Study Protocol to be submitted to the study session

Cod.: FARM8ZBT93

A. Characteristics of the study

A1. PRINCIPAL INVESTIGATOR

First name NERA	**Last name (Family name)** AGABITI	**Year of birth** 07/11/1959	**Gender** F
Email agabiti@asplazio.it	**Tel.** 06 83060403	**Fax** 06 83060374	**Cell.**

A2. INSTITUTION

Institution	AUSL Roma E di Roma (SEDE USL)		
Unit:	Dipartimento di Epidemiologia, U.O.C. Epidemiologia Clinica		
Address	B.GO SANTO SPIRITO, 3	ROMA (RM)	Web Site: www.epidemiologia.lazio.it

A3. AREA-TOPIC

AREA	B - Pharmacoepidemiological studies aimed at defining the benefit-risk profile of treatments and the impact of strategies for improving the appropriateness of drug use
Topic	4 - Assessment of the outcome and appropriateness of therapeutic strategies used in patients affected by severe asthma and frequently relapsing COPD.

A4. PROPOSAL TITLE

Title	Long-term outcomes and adverse events of therapy with inhaled corticosteroids, long-acting beta-2-agonists and anticholinergic drugs in hospitalised patients with Chronic Obstructive Respiratory Disease (COPD) - a cohort study based on health information systems in three Italian regions.				
Running title	OUTCOMES OF INHALED THERAPY IN COPD COHORT				
Key words	ADVERSE EVENTS	COHORT	COPD	INHALED THERAPY	SURVIVAL

A5. PHARMACOLOGICAL TREATMENT

n°	Drug			Marketed (in Italy or abroad)		Not Marketed (neither in Italy nor abroad)
	Active ingredient	**Reimbursement class within the NHS (A, C, H)**	**Drug for treatment group (T) drug for standard group (C)**	**Patent/Off patent**	**Approved indications /Other indications**	
1.	*ATC: R03A*	*A*	*T*	*Patent*	*Approved indications*	
2.	*ATC: R03B*	*A*	*T*	*Patent*	*Approved indications*	
3.	*ATC: R03C*	*A*	*T*	*Patent*	*Approved indications*	
4.	*ATC: R03DA*	*A*	*T*	*Patent*	*Approved indications*	
5.	*ATC: H02AB*	*A*	*T*	*Patent*	*Approved indications*	

6.	*ATC: V03AN01*	*A*	*T*	*Patent*	*Approved indications*	
7.	*ATC: J01*	*A*	*T*	*Patent*	*Approved indications*	
8.	*ATC: R05-R06-R07*	*A*	*T*	*Patent*	*Approved indications*	
9.	*ATC: C01, C02, C03, C07, C08, C09, C10*	*A*	*T*	*Patent*	*Approved indications*	
10.	*ATC: B01*	*A*	*T*	*Patent*	*Approved indications*	
11.	*ATC: A10*	*A*	*T*	*Patent*	*Approved indications*	
12.	*ATC: M05B*	*A*	*T*	*Patent*	*Approved indications*	

A.5a. Non pharmacological treatment

not applicable

A.6. STUDY DESIGN

Observational

Observational

- Cohort ***Number of Patients:*** *40000*

Number of Case-patients:

- Prospective

Number of Clinical Centres*:

A.7. ESTIMATION OF THE STUDY DURATION:

Estimation of the complete duration of the study*: *36 (months)*

Duration of recruitment (if applicable): *(months)*

Treatment duration (if applicable): *(days)*

Duration of follow up (if applicable): *(days)*

A.8. STUDY POPULATION

Setting of the study: *Other: health information systems*

Special populations: *Yes Eldery (65-74 y); Eldery (75+ y);*

A.9. OUTCOME(S)

Follow-up at 12, 24, 36 and 48 months for:

1. Mortality (all causes, respiratory, cardiovascular)
2. COPD exacerbation
3. Adverse cardio- and cerebrovascular events
4. Pneumonia
5. Osteoporotic fractures

TOTAL COST: 350.663

B. Study Protocol

B1. ABSTRACT

Background
There is evidence that inhaled corticosteroids (ICS), long-acting beta-2-agonists (LABA) and anticholinergics for Chronic Obstructive Pulmonary Disease (COPD) reduce symptoms and exacerbations and improve lung function, but no conclusive results exist on long-term benefits such as survival. A large scientific controversy is ongoing on potential adverse events.
Objectives
The main objectives are:
1. To measure long-term outcomes and adverse events of inhaled drugs in the cohort under study over a 4-year period follow up
2. To compare effectiveness of the different drugs (both "monotherapy" and "combined therapy") in term of long-term survival or exacerbations
3. To compare incidence of side effects of inhaled therapy (ICS, LABA and anticholinergics) among users versus non users
Methods
Design: longitudinal population-based cohort study. From the Hospital Information Systems (HIS) 2006-2007 in three Italian regions, about 40,000 resident patients 45+ years old with COPD (ICD-9-CM codes) will be enrolled. Record linkage procedures with Mortality Register, HIS, Emergency Information System, Drug Dispense Register will be performed to define exposure (ICS, LABA, and anticholinergics), potential confounders, and to measure outcomes over a 4-year period starting from the date of discharge. Outcomes: all-cause, respiratory and cardiovascular mortality, incidence of adverse events, and COPD exacerbations. Through Cox-proportional-hazard models for each drug, comparison will be made between users versus non-users. Subgroup analysis will consider mono- versus poly-therapy. Sensitivity analyses will take into account different subgroup susceptibility or different definitions of chronic exposure.
Expected results
This study gives insights into:
1. real-life utilization patterns of inhaled drugs and other respiratory medicines for a disease with large impact on population health, hospital care, drugs use and costs in Italy
2. appropriateness and adherence to clinical guidelines
3. comparative long-term effectiveness of different inhaled drugs
4. incidence of long-term adverse events and risk/benefit ratio of inhaled drugs
5. identification of subgroups of COPD patients particularly susceptible to beneficial/adverse events.
Results may have a strong impact on current clinical practice in our country.

