

CLINICAL REVIEW

The Burden of Obstructive Lung Disease Initiative (BOLD): Rationale and Design

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ABSTRACT

Quantifying COPD prevalence worldwide is needed to document COPD's effect on disability, health care costs, and impaired quality of life and to inform governments and health planners. As an adjunct to data obtained from population-based studies, and for countries where a fully powered prevalence survey cannot be done, modeling of COPD prevalence and its economic burdens can help estimate potential health care needs and costs. For comparability, standardized methods for prevalence surveys are needed that can be used in countries at all levels of economic development. The Burden of Obstructive Lung Disease (BOLD) Initiative has developed a set of methods for estimating COPD prevalence and a model for assessing its economic impact, and piloted these methods in China and Turkey. The methods were revised to reflect the findings in the pilot studies, and BOLD is now making the standardized methods available worldwide. The BOLD Operations Center provides training,

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materials, quality control, and data analysis. **BOLD emphasizes data quality control at every stage of the process. Data from paper forms completed in the field are entered electronically to a specially designed secure Web platform. Pre- and post-bronchodilator spirometry testing is done on all participants, and all spirometry data are reviewed for quality. Questionnaires are used to obtain information about respiratory symptoms, health status, exposure to risk factors, and economic data about the burden of COPD. BOLD's standardized methods will provide a uniform way to compare COPD burden within and between countries, and where differences are found, to explore explanations for these differences.**

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of morbidity and mortality in the US (1). Worldwide, COPD is projected to rank fifth in burden of disease and third with respect to mortality in 2020 (2, 3). Even so, COPD fails to receive adequate attention from the health care community and governments and is virtually unknown among the public. A major problem is the lack of information about the prevalence and economic and social burden of COPD, especially in developing countries. This lack of information leads to an incomplete understanding of the substantial impact of the disease on quality of life and direct and indirect health care costs.

An accurate database of COPD prevalence and a tool to project economic and social burden would help inform governments and health planners. The database should document the impact of the disease with regard to disability, health care costs, and impaired quality of life. To be most useful, such a database should be developed from population-based studies using standardized methods. The first step, then, is to develop standardized methods that can be used in countries at all levels of economic development. The availability of standardized methods will make it possible to estimate prevalence and compare prevalences within and between geographic areas. Standardized methods will also allow investigators to explore differences in COPD observed between different areas and quantify the risks attributable to different exposures. As an adjunct to COPD prevalence data obtained from population-based studies, and for countries where a fully powered prevalence survey cannot be done, modeling of COPD prevalence and its economic burden could be used to estimate health care needs and costs.

The Burden of Lung Disease (BOLD) Initiative was designed to develop robust models that can be used to estimate the prevalence and current and future economic burden of COPD.

OVERVIEW OF THE BOLD INITIATIVE

BOLD's primary objectives are to: 1) measure the prevalence of COPD and its risk factors in various areas around the world; 2) estimate the burden of COPD in terms of its impact on quality of life, activity limitation, respiratory symptoms, and use of health care services; and 3) develop a model to project future burden of disease for COPD.

Secondary objectives are to: 1) compare different diagnostic criteria for COPD, including those proposed by the American Thoracic Society/European Respiratory Society (4) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2, 3); 2) determine the extent to which variations in risk factors contribute to variations in the prevalence of COPD; 3) describe the distribution of COPD according to age, sex, and smoking history; 4) describe the main clinical symptoms reported by subjects diagnosed with COPD; 5) assess the sensitivity and specificity of selected clinical symptoms for COPD using lung function testing as the gold standard; and 6) characterize the clinical management of COPD in selected broad geographic areas.

Recognizing the importance of standardizing methods worldwide, BOLD worked collaboratively with PLATINO, an initiative of the Latin American Thoracic Society, to develop the BOLD methods. PLATINO used these methods to estimate COPD prevalence in 5 Latin American countries (5), and the BOLD Initiative piloted the methods in 2 countries, China and Turkey. Lessons learned from PLATINO and the BOLD pilots were incorporated into the final BOLD methods, which now are available for implementation worldwide. Three countries have been trained and will collect data in 2004 and 2005, and BOLD is presently enrolling countries for 2005 and 2006. The BOLD protocol and application form are available on the BOLD web site (www.boldcopd.org).

The BOLD Executive Committee developed the initial protocol and provides ongoing scientific oversight for the study by means of annual face-to-face meetings, monthly conference calls, and e-mail communications. The BOLD International Advisory Board provides an additional level of review and also acts in an advisory capacity. The BOLD Operations Center (OC) provides the overall administration and supervision of the BOLD Initiative.

