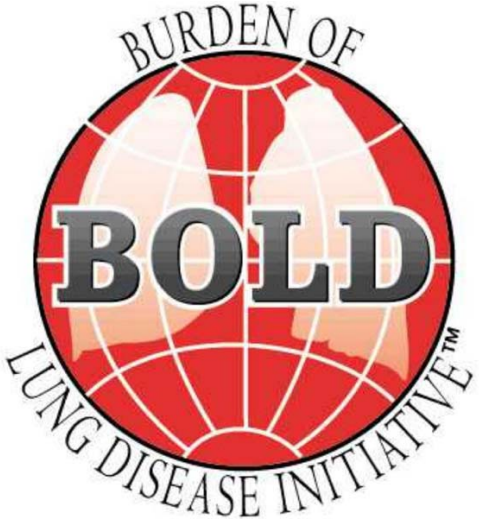
BURDEN OF OBSTRUCTIVE LUNG DISEASE (BOLD)

Chapter 1

Protocol



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OVERVIEW

The BOLD project will develop a standardized protocol to obtain information about the prevalence and burden of COPD, and will implement this protocol in a number of countries throughout the world. This work will be accomplished in three phases:

Phase 1 (June - December 2001) planning phase: development of a "cookbook" of standardized methods for estimating COPD prevalence and establishment of an Operations Center.
Phase 2 (June 2002 – March 2004) pilot projects: planning, execution, and data analysis of pilots; "cookbook" revised.
Phase 3 (March 2004 –December 2006) standardized methods available. All countries encouraged to plan prevalence surveys. Operations Center provides coordination, training, materials, and data analysis.

The BOLD project can be defined by a number of operational and scientific objectives. The former define the work to be accomplished in each phase of the project, and the latter define the scientific aims of the project

OPERATIONAL OBJECTIVES

Phase 1: Specific Objectives

- Develop a basic "cookbook" of standardized methods that can be used to estimate COPD prevalence in countries with citizens of all income levels.

Phase 2: Specific Objectives

A. Prevalence Surveys

- Design, plan, and execute prevalence surveys in a limited number of pilot sites.
- Evaluate quality control procedures and refine them as needed.
- Test communications systems and revise them as needed.
- Test data entry and management systems and refine them as needed.
- Generate valid COPD prevalence estimates for the pilot sites.
- Finalize the "cookbook" for use in Phase 3.
- Develop rough budget estimates for use by sites wishing to participate in phase 3.

B. Burden of Disease Model

- Develop a model for estimating the burden of COPD using prevalence, smoking, and mortality data that may exist (or may need to be generated) locally.

- Test the model using pilot data.

Phase 3: Specific Objectives

- Make standardized methods available to as many countries/investigators as are interested.

- Maintain an Operations Center to provide oversight, training, materials, quality control, and data analysis.

- Use prevalence and burden of disease data to support the Global Initiative for Chronic Obstructive Lung Disease (GOLD)

SCIENTIFIC OBJECTIVES

Primary Objectives

1. Measure the prevalence of COPD and its risk factors in various countries 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.

3. Develop a validated model to project future burden of disease for COPD.

Secondary Objectives

1. Compare the impact on COPD prevalence of using various definitions of COPD, including those proposed by the American Thoracic Society[1], The European Respiratory Society[2], and GOLD[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 as the gold standard.

6. Characterize the clinical management of COPD in selected broad geographic areas.

BACKGROUND

COPD is the fourth leading cause of morbidity and mortality in the US and worldwide is projected to rank fifth in burden of disease in 2020[3], yet COPD fails to receive adequate attention from the health care community and governments. A major problem is the incomplete information about the causes, prevalence, and burden of COPD, especially in developing countries, and lack of understanding of the substantial impact of the disease on quality of life and health care costs.

COPD is defined as a disease state characterized by airflow limitation that is not fully reversible[3]. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Removal from the exposure usually slows the progression of disease[3]. COPD, once present, may have a lengthy and costly course.

A diagnosis of COPD should be considered in anyone, particularly smokers**,** with symptoms of cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease. Cigarette smoking is by far the most important risk factor in most countries, but other factors, such as heavy occupational exposures to particulates and indoor and outdoor air pollution, can be causally related to COPD when the exposures are sufficient[3]. Genetic risk factors may modify the risk, but these are poorly understood at present.