B2. BACKGROUND AND RATIONALE

Chronic obstructive pulmonary disease (COPD) is the 4th-leading cause of mortality and 12th-leading cause of disability worldwide and its global burden is increasing (1). COPD - generally considered a respiratory condition only - has important systemic effects, and chronic systemic inflammation has been proposed as a possible link (2). The care of patients with COPD has changed radically over the past two decades and novel therapy can improve the health status of patients with COPD and modify its natural course (3). Pharmacological therapy, pulmonary rehabilitation, long-term nocturnal noninvasive mechanical ventilation, domiciliary oxygen therapy, and disease management programs are recommended by the Scientific Guidelines (4).

Over the past 20 years, several drugs, such as inhaled corticosteroids (ICS), long-acting beta-2-agonists (LABA), and anticholinergics, have been introduced for patients with stable COPD as long term therapy. They have different mechanisms of action and therefore could have an additive effect when combined. Increasing evidence suggests that LABA and ICS have complementary and synergistic effects, when delivered as combination therapy from a single inhaler. In this respect, two preparations comprising combinations of salmeterol+fluticasone propionate (SFC) and formoterol+budesonide (FBC) are currently available and employed for treatment of more severe disease. In the last few years a novel anticholinergic drug, tiotropium, has had a large impact in clinical practice.

Several trials and observational studies have been conducted to compare efficacy of different inhaled drugs,

but results are not conclusive. While inhaled therapy with ICS, LABA, and anticholinegics have generally been shown to slow the decline of quality of life, reduce symptoms and rates of exacerbations, and favourably affect lung function parameters, relatively few studies have evaluated clinical long-term effects such as survival. A great controversy is ongoing on potential adverse events. Much attention has been paid to the increased risk of pneumonia in relation to inhaled ICS and the higher rates of cardiovascular adverse events in relation to both LABA and anticholinergics and further investigation is required (5, 6). New studies are needed to assess the relative effects of combined therapies, to examine the convenience of using different inhaler devices, and to identify specific subsets of patients with COPD who mostly benefit from inhaled drugs (5,7).

Efficacy and safety of inhaled therapy in COPD - summary of evidence
LABA plus ICS - Several large-scale studies in patients with moderate-to-severe COPD have demonstrated that treatment with LABA plus ICS leads to significantly greater improvements in lung function, exacerbations, health status and breathlessness, compared with placebo or monotherapy of component drugs (3,5). They are also more effective than in ICS alone or placebo in reducing mortality, while no beneficial effect on survival has been proven compared to LABA monotherapy even with additional information from the TORCH trial (5). In the meta-analysis by Sobieraj et al addition of an ICS to a LABA was associated with an increased risk for pneumonia and oral candidiasis compared with LABA monotherapy (8). Evidences of beneficial effect on survival come from observational studies. Using data from the UK General Practice Research Database, Soriano et al found that 3-year survival in 1,045 COPD patients treated with ICS and LABA was higher than in 3,620 COPD patients who regularly used other bronchodilators (78.6% versus 63%). The survival advantage observed was highest in combined users and mortality decreased with increasing number of prescriptions (9). These findings were successively confirmed in other population studies from USA (10).

ICS - Recent studies on ICS therapy in stable COPD have yielded conflicting results regarding survival and risk of adverse events. Among patients with COPD, ICS therapy does not affect 1-year all-cause mortality while it is associated with a higher risk of pneumonia (7). Long term use of ICS (more than 6 months) versus placebo did not significantly reduce the rate of decline in lung function, and did not produce statistically significant effects on mortality (11). Again, observational studies yielded different findings. Sin and Tu conducted a population-based cohort study on over 22.000 people hospitalized with COPD in Canada and suggested that inhaled corticosteroid therapy (within 90 days post discharge) is associated with reduced COPD-related morbidity and mortality in elderly patients (12). Similarly, among 1700 people with COPD recruited from two managed care populations in USA, Mapel et al found that COPD patients who used ICS alone or in combination with LABA had substantially improved survival (13).

Anticholinergics - Several RTCs have examined the relative efficacy of ipratropium and LABA. Long term use (at least four weeks) of ipratropium bromide (IpB) plus LABA versus LABA alone slightly differ from regular long term use of IpB or LABA both monotherapy in term of symptoms and exercise tolerance (14). A large 4-year trial showed that tiotropium is associated with improvements in lung function, quality of life, and number of exacerbations during a 4-year period but did not significantly reduce the rate of decline in lung function (15). A recent review found that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, myocardial infarction, or stroke among patients with COPD (6). Controversal evidence on efficacy and cardiovascular adverse events (tachycardia, myocardial infarction, heart failure or stroke) comes from observational studies (16,17).

