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Multi-Center Survey of COPD in Five Major Latin-American Cities
The "PLATINO" Survey

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Proposal by
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Table of contents

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BACKGROUND TO THE PROPOSAL

In September 2001, a meeting was convened in Berlin with representantives of the Asociación Latinoamericana del Tórax (ALAT), two directors of Boehringer-Ingelheim and Dr. Ana Menezes to discuss the possibility of a survey for measuring the prevalence of COPD in some cities of Latin America.

ALAT and Boehringer-Ingelheim invited Dr. Menezes to be the main coordinator of the project. At that time, it was decided that the following countries (and cities) would participate in the survey: Argentina (Buenos Aires), Brazil (São Paulo), Chile (Santiago), Colombia (Bogota) and Mexico (Ciudad of Mexico). One researcher from each country was appointed as the Site Principal Investigator (PI).

A next meeting is planned for January 2002, in São Paulo, and Dr. Menezes was asked to prepare a draft study proposal for discussion at this meeting. In order to prepare the proposal, it was agreed that some ancillary studies should be carried out by Dr. Menezes and her team. These included a systematic review of the literature on COPD epidemiology (international and Latin America literature); collection of relevant data for the Latin American sites, including socio-demographic information, morbidity and mortality due to respiratory diseases (especially COPD), and seasonality of respiratory diseases.

The present proposal presents the results from these ancillary studies and describes the justification, objectives, methods, logistics, timetable and budget for the proposed survey.

1. INTRODUCTION

The international literature shows that the prevalence of Chronic Obstructive Pulmonary Disease (COPD) in many developed countries is increasing (Hurd, 2000; Pauwels, 2000; Petty, 2000) There is also limited evidence from Latin America that COPD is a growing cause of death, but information on prevalence is scant (Brasil, Datasus). To obtain a detailed picture of its worldwide distribution, it is necessary to know its prevalence in less developed countries. It is possible that, due to the high frequency of smoking - the main risk factor for COPD - in these countries, this disease may represent a major public health problem that has not yet been recognized as such.

The present proposal is aimed at measuring the prevalence of COPD in five major cities in Latin America - Buenos Aires, São Paulo, Santiago, Bogota and Ciudad of Mexico - in order to provide information to fill this knowledge gap. Before describing the project itself, it is important to provide some background information on Latin America, especially about the countries included in the project.

1.1. LATIN AMERICA: SELECTED POPULATION AND GEOGRAPHICAL CHARACTERISTICS

The countries included in the study - Argentina, Brazil, Chile, Colombia, and Mexico - were chosen because of their importance, population size and due to the availability of collaborating research centers. In geographical terms, they represent the different geographical areas of Latin America (see Figure 1, blue areas). The largest city in each of these countries was selected. The study is not intended to be representative of Latin America. A truly representative sample would not be possible given logistic, time and budgetary constraints. Nevertheless, it will be the first multi-center study on COPD prevalence in Latin America using a standardized methodology.

Figure 1 - Map of Latin America

Table 1 shows the population of the countries and metropolitan areas included in the study (Argentina:www.indec.gov.ar; Brasil:www.ibge.gov.br; Chile:www.ine.cl; Colombia: www.dane.gov.co; Mexico:www.inegi.gob.mx.). Brazil is the largest country in size and population (170 million inhabitants) and Chile is the smallest (13 million). Santiago is the city with the smallest population (5.2 million) in the sample.

TABLE 1 - POPULATION OF COUNTRIES AND METROPOLITAN AREAS INCLUDED IN THE EPOC STUDY.

COUNTRIES/ CITIES	**LAST CENSUS**	**POPULATION**	**2000-2001 ESTIMATES**
Argentina/	1991	32.615.528	
Buenos Aires		12.594.974	14.214.701
Brazil/	2000 (preliminary	169.544.443	_
São Paulo	results)	9.713.692	
Chile/	1992	13.348.401	
Santiago		5.257.937	6.189.964
Colombia/	1993	37.500.000	40.000.000
Bogota		7.000.000	
Mexico/	2000	97.361.711	_
Ciudad of Mexico		13.083.359	

Although the study will be restricted to urban areas, it is important to recognize that these account for the vast majority of the population in the countries studied. Argentina, Brazil and Chile have more than 80% of their population in urban areas, whereas Colombia and Mexico have 60%-70% (Table 2). In all countries, urbanization continues to increase.

TABLE 2 - PROPORTION OF THE POPULATION LIVING IN URBAN AND RURAL AREAS OF THE COUNTRIES INCLUDED IN THE EPOC STUDY

COUNTRIES	URBAN/RURAL (LAST CENSUS)
Argentina	86.9% / 13.1% (1991)
Brazil	81% / 19% (2000)
Chile	96.5% / 3.5% (1992)
Colombia	65%/35% (1993)
Mexico	60%/40% (1999)

When conducting studies of the prevalence of respiratory diseases, one must take into account seasonality. The three cities located further from the Equator (Buenos Aires, São Paulo and Santiago) have four marked seasons with the winter lasting from June to August-September. In Bogota and Ciudad of Mexico there are a rainy and a dry season (Table 3). The issue of seasonality will be further discussed below.

TABLE 3 - SEASONALITY IN LATIN AMERICAN CITIES

CITIES	MONTHS
Buenos Aires	June to August
São Paulo	June to August
Santiago	June to August
Bogota	Rain – April to May, November
Ciudad of Mexico	Rain – December to February

2. REVIEW OF LITERATURE ON COPD

The literature on COPD is vast, but the following review was concentrated on issues that are directly relevant to the proposed study. It is aimed at answering the following questions:

- What are the relevant methodological issues regarding the operational definition of COPD, that should be taken into account when developing questionnaires and measurement procedures? (see Section 2.1)

- What information is available on the prevalence of COPD and of its main risk factor – smoking - in Latin America (including its age and sex distribution)? (see Section 2.2)

- What is the seasonality of respiratory symptoms in the study areas, and how may this affect COPD estimates? (see Section 2.3)

- What else is known about the epidemiology of COPD that may be relevant to the present survey? (see Section 2.4)

2.1. DEFINITIONS OF COPD

Before reviewing the international and Latin American literature, there are some methodological issues that should be considered regarding the definition of a COPD case.

Until recently, COPD was a loose term used to describe several different diseases, being based more on clinical assessment than on functional measurements. In the recent past, COPD became essentially defined in functional terms, including only obstructive chronic bronchitis and emphysema. Therefore any comparison between prevalences from different studies will be distorted if one does not consider differences in definitions as will be seen below.

Due to these changes in case-definitions, studies carried out long in the past have limited relevance for prevalence estimates. Thus, the international literature on prevalence of COPD and smoking was reviewed. A MEDLINE search using the keywords “COPD”, “prevalence”, “smoking” and “adults” was carried out for papers published since 1990. Only the most relevant studies are shown in Tables 4-5. Table 4 presents the definitions used in 11 studies carried out in the region.

Two problems are evident. First, different studies used different criteria. Few studies used more than one criterion. Secondly, even when the same criteria were apparently used, often the cutoffs were different from one study to another. One easily realizes that it is difficult if not impossible

to compare the reported prevalences. This fact highlights the need for a multi-center study using standardized definitions and methods.