The primary emphasis in BOLD is on building rigorous quality into the methods. The OC, located at the Kaiser Permanente Center for Health Research in Portland, Oregon, supervises all aspects of the protocols. All spirometry data are reviewed for quality control by the pulmonary function reading center in Salt Lake City, Utah, under the direction of Robert Crapo, MD. Spirometry data and quality scores are returned to the field site so that they can be used for feedback and continued training of the field staff.

An additional part of the BOLD Initiative is the development of an interactive, Web-based model to estimate the economic burden of COPD. This model, once completed,

will be accessible to all on the BOLD web site so that country-specific estimates of the prevalence and economic burden of COPD can be compared.

DESIGN FEATURES

Participants

BOLD is designed primarily as a COPD prevalence survey among non-institutionalized adults aged 40 years and over. This age range was chosen for efficiency, as the prevalence of COPD climbs steeply over age 40. Participating sites are expected to recruit a minimum of 600 persons, preferably split evenly between men and women.

In order to develop valid estimates of future burden of disease, participating sites are encouraged to survey an additional cohort on the prevalence of smoking and other key risk factors. The additional cohort, made up of at least 600 men and women aged 18–39 years, will not be asked to provide lung function measurements. Completion of this portion of the study is not required for a site to participate in the primary prevalence survey. Sites that include a younger age group may choose to follow this cohort prospectively with or without spirometry.

Target population

All sites wishing to participate in the collaborative analysis are required to recruit participants from a well-defined target population meeting the characteristics described below. This population, along with the sampling frame and sampling methodology used to select individuals from it, must be approved in advance by the OC.

The target population should ideally be defined by meaningful administrative boundaries for which other types of routinely collected information, such as census and air pollution data, are also available. In order to avoid sampling populations that may have limited generalizability, the area should have a total population, including all ages, of at least 150,000 people. A target population may be a well-defined area within some larger administrative boundary, so long as it meets the requisite sample size requirements and is representative of the larger population in terms of housing stock, socioeconomic status, and air quality, in order to maximize the generalizability of the data. In this case, participating sites are required to document to the extent possible the comparability of the selected administrative area with the larger population.

Sampling

Participating sites are expected to select a true population-based random sample from non-institutionalized individuals living within their target population. This may take the form of, for example, a simple random sample, a stratified random sample, or some form of cluster sample. Although the OC

must review and approve the sampling methodology and has a sampling expert to assist in this process, individual sites are required to identify local sampling experts who can advise on this portion of the study and assist in its implementation as needed.

The proposed sample size of 600 individuals is designed to provide an acceptable level of precision for estimating prevalence at any given site. Because this sample size will result in a fairly limited number of individuals with COPD at any given site (e.g., 90 if the prevalence is 15%), investigators are free to recruit more than the minimal sample size of 600 in order to maximize the utility of results from their specific site, and to further analyze the data.

Data collection

Study participants complete a questionnaire covering respiratory symptoms, health status, activity limitation, and exposure to potential risk factors, such as tobacco smoke, occupational risk factors, and biomass exposure. They also perform pre- and post-bronchodilator spirometry tests. Data for BOLD consist of electronic spirometry records that provide the 1-second and 6-second forced expiratory volumes (FEV₁ and FEV₆) and the forced vital capacity (FVC), responses to questionnaires administered to individual participants, individual tracking data to document the final outcome for each person invited to participate, and aggregate data about the target population. The last may include demographic data, information on socioeconomic status, and data on air quality for the geographic area in which the target population resides.

Questionnaires

The BOLD Core questionnaire was developed where possible from pre-existing validated questionnaires that had already been used in multi-national studies. The questionnaire obtains information about respiratory symptoms (cough, sputum, wheezing, shortness of breath); exposure to potential risk factors, including smoking; occupation; respiratory diagnoses (e.g., asthma, emphysema, COPD, chronic bronchitis); co-morbidities; health care utilization; medication use; activity limitation; and health status. It includes sections taken from the 1978 ATS/DLD Respiratory Symptom Questionnaire (6) and the questionnaires used in the European Community Respiratory Health Study (7), the CNR study (8), and the OLIN study (9). It also includes the SF-12 to assess overall health status (10).