Beta-2agonists - Safety of long-acting beta agonists (LABA) has been questioned and a detrimental effect on asthma control has been suggested as well as an increased risk of death (18). This evidence reinforced the international recommendations, confirming that use of LABA remains the preferred add-on therapy to ICS for patients whose disease cannot be adequately controlled with ICS, and that LABA should not be prescribed as a monotherapy. Regarding stable moderate-to-severe COPD, a recent review supports the beneficial effects of LABA and did not confirm previous data about an increased risk for respiratory deaths (19).

Methodological issues in observational studies aimed at evaluating health care outcomes
A fervent methodological dispute is still ongoing on how to define exposure time-windows, and how to properly take into account overlapping exposure and follow-up times. In 2001, Sin and Tu conducted a population-based cohort study on over 22.000 people hospitalized with COPD in Canada treated with inhaled drugs and chose an exposure time-span of 90 days after discharge index, defining as "exposed" all subjects with drug prescriptions in that period, while lack of prescription was considered "non-exposed". Furthermore, all exposed subjects were considered under treatment from the first day of follow-up till the last, regardless on when the prescription was actually filled (intent-to-treat assumption); analogously, non-exposed subjects were considered out-of-treatment for the whole period, regardless whether they received treatment after the 90-day period (12). This approach was criticized by Suissa, who declared the study as affected by "immortal-time

bias" (20). This bias results from cohort studies with follow-up time during which a subject cannot, by definition, incur the outcome event under study. That is, when the exposure time overlaps follow-up times, patients who die during the exposure time by definition cannot obtain the drug in question and as such will be classified as non-exposed. This is believed to result in underestimation of person-time without ICS/LABA treatment leading to overestimation of any treatment effect. In a more appropriate time-dependent analysis (according to Suissa), Fan et al examined 8033 patients with COPD in USA and the use of ICS was not associated with a decreased risk of mortality or exacerbations (21). Successively, Kiri et al applied two different designs - free of immortal time bias but still treating the exposure variable in a time-fixed fashion - using the UK General Practice Research Database. They found a protective effect of ICS use on both readmissions and mortality risks and concluded that immortal time bias cannot account for the risk reduction associated with ICS exposure in observational studies (22). Mapel et al criticized the "time-dependent" approach advocated by Suissa and Fan, stating that it is methodologically correct to use time-dependent exposures only when the variations of exposure in time are not related with the outcome or other factors affecting the outcome (as the health status of the patient). They stated that the time-dependent approach would increase bias rather than diminish it (13).

Strengths of large observational studies based on health information systems and expected results
In recent years, there has been enormous growth in the use of large health care databases to evaluate quality of care all over the world. In Italy, experience on this topic has been increasing in the last decade, especially in the Lazio region (23). The commonly used data sources are hospital information systems, mortality registers, and pharmacy dispensing databases. These data, routinely collected for administrative purposes, contain also information on clinical severity, procedures and therapy and have numerous strengths: 1) their large size allows to study rare events, 2) represent routine clinical care and allow to study real-world effectiveness, utilization patterns and appropriateness, 3) low cost and easy access. Regarding drugs, observational post-marketing studies are of paramount importance in order to assess the real-life effectiveness of drugs in populations often excluded from pre-marketing RTCs (for example elderly patients with multiple co-morbidities), and to assess whether an intervention does more good than harm when provided under usual circumstances of health-care practice. Moreover, in the case of COPD patients, interactions between respiratory and cardiac drugs are expected and may influence outcomes. Evidence is very limited in this respect and further research is required.

This study will enroll over 40.000 patients with mild-severe COPD, one of the largest sample available in European contest. The large numbers will enhance the precision of effect estimates and improve detection of adverse events. It will contribute to the knowledge of:
1) real-life utilization patterns of inhaled and other respiratory drugs for a disease with high impact on population health, hospital care, drugs use and costs in Italy
2) appropriateness and adherence to clinical guidelines
3) efficacy of different inhaled drugs over a 4-year period
4) incidence of long-term adverse events and risk/benefit ratio
5) concomitant prescribing patterns of drugs for co-morbidities, with special attention to cardiovascular disease and diabetes
6) potential interaction of concomitant diseases and related prescribing patterns on the exposure-outcomes association of inhaled therapy.
Moreover, it will give an important contribution to the scientific controversy about methodological issues in post-marketing observational studies.
Finally, it will allow to address specific scientific questions that are all still open with potential strong impact on current clinical practice in our country. Among them: Is "combined LABA-steroid therapy" in one inhaler more effective than different devices therapy? - Are there subgroups of COPD patients particularly susceptible to cardiovascular side effects of LABA or anticholinergic therapy?