TABLE 4 - STUDIES ON COPD ACCORDING TO DIFFERENT CRITERIA

STUDIES	DEFINITIONS AND CUTOFFS					
	ERS	**ATS**	**GOLD**	**Fixed ratio**	**Symptoms**	**Medic.Diag.**
IBERPOC (1997); Spain (2000), Sobradillo Peña, 2000	FEV1/FVC < 88% predicted males and 89% for females					
III NHANES STUDY 1988-1994 Celli	FEV1/FVC < 88% predicted males and 89% for females	FEV1/FVC ≤ lower limit of normal	FEV1/FVC < 70% and FEV1 < 80% of predicted	FEV1/FVC ≤70%		
Canada (1994-1995) Lacasse, 1999						Diagnosis of chronic bronchitis or emphysema by the doctor
Norwegian (1987-1988) Bakke, 1991			FEV1/FVC < 70% and FEV1 < 80% of predicted			
Italy (1988-1991) Viegi, 2000	FEV1/FVC < 88% predicted males and 89% for females	FEV1/FVC < 75% (ATS=1986)		FEV1/FVC < 70 %		
England – Manchester (1992-1994) Renswick, 1996	FEV1/FVC < 65% for age <= 65 y For age > 65 y = FEV1/FVC % > 65%					
England (1999) Dickinson, 1999	FEV1 < fifth centile of predicted or > 15% mean diurnal variation of PF					
Sweden (1998) Montnémery, 1998					Symptoms	
Finland (2000) Hertzen, 2000				FEV1/FVC ≤69%		
Sweden and Finland (2001) Lindström, 2001					Symptoms	
Poland (2001) Zielinski, 2001	FEV1/FVC < 85% predicted					

Table 5 shows that prevalences of COPD in these studies ranged from 3.9% to 60.7%. The high variability is not surprising, due to the discrepancies in the criteria used for defining COPD. Prevalences were higher in men than in women, and lower prevalences were observed with the GOLD criteria and when medical diagnosis was used. Most of the studies comprised subjects aged 40 years or more. Prevalences of smoking ranged from 13% to 40% with the exception of Poland where current and ex-smokers were in the same category.

TABLE 5 - INTERNATIONAL REVIEW OF LITERATURE ON COPD PREVALENCE AND SMOKING

COUNTRY/ AUTHOR/ YEAR OF PUBLICATION	AGE	COPD PREVALENCE					SMOKING PREVALENCE
		ERS	ATS	GOLD	Fixed ratio	Medic.Diag.	
Spain Sobradillo, 2000	40-69 y	M=14.3% F=3.9%					25.4%
III HAINES STUDY 1988-1994 Celli	>30 y	M=28.6% F=30.1%	M=14. 6% F=13. 3%	M=8. 1% F=7.0%	M=19.1% F =13.1%	M=5.8% F=9.4%	37 to 40% (1994)
Canada Lacasse, 1999	55- >74 y					55-64 y - 4.6% 65-74 y - 5.0% >=75 y - 6.8%	30%
Norwegian Bakke, 1991	18-73 y			G=4. 5% M=4 .8% F= 4. 2%			29%
Italy Viegi, 2000	>=46 y	M=14.5% F=12%	M=60.7% F=53.4%		M=33.1% F=22.2%		27.5%
England – Manchester Renswick, 1996	> 45 y	26.4% - <65 y 29.7% > 65 y					29.2%
England Dickinson, 1999	60-75 y	16.4%					15.9%
Finland (2000) Hertzen, 2000	> 30 y	M=11% F=5%					36% males 13% females
Poland Zielinski, 2001	Mean age = 51.8	24.3%					80% (current and ex-smokers)

Bartolome Celli, in his paper on population impact of different definitions of airways obstruction (Celli, submitted to publication) clearly shows how much estimated prevalences can vary according to the criterion used. He reanalyzed the United States' NHANES III using five definitions. Table 6 shows the estimated prevalences in this sample for individuals aged 30 years or more according to five definitions, as well as the results from the survey carried out in Pelotas, 2000, by the author of the present proposal (Menezes,unpublished data). The outcome relating to medical diagnosis could not be compared because it was not measured in the same way in both studies.

TABLE 6 - COPD PREVALENCES WITH FIVE DIFFERENT CRITERIA IN THE NHANES III AND IN THE PELOTAS 2000 STUDIES

STUDY	COPD PREVALENCES				
	LLN (ATS)	FIXED RATIO	GOLD	ERS	MEDICAL DIAGNOSIS
III NHANES 1988-1994	13.9%	16.0%	7.5%	29.4%	7.7%
PELOTAS 2000 (unpublished data)	58.9%	14.7%	8.9%	27.4%	-

With the exception of the LLN definition, results are strikingly similar in the US and in Pelotas. The reasons for the discrepancy in the LLN indicator are still being investigated, but these results suggest that lower limit of normal can be different from one population to another (in the Pelotas study the lower limit of ATS was used).

The need to standardize definitions in order to allow international comparisons led to the development of the BOLD (Burden of Obstructive Lung Disease) project, coordinated by Dr. Sonia Buist, which is aimed at carrying out simultaneous prevalence studies in different countries. The methods for this project are under development, and every effort should be made to have comparable indicators in the BOLD and EPOC surveys.

The above findings reinforce the need for collaborative studies in different sites using multiple definitions and cutoffs in order to allow comparison with the international literature. There is also a great need to standardize data collection procedures in order to be able to compare results.

After many meetings with the coordinators of the EPOC survey and the BOLD survey it was decide that both surveys should have the same protocol in order to allow further comparisons. Dr.

Menezes and all the PIs from the EPOC study agreed with Dr. Sonia Buist and William Vollmer from the BOLD study about several itens in two meetings (one in Mazatlan, Mexico and another in Atlanta, ATS meeting). After the meeting in Mazatlan it was decided that the EPOC survey would have a name of PLATINO study.

People from Boehringer-Ingelheim were present in Atlanta and they also agreed that would be important to have both projects (PLATINO and BOLD) running together.

2.2. PREVALENCE OF COPD AND SMOKING IN LATIN AMERICA

This section includes three sub-sections: data on the burden of disease due to respiratory illness, specific studies of COPD prevalence and surveys on smoking prevalence in Latin America.

2.2.1. BURDEN OF RESPIRATORY DISEASE IN LATIN AMERICA

Like information on COPD prevalence, data on the burden of disease – morbidity and mortality due to respiratory conditions – may be hard to compare due to the use of different definitions and to the variable coverage of death registration systems.

Two main sources of data were used in this review:

a) The publication on "The Global Burden of Disease" (Murray and Lopez, 1996, in which a major attempt was made to produce comparable information from different parts of the world, and
b) National sources on death statistics.

The Burden of Disease results refer to symptomatic cases of COPD, that is, these estimates do not include deaths due to other conditions for which COPD may have been a contributing cause. Therefore, they are likely to underestimate the true magnitude of the problem. Despite this, Table 7 shows that there were an estimated 57,000 COPD deaths in Latin America in 1990, and this is rising to reach 95,000 in 2000.

TABLE 7 – MORTALITY FROM COPD IN LATIN AMERICA (symptomatic cases)

AGE GROUP (years)	DEATHS 1990		DEATHS 2000 (Projected)	
	Number ('000s)	Rate (per 100 000)	Number ('000s)	Rate (per 100 000)
Males				
0-4	0	0.0	0	0.0
5-14	0	0.0	0	0.0
15-44	1	0.9	1	0.9
45-59	4	17.7	5	17.4
>=60	29	202.0	46	234.0
All ages	34	15.2	53	19.8
Females				
0-4	0	0.0	0	0.0
5-14	0	0.0	0	0.0
15-44	1	0.8	1	0.8
45-59	3	12.1	5	16.7
>=60	19	115.8	36	150.8
All ages	23	10.4	42	15.7
TOTAL	57	12.8	95	17.8

Another way of measuring mortality is by using "Years of Life Lost" (YLLs) due to premature mortality. The change in rank order of YLLs for the 15 leading causes in the world , from 1990 to 2020, shows that COPD which was in the 16th place in 1990 will occupy the 10th place in 2020.

It is also interesting to observe that, according to yet another measure of health outcomes - 'Disability –Adjusted Life Year' (DALYs) – COPD is predicted to rise from the 12th cause of lost DALYs in 1990 to the 5th cause in 2020. For developing countries, COPD is expected to be the 4th cause for males and the 3rd for females in 2020 (Murray and Lopez, 1996).

Substantial efforts were made to obtain mortality data for COPD for the countries included in the study. The main sources available are the web sites of the National Statistical Bureaus or Ministries of Health (Argentina:www.indec.gov.ar; Brasil:www:datasus.gov.br; Chile: www. epi.minsal.cl; Colombia:www.minsalud.gov.co; Mexico:ssa.gov.ar). Results are summarized in Table 8.

TABLE 8. INFORMATION FROM DEATH STATISTICS ON THE IMPORTANCE OF COPD DEATHS.

Country	Year	Rank of COPD in all-age mortality
Argentina	**-**	**6th**
Brazil	**1998**	**10th**
Chile	**1998**	**9th**
Colombia	**1994**	**7th**
Mexico	**1999**	**10th**

From the above data, it is evident that COPD is one of the leading causes of death and disability in Latin America. It must be stressed that these refers to deaths at all ages. Had it been possible to restrict the analyses to deaths at ages 40 years or older, the COPD rank would certainly be higher.