Participants also are expected to complete an occupational questionnaire and (for current cigarette smokers) a “stages of change” questionnaire (2) that assesses readiness to quit smoking. For countries where it is applicable, there is also an optional questionnaire to assess exposure to biomass fuels used in the home for either heating or cooking. The questionnaires must be administered by trained and certified staff; self-administration of questionnaires is not allowed.

Supplemental questions

Individual sites may ask additional questions to reflect factors either unique to that site or of particular interest to the local investigators. Local sites are responsible for developing their own data entry applications for supplemental data and for integrating supplemental data with the main study data set for local analysis.

Spirometry

The single most important outcome measure obtained as part of the BOLD protocol is spirometry before and after administration of 200 µg (2 puffs) of albuterol/salbutamol. The use of a bronchodilator is important because present diagnostic criteria for COPD recommend the use of post-bronchodilator values for the diagnosis and classification of severity (2). Although standardized methods for performing spirometry are available and widely used, no single standard is universally applied in practice. Proper training and ongoing quality control are essential to obtaining consistently high-quality measurements over time. The methods developed for BOLD meet or exceed the ATS standards (11) for acceptable equipment and technique. The BOLD methods were developed assuming that testing will often be done in the field, i.e., not in a climate-controlled pulmonary function laboratory. The primary spirometry measurements to be used for analysis include the FEV₁, the FVC, and the FEV₆, allowing comparison of FEV₁/FVC and FEV₁/FEV₆ as measures of airflow limitation. The FEV₆ has been demonstrated as a viable surrogate for the FVC and has important advantages—it requires only 6 seconds of exhalation time and has about 25% less variability than the FVC (12). In epidemiologic studies, there are significant advantages to requiring only 6 seconds of maximal exhalation, such as less coaching time, less chance of dizziness, and less physical discomfort to participants than a complete exhalation.

To optimize quality control in the BOLD study, sites are required to use the ndd EasyOne™ Spirometer, which was chosen because it provides a high degree of accuracy, robustness, portability, and ease of storage. It can be used easily in the field and where there is no electric power available—it operates on batteries and requires no calibration with a 3-liter syringe. The ndd spirometer has been approved by the BOLD pulmonary function reading center as meeting predetermined performance criteria relating to reliability of measurement, suitability for field use, and ease of access to data.

Other clinical measurements

Each participant's height and weight are measured by trained field staff. Use of a wall-mounted stadiometer is recommended for height measurement to provide maximum quality control. Height and weight are measured with participants wearing indoor clothing without shoes.

Data management

Once data collection is completed for any given site, the OC provides that site with an electronic copy of its own fully cleaned and edited data for use in conducting site-specific analyses. The OC also provides each site with a statistical report summarizing the key study outcomes. A copy of the data is also retained at the OC for pooled, cross-site analyses.

Spirometry

Each site sends its spirometry data electronically to the OC, which in turn sends them to the pulmonary function reading center. The pulmonary function reading center grades each maneuver and assigns an overall quality score to initial effort, FEV₁, and FVC based on ATS acceptability and reproducibility criteria. The FEV₆ is not specifically graded, but since the quality assessment process focuses on total exhaled volumes and the length of exhalation, the quality of the FEV₆ is indirectly assessed during this process. The pulmonary function reading center also reviews the quality of spirometry from each technician in order to monitor for decline in the quality scores. The OC uses this information to initiate corrective action as needed. For example, if the quality of an individual technician's spirometry falls below a critical level, the technician must stop testing study participants and be re-trained and re-certified before returning to fieldwork.

The transmission of spirometry records is done through secure encrypted Internet transfer. Transfer of data between the OC and the pulmonary function reading center uses this same method. Data are transmitted using a standard format (for example, in an Access database) on a regular basis (for example, once each week) to the server at the OC. Use of the same type of spirometers and software throughout the project makes training more efficient and data compilation and transfer easier and less susceptible to error. Data transferred to the OC also remain stored at the local site in their original form (e.g., paper forms and electronic databases).

Questionnaire data

Questionnaires are administered using paper copies. Individual questionnaire data are entered in Web-based forms and transmitted by Internet directly to the OC. The data entry application performs a variety of edit checks to make sure that ineligible values are not allowed and suspect values are verified. The OC performs additional, more detailed edit checks after receiving the data.

Quality control

The BOLD project employs several measures to assure a high level of quality control in all aspects of the study. Formal written procedures exist in an extensive manual of procedures for all aspects of the study, including the questionnaire, lung function testing, data management system use, and study sample selection. Prior to undertaking the protocol, staff must

be trained and certified in study procedures. Two or 3 staff members from each site are required to attend a central training session to be trained as “master trainers” of additional staff at their sites. This “train-the-trainer” approach has been chosen to reduce the cost burden to sites for a training week in a distant location, and to deal with the language barriers that a central training of field staff would pose. The OC monitors training and assumes responsibility for assuring that all staff on the study are properly certified.

