Norwegian study) as a combination of FEV₁/FVC less than 0.7 and FEV₁ less than 80% predicted. The overall prevalence of airflow limitation was 5.2%, while 8.2% reported a previous and/or current diagnosis of OLD. A model has been developed from this Third National Health and Examination Survey to estimate prevalence of COPD from the known smoking status of the population. With this model, it was estimated that 1.8 million people suffer from COPD in Spain, 3.0 million in the UK, 2.7 million in Germany, 2.6 million in Italy and 2.6 million in France.

The Global Burden of Disease Study has estimated the worldwide prevalence of COPD as 834 per 100,000 people, which yields approximately 44 million cases of COPD worldwide. In countries with established market economies the prevalence rate was estimated to be a low as 535 per 100,000. This estimate covers all ages. Since most cases of COPD usually become clinically apparent after the age of 45 years, this study grossly underestimates the prevalence of the disease in adults and the elderly. For countries with a life expectancy of 80 years or longer, and with more than 20% being smokers, these estimates are much too low.

II. Incidence

Longitudinal studies of lung function have shown that the development of airflow limitation is heavily dependent on smoking habits and dust exposure. The decline in FEV₁ seems to occur along a slowly accelerating curvilinear path. However, the distribution of the decline in lung function has a very wide range. Some relatively small studies did not show the development of FEV₁/FVC ratios below 0.70 in non-smoking males, followed up over 10-25
years.
A community study in Finland in 1961, of a population aged 40-64 years, was re-examined in 1971. The average incidence of an FEV₁/FVC less than 0.6 was 0.2% per year for the whole population and almost 1% per year in continuous smokers. In Zutphen, the Netherlands, the incidence of chronic non-specific lung disease (CNSLD) was studied from 1965-1985 in a population of males aged 40-59 years. CNSLD was defined as respiratory symptoms, such as regular cough and sputum production for longer than 3 months, or episodes of wheezing and shortness of breath reported to the survey physicians; or a diagnosis by a clinical specialist of CNSLD, including chronic bronchitis or emphysema. The average incidence was estimated to be 1.5% per year and remission did occur. The figures may imply that asthmatics may have been included in this survey. A 13-year follow-up study between 1968 and 1981 was conducted in a population aged 19-70 years in Krakow, Poland. COPD was defined as an FEV₁ below 65% predicted. The average incidence per year was 0.5%. The incidence was almost two times higher in males than in females and a considerable number of new cases of COPD were seen in non-smokers in this community.

The experts of the Global Burden of Disease Study were encouraged to make informed estimates of incidence of COPD in the eight health regions. The estimate for countries with established market economies was calculated to be 84 per 100,000 individuals, which is the less than one-fifth of that observed in Krakow, Poland. The observed incidence of COPD varies greatly in the available literature, partly due to the use of different indices of disease and partly due to reports of studies of small populations that were not followed for a sufficient length of time.

Precise estimates of the incidence of physician-diagnosed COPD, or spirometric airflow limitation, as defined by GOLD (FEV₁/FVC less than 0.7 and FEV₁ less than 80% predicted) are lacking for many countries. The overall incidence of FEV₁/FVC less than 0.7 over a 9-year period was 9.8% in an adult general population aged 18-74 years in Western Norway. In those aged 60-74 years, the incidence was 23%.

III. Disability-Adjusted Life Years Lost

Disability-adjusted life years (DALYs) have been used by the World Bank and supported by the WHO as a measure of the burden of disease. DALYs are the sum of years lost due to premature mortality and the amount of years lived with disability, adjusted for the severity of the disability. The disability weight for untreated COPD was estimated to be 0.43, using a person trade-off method, where death is weighted as 1.0 and perfect health as 0. Estimated DALYs for the world were calculated to be 29 million in 1990 and from this 2.3 million DALYs are accounted for by countries with established market economies. In 1990, COPD was the twelfth most common cause of disability in the world. According to the projection from the Global Burden of Disease Study, COPD will rank fifth as a cause of disability in 2020 and will be responsible for 4% of the total DALYs lost. Only ischaemic heart disease, depression, traffic accidents and cerebrovascular disease will be a greater burden.