B3. OBJECTIVES OF THE STUDY

Primary objectives

1. To measure long-term outcomes and adverse events of inhaled drugs in the study cohort over a 4-year follow up period

2. To compare effectiveness of the different drugs (both "monotherapy" and "combined therapy") in terms of long-term survival or exacerbations

3. To compare the incidence of side effects of inhaled therapy (ICS, LABA and anticholinergics) among users versus non users

Secondary objectives

1. To describe the use of inhaled drugs in a cohort of moderate-severe COPD patients in three Italian regions

2. To compare the prescribing pattern of inhaled drugs with the Guidelines on COPD management and therapy

3. To identify subgroups of COPD patients particularly susceptible to beneficial effects of the different inhaled therapies by testing the potential effect modification of
o disease severity (i.e. moderate versus severe COPD)
o socio-demographic characteristics (i.e. gender, age)
o co-morbidity status (i.e. coexisting cardiovascular disease or diabetes)
o concomitant exposure to cardiovascular protective agents (e.g. low-dose acetylsalicylic acid, HMG CoA reductase inhibitors, etc.)

4. To identify subgroups of COPD patients particularly susceptible to or protected from side effects of the different inhaled drugs by testing the potential effect modification of
o disease severity (i.e. moderate versus severe COPD)
o socio-demographic characteristics (i.e. gender, age group)
o co-morbidity status (i.e. coexisting cardiovascular disease or diabetes)
o concomitant exposure to cardiovascular protective agents (e.g. low-dose acetylsalicylic acid, HMG CoA reductase inhibitors, etc.)

B4. METHODS

A. Study design (flow chart ANNEX Part A Figure 1)

The present observational study is a population based prospective cohort study. No active enrolment will be performed, but the cohort will be systematically recruited on the basis of data routinely collected in three Italian regions (Emilia-Romagna, Lazio, Lombardia).

B. Data sources (details ANNEX part B)

The principal data sources used for the study are Mortality Information System (MIS), Hospital Information System (HIS), Healthcare Emergency Information System (HEIS), and drug dispense registry (Pharm).

C. Study population (details in ANNEX Part C)

From HIS all patients aged 45+ years and resident in the study areas with acute exacerbation of COPD during a two-year period (2006-07) will be enrolled. We assume that people hospitalized for acute COPD exacerbations represent moderate-to-severe cases of COPD patients (24). For those patients with more than one admission for COPD the first admission will be considered as index admission.

D. Exposure (details ANNEX Part D)

Exposure will be defined on the basis of all prescriptions (of specific categories) occurring from index hospital discharge (start to follow-up) to event/censoring, for 36/48 months for each subject.
The reference date is the date of discharge referring to the index admission.

Types of exposure
Main exposure is intake of drugs belonging to the following ATC groups:
Selective beta-2-adrenoreceptor agonists, Aticholinergics, Corticosteroids (glucocorticoids) (inhaled)

Comparisons will be made between

drug users of the following ATCs:
1. inhaled long-acting beta-2-agonists

2. inhaled anticholinergics
3. inhaled glucocorticoids

versus

non users (=control group): patients treated with any drug not in the user group or not treated.

Exposure assessment
For each patient of the cohort the Pharm database will be searched for all prescriptions of drugs referring to the 36/48 months following the reference date.
Drug use is defined as days of therapy covered by the cumulative prescribed drugs of each ATC group, calculated on the basis of the defined daily doses (DDD) of each single drug.
Chronic use will be defined a priori on the basis of a minimum cut-off of therapy days in a given time-window.

The following issues will be addressed in exposure assessment:
1. Immortal time bias
2. Sensitivity to time-window chosen
3. Time-dependent exposure
4. Dose-response relationship

E. Outcomes (details ANNEX Part E)

Follow-up at different time intervals will be considered: 12, 24, 36 and 48 months after the reference date.
Through individual record linkage with health information systems the following outcomes will be identified:

o All cause- mortality
o Respiratory mortality
o Cardiovascular mortality
o COPD exacerbation defined as either a hospital admission/emergency visit for COPD or COPD-related causes or a prescription for an oral corticosteroids with/without systemic antibiotic
o Adverse cardio- and cerebrovascular events
o Pneumonia
o Osteoporotic fractures

Composite endpoints will be also examined.

F. Potential Confounders/effect modifiers

A number of covariates that might influence outcomes in COPD are defined as potential confounders or effect modifiers to be considered in the analysis.

F.1 Potential proxy measures of COPD severity (details ANNEX Part F.1)

o Concomitant exposure to other respiratory drugs for chronic management of COPD
o Exposure to respiratory drugs for chronic management of COPD in the previous 12 months
o History of acute exacerbations of COPD in the previous 12 months
o Diagnosis of chronic respiratory diseases other than COPD (index admission plus previous 2 year - period hospital admissions)
o Diagnosis of pulmonary infections (index admission plus previous 2 year-period hospital admissions)
o Diagnosis of respiratory failure in the index event
o Diagnosis of acute pulmonary symptoms / conditions in the index event

F.2 Co-morbidities (details ANNEX Part F.2)

Co-morbidity status will be ascertained on the basis of diagnoses (ICD-9-CM codes) registered both in the HIS and in HEIS.

Following validated CM ICD-9-CM coding algorithms, we define selected chronic coexisting conditions (co-morbidities) that can influence the prognosis of a COPD, including ischemic heart disease, congestive heart failure, arrhythmia, diabetes, hypertension, cerebrovascular disease, liver disease, renal disease,

depression (23).
We define co-morbidities both in the index event and in the previous 24 months hospital admissions. In order to deal with the known limit of administrative data in distinguishing present-at-admission diagnoses from other acute events potentially related with the care delivered, we adopt specific coding algorithms for the index event aimed at defining only chronic conditions, The coding algorithm for the previous 24 months admissions and for HIES included both acute and chronic ICD-9-CM coded diagnoses. For each patient the clinical history will be retrieved through linkage with HIS and HIES in order to screen for co-morbidities.