The ndd EasyOne™ Spirometer approved for use in this study meets the highest standards of quality control while still being affordable and suitable for field use. Staff from the pulmonary function reading center direct the training of master trainers in lung function testing from each site and supervise ongoing quality control monitoring of pulmonary function technicians, as described above.

The OC has developed detailed instructions for administering and coding each study questionnaire to assure maximum comparability in how the questionnaires are administered and responses are scored. Participating sites must translate the questionnaires into their local language following a standardized protocol. The OC back-translates each questionnaire into English as a further quality control check, and differences between the original and back-translated versions are reconciled. The protocol specifies the requirements for the original and second language of the individuals who do the forward and back translations. The OC maintains the original and back-translated versions of all versions of the questionnaires.

The data entry system for the study uses real-time edit checking, along with double entry of selected fields, to assure that errors in data entry are minimized and the final data set is as clean as possible.

Primary outcome

As stated in the Overview, BOLD’s primary objectives are to 1) measure the prevalence of COPD and its risk factors in various areas around the world; 2) estimate the burden of COPD in terms of its impact on quality of life, activity limitation, respiratory symptoms, and use of health care services; and 3) develop a model to project future burden of disease for COPD.

An important secondary objective is to compare different diagnostic criteria for COPD. We are well positioned to do this, because we obtain pre- and post-bronchodilator lung function data plus symptom and health status information. GOLD states that “The presence of a post-bronchodilator $FEV_1 < 80\%$ predicted, together with an $FEV_1/FVC < 70\%$, confirms the presence of airflow limitation that is not fully reversible. In patients with $FEV_1 \geq 80\%$ predicted, $FEV_1/FVC < 70\%$ may be an early indicator of developing airflow limitation” (2).

Operationally, we will initially define COPD as a post bronchodilator $FEV_1/FVC < 70\%$ and further designate severity using the GOLD criteria (2). To obviate the need to develop

reference values for each country site, we will use common reference values as developed by the US NHANES 3 Study (13).

Using a post-bronchodilator $FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ predicted to define COPD will inevitably result in some misclassification with asthma, especially in older adults and longstanding disease. To minimize this misclassification, we obtain information about doctor diagnosis of asthma and about current medications on the assumption that most asthmatics with significant irreversible asthma will have a diagnosis of asthma and will probably be on asthma medications.

Data analysis

The OC conducts limited site-specific analyses as well as more comprehensive analyses of the trial-wide data.

Site-specific analyses

The OC continually checks on each site’s data during data collection as part of its ongoing quality control activities. It then follows up with each site to attempt to resolve data discrepancies rapidly. At the conclusion of each site’s data collection activities, the OC generates a basic statistical report for each site’s data and returns this report to the site, along with the site’s cleaned data set. The report includes response rates, characteristics of responders and non-responders, univariate statistics on all study variables, and properly weighted tables showing COPD prevalence estimates. Prevalence estimates are shown both overall and for selected subsets of the population, such as men and women, smokers, non-smokers, and ex-smokers. The report also summarizes the derivation of weights used for computing the prevalence estimates and their standard deviations. Each site may use its report as a basis for further investigation or for presentations and publications, at the judgment of the local principal investigator.

Analyses of study-wide data

The OC will conduct analyses of study-wide (cross-site) data at the end of the study. Data used in trial-wide analyses will be weighted according to the sampling design used by each site.

Economic burden analyses

The burden of disease model is a policy model that estimates the current and future economic burden of COPD. The model was developed to use aggregate estimates from the prevalence survey and site-specific cost and population estimates to provide an estimate for each site of current and future costs related to COPD. Costs per capita and per patient with COPD and costs for categories of COPD severity can be determined. Model simulations and calculations are conducted on a standard spreadsheet platform with an interface that allows for changes in input parameters to conduct sensitivity analyses.