IV. Causes

. Tobacco smoke
. Occupational dust
. Outdoor and indoor pollution
. Socioeconomic status
. Genetic factors

V. Financial Burden

Among respiratory diseases COPD is the leading cause of lost work days. In the EU (distinguished as 25 member states plus Norway and Switzerland throughout this chapter), approximately 41,300 lost work days per 100,000 population are due to COPD. The number is far lower in Central and Eastern Europe, where merely 4,300 lost work days per 100,000 individuals are due to COPD. Productivity losses amount to a total of €28.5 billion annually. Accordingly, indirect costs represent the major financial burden in COPD.

The total of COPD-related expenses for outpatient care is €4.7 billion. The annual number of consultations per 100,000 population ranges from 40,900 in Greece to 4,100 in Turkey, with an average of 17,300 within the EU. Inpatient care generates costs of €2.9 billion, followed by expenses for pharmaceutical at €2.7 billion.

Research Prospects

The priorities of research according to the European Lung White Book of the European Respiratory Society (ERS) should be the following:

- To create a stronger foundation for fighting COPD by acquiring accurate data on illness, exacerbations, natural history, deaths and cost.
- To perform scientific surveys with spirometric of forced expiratory volumes in population samples in all European countries to improve knowledge of the distribution of COPD.
- To establish higher standards of COPD care through studies on the effectiveness of current prevention, education, medication and rehabilitation.
- To develop new therapeutic modalities that can inhibit the decline in lung function.
- To establish studies of the most effective smoking cessation intervention, and techniques to prevent people from starting to smoke.
- To guide caregivers and care-payers in the most efficient and effective ways to manage this disease.

VI. The situation in 5 years’ time will be likely more favourable. In this regard, a more complete picture will be available on the prevalence, incidence and natural history of COPD. More knowledge will be available on the genetic factors that may influence the development of COPD. New drugs for COPD will be available to improve symptoms and the natural history of the disease.

VII. In summary, COPD is the only leading cause of death that is increasing in prevalence worldwide. Awareness of the increased burden of COPD in Europe has to reach governments, industry and the public. Europe should implement strategies for effective prevention, diagnosis and treatment of this disabling and life-threatening disease.

VIII. Today’s Status of COPD Exacerbations

The natural history of COPD is one of a progressive lung function reduction, mainly
expressed by an accelerated decline in the FEV$_1$, associated with limited exercise activity and health status (quality of life) deterioration and interspersed with varying frequency of episodes of COPD-Exac of symptoms. Although there is no consistently used definition for COPD-Exac, with repeated imprecise attempts to gain consensus, recently a consensus statement defined COPD-Exac as “a sustained worsening of the patient’s condition, from the stable state and beyond day to day variations that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD”. An amendment of the latter consensus definition, qualified for operational purposes, recommends the following replacement “…and may warrant additional treatment...” to incorporate all COPD-Exac of similar magnitude in which additional therapy was not necessarily sought.

Between 1990 and 1996 annual hospital admissions due to physician-defined OLD varied between 360 and 460 per 100,000 per year among inhabitants of Nordic countries. Admission rates have been increasing in females and the elderly. In those older than 60 years of age, the rates are more than 1,000 per 100,000. Thirty per cent had re-admissions during the same year. The average length of hospital stay was 9 days for patient with COPD and 5 days for patients with asthma. In contrast, admission rates due to asthma have declined considerably over the last 15 years. Hospitalisation rates for OLD are also dependent on the organisation of emergency units as well as the availability of hospital beds. Most of the admissions are recurrent admissions in elderly COPD patients. The number of hospitalisation for COPD for 1994 in Germany was 125,508 (1993), in the UK 73,342, Spain 45,624 and Italy 40,190.