The prescribing patterns of drugs other than respiratory will be also examined to obtain an integrated definition of co-morbidity status. (for ATC see ANNEX Part F)

F.3 Socio-demographic variables

Categories for potential subgroup analysis:
Age groups: 45-64; 65-74; 75-84; 85+ years aged
Gender: M/F

F.4 Hospital factors

Since structural characteristics of hospitals and quality of hospital care have an influence on health outcomes in various settings, the hospital where patients were treated in the index admission will be considered in the analysis.

G. Sample size estimate

The three study areas comprise about 8,2 Million residents aged 45 years and older (census 2001). Considering that in the city of Rome (1,33 Million residents aged 44+) the prevalence of COPD cases is about 3900 in one year, about 24,000 cases can be expected in the entire study area in one year. In a two-year recruitment period, at least 40,000 cases of COPD will be enrolled in the cohort.
Results of a preliminary evaluation of the use of beta-2-agonists, anticholinergics and inhaled corticosteroids in a COPD cohort in Rome showed, that the proportion of COPD patients treated with these drugs is about 80%, whereas for the remaining 20% no prescription of any of these drugs was retrieved.
The incidence of expected outcomes in one year varies between 24% for mortality, 13% for hospital admissions due to acute events and 2.2% for cardiovascular adverse events (6, 9), a population of 40000 persons would allow to estimate relative risks for exposed versus non exposed persons between 0.8 and 0.9, with a 95% confidence interval and a power of 80%, considering the rarest event.

H. Statistical analysis

The present analysis is intended to simulate as far as possible the trial approach in an observational setting, following the experiences reported in scientific literature (26).
For every treatment in study, comparison will be made between users of the treatment versus non-users. In the first step, non-users will be defined as all members of the cohort who have not been exposed to the treatment or exposed to a predefined low level of treatment not sufficient to be considered as minimum treatment; this will include also users of other drugs for the same condition. In a sensitivity analysis, users of drugs belonging to the same ATC group as the drug in study will be excluded from the control group (e.g. studying long-acting beta-2-agonsits, users of short-acting beta-2-agonists will be excluded in sensitivity analysis from the control group).
As further sensitivity analysis, patients switching from one exposure to another, or adding a new treatment to the one being studied, will be censored at the time of switching/adding, so to contribute as person-time to only one exposure category.
Subgroup analysis will be performed considering mono- versus poly-therapy (e.g. patients treated with long-acting beta-2 agonists plus corticosteroid).

H.1 Preliminary analysis - drug use patterns in COPD patients in three Italian regions:

As a first descriptive step, for the entire cohort, COPD related drug use during a 24 months period after index admission will be described, using PHARM data and considering any ATC group (and single active principles within the groups) used for COPD treatment according to clinical guidelines,
The drug intake patterns in COPD patients, for all COPD related ATC groups will be taken into consideration

(see ANNEX Part H).

H.2 Main analysis

The main analysis will focus on three drug groups indicated for COPD maintenance treatment according to clinical guidelines (see exposure).
For each drug group, a separate multivariate Cox proportional-hazards model will be implemented, comparing users versus non-users for every single outcome.
The model will adjust for age, gender, severity (at least one indicator from the list reported above), and hospital of index admission, regardless whether these factors are associated with the outcome, since there are strong scientific evidences on their predictive power on survival in COPD patients. Furthermore, co-morbidity factors (of the index admissions and the previous two years), will be taken into account. In particular, groups of diagnoses will be selected by a stepwise procedure (significance level for entry of 0.10 and for stay of 0.05). Adjusted hazard ratios (and 95% confidence intervals) will be estimated, and adjusted survival curves will be derived and plotted for all comparison groups.
Finally, the opportunity of adjustment for multiple testing will be evaluated.

H.3 Sensitivity analyses

Sensitivity analyses will focus, as previously described, on the following aspects:
o Different definitions of "chronic exposure": the time-window defining chronic drug use will be altered, choosing several options, both shorter and longer (from 4 weeks to one year of cumulative exposure. Furthermore, chronic use will be defined also on the basis of time needed to accumulate a certain amount of drug (for different cut-offs), and survival analyses will be applied starting from the end of the accrual period to the occurring of event or censoring
o Different definitions of "chronic effects": different time-windows for the occurring of endpoints will be evaluated to disentangle short/mid/long-term effects of chronic drug treatments
o Dosage: chronic use will be classified not only as present/absent, but also average daily dose will be used to define low/mid/high dosage, to be evaluated as effect modifier of the main study association
o Different study designs: propensity score matching and nested case-control designs will be applied as alternative approaches, addressing the previous points at the same time
o Different exclusion criteria: analyses will be re-run excluding subgroups of individuals (asthma patients, subjects switching to/adding a new treatment, etc.)

I. Validation study

One of the units in this project is the Respiratory Physiology Unit in the Columbus Hospital, Catholic University, in Rome, which comprises both, hospital and ambulatory settings. Their participation offers the opportunity to retrieve detailed clinical information for a subgroup of patients from the cohort. Comparison of clinical information (including functional parameters) with data extracted from information systems will be an important instrument to validate the contribution and quality of each data source. In particular, it will allow a validation of the algorithms used for the COPD case definition, attribution of severity levels, co-morbidity status and drug therapy.