2.2.2. EPIDEMIOLOGICAL STUDIES ON COPD

The review of the epidemiological literature on COPD in Latin America followed a systematic search. Several data sources were used to identify the relevant literature. The most comprehensive literature databases were searched. These included MEDLINE, LILACS (Latin American Health Sciences Literature Database) and governmental sources. The keywords used were “COPD”, “EPOC”, “DPOC”, “SMOKING”, “TOBACCO”, “TABACO”, “ADULTS” (or no limits of age), and SOUTH AMERICA/ LATINAMERICA/ MEXICO/ COLOMBIA/ CHILE/ ARGENTINA/ BRAZIL”. Key informants (local coordinators of each centre of the study) were also contacted.

About 112 citations on COPD (68 from MEDLINE and 44 from LILACS) were identified in the LA review. Unfortunately only two studies were population-based studies and both were from the author of this project.

Table 9 shows the main results of these two studies in Brazil. Results based on spirometry from the 2000 study were already presented in Table 6.

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TABLE 9 - POPULATION-BASED STUDIES ON CHRONIC BRONCHITIS AND COPD IN PELOTAS-BRAZIL

STUDIES	Sample	Age	Symptoms*	Medical diagnosis	Smoking Prevalence
Chronic Bronchitis Menezes, 1994	939	40-69 y	12.6%	5.2% **	36.3%
COPD Menezes, 2000 (unpublished data)	1 047	40-69 y	7.8%	3.2% ***	29.4%

***** Symptoms of cough and sputum production during the majority of days for at least three months in the previous two or more years.

****** Medical diagnosis of chronic bronchitis.

******* Medical diagnosis was investigated only for subjects who reported symptoms of chronic bronchitis.

Considering the prevalence of symptoms of chronic bronchitis it seems that there was a reduction from 1992 to 2001. It is possible that the reduced prevalence of smoking in 2000 can partly explain some of this reduction. Another point which should be mentioned is that the second study was done in summer, and the first one was during the winter. Most of the difference between the two studies was related to the duration of the cough and sputum "in the last 3 months". This finding highlighted the need for taking seasonality into account when investigating COPD prevalence (see section 2.3).

2.2.3. LITERATURE ON SMOKING PREVALENCE

Given the limited information available on COPD prevalence, it is important to describe how many Latin Americans are affected by the main risk factor for respiratory diseases – cigarette smoking.

The review of literature on smoking in LA resulted in many studies being identified (301 citations from MEDLINE and 401 from LILACS). From these 702 citations, 16 from MEDLINE and 14 from LILACS were identified as relevant papers (see Annex I, Table 2).

Most studies were limited to small geographical areas, which makes their extrapolation to the whole country problematic. Fortunately, for most countries included in the EPOC study at least one nationally representative study is available. These are summarized in Table 10.

TABLE 10 - PREVALENCE OF SMOKING IN NATIONAL SAMPLES OF LATIN AMERICAN COUNTRIES INCLUDED IN THE EPOC STUDY

COUNTRY/ STUDY	AGE	SMOKING PREVALENCE		
		TOTAL	MALES	FEMALES
Argentina	Adults	33,5%	36%	32%
Brazil (1989) *	>= 15 years	32.6%	40%	26%
Chile (2000)**	12-64 years	45.4%	49.6%	41.7%
Colombia (1998) ***	18-69 years	18.9%	26.8%	11.3%
Mexico (1998) ****	12-65 years	27.7%		

* Pesquisa Nacional sobre Saúde e Nutrição (INAN)

** Quarto Estudio Nacional sobre Consumo de Drogas (CONACE)

*** II Estudio Nacional de Factores de Riesgo para Enfermidades Cronicas (information from Carlos Torres)

**** Encuesta Nacional de Adicciones (Mexico: www://ssa.gob.mx)

Prevalences of smoking in these countries range from 11.3% in females (Colombia) to 49.6% in males (Chile). For both sexes combined, the median prevalence of smoking is around 30%, being higher among males than females. Chile has the highest prevalences.

Based on the other studies reviewed (see Annex I, Table 3), the following conclusions can be reached:

- The majority of studies in these countries show rising prevalences of smoking in females.
- Some studies show that smoking prevalences are decreasing among males.
- Most studies show increasing prevalences of smoking among teenagers, particularly girls.

2.3. SEASONALITY

It is known that seasonality has a role in respiratory morbidity and mortality worldwide. In Southern Brazil, for example, where hospital statistics are highly realiable and the four seasons are well defined, the highest number of hospitalizations for COPD is observed during August (10, 357 hospitalizations) and the lowest in February (7 357 hospitalizations), since these months correspond to winter and summer, respectively (Brasil, DATASUS).

On the other hand, during the winter or rainy season spirometries could be delayed because of more respiratory infections. The conclusion was to do the project in the best logistic way without considering seasonality.

2.4. RISK FACTORS

Several risk factors for COPD are well recognized in the literature. Testing associations between COPD and risk factors is a secondary objective of this survey. The main known risk factors will be presented here, with emphasis on how knowledge about such factors may help define the study sample and prepare the questionnaires.

2.4.1. AGE

Although many published papers indicate age as a risk factor for obstructive chronic diseases, it should be pointed out that this might be due to the cumulative effect of other factors such as smoking (Burrows, 1981). Since age is a potentially confounding variable, it is important to adjust the outcome COPD for age in all analyses. Also, since COPD is rare below the age of 40 years, it is proposed that the planned survey should be limited to subjects are 40 or more. Stratification by age groups (within those aged 40 or more) would be logistically complicated and is not being proposed.

2.4.2. SEX

Most studies (see Table 5, for example) show that males have higher COPD prevalences than females. This seems to be largely due to the fact that, in virtually all societies, men still smoke more than women. Adjustment for smoking in the analyses of sex differentials is important: for example, in the Pelotas study, the odds ratio of COPD for males was equal to 2.2 in the crude analysis, dropping to 1.3 in the adjusted analysis (Menezes, 1994). The proposed survey should include men and women; there is not need for a priori stratification by sex since the proportion of men and women will be roughly similar (with a slight preponderance of females in this age range).

2.4.3. SOCIO-ECONOMIC STATUS

Several studies show inverse associations between socio-economic level and COPD (Yamaguchi, 1988; Burr, 1987). One of the possible reasons for this is that smoking is also inversely associated with socio-economic status. However, even when adjustment for smoking is done, the association may remain. This seems to demonstrate the presence of other COPD determining factors like intra-uterine life factors, weight at birth, poor diet, among others related

to socio-economic factors (Strachan,1992). It is important that the proposed survey should include members of all social groups in the same proportion as these are present in the societies being studied.

2.4.4. SMOKING INTENSITY AND DURATION

Due to the long latency period between exposure and disease onset, for many years the harmful effects of smoking were not recognized. Nowadays, however, smoking is known to be the main COPD risk factor, and this risk is directly related to the amount and time of smoking. Literature is unanimous regarding the association between COPD and active smoking. The survey should collect detailed information on smoking frequency, both current and in the past.

2.4.5. TYPE OF CIGARETTES SMOKED

Types of cigarettes vary according to the type of tobacco (black or blonde), the type of wrapping (paper, maize leaves, etc) and to the presence of filter. Although currently most cigarettes are paper-wrapped, blonde tobacco with filter, many of the subjects who are now aged 60 or more may have smoked other types in the past. Menezes showed an important independent association between chronic bronchitis and use of maize leaf cigarette (Menezes, 1995). Information on types of cigarette consumed in the subject's lifetimes must be collected.

2.4.6. INDOOR BIOMASS POLLUTION

Several studies from Padilha in Mexico showed an association between stoves burning biomass fuel and spirometric and clinical signs of COPD in non-smoking women, even after adjustment for confounding variables (Pérez-Padilha,1996, Pérez-Padilha, 1999, Bruce, 2000, Regalado (submitted to publication). Another study from Colombia – a hospital-based case control study in Bogota - also showed an association between obstructive airway disease and exposure to woodsmoke in women (Dennis, 1996). It is proposed that the survey should collect information on indoor biomass pollution in the past.