In the UK, general practice annual consultation rates in 1991-1992 for COPD per 10,000 population increased with age from 417 at age 45-64 to 886 at age 65-74 and 1,032 at age 75-84 years, values that are two to four times the equivalent consultation rates for angina pectoris. The use of outpatient services for COPD patients also increases steeply with age. The mechanisms by which COPD-Exac could contribute to accelerated deterioration in health status and to progressive compromise of lung function in COPD are insufficiently known and remain elusive, being highly likely that several mechanisms are involved. Since COPD-Exac are a vital source of the morbidity and mortality found in COPD, there has been considerable interest in the identification (definition and characterisation), triggers (aetiology), mechanisms (pathobiology, pathophysiology, pathogenesis), management, therapy, and prevention.

Despite that the heterogeneity of COPD is being appreciated increasingly, this is not always taken into consideration in studies of COPD-Exac, which are also heterogeneous into its own right. It has been demonstrated that the frequency of COPD-Exac increases with increased disease severity, mostly in patients with advanced (severe) stages (GOLD-Stage III) of the disease (FEV$_1$<50% predicted), who are often prone to frequent and repeated episodes (named frequent exacerbators). According to data from three larger European clinical trials (Copenhagen, Euroscop, and Isolde) to assess the efficacy of regular administration of inhaled glucocorticosteroids in patients with COPD to reduce the FEV$_1$ decline over a 3 year period, COPD-Exac are uncommon in mild-to-moderate COPD while they are a characteristic feature of moderate-to-severe stages. Thus, it has been shown that there is increasing in frequency from on average less than one exacerbation per year in patients with an FEV$_1$$>$1.5 L to more than 2.5 per year in patients with very severe COPD (FEV$_1$$<$1.25 L); notwithstanding, 20% of patients in the latter COPD subset had no COPD-Exac during this 3 year period of study. COPD-Exac have a dramatic impact on daily health status, contribute to the decline of lung function and are one of the principal culprits of the elevated mortality due to the disease. Moreover, the burden of COPD-Exac to the healthcare services is enormous; causing the expenditure of huge resources and increasing dramatically economic costs (see
All over the year, although more heavily in winter, there is an increasing rate of admissions to hospital for COPD-Exac and, in terms of healthcare resources and service delivery, imposing a further impressive spanner in the works.

While understanding of the nature and triggering factors of COPD-Exac has increased greatly in recent years, these advances have been useful to confirm and test their complexity and their heterogeneous nature, which vary enormously from individual to individual. This heterogeneity that encompasses several different factors causes, such as bronchial infections, essentially due to bacteria and viruses, air pollutants, and/or climate with its potential unknown interaction, represents an additional problem as an increase in the underlying inflammatory response of the lungs may not be commonplace to all COPD-Exac.

Furthermore, while it is accepted that COPD includes also an abnormal inflammatory response of the lungs to external aggressive agents, it is unknown whether or not the airway inflammatory process is necessarily accentuated during COPD-Exac. Accordingly, it is highly likely that that the heterogeneous nature of the stimuli that can lead to COPD-Exac will initiate different pathobiological processes with different clinical sequelae. COPD-Exac are by their nature heterogeneous at a cellular level, possibly with different clinical implications. Increased neutrophils and eosinophils (less frequently) have been reported repeatedly in COPD-Exac. Similarly, the levels of cytokine release seem equally heterogeneous among COPD-Exac, and this may have also considerable clinical and therapeutic consequences in that the high circulating levels of some of these mediators, such as tumour necrosis factor (TNF)-alpha, may then contribute to cachexia and muscular weakness, a well-known COPD phenotype in advanced stages. Likewise, the elevated levels of plasma fibrinogen and interleukin-6 demonstrated in acute COPD can lead to a hypercoagulability state with thrombotic consequences, hence facilitating an enhancement of the systemic effects of the disease. Cardiovascular co-morbidities, depression, osteopaenia, and fluid retention, altogether reported as systemic effects in COPD can be modulated by the release of all these molecules. Furthermore, we ignore what can be the links and/or pathways with the frequent coexistence of acute hypoxemic or hypercapnic respiratory failure during the more severe episodes of COPD-Exac. In sum, it is highly plausible that different COPD-Exac may lead to different pathogenic mechanisms, hence contributing to specific clinical and therapeutic implications.