Table 1. Estimated half-width of 95% confidence interval for estimating prevalence assuming simple random sampling*

Sample size	Prevalence (%)									
	6	9	12	15	18	21	24	27	30	33
200	3.3	4.0	4.5	4.9	5.3	5.6	5.9	6.2	6.4	6.5
250	2.9	3.5	4.0	4.4	4.8	5.0	5.3	5.5	5.7	5.8
300	2.7	3.2	3.7	4.0	4.3	4.6	4.8	5.0	5.2	5.3
350	2.5	3.0	3.4	3.7	4.0	4.3	4.5	4.7	4.8	4.9
400	2.3	2.8	3.2	3.5	3.8	4.0	4.2	4.4	4.5	4.6
450	2.2	2.6	3.0	3.3	3.5	3.8	3.9	4.1	4.2	4.3
500	2.1	2.5	2.8	3.1	3.4	3.6	3.7	3.9	4.0	4.1
600	1.9	2.3	2.6	2.9	3.1	3.3	3.4	3.6	3.7	3.8

*Ignores finite sample correction factor.

The BOLD model is a multi-state Markov model that follows a cohort of patients over a fixed time duration. The model includes health states for patients with COPD and patients that are “at-risk” for developing COPD. The “at-risk” population is important for estimating the future burden associated with COPD. The model is divided into 10 mutually exclusive health states: 1) Smoker; 2) Never Smoker; 3) Former Smoker; 4) Non-smoker COPD Stage I (2, 3); 5) Non-smoker COPD Stage II; 6) Non-smoker COPD Stage III/IV; 7) Smoker COPD Stage I; 8) Smoker COPD Stage II; 9) Smoker COPD Stage III/IV; and 10) Dead. Patients move between the health states based on annual transition probabilities. The transition probabilities were obtained through published literature or empiric analyses.

The information from the prevalence surveys is used to populate the model for each of the BOLD sites. Information obtained from the prevalence surveys is compiled as gender-specific summary information. Parameters used in the model include estimates of prevalence, smoking rates, and health care utilization rates. Exacerbation rates are included in the economic model and are thus included in the current and future cost projections. The cost information used in the economic model is based on local unit cost estimates for hospitalizations, healthcare provider visits, and medications. Additionally, estimates of incidence rates for COPD, mortality rates, and smoking prevalence in younger populations are used to determine future costs associated with the disease.

Current and future costs are estimated for lost productivity as well as direct medical expenditures. Lost work time due to COPD is estimated from the prevalence survey and multiplied by local wage rates to estimate the cost of lost productivity.

The model allows for sensitivity analysis by varying the values of key variables, helping to understand how policy might affect the current and future burden of COPD. The sensitivity analyses focus on variable distributions, prevalence estimates, smoking rates, risk from non-smoking environmental exposure, and COPD incidence rates. In addition to the built-in scenarios, model users will be able to vary other input parameters to evaluate the impacts of these changes on overall costs.

The model can provide decision-makers with a tool to estimate the current and future economic burden associated

with COPD in their region. Decision-makers can estimate the resources that will be required to treat patients with COPD 5, 10, or 20 years into the future. A final application of the model could be the economic evaluation of various interventions that might affect patients with COPD, whether the interventions reduce exacerbation rate or change disease progression, and the economic implications of new interventions.

Sample size

The proposed sample size for BOLD (a minimum of 600, divided evenly between men and women) is designed to provide an acceptable level of precision for estimates of prevalence at any given site assuming simple random sampling. It also will allow for the reduced precision that may result from alternative design, such as cluster sampling, that many sites are expected to use.

Table 1 shows the level of precision that can be expected for various estimates of prevalence. The entries in the table represent the half-width of a 95% confidence interval and are computed under the assumption that the finite population correction factor can be ignored. Thus, for example, with an estimated prevalence of 15%, a 95% confidence interval for each gender would be 15% ± 4%, while the comparable confidence interval for the sample as a whole (assuming equal prevalences for men and women) would be about 15% ± 2.9%. If, as is likely, the prevalence of COPD differs for men and women, the figures shown in Table 1 will likely underestimate the true margin of error. Even with a design effect of 1.5 due to clustering, the effective sample size for the whole site would still be 400, resulting in confidence intervals ranging in width from 5 to 9 percentage points for the prevalences we anticipate.

SUMMARY

The BOLD initiative offers standardized methods for measuring the prevalence of COPD and its risk factors in various countries around the world; estimating the burden of COPD in terms of its impact on quality of life, activity limitation, respiratory symptoms, and use of health care services; and making available worldwide a model to project

future burden of disease for COPD. The information that BOLD gathers will be invaluable in documenting COPD's considerable effect on disability, health care costs, and quality of life to inform governments and health planners. The ultimate goal is to use this information to provide resources to improve COPD treatment and quality-of-life for patients.

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