2.4.7. WORK EXPOSURES

On the same way as indoor pollution can be associated with COPD, occupational smoking exposures can also be associated with this disease. Some studies with representative samples have shown that subjects exposed to dust show high COPD prevalence (Higgins, 1973). Bakke in Norway (Bakke, 1991) found an odds ratio of 3.6 for COPD in people highly exposed to asbestos, quartz, dust, gases, and aluminum. and on occupational history with emphasis on

exposure to dust, smoke and other pollutants. The survey should collect a detailed occupational history with emphasis on exposure to dust, smoke and other pollutants.

2.4.8. ENVIRONMENTAL POLLUTION

The role of environmental pollution on COPD is harder to study in a survey as there is usually not sufficient variability within a single site to detect an association. Even the comparison of the 5 sites in the study will not provide sufficient degrees of freedom to test an association. Berglund (1999) found an association among long-term ambient concentrations of air pollutants and chronic cough and sputum; in the AHSMOG STUDY the greatest decrement in lung function associated with PM_{10}(100) was found in men whose parents had chronic airway disease (Abbey, 1998). The survey does not intend to measure environmental pollution, although it should be asked to the subjects if they were exposed to any pollution (self-report).

This was one of the points discussed in São Paulo and the following reasons support the conclusion of not studying air pollution in the EPOC SURVEY:

The only way to integrate an assessment of the role of air pollution in the study is if, in the metropolitan areas included, the following conditions could be satisfied:

1) There should be accurate measurements of air pollution according to easily delimited geographical areas (e.g. neighborhoods or groups of census tracts). This would allow to relate each individual included in the sample to a given level of pollution.

2) There should be enough variability in air pollution levels between these areas in the same metropolitan area – thus allowing a dose-response analysis. In other words, if levels of pollution are more or less the same in the whole metropolitan areas there will not be sufficient heterogeneity for the study.

3) Migration rates (from one neighborhood to another, or from other cities to the metropolitan area) should not be very high, since otherwise it will not be possible to characterize exposure in the past, since COPD takes many years to develop.

4) Of the five metropolitan areas included, most should allow this type of analyses (it now seems that they may be possible in Mexico, Santiago and perhaps in São Paulo).

If these conditions are satisfied, then the sampling for each of these metropolitan areas would be stratified by pollution level (as well as stratified for other variables if applicable). We would have to recalculate sample sizes to accomodate this new objective, which would almost certainly lead to larger samples.

It is our belief that given the above difficulties, these analyes will be very difficult to carry out.

2.4.9. GENETIC FACTORS

A number of studies has been carried out in order to assess the role of genetic factors in determining COPD, but major evidences refer to emphysema due to alpha-1-antitripsine deficiency (Koyama, 1998), which stands for only 1% of COPD cases. It is proposed that the survey should collect information on family history of COPD.

2.4.10. CHILDHOOD ACUTE RESPIRATORY INFECTION (ARI)

Although many studies show a possible association between respiratory diseases during childhood and COPD, some caution would be advisable when interpreting their results. Most studies may be affected by recall bias, since they are cross-sectional studies with a retrospective component. For example, in the Brazilian study, adults who reported "lung problems during childhood" showed twice chronic bronchitis risk compared to those who did not report them (Menezes, 1994). On the other hand, at least two cohort studies found significant associations. Ding's prospective study in China (Ding, 1992) followed up a group of children who were hospitalized due to lower tract respiratory infection for 30 years showing a prevalence of chronic bronchitis 12.2% compared to 2.2% in the control group. Yamaguchi's study in Japan (Yamaguchi, 1988) found respiratory infections during childhood as a significant risk factor for chronic bronchitis. Information on past history of pulmonary disease will be collected in the present survey, but since this will be based on self-report, any positive associations will have to be interpreted with caution.

3. JUSTIFICATION

Prevalence of COPD is increasing in many developed countries and there is some evidence from Latin America that COPD is a growing cause of death.

However, information on prevalence of COPD from Latin America is poor and it would be very important to fill this knowledge gap.

For developing countries, COPD is expected to be the 4th cause for males and the 3rd for females in 2020 for "Disability–Adjusted Life Year" (Murray and Lopez, 1996)

This survey aims to measure the prevalence of COPD in five major cities of Latin America. Although is not a representative study of all Latin America it will be the first multi-center study on COPD prevalence in LA with standardized methodology.

4. OBJECTIVES

4.1. Main objective:

To measure the prevalence of COPD in 5 Latin American metropolitan areas.

4.2. Secondary objectives:

- To measure and compare COPD prevalences using different definitions, including ATS, ERS, GOLD, FIXED RATIO AND SYMPTOMS;
- To measure the prevalence of known risk factors for COPD including socio-economic status, smoking, type of cigarette smoked, indoor biomass pollution, work exposure, environmental pollution, genetic factors and history of severe respiratory disease in childhood;
- To describe the distribution of COPD according to age, sex, smoking and the presence of other risk factors;
- To describe the main clinical symptoms reported by subjects diagnosed with COPD;
- To assess the sensitivity and specificity of COPD clinical findings, using lung function as the “gold standard”;
- To compare COPD prevalence in Latin America with that reported from other countries (mainly developed ones);
- To correlate the subject’s awareness of suffering from COPD with actual diagnosis;
- To describe how this disease is being managed in terms of drug therapy, clinical and laboratory investigations, and other relevant aspects;
- To describe the social and economic consequences of COPD, in terms of work limitations, absenteeism and other relevant issues.

5. METHODOLOGY

The methodology section will cover the following topics:

5.1. Design
5.2. Target population
5.3. Sample size
5.4. Sampling
5.5. Outcome variables: diagnostic criteria
5.6. Identification variables
5.7. Variables on demographic and risk factors
5.8. Site team composition, selection and training
5.9. Logistics
5.10. Cluster sheet
5.11. Pilot study
5.12. Data processing and analysis
5.13. Conceptual model for the analysis

5.14. Quality control
5.15. Ethical issues

5.1. Design

A cross sectional design will be used, aimed at obtaining representative samples of adults aged 40 years of age or more (no upper limit of age), living in five major metropolitan areas in Latin America: Mexico City, Santiago, Bogota, Buenos Aires and São Paulo. Multi-stage cluster sampling will be used.

5.2. Target Population

The target population will include adults aged 40 years of age or more of both sexes. Subjects under 40 years will not be included because COPD prevalence is low at this age range.

5.3. Sample size

As described above, the primary objective of the study is to estimate COPD prevalences in the five metropolitan areas. To calculate the required sample size, the following information is needed:

5.3.1. Estimated prevalence of COPD in the study areas

Sample size calculations require a rough estimate of the prevalence of COPD in the metropolitan areas to be studied. Much effort was dedicated to obtaining such estimates, but results were disappointing (in fact, if good estimates were available there would be no reason to do the survey now being proposed!).

Only one population-based study using spirometric measurements was located in Latin America; this was carried out in Pelotas by the author of this proposal (Literature Review). Using different definitions, this study showed prevalences among adults aged 40-69 years ranging from 7.8 to 58.9.%. These estimates are very similar to those obtained by Celli when analyzing the NHANES III (Celli, submitted to publication). Using the LLN definition, the estimated prevalence was 58.9%, but as mentioned above there are serious concerns regarding the accuracy of this estimate.

When prevalence estimates from spirometric tests are not available, one option is to estimate COPD prevalence based on the frequency of smoking. Table 8 shows the information available

from Latin American countries. Current smoking prevalences ranged from 11.3% to 49.6%. Had the studies been restricted to those aged 40 years or more, higher prevalences would be found.

Stang (2000) located four studies in the international literature providing sufficient information on smoking and spirometric results that allowed them to estimate predictive equations. However, this model requires very detailed breakdowns of smoking status (current, ex or non-smoker) by age, sex and race, which are not readily available in Latin America, so that the method cannot be used to estimate COPD prevalence.

In view of these data limitations, the safest option for calculating sample size is to cover a wide range of prevalence scenarios. Table 5 with the review of international spirometric studies showed that COPD prevalences ranged from 4 to 61%, according to the country and criteria used. A large proportion of the estimates ranged from 5 to 20%. Smoking prevalences in these sites were similar to those observed in Latin America (Table 8). Sample size calculations, therefore, were made to cover the range of 5 to 60% prevalences (Table 9 bellow).