A state-of-the-art database of COPD prevalence should be available to inform governments and health planners. The database needs to document the impact of the disease with regard to disability, health care costs, and impaired quality of life. The COPD database should be developed from population-based studies using standardized methods, so the first step must be to develop standardized methods that can be used in countries with citizens at all income levels. Investigators in many countries could use these methods within and between countries to quantify and compare prevalences and costs.

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. One of the major aims of the BOLD program, therefore, is to develop robust models that can be used to estimate the prevalence and cost of COPD.

DESIGN

Adults Aged ≥40 Years

BOLD is designed primarily as a COPD prevalence survey among non-institutionalized adults aged ≥40 years. Individuals in this age range will be asked to complete a questionnaire covering respiratory symptoms, health status, activity limitation, and exposure to potential risk factors, such as tobacco smoke. These individuals will also be asked to provide measurements of lung function before and after administration of a short-acting bronchodilator. Participating sites are expected to recruit a minimum of 300 men and 300 women in this age range.

Adults Aged 18-39 Years

In order to develop valid estimates of future burden of disease, participating sites will also be encouraged to survey an additional cohort of non-institutionalized individuals aged 18-39 years on the prevalence of smoking and other key risk factors in these groups. These individuals will not be asked to provide lung function measurements. Completion of this portion of the study is strongly encouraged, but it is not a requirement for participation in the primary prevalence survey.

METHODS

Selection and Recruitment of Study Population

All sites wishing to participate in the collaborative analysis will need 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 Operations Center (OC).

Target population

The target population should ideally be defined by meaningful administrative boundaries for which other types of routinely collected information, such as air pollution and census data, are also available. In order to avoid sampling populations that may have only 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. For instance, rather than attempting to take a true random sample from all of Guangzhou, China, an investigator may choose to sample only one (or more) of the administrative districts that comprise Guangzhou. For the purposes of BOLD, the resulting population need not be "representative" of all of Guangzhou, although this may be an important consideration for the local investigator. For instance, the prevalence of COPD within a single administrative district from Guangzhou may not be representative of the prevalence of COPD within the city as a whole. This needs to be balanced against the relative cost of and logistical feasibility of doing the survey in one administrative district versus the whole city. If the investigator does choose to sample from a particular administrative area, that area should ideally be known to be 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 latter case, participating sites should attempt to document the comparability of the selected administrative area with the larger population and to share this information with the Operations Center.

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. While the OC in Portland, Oregon, USA, must review and approve of the sampling methodology and has a sampling expert to assist in this process, it is essential that individual sites identify

local sampling experts who can advise on this portion of the study and assist in its implementation if needed.

Recruitment

The goal for each center is to collect complete spirometry and questionnaire data on 300 men and 300 women aged ≥40 years. Those centers that are also recruiting a younger cohort should complete the minimal questionnaire on 300 men and 300 women aged 18-39 years. In order to characterize properly the response rates and compare the characteristics of responders and non-responders, each center must keep careful records concerning the ultimate outcome of each participant it attempts to recruit.

As noted in the sample size section, the proposed sample size of 600 individuals is designed to provide an acceptable level of precision for estimating prevalence at any given site. However this sample size will result in a fairly limited number of individuals with COPD at any given site (e.g,. 60 if the prevalence is 10%), although this won't be a problem for the analysis of trialwide data. As a result, investigators may wish to recruit more than the minimal sample size of 600 in order to maximize the utility of results from their specific site.

Questionnaires

The BOLD Core questionnaire has been developed where possible from pre-existing validated questionnaires that have already been used in multinational studies. The intent is to obtain information about respiratory symptoms (cough, sputum, wheezing, shortness of breath), exposure to potential risk factors, occupation, respiratory diagnoses (asthma, emphysema, COPD, chronic bronchitis, etc.), co-morbidities, health care utilization, medication use, activity limitation, and health status. It includes sections taken from the 1978 ATS/DLD Respiratory Symptom Questionnaire and the questionnaires used in the European Community Respiratory Health Study and the US Lung Health Study. It also includes the SF-12 to assess overall health status.

All participants are expected to complete the BOLD Core, Stages of Change and Occupational questionnaires. There is also a Minimal Data/Refusal questionnaire for participants who are not willing to participate in the full protocol. All questionnaires need to be administered by trained staff. Self-administration of questionnaires is not allowed.