J. Organizational characteristics

Co-ordinating Centre:
The Department of Epidemiology of the Local Health Authority Rome E (DEP) is a 30 year old public health and research institution. The DEP acts as a referral centre for epidemiology at a regional level. It is involved in a large number of international, national and local collaborations, and has coordinated several European and Italian multi-centre studies. In recent years, outcomes research has become one of the main topics treated by the DEP. The DEP runs the mortality information system of the Lazio region and has large experience in the use of administrative data in epidemiological studies. Since 2008, also drug prescription data are available. The Cochrane Review Group on Drug and Alcohol has the editorial base in the DEP. As part of the Cochrane collaboration, the group has also been involved in the preparation of WHO clinical guidelines on pharmacotherapy for opioid dependence.
In the present project, the DEP is responsible for the coordination of all activities performed by the four study groups, including also organisational/administrative issues. The data analysis will be performed by the Co-ordinating Centre.

Unit-1
CeVEAS (Centre for the Evaluation of the Effectiveness of Health Care) is a Department of the Provincial Health Authority of Modena, but operates within seven Local Health Authorities of the Northern area of the Emilia Romagna Region. CeVEAS was founded in 1999 to evaluate health interventions and health policies (in particular pharmaceutical policies) mainly through the analysis of scientific literature, and to facilitate the access to the best evidence on health care through the transfer of relevant knowledge to physicians, policy makers and citizens. CeVEAS collaborates with several stakeholders, such as Local Health Units and Regional Health Agencies, the Italian National Health Institute and the Italian Drug Evaluation Agency, and is a WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development in Reproductive Health.
Many of its activities and specific projects require a multidisciplinary approach; for this reason, different clinical and non clinical specialists work at CeVEAS, like general practitioners, specialists in cardiology, pharmacology, pneumology, neurology, endocrinology, ginecology, pediatrics, epidemiology, pharmacy, scientific communication, statistics, library services.

Unit-2
The Department named "Epidemiologic Observatory" of the Health Directorate of the Lombardy region has the typical tasks of an epidemiologic observatory, with emphasis on the followings: a. To collect all the available information useful to describe the health status of the citizens and the distribution of the diseases; b. To periodically produce health statistics; c. To collaborate in conducting efficiency, efficacy and outcome evaluations; d. To collect all the sanitary activities performed by the Lombardy region's providers (hospital discharges, outpatients activities, drug consumptions, ...); e. To collect and produce information to help conducting costing evaluation activities. The office directly operates on the major databases available at a regional level (population, mortality, health demands, ...), and a specific effort has been devoted to the building of an integrated system of information regarding individual subjects and their sanitary consumes all over the region.

Unit-3
The Respiratory Physiology Unit in the Columbus Hospital, Catholic University, in Rome is involved in three different activities:
- Out-patient clinic
- In-patient consultant activity
- Research in clinical epidemiology and in RCT of pharmacological and non-pharmacological treatments of the obstructive respiratory diseases.
The staff of the Unit includes:
One senior clinician
One junior clinician
Two MD training in respiratory medicine
Two technicians.

K. Feasibility.

Nera Agabiti has participated in national and international epidemiological studies on respiratory and cardiovascular diseases. In the last years, she has contributed to the development of standardized methodology for outcome indicators, risk adjustment and comparative performance of providers and inequity of care, using data from health information systems.

L. Timing.

A flow chart is attached in the ANNEX Part L (Figure 2)

M. Good clinical practices.

not applicable

N. Ethical aspects

Since this is an observational study based on data already collected by existing information systems, patients won't face any additional risk due to their participation in the study. All rules established by the Italian law about confidentiality (D.Lgs 675/96 followed by D.Lgs 196/2003) will be observed. Data linkage will be

conducted only by the legally authorised regional personnel. All analysis will be conducted using the databases without identifiers. Only aggregate results will be communicated. Notification of the new study will be sent to the ethical committees of the involved areas, as prescribed by the AIFA guide lines for observational studies.

B5. REFERENCES

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C. Budget

C1. Personnel

Subject	Degree	Participating centres	Contract	Specify	Tasks	Specify	Duration (in months)	% of full time equivalent	Salary (€)	Quantity	Total (€) (salary*quantity)
1.	*MD*	*Coordinating centre*	*Other (specify)*	*Dirigente Medico, operante presso il Dipartimento di Epidemiologia ASL RM/E*	*Coordination , Data analysis , Study monitoring , Other (specify)*	*methodology*	*36*	*19*	*46.528*	*1*	46.528
2.	*MD, MSc*	*Coordinating centre*	*Other (specify)*	*Dirigente Medico, operante presso il Dipartimento di Epidemiologia ASL RM/E*	*Coordination , Other (specify)*	*methodology*	*36*	*4*	*18.990*	*1*	18.990
3.	*Pharmacist, MPH*	*Coordinating centre*	*Contratto a tempo det.*		*Coordination , Data analysis , Study monitoring , Other (specify)*	*methodology*	*36*	*17*	*33.485*	*1*	33.485
4.	*Statistician*	*Coordinating centre*	*Other (specify)*	*Dirigente Statistico, operante presso il Dipartimento di Epidemiologia ASL RM/E*	*Data analysis , Other (specify)*	*methodology*	*36*	*17*	*35.610*	*1*	35.610
5.	*Analyst*	*Coordinating centre*	*Contratto a tempo det.*		*Data analysis*		*36*	*17*	*30.717*	*1*	30.717
	Secretary	*Coordinating*	*Co.Co.Pro*		*Other*	*secreterial*	*36*	*8*	*5.704*	*1*	