5.3.2. Margin of error

Studies aiming at high precision – small margins of error – require large samples. In the present study, it is proposed that margins of error should range between 2 and 4 percentage points, depending on the magnitude of the prevalence (see below).

5.3.3. Level of confidence

The survey result will have a 95% probability of being within the margin of error described above, relative to the actual prevalence.

5.3.4. Design effect

In cluster surveys, investigators have to take into account that subjects living in the same cluster may be more similar to one another than would be true for a random sample of the whole population. This degree of similarity is referred to as “intra-class correlation”, or ICC, and it results in the variance of the estimate of interest (in this case, COPD prevalence) being smaller in a cluster survey than it would be in a true random sample of the population. Using the ICC and the proposed cluster size, it is possible to calculate the “design effect”, a value by which the estimated sample size should be multiplied in order to make the cluster sample equivalent to a random sample.

Limited information is available on the intra-class correlation for COPD estimates from anywhere in the world, and less so for Latin America. When preparing this protocol, the investigator reanalyzed data from the 2000 COPD survey in Pelotas, Brazil, arriving at the results shown in Box 1.

BOX 1. DESIGN EFFECT IN PELOTAS 2000 COPD SURVEY

Outcome: ATS
Intra-class correlation = -0.021
Design effect (clusters of 15 subjects) < 1.00

Outcome: GOLD
Intra-class correlation = -0.005
Design effect (clusters of 15 subjects) < 1.00

Outcome: ERS
Intra-class correlation = 0.005
Design effect (clusters of 15 subjects) = 1.05

Outcome: FEV1/FVC <= 70%
Intra-class correlation = 0.003
Design effect (clusters of 15 subjects) = 1.03

Outcome: Cough/phlegm symptoms
Intra-class correlation = -0.091
Design effect (clusters of 15 subjects) < 1.00

The results in Box 1 show that design effects are small for the spirometric measurements. However, to be on the safe side, a design effect of 1.5 is being proposed.

5.3.5. Sample size calculations

Table 11 shows sample size calculations for COPD with the following parameters: margin of error from 2% to 4%, design effect of 1.0 and 1.5 and prevalences from 5% to 60%.

TABLE 11 – SAMPLE SIZE CALCULATIONS FOR COPD

DESIGN EFFECT		1.0			1.5		
MARGIN OF ERROR		2%	3%	4%	2%	3%	4%
ESTIMATED PREVALENCES	5%	475	211	119	713	317	178
	7%	651	289	163	977	434	244
	10%	900	400	225	1350	600	338
	15%	1275	567	319	1913	850	478
	18%	1476	656	369	2214	984	554
	20%	1600	711	400	2400	1067	600
	25%	1875	833	469	2813	1250	703
	30%	2100	933	525	3150	1400	788
	40%	2400	1067	600	3600	1600	900
	50%	2500	1111	625	3750	1667	938
	60%	2400	1067	600	3600	1600	900

Formula for required target sample = n = 4*p*(1-p)*deff/e^2

5.3.6. Sample size estimates

A series of sample size calculations were carried out using different combinations of estimated prevalences and margins of error. Using clusters of 15 subjects, 95% confidence level, a design effect of 1.5, a total sample of 800 individuals (red color in Table 11) in each metropolitan area would result in:

- prevalences of up to 5% will have a margin of error no larger than 2 percent points;
- prevalences between 6% and 10% will have a margin of plus or minus 3 percent points; and
- prevalences of 18% to 30% will have a margin of error no greater than 4 percent points.

To include 800 individuals in the sample, it is proposed that 1,000 should be invited to participate, thus allowing for non-response (refusals, contact failures, etc). Given an average cluster size of 15 subjects, around 68 clusters will be required in each site. In each metropolitan area, the number of households per cluster will have to be calculated to yield on average 15 adults aged 40 years or over. This number is obtained by dividing 15 by the product of the proportion of the total population aged 40 years or over and the average number of persons per household. For example, in Pelotas this is equal to 15/(0.30 x 3.5), or 14 households.

The total size of the study, therefore will be of 4,000 individuals in the five metropolitan areas. It is important to stress that the margins of error will apply to each metropolitan area in the study. Subgroup analyses (for example, sex, age or smoking specific prevalences) will have larger margins of error within each metropolitan area. However, data from the five areas may be pooled for subgroup analyses, resulting in higher precision.

Pooled analyses may also be carried out to investigate the effect of risk factors on COPD prevalence. Sample size calculations for these are being prepared. It is envisaged that, with a total sample size of approximately 4,000 subjects, there will be sufficient statistical power to detect even weak associations.

5.4. Sampling

In order to obtain probabilistic samples that are representative of the five metropolitan areas, the following approach is being proposed (there may be slight variations determined by the availability of background data for building the sampling frame).

- Each metropolitan area will be stratified into the main municipality and surrounding towns. The number of clusters to be selected will be proportional to the population in these two strata.

- Rural areas in these municipalities and towns will not be included in the sampling frame.

- Census tracts (or similar units) will be listed in each of the two strata, and selected with probability proportionate to the census tract population.

- In each census tract selected, a sketch map will be drawn (if not already available) and the blocks or similar units will be numbered.

- One block will be randomly selected in each tract.

- Within this block, one street corner will be randomly selected.

- Moving around the block in a clockwise direction, every second household will be visited until the required number of households are included. A cluster form will be filled with information on the composition of the household (age and sex distribution).

- All persons aged 40 or more, living in the selected households, will be invited to participate in the study. If more than one person is available in a given household, all will be included (the analyses will take into account this fact).

In most of these cities, the Census Bureau or a similar institution may already have a master sample for the metropolitan area. If this is available, it will be examined in order to assess if it would be appropriate for the proposed survey.

5. 5. Outcome variables: diagnostic criteria

As discussed in the Introduction, there is wide consensus that spirometric measurements are the gold standard for the diagnosis of COPD in prevalence surveys (Celli, 2000). However, there is no consensus on a single index and cut-off for diagnosis. Therefore we propose to use multiple criteria so that the study results may be compared to the existing literature. These will include:

ATS – FEV1/FVC < lower limit of normal
ERS – FEV1/FVC < 88% of predicted (males)
FEV1/FVC < 89% of predicted (females)
GOLD – FEV1/FVC < 0.70 AND FEV1 < 80% of predicted
FIXED RATIO – FEV1/FVC <= 0.70

After the meeting in Mazatlan (Mexico) it was decided that the definition of COPD in this project will be based on Fixed Ratio criteria (FEV1/FVC < 70% post bronchodilator - BD), although it will be possible to evaluate all parameters cited above. The reason for choosing this criteria is because there are no predicted values for lung function for all the sites enrolled in the project.

Exclusion of asthma – subjects will be considered as possible asthmatics if they have a positive response with a FEV1/FVC >= 70% after BD. If they have a positive response after BD but FEV1/FVC stays < 70% they will not be excluded. Patients with self reported asthma will also be kept in the group of COPD.
Although it is well known that symptoms and medical diagnoses underestimate the frequency of COPD, we also plan to collect information on these indicators, since one of our secondary objectives is to compare these with spirometric measurements. The following definitions will be used:

Chronic bronchitis - subjects reporting cough with expectoration during 3 months of the year, for at least two consecutive years.

Medical diagnosis of bronchitis or emphysema – subjects reporting that they have been diagnosed with bronchitis or emphysema

In addition, clinical information will be collected on history of cough, phlegm, wheezing, etc. The personal history of important respiratory conditions (e.g. leading to hospital admission) since childhood will also be collected.

5.6. General exclusion criteria for the study:

- Institutionalized subjects.
- Subjects with mental diseases.
- Other conditions to be specified.

5.6.1. Exclusion criteria for spirometry:

- Subjects with current tuberculosis (questions about current and ever treated tuberculosis).
- Heart attack in the last three months.
- Upper pulse limit over 120 beats/minute.
- Lower pulse limit < 60 beats/minute.
- Pregnant women (self reported).
- Thoracic or abdominal surgery in the last 3 months.
- Other conditions to be specified
- Respiratory infection in the past 3 weeks (Cough and sputum in the last 3 weeks - if the subject answered yes, but is willing to have you return at a later date, then make a new appointment and do so. If not, ask what was the last day of the respiratory infection and do the spirometry).