Supplementary questions for local use only

In addition to the Core questionnaire and Stages of Change and Occupational questionnaires, individual sites may choose to add additional questionnaire items reflecting factors either unique to that site or of particular interest for the local investigators. With one exception, the OC will not collect this information. Local sites are responsible for developing their own data entry applications for these data and for integrating these data with the main study data set for local analysis. The one exception is the BOLD Biomass questionnaire, which covers exposure to biomass fuels used for cooking or heating. Individual sites have the option of asking their study participants any or all of these questions and entering the resulting responses in the BOLD database.

Investigators should not attempt to integrate additional questions into the existing BOLD questionnaires, since to do so would threaten the integrity of the data. Rather, additional questions should be placed in a separate questionnaire(s) and asked after all of the BOLD questionnaires. Any additional questionnaires should contain the same study ID as used on the regular BOLD questionnaires so that the data from the various questionnaires can eventually be merged together.

Spirometry

The single most important outcome measure obtained as part of the BOLD protocol is spirometry before and after the administration of an inhaled, short-acting bronchodilating agent. This measure will be used to determine whether the participant has COPD.

Although standardized methods for performing spirometry are available and widely used, no single standard is universally applied. 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[4,5] for acceptable equipment and technique, and were developed with the assumption that testing will often be done in the field, i.e., not in a climate-controlled pulmonary function laboratory.

To optimize quality control in the BOLD study, sites are required to use the NDD EasyOne™ Spirometer. This spirometer has been approved by the pulmonary function reading center (PFRC) as meeting predetermined performance criteria relating to reliability of measurement, suitability for field use, and ease of access to data.

Other Clinical Measurements

BOLD study staff need to record height and weight for each participant. Ideally, height should be measured using a wall-mounted stadiometer, since this provides maximum quality control.

Data Entry and Management

Data for BOLD will consist of electronically generated spirometry records, responses to questionnaires administered to individual participants, individual tracking data, and aggregate data about the target population. The last may include demographic data, information on socio-economic status, and data on air quality for the geographic area in which the target population resides.

Once data collection is completed for any given site, the coordinating center will provide that site with an electronic copy of their own data for their use in conducting site-specific analyses. A copy of the data is also retained at the coordinating center for pooled, cross-site analyses.

Spirometry

All spirometry data will be sent electronically to the OC and then to the Pulmonary Function Reading Center (PFRC), which will grade each maneuver and assign an overall quality score to the participant's data. The PFRC also will review the quality of maneuvers from each

pulmonary function technician in order to monitor for quality drift and will initiate corrective action when needed.

The actual transmission of spirometry records is done through secure, encrypted Internet transfer. Transfer of data between the OC and the PFRC uses this same method. Data will be 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. The use of the same spirometers and software makes this both practical and easy. Duplicate data remain stored at the local site. The spirometry measurements to be used for analysis include FVC, FEV_1, FEV_6, peak flow, and total expiratory time. This will allow comparison of FEV_1/FVC and FEV_1/FEV_6 as measures of airflow limitation.

Questionnaire Data

Individual questionnaire data are entered in web-based forms and transmitted by Internet directly to the OC. The data entry application will perform 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 receipt of the data.) The data entry application may also require mandatory double entry of some key fields, although in general it will not be necessary to double enter all data.

Summary data about site

Finally, aggregate data about the target area will be sent to the OC either by fax or electronically.

Participant Safety

Participation in BOLD should carry minimal direct health risk. In addition to measurement of height and weight, which carry no health risk, participants complete spirometry before and 20 minutes after administration of an inhaled, short-acting bronchodilator. The spirometry maneuver itself is generally safe. The primary risk associated with it is fainting in older participants with impaired lung function. To minimize the risk, spirometry is done with participants in a seated position, and staff are trained to watch for signs of dizziness or other problems and to stop the maneuver if necessary. Infection risk is minimized by using disposable mouthpieces. Additionally, participants with obvious upper respiratory infections are asked to reschedule their testing if possible.

The only other health risk is associated with the use of a bronchodilator, which may cause some jitteriness and tachycardia. In order to minimize these risks, the BOLD protocol calls for the use of only two puffs of albuterol, rather than the four-puff dose that is more routinely recommended for testing hyper-reactivity. This is felt to be a very safe dosage, even if the participant has recently had to use their own inhaler for quick relief of symptoms in the few hours preceding the testing. The BOLD Executive Committee adopted this approach in part because many sites are expected to perform testing in the home environment, where appropriate medical back-up would not be readily available.