6.		*centre*			*(specify)*	*supply, budget, meetings*					5.704
7.	*Statistician*	*Unit Code 1*	*Contratto a tempo det.*		*Data analysis*		*36*	*11*	*25.667*	*1*	25.667
8.	*Farmacist, MPH*	*Unit Code 1*	*Contratto a tempo det.*		*Data analysis , Other (specify)*	*methodology*	*36*	*6*	*17.500*	*1*	17.500
9.	*MD*	*Unit Code 1*	*Contratto a tempo det.*		*Data analysis , Other (specify)*	*methodology*	*36*	*7*	*22.917*	*1*	22.917
10.	*MD*	*Unit Code 1*	*Contratto a tempo det.*		*Other (specify)*	*methodology*	*36*	*1*	*6.667*	*1*	6.667
11.	*Diploma*	*Unit Code 1*	*Contratto a tempo det.*		*Other (specify)*	*methodology*	*36*	*6*	*5.000*	*1*	5.000
12.	*Engineer, Biostatistician*	*Unit Code 2*	*Other (specify)*	*Dirigente, Regione Lombardia*	*Other (specify)*	*dataset, methodology*	*36*	*5*	*13.750*	*1*	13.750
13.	*MD*	*Unit Code 3*	*Other (specify)*	*Dirigente Servizio Sanitario Nazionale*	*Data analysis , Other (specify)*	*methodology, validation study*	*36*	*4*	*20.000*	*1*	20.000
14.	*MD*	*Unit Code 3*	*Dottorato di ricerca (o equivalente)*		*Other (specify)*	*validation study*	*36*	*8*	*16.250*	*1*	16.250
	Total (€)						**504**		**298.785**	**14**	**298.785**

C2. Supplies

nº	Categories of supplies	Total budget for the entire project and for all participating centres (€)	Brief description, if needed (200 car.)
1.	***Hardware***	***5.000***	
2.	***Software***	***0***	
3.	***Stationery***		
4.	***TOTAL (€):***	***5.000***	
5.	***Drug(s) cost for not approved indications:***		***Drug(s) will be provided by:***

C3. Services

nº	Services	Total budget for the entire project and for all participating centres

C4. Meetings, conferences, workshops

nº	Activities	Total budget for the entire project and for all participating centres (€)	Brief description, if needed (200 car.)
1.	***Organization of scientific conferences related to the study project***	***10.000***	***oragnisation of a two-day seminar with experts from abroad (Europe, USA) and from Italy on methodological issues regarding the p.roj.ect***
2.	***Participation in scientific conferences***	***2.000***	***presentation of intermediate results, methodological exchange with c.oll.eag.ues***
3.	***Coordination meetings***	***3.000***	***three meetings of all participating units in R.ome***
	Total (€)	**15.000**	**0**

C5. Overall expected costs for each of the items indicated below and for each year of the project

Items	Expected costs for the 1st year (€)	Expected costs for the 2nd year* (€)	Expected costs for the 3rd year* (€)	Total Costs (€)
Personnel	***119.514***	***119.514***	***59.757***	298.785 {C1 (**)}
Supplies	***5.000***	***0***	***0***	5.000 {C2 (**)}
Services	***0***	***0***	***0***	0 {C3 (**)}
Travels / Meetings/ Courses	***10.000***	***3.000***	***2.000***	15.000 {C4 (**)}
Overhead (max 10% of total)	***13.451***	***12.251***	***6.176***	31.878
Total (€)	147.965	134.765	67.933	350.663

C6. Distribution of costs betweeen coordinating and participating centres

	Total Costs (€)	%
Coordinating centre	***210.138***	59,93 %
Transfers to other centres	***140.525***	40,07 %
Total Costs (€)	350.663	100 %