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* Betablocker is not an exclusion criteria.

*** The subject should be advised to see a cardiologist if the pulse beats is over 120 or below 60/minute.**

5.7. Identification variables

Each questionnaire will have a unique six-digit number made up by:

- site number (1 digit)
- census tract number in the site (2 digits)
- household number in the census tract (2 digit)
- subject number in the household (1 digit)

In addition, the identification block will include:

- date of the interview;
- hour of the interview;
- name of the interviewer;
- subjects name (for revisit purpose only – to be erased from data files for confidentiality reasons);

- full address and instructions on how to reach the house
- subject's telephone (if available)

5.8. Variables on demographic and risk factors

These will include:

- sex – dichotomous variable: male or female.
- age – discrete variable: years completed until the interview date.
- civil status – single, married (or living with a partner), widow, and separated or divorced.
- ethnic group – to be defined locally and collected in two different forms: by self-classification and according to the observation of the interviewer.
- education level – discrete variable: completed education years.
- income – continuous variable: monthly family income in local currency in the last month (obtained by adding the incomes of all family members)
- migration status – how long the subject has lived in the metropolitan area and previous place of residence
- occupation – using local classification; particular emphasis to be given to occupations known to be related to COPD
- occupational exposure to powder, dust, smoke, gas or chemicals: duration of exposure, intensity of contact, frequency of contact and type of work.
- smoking history – amount, age at beginning and stopping, type of cigarette, inhaling, etc
- passive smoking – intensity and duration of exposure at home and in the workplace
  housing characteristics - walls, roof, floor, crowding
- domestic biomass pollution – exposure to smoke from cooking, heating or lighting fluids
- family history of lung disease - chronic bronchitis, asthma or bronchitis, emphysema, tuberculosis, lung cancer, other
- cause of death of parents (if applicable)
- anthropometric status – weight, height, body mass index (see below under "Instruments").

5.9. Variables related to medical management and consequences of COPD:

- awareness of the presence of COPD
- health services utilization (outpatient, admissions)
- clinical and laboratory investigations performed
- drug management
- prevention of COPD consequences (vaccinations, avoidance of smoking)
- impact of COPD on disability, absenteeism and social life

5.10. Questionnaire

The questionnaire to be used in this survey will be jointly developed by the main coordinator of the PLATINO project and the coordinators of the BOLD study. It will be a short version of the ATS-DLD questionnaire used in the study in chronic bronchitis in Brazil by the author of this project. Spanish and Portuguese versions will be prepared.

The draft questionnaire will then be tested in no less than 20 interviews at a convenient location (for example, in a general practice clinic) in each site, and feedback will be provided to the central coordination regarding adaptations that may be required. The central coordination will then distribute the revised version to all sites. To ensure the comparability of the results, no changes in the questionnaire are allowed without clearance from the central coordination – it is not envisaged that any changes will be required, but some limited local adaptation may be needed. The database for entering the questionnaire data will also be centrally prepared.

5.11. Measuring equipment and techniques:

The measurements will include spirometry and anthropometry, since weight and height information are required for calculating lung function.

Weighing scale. Electronic weighing scales with a precision of 100 g (model to defined) will be used. Subjects will be weighted without shoes and wearing light clothes. The type and quantity of clothes will be recorded for later subtraction from the gross weight.

Stadiometer. Standing height will be assessed with stadiometers with a precision of 0.1 cm (model to be defined). The technique will follow that recommended by Lohman (Lohman, 1988) Subjects will not wear shoes. They will be asked to stand the feet drawing at the bottom of the stadiometer and to their heads straight in the Francfort plane while their height is being checked.

Spirometry. Try to perform the spirometry before the questionnaire and 15 minutes after the BD do the post BD test. All subjects should do spirometry with BD (see exclusion criteria for spirometry). It should be done preferentially at home since it is a very safe test (Lung Health Study). It should be performed according to the international guidelines. Subjects should perform the test sitting in a chair (to prevent any fall if they feel dizzy). The same portable spirometers should be used in all sites. We are proposing to use the NDD (American) with the following advantages: considerably cheap (1800 USD), very small (fits in a pocket), with batteries (2 AA) and having a considerable memory (at least for 400 tests with graphs).NDD saves the 3 best tests. Database formed is an Access database compatible with anything (can be exported to dbase etc). Downloading is very simple, and it can print directly to a parallel port printing. A disposable mouthpiece should be used.

Every day the spirometers must be calibrated with a 1 litre syringe. A noseclip must be used by all subjects and it has to be asked if he/she did use a bronchodilator during the last hour prior to the test or if he/she smoke a cigarette (if he/she used a BD or smoked a cigarette in the last hour delay lung function test one hour after the last cigarette or inhaler).

Ask if the subject had used any BD in the last hour or in the last 24 hours. If possible wait until enough time has elapsed or reschedule the subject for another time. If the subject doesn't want to wait do the spirometry and write in the questionnaire which drugs he/she used and when.

Reversibility will be assessed by the GOLD criteria: an increase in FEV1 of 200ml and 12% after an inhalation of 200mcg of sallbutamol with a metered dose inhale with a spacer. The BD test should be with salbutamol 200 mcg through a volumetric spacer and repeated after 15 minutes.

Record first two technically satisfactory manoeuvres (up to eight attempts) and the number of rejected attempts.

5.12. Site team composition, selection and training

Each site team will include a Principal Investigator, a technical coordinator, a data manager, data entry clerks, a secretary, two supervisors and eight interviewers.

The Site Principal Investigator will be a senior pneumologist or epidemiologist who will be in charge of preparing the site protocol, submitting the protocol to the ethical committee, contacting local authorities, recruiting staff and overseeing all aspects of the study. It is envisaged that this person should dedicate no less than 20% of his/her time to the study.

The Site Technical Coordinator will be an experienced epidemiologist who will dedicate 100% of his/her time to the project. This person will be directly responsible for staff selection and training and will be in charge of sampling, deploying staff in the field, quality control, general supervision, and data management. The main coordinator of the study (Dr Menezes) will visit each of the centers to supervise the training, data collection and quality control activities.

The Site Data Manager will be a statistical technician who will be directly responsible for overseeing data entry and who will personally carry out data cleaning, editing, and preparation of data files for submission to the central study coordination. One or more data clerks, as required, will work under the data manager.

A Site Secretary will be in charge of copying, distributing and collecting questionnaires and other administrative activities related to the study.

Ten field workers will be selected in each site, of whom two will become field supervisors. They will, if possible, have University degrees in health, nutrition or social work fields. It is essential that they should dedicate 100% of their time to the project for 12 weeks. Training will last 1-2

weeks, consisting of meetings with the general coordinator and discussion of the study methodology and logistics. Afterwards, questionnaires and procedures will be read, and dramatizations, supervised interviews, and daily discussions of upcoming problems and doubts will take place. For weight, height and spirometry measurements, a specific training exercise will be carried out at a location with convenient volunteers, for example, a University clinic.

A pilot study will be carried out. It is recommended that about 15 candidates should be trained for selecting 10 field workers.

The two most competent trainees will be selected for being field supervisors. They will repeat 10% of all interviews, each being in charge of four interviewers. They will also revise and correct every questionnaire submitted by the latter.

Eight field workers will carry out the interviews and measurements. The field workers will be submitted to a special training course on spirometry and will receive a certificate to this effect.

5.13. Logistics

Experience from the Pelotas survey shows that it is possible to complete an interview and all measurements in one hour. Sufficient time must be allowed to reach the cluster, locate eligible subjects at home, and carry out all measurements.

For security and logistical reasons, interviewers will work in pairs. Both members of each pair will be trained both in interviewing technique and in spirometry, but one will be designated as the lead spirometrist.

Each pair will be expected to complete two clusters (30 interviews) in a 6-day week. Therefore, the 68 clusters in each participating site could be covered by 4 pairs of interviewers in 9-10 weeks. These calculations assume that each pair will carry a full set of equipment.

The two supervisors will repeat a short interview and re-measurement session with 10% of all subjects included, as well as to closely follow the work of each interviewer.