The other risk associated with BOLD relates to confidentiality of participant data. Individual-level risk factor and health data are to be transmitted to the OC and to the PFRC. All such data

are transmitted to the OC through a secure, encrypted transmission process. Once received at the OC, data are stored on password-protected databases to which access is restricted to authorized personnel. Furthermore, participants will be identified in these data files only by an anonymous study ID. No information relating to participant name, address, phone number, or governmental ID number (such as Social Security number in the US) will be transmitted to the OC. Some identifying information will need to be collected by the local sites, however.

Finally, all sites participating in BOLD, including the OC and the PFRC, need to receive the requisite human subjects approvals as mandated by local or state regulations for their country. The OC will require assurance that such approval has been obtained before allowing sites to transmit data, and will furnish to sites on request copies of human subjects approvals and data handling procedures for the OC and the PFRC.

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 for all aspects of the study, from the selection of the study sample to the questionnaire, lung function testing, and the use of the data management system. Prior to undertaking the protocol, staff must be trained and certified in study procedures. One or two members of each site will attend a central training session to be trained as "master trainers" and be certified to train additional staff at their sites. The OC monitors training and assumes responsibility for assuring that all staff who participate in the study are properly certified.

The nddEasyOne™ Spirometer that is 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 PFRC direct the training of master trainers in lung function testing from each site and supervise ongoing quality control monitoring of pulmonary function technicians.

The OC has developed detailed instructions for administering and coding each study questionnaire to assure maximum comparability in how the questionnaire is administered and responses are scored. Participating sites must conduct a forward translation of the questionnaires following a standardized protocol, and the OC will back-translate the questionnaire as a further quality control check. The OC will maintain the original and back-translated versions of all translations that are made of the questionnaire.

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 dataset is as clean as possible.

Finally, prospective sites must have their target population and sampling strategy approved by the OC, which has contracted with a sampling expert to assist in this evaluation. Clinical centers are also expected to have local access to individuals with expertise in sampling.

Primary Outcome

COPD is defined as airflow limitation that is largely irreversible, as documented by post-bronchodilator spirometry. We propose to compare three separate definitions of COPD, as described in Table 1. The new GOLD definition (3) will be considered the "standard" definition:

> *"Diagnosis of COPD is based on a history of exposure to risk factors and the presence of airflow limitation that is not fully reversible, with or without the presence of symptoms. [A post-bronchodilator] FEV1/FVC <70% and a post-bronchodilator FEV1 <80% predicted confirms the presence of airflow limitation that is not fully reversible."*

Table 1. Definitions of COPD to be evaluated in BOLD

Source of Definition	Algorithm
American Thoracic Society	$FEV_1/FVC < 0.75$
European Respiratory Society	$FEV_1/FVC < 88\%$ of predicted (men) $FEV_1/FVC < 89\%$ of predicted (women)
GOLD	$FEV_1/FVC < 0.70$ (stage 1) $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ of predicted (stage 2)

Data Analysis

The (OC) will conduct limited site-specific analyses as well as more comprehensive analyses of the trial-wide data.

Site-Specific Analyses

In addition to performing edit checks on each site's data as part of its ongoing quality control activities, the OC will generate a basic statistical report for each site's data and return this report to the site, along with the site's cleaned dataset, at the conclusion of each site's data collection activities. This report will include response rates, characteristics of responders and nonresponders, univariate statistics on all study variables, and tables showing (properly weighted) COPD prevalence estimates, both overall and for selected subsets of the population. The report will also summarize the derivation of weights used for computing the prevalence estimates and their standard deviations. This basic statistical report may form the basis of a site-specific paper or may be used in conjunction with other locally conducted analyses to develop site-specific manuscripts. Primary responsibility for developing site-specific manuscripts rests with the local principal investigator.

Analyses of Trial-wide Data

The OC will also conduct analyses of trial-wide (cross-site) data for manuscripts approved by the publication committee. At a minimum, these trial-wide manuscripts are expected to address each of the primary and secondary aims as outlined in the BOLD protocol. Additional manuscripts will also be proposed. Data used in trial-wide analyses will be properly weighted according to the sampling design used by each site.

Economic Burden Analyses

The burden of disease model will primarily be a policy model that will provide estimates of the current and future economic burden of COPD. The model will utilize aggregate estimates from the prevalence survey and local cost and population estimates to provide a site-specific estimate of the current and future costs related to COPD. Model simulations and calculations will be conducted on a standard spreadsheet platform (for example, MS Excel) with an interface that will allow for changes in input parameters to conduct sensitivity analyses.