In each site, a survey headquarters will be established which will serve as the basis for all operations.

5.14. Cluster sheet

While conducting data collection on a given cluster (census tract), each interviewer will complete a cluster sheet with data on number of households, full address, number of subjects in each household, number of adults with aged 40 years or more, and interview status (interviewed; refused; not contacted after repeated attempts). In case of non-response, the field worker should

attempt to obtain information on age and sex of the non-responder, by asking other family members or neighbors (small questionnaire, see Annex II).

5.15. Pilot study

In each site included in the study, one additional census tract will be selected for the pilot study. This will include interviews and spirometry in 20 households during a weekend. The technical coordinator and the two field supervisors will carry out this study jointly with the interviewers. After this pilot study, the questionnaires will be entered into the computer to test the database structure. Finally, each team will assess the pilot study results jointly with the central study coordination, in order to correct possible problems that were identified.

5.16. Data processing and analysis

This will include coding of open questions (which will be kept to a minimum), revision of the questionnaires, data entry and cleaning. The questionnaires will be coded by the interviewers and revised by the local supervisors. Data entry and cleaning – using centrally prepared routines – will take place in each site. Data will be entered twice in a Epi-Info database. The data files will then be sent to the Coordinating Center for final editing. Only after the data sets are "closed", that is, fully cleaned, edited and approved by the Coordinating Center, will any publications of results be allowed.

Analyses will be run using the SPSS/PC statistical program, and the STATA program. They will include:

- descriptive data analysis (univariate analysis), with calculation of means, standard deviations and medians for continuous variables, and of proportion measures for categorical ones;

- bivariate analyses to test associations between the outcomes (COPD measures according to different definitions) and risk factors, using the Pearson chi-squared test and the test for linear trend in proportions, when applicable;

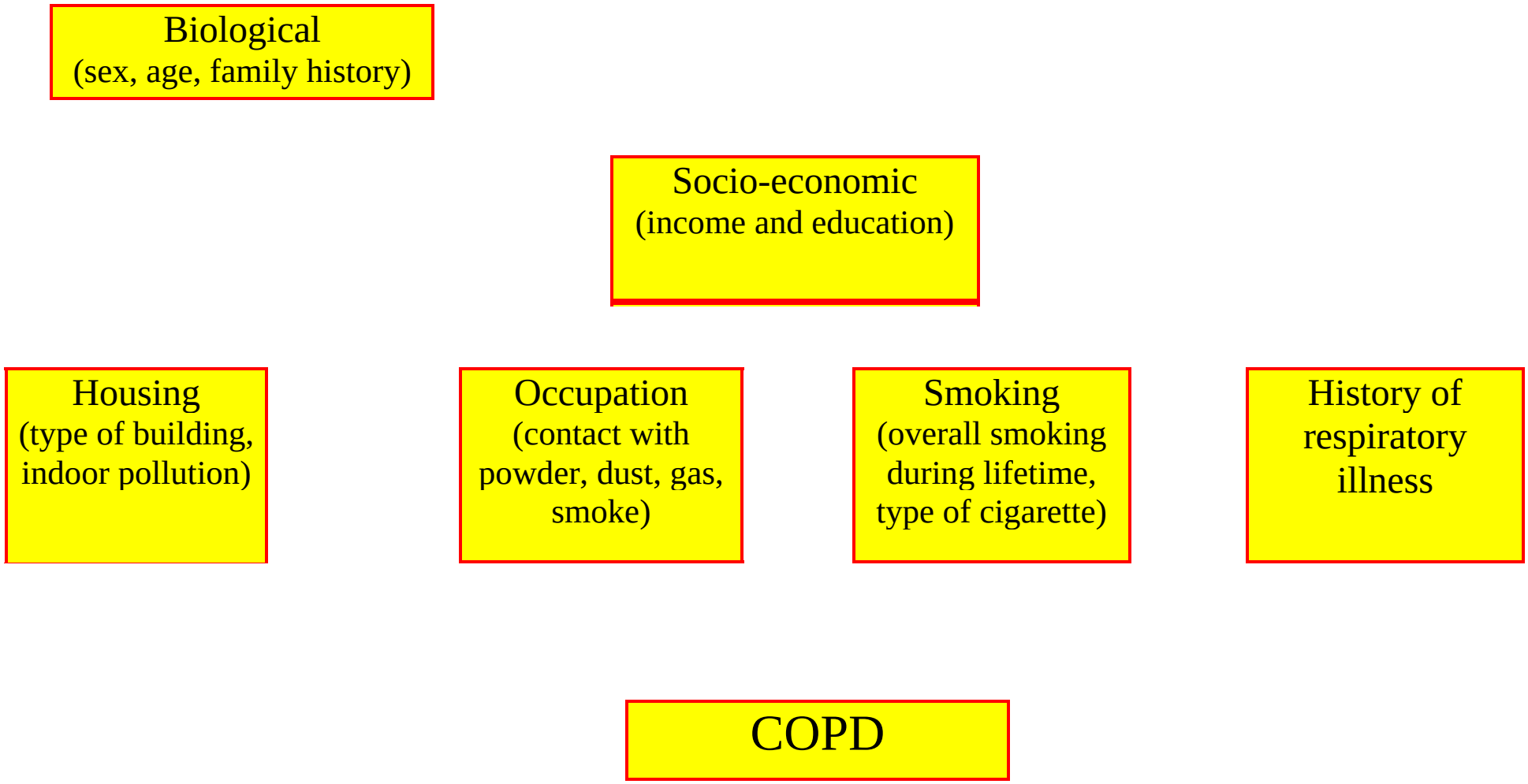
- multivariate analyses using non-conditional logistic regression, according to a previously defined conceptual model that takes into account the hierarchical relationships between risk factors (Figure 3). Confounding variables will be kept in the model if they reach a P level of 0.20, and the 0.05 P level will be used for characterizing significant risk factors.

5.17. Conceptual model for the analysis (Figure 3)

A conceptual model will be used for laying out the expected associations between risk factors and how these may affect the outcomes. The biological factors – age and sex and family history –

may affect COPD independently of other factors, or may interact with these. Socio-economic factors constitute distal determinants that influence COPD prevalence either by acting through known proximate determinants (such as smoking or occupational exposures), or by other unknown mechanisms. Variables in each level of causal determination will be adjusted for other variables in the same level and, if applicable, for those in higher levels (Victora, 1997).

FIGURE 3 – ANALYSIS MODEL FOR COPD ASSOCIATED RISK FACTORS



5.18. Quality control

Several measures will be taken to ensure strict quality control in the study. These will include:

- Use of pre-tested, standardized data collection forms and detailed interviewer guides
- Translation from Portuguese into Spanish and back-translation of questionnaires and other forms
- Careful selection and evaluation of interviewers
- Thorough training course on interviewing techniques
- Central training of all Site Technical Coordinators on anthropometric and spirometric measurements, followed by standardization sessions with assessment of intra and inter-observer variability
- Local training at each site by the Site Technical Coordinator on anthropometric and spirometric measurements, followed by standardization sessions with assessment of intra and inter-observer variability (under supervision of Rogelio Padilha from Mexico). All spirometric data will be transmitted on a regular basis (weekly) to Rogelio Padilha in Mexico's city and he will be responsible for the quality control of spirometries
- Frequent calibration of weighing and spirometric equipment
- Regular standardization sessions (every two weeks) throughout the data collection period
- Repeated attempts (no fewer than 3) to interview all subjects in order to reduce non-response
- Repetition of 5-10% of all interviews and measurements by a field supervisor using a shortened version of the questionnaire, with calculation of the kappa statistic for inter-observer reliability
- Simultaneous data entry with range/consistency checks and digit preference analysis by interviewer

5.19. Ethical issues

The study entails a level of risk to participants that is no greater than that associated with routine medical examination. Written informed consent will be requested from all subjects interviewed. The confidentiality of the data collected will be guaranteed. Spirometry results will be delivered to all subjects. Those with pulmonary function deficits will receive a written referral note to be taken to a clinic affiliated with the local institution carrying out the research. Ethical approval in each country will be sought at the required levels (i.e., institutional and/or national).

5.20. Refusals

A small questionnaire concerning sociodemographic, smoking and health status data should be performed in all subjects who refused to participate in the study.

6. LIMITATIONS OF THE STUDY

The main limitation of the study is the fact that although it will provide representative information for five of the largest metropolitan areas in Latin America, it cannot be extrapolated to the whole region, since smaller urban areas and rural populations are not included. Nevertheless, it will be one of the largest collaborative studies on COPD ever carried out, and its results will produce important information for assessing the distribution and risk factors for this important condition.

When studying associations with risk factors, it will be important to take into account the possibility of reverse causality, that is, that diseased individuals may avoid some risk factors (such as smoking or occupational exposures). One possible way to avoid such bias is to collect information about exposures in the past, before the first symptoms of COPD appeared.

7. STUDY ORGANIZATION

The organizational framework for the multicenter study is described in Figure 4 (see below). ALAT, Boehringer-Ingelheim, Dr. Menezes and the Site Principal Investigators will make up the Steering Committee which will have full responsibility for the design and implementation of the study.

The Executive committee comprises Dr. Menezes, Rogelio Padilha and the present director of the department of DPOC in Latin América .

The Advisory Committee comprises prominent external experts on the subject who, when requested by the steering committee, will provide guidance on study design, implementation and analysis.

The main coordinator of the study - Dr. Menezes – is an experienced epidemiologist and pneumologist from the Universidade Federal de Pelotas (UFPEL) in southern Brazil.

The study secretariat and the units of epidemiology, biostatistics and computing will be also located in Pelotas. Each study center will have a Site Principal Investigator who will be responsible for the field work in these places: Dr. Rogelio Pérez-Padilha from Mexico, Dr. Gonzalo Valdivia from Chile, Dr. Ricardo Gene from Argentina, Dr. Carlos Torres from Colombia and Dr. Jose Jardim from São Paulo. Dr. Menezes will visit all sites before and during the study.

ORGANIZATION FRAMEWORK FOR THE STUDY

STEERING COMMITTEE
ALAT, Boehringer-Ingelheim,
Ana Menezes
5 Principal Investigators

EXECUTIVE COMMITTEE
(Operational committee)
Ana Menezes
Juan Luna (Director, ALAT COPD)
Rogelio Padilha

ADVISORY COMMITTEE
Bartolomé Celli
Sonia Buist,
Marc Miravitlles, William
Vollmer, Roberto R.Roisin

GENERAL COORDINATION
AND STUDY SECRETARIAT
Pelotas (Brazil)
Ana Menezes

UNIT OF EPIDEMIOLOGY
Cesar Victora, Pelotas (Brazil)

UNIT OF BIOSTATISTICS/COMPUTING
Cesar Victora and Aluisio Barros, Pelotas
(Brazil)

BUENOS AIRES CENTER
P.I.: Ricardo Gene

SÃO PAULO CENTER
P.I.: José Jardim

SANTIAGO CENTER
P.I.: Gonzalo Valdivia

BOGOTA CENTER
P.I.: Carlos Torres

MEXICO CENTER
P.I.: Rogelio Padilha

8. PUBLICATION AND DATA OWNERSHIP ISSUES

Detailed guidelines for publication and data ownership should be discussed with the Steering Committee and Principal Investigators. This item could be presented in a next meeting. Some of the guidelines will be described below:

1. PUBLICATION GUIDELINES

The General Coordinator will present the final report of the study by late 2003 or early 2004 to Boehringer-Ingelheim (BI) and to the Steering Committee of the EPOC SURVEY (ES). The exact date will depend on the timetable of the study.

Cross-site papers.

The main paper on the study will present a summary of the methodology and the main results from all five centers. It will be submitted for publication soon after results from all sites are available, after approval by the Steering Committee. The authorship will be defined by the Steering Committee, but the General Coordinator and all Site PI's will be included as individual authors. The names of individual authors will be followed by the "PLATINO Study Group", comprising the names of local investigators involved in the study (listings to be provided by the PI's).

The full study protocol will also be published. There is a growing interest in making protocols widely available, and some electronic journals, for example, BioMed Public Health, encourage such publication. Approval and authorship guidelines for protocols are the same as described above.

If any of the investigators involved in the study have special interest in pursuing a specific topic using data from all sites, they should obtain consent from the Steering Committee. These papers must be approved by the Steering Committee before publication. Authorship by up to three individual authors involved in the analysis and writing up and by the "PLATINO Study Group" is recommended. A list at the end of the paper will include members of the country teams who, according to their PI, were involved in the collection of data reported in the paper; these will not necessarily include all members of the country research team.

Site-specific papers.

Principal investigators are encouraged to publish site-specific findings in a timely manner, if possible within one year of completion of each survey. Publication of these papers should not wait for completion of the whole study in all sites. The Steering Committee will provide assistance in writing up results for publication, upon request from the study sites. All papers should be submitted to the Steering Committee for review prior to publication.

Members of the Steering Committee who made substantial contributions may be invited to be co-authors on an individual basis at the discretion of the local PI (The order of author's names in publications based on country-specific analyses will be the responsibility of the site Principal

Investigator). Authorship should follow international recommendations, i.e. all authors should have contributed substantially (see http://bmj.com/advice/article_submission.shtml).

Presentations at local, regional and international meetings**.**

Country team members are encouraged to present results from the ES in such meetings. Local approval by the PI is required. The Steering Committee should receive a copy of the abstract at the time it is being submitted. Presenters are encouraged but not required to share their presentation materials with ALAT and BOEHRINGER. Acknowledgement of ALAT/BOEHRINGER support should be included in the presentation along the lines suggested below.

2. DATA OWNERSHIP

The contract between ALAT and BOEHRINGER will specify that all data derived from the ES are a joint property of ALAT and BOEHRINGER. The institutions to which individual PI's are affiliated will share with ALAT/BOEHRINGER the ownership of their site-specific data sets.

As soon as the data sets from a specific survey are entered and cleaned, a copy should be made available to ALAT/BOEHRINGER. This should always take place within one year from the end of data collection.

ALAT/BOEHRINGER will examine requests for data use before their transfer into the public domain from individuals or institutions not involved in the PLATINO data collection on a case-by-case basis. These applications should include a detailed plan for analyses and publications, list the specific variables being requested and indicate how each of these variables will be used in the analysis. Complete data sets will not be released. ALAT/BOEHRINGER will then consult with the local PI's. If all parties agree that they are not interested in taking the lead in the analyses being suggested, the partial data set may be released.

Two years after publication of the main cross-site results paper, the full data set will be made available in the public domain. The anonymity of all study participants will be ensured.

3. ACKNOWLEDGEMENT TO ALAT/BOEHRINGER SUPPORT

The following language is recommended when acknowledging the research: "This work is a part of the Multi-Centre Survey of COPD in Five Major Latin-American Cities (THE PLATINO STUDY), coordinated by Associacion Latino-Americana del Torax and supported by BOEHRINGER-INGELHEIM."

4. COORDINATION OF PUBLICATIONS

The Steering Committee will be responsible for:

- Preparing of a list of expected publications from each site involved in the study.

- Encouraging PI's to produce these publications in a timely manner, and offering assistance if required.
- Setting up writing committees for the papers and a mechanism for review of the final drafts that are submitted for publication.
- Reviewing papers before publication with the goal of maintaining internal consistency of material, methods, analyses and interpretation.
- Examining requests for data analysis and publication by individuals or institutions external to the PLATINO.

9. TIME TABLE

Year	2002						2003												2004					
Month	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6
Finalization of proposal	●																							
Development of instruments		●	●																					
PI meeting																				●				
Coordinator training (Pelotas)				●																				
Visits to sites (Menezes)					●	●				●		●												
Data collection: Brazil		**P**	**T**	**F**	**F**	**D**																		
Data collection: Chile					**P**	**T**	**F**	**F**	**D**															
Data collection: Mexico									**P**	**T**	**F**	**F**	**D**											
Data collection: Colombia									**P**	**T**	**F**	**F**	**D**											
Data collection: Argentina												**P**	**T**	**F**	**F**	**D**								
Data analysis (Pelotas)											●	●	●	●	●	●	●	●	●	●	●	●	●	
Preliminary report																				●				
Preparation of papers																					●	●	●	
Final report																								●

P = pretest of questionnaire
T= training and pilot study
F = field data collection
D=data entry and cleaning

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