Base case analyses of the estimate of the current and future economic burden of COPD will be conducted for sites participating in the pilot phase of the project. In the base case analysis, information obtained from the prevalence survey will serve as input parameters for the economic model. The inputs will be based on gender-specific summary information. Parameters that will be used in the model include estimates of prevalence, smoking rates, and healthcare utilization rates. The cost information used in the economic model will be based on local unit cost estimates. Cost estimates for hospitalizations, physician (or other healthcare provider) visits, and medications will be incorporated in the model. Additionally, estimates of incidence rates for COPD, mortality rates, and smoking prevalence in younger populations will be used to determine future costs associated with the disease.

Current and future costs will be estimated for direct medical expenditures as well as costs related to lost productivity. Lost work time due to COPD will be estimated from the prevalence survey and used in conjunction with local wage rates to calculate the cost of lost productivity due to COPD.

In the base case analysis, prevalence estimates from the survey will be combined with cost data to estimate the overall costs associated with COPD and its treatment. In addition to overall estimates of cost, costs per capita and per patient with COPD will be calculated. Costs will also be determined for categories of COPD severity. Estimates of the future burden of COPD will be calculated by incorporating information on COPD incidence, mortality, and smoking patterns. Estimates of future costs will include overall costs, per-capita estimates, and estimates per patient with COPD.

Several sensitivity analysis scenarios will be built into the model for use in understanding how changes in key input parameters affect estimates of the current and future burden of COPD. The sensitivity analyses included in the model will focus on parameter 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 impact of these changes on overall costs.

Two examples of the included sensitivity analyses are cost estimates incorporating distributional information on the input parameters and changing smoking patterns. Instead of relying on point estimates to generate estimates of overall costs, we will include information on the distributions associated with the point estimates. In this sensitivity analysis, a value will be randomly drawn from the distribution of possible values for the input parameters. This process will be repeated multiple times, which will provide a distribution of potential cost estimates. Thus, instead of

having a single estimate, we will have an estimate of costs as well as information on the distribution of possible costs.

Another sensitivity analysis will involve modifying smoking rates to determine how smoking patterns influence future economic estimates of COPD. In this sensitivity analysis, smoking rates can be changed with an attendant cost estimate or without a cost estimate. That is, changing smoking rates can be attributed to an intervention and its costs or to secular changes in smoking patterns. These estimates will provide information on how resources focused on influencing smoking rates may affect the future costs associated with COPD.

Sample Size

The proposed sample size for BOLD (300 men and 300 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 2 shows the level of precision that can be expected for various possible 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 approximately 15% ± 2.9%. If, as is likely the case, the prevalence of COPD differs for men and women, the figures shown in the table below 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 are likely to see.

Table 2. Estimated half-width of 95% confidence interval for estimating prevalence assuming simple random sampling*

sample	Prevalence (%)									
size	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

* ignores finite sample correction factor

Translation of Study Documents

The OC will produce the official English-language versions of the protocol, MOP, and study questionnaires. Individual centers wishing to administer the questionnaire in a different language are expected to provide for the forward translation using a standardized translation protocol. The OC will conduct a back-translation of all non-English questionnaires and work with individual

sites to assure that each translated version is as comparable as possible to the original English-language version.

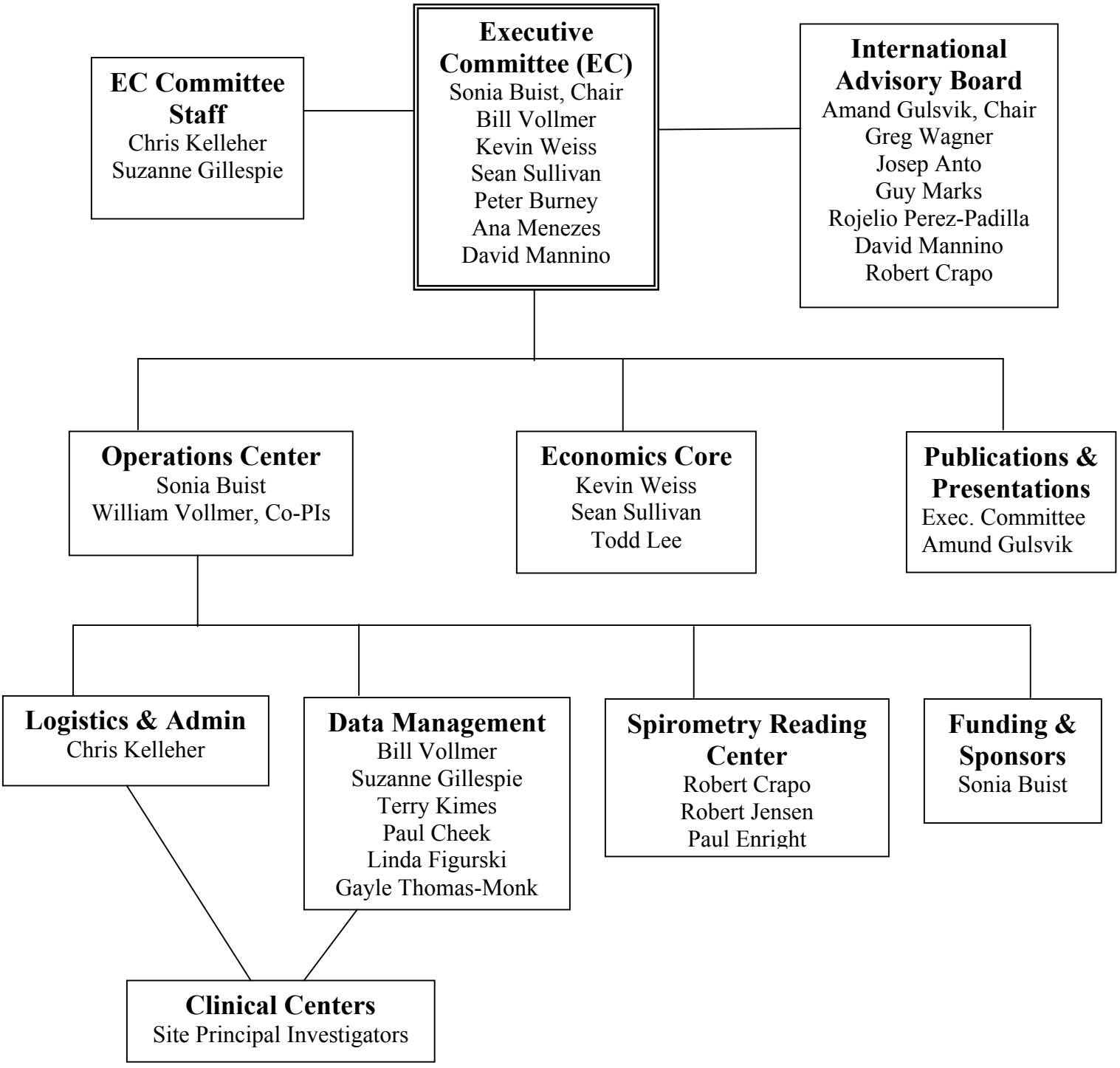
ORGANIZATIONAL STRUCTURE

An executive committee developed the initial protocol and provides ongoing scientific oversight for the study. Dr. Sonia Buist is the chair of the executive committee. Dr. William Vollmer and Dr. Buist direct the OC, which is located in Portland, Oregon, USA. The operations center comprises three functions: Logistics and Administration, under Chris Kelleher; Data management, under Dr. William Vollmer; and Funding and Sponsors under Dr. Sonia Buist. Drs. Kevin Weiss and Sean Sullivan are responsible for the economic core component of the study. A Publications Committee will oversee the publications that are produced from this project.

Dr. Peter Burney will advise on all aspects of the study. He brings to the study not only his expertise in the field of epidemiology, but also his experience in directing the original and follow-up ECRHS studies, which helped to form the model for how BOLD is structured. Dr. Ana Maria Menezes provides formal linkage with the PLATINO study, which is a parallel COPD prevalence survey being carried out in five countries in Central and South America. Drs. Buist and Vollmer also are members of the PLATINO steering committee. Investigators from PLATINO and BOLD have worked closely together to assure that the protocols for these two studies are as comparable as possible, thus facilitating direct comparisons of results and joint analyses of data.

Other components of BOLD include the PFRC, directed by Dr. Robert Crapo in Salt Lake City, Utah, USA, and an international advisory board chaired by Dr. Amund Gulsvik from Bergen, Norway. The role of the international advisory board is to review and advise on the standardized methods, review and advise on applications for BOLD sites (countries), advise on future directions, and advise on analyses.

BOLD ORGANIZATION CHART



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