D. Participating centres

D1. CURRICULUM VITAE OF THE PRINCIPAL INVESTIGATOR; up to 5 publications

Principal Investigator

First Name	NERA
Last name (Family name)	AGABITI
Curriculum Vitae	***Medical Degree at the Catholic University of Rome: 1985*** ***Post Doc in Respiratory Diseases at the Catholic University of Rome: 1989*** ***Post Doc in Preventive Medicine and Public Health at the University of Rome: 2001*** ***Main work experience:*** ***o 1985-1990 practitioner for respiratory health management and treatment, pneumologist at the outpatient respiratory laboratory for COPD patients, and participation in clinical pharmacological trials on respiratory drugs at the Catholic University Hospital in Rome; primary care practitioner and emergency care services in Macerata, Italy;*** ***o Since 1990 epidemiologist at the Department of Epidemiology ASL RM/E.*** ***Attendance of national and international courses in Epidemiology, Statistics and Health Technology Assessment;*** ***participation in national and international scientific meetings/conferences/workshops;*** ***responsible for the scientific organization of regional workshops;*** ***teacher in epidemiological courses and conferences at regional and national level;*** ***First author or co-author of about 190 scientific articles, technical reports, abstracts, and book chapters;*** ***Member of:*** ***o Reviewers list for international journals (e.g. Epidemiology, Canadian Medical Association Journal, Journal of Epidemiology and Community Health);*** ***o Editorial Board of the scientific journal "The Open Health Services and Policy Journal";*** ***o Technical boards at regional level - in collaboration with Scientific Societies and other Governmental Institutions - to enhance cardiovascular epidemiology, to promote the quality of emergency cardio- and cerebrovascular care, to develop and validate new organizational model of integrated care and to build standardized quality of care indicators (in particular, health care outcomes indicators on the basis of routine health information systems datasets);*** ***o Regional technical board in cardiovascular and respiratory fields;*** ***Participation in epidemiological studies:*** ***o Italian cross-sectional studies on asthma and air pollution in children (SIDRIA study group);*** ***o occupational longitudinal cohort studies in Lazio Region;*** ***o evaluation of quality of health care using data from routine health information systems for cohorts of hospitalized patients with different medical and surgical conditions; contribution to the development of standardized methodology for outcome indicators, risk adjustment and comparative performance of providers;*** ***o collaborative projects on health outcomes research and inequity in health care (Ministry of Health);***

	o project on "Hip Replacement Registry" project in Lazio Region (Ministry of Health); *o development of the "Emergency Stroke Registry" in Lazio Region;* *o European Project HEAPSS - Health Effects of Air Pollution on Susceptible Subpopulations;* *o Italian translation of International Classification of Disease and Causes of Death - 9th revision, clinical modification, 1997.* *Main areas of interest: environmental air pollution, tobacco smoke pollution, asthma/atopy in children, respiratory health in adults, cardio- and cerebrovascular epidemiology, health care outcomes, health technology assessment, hospital information systems, socioeconomic factors, inequity in health, interventional cardiology and heart surgery, orthopedic surgery.*
Publication 1	*Agabiti N, Cesaroni G, Picciotto S, Bisanti L, Caranci N, Costa G, Forastiere F, Marinacci C, Pandolfi P, Russo A, Perucci CA (The Italian Study Group on Inequalities in Health Care). The association of socioeconomic disadvantage with postoperative complications after major elective cardiovascular surgery. JECH 2008, 62: 882-889.*
Publication 2	*Cesaroni G, Forastiere F, Agabiti N, Valente P, Zuccaro P, Perucci CA.Effect of the Italian smoking ban on population rates of acute coronary events. Circulation. 2008 Mar 4;117(9):1183-8.*
Publication 3	*Agabiti N, Picciotto S, Cesaroni G, Bisanti L, Forastiere F, Onorati R, Pacelli B, Pandolfi P, Russo A, Spadea T, Perucci CA (The Italian Study Group on Inequalities in Health Care). The influence of socioeconomic status on utilization and outcomes of elective total hip replacement: a multicity population-based longitudinal study. Int J Qual Health Care. 2007 Feb;19(1):37-44.*
Publication 4	*Agabiti N, Ancona C, Forastiere F, Arcà M, Perucci CA.Evaluating outcomes of hospital care following coronary artery bypass surgery in Rome, Italy. Eur J Cardiothorac Surg. 2003 Apr;23(4):599-606; discussion 607-8.*
Publication 5	*Forastiere F, Stafoggia M, Tasco C, Picciotto S, Agabiti N, Cesaroni G, Perucci CA. Socioeconomic status, particulate air pollution, and daily mortality: differential exposure or differential susceptibility. Am J Ind Med. 2007 Mar;50(3):208-16.*

D2. LIST THE INVESTIGATORS IN CHARGE OF THE UNITS INVOLVED IN THE STUDY; up to 3 publications

Unit code 1

First Name: NICOLA	*Last Name: MAGRINI*	*Gender: M*	*Year of birth: 1961*
Tipo Istituzione: Struttura pubblica sanitaria (es. Regione,Ospedale,ASL)			
Institution: AUSL DI MODENA		*Unit: CEVEAS, CENTRO PER LA VALUTAZIONE DELLA EFFICACIA DELL'ASSISTENZA SANITARIA, AZIENDA USL DI MODENA, CEVEAS, CENTRO PER LA VALUTAZIONE DELLA EFFICACIA DELL'ASSISTENZA SANITARIA, AZIENDA USL DI MODENA*	
Address: Viale Muratori, 201 - 41100 MODENA (MO)			
Tel: 059 435200	*Fax: 059 435222*	*Email: n.magrini@ausl.mo.it*	*Web Site: WWW.CEVEAS.IT*

Curriculum: Current position
Head,
CeVEAS
NHS Centre for the Evaluation of the Effectiveness of Health Care
WHO Collaborating Centre for evidence-based Research Synthesis and Guideline Development in Reproductive Health; Azienda USL di Modena

Other current positions:
° Chairman of the Ethics Committee of Reggio Emilia Hospital (since 1997)
° Founder member of the Italian Cochrane Center - Association for the Research on the Effectiveness of Health Care - (AREAS-CCI) (since 1996)
° Member of the WHO Expert Advisory Panel on Drug Evaluation (2007-2011)

He graduated in Medicine at the University of Bologna and specialised in clinical pharmacology in Milan. He trained in RCT methodology and metanalysis at Mario Negri Insitute in Milan in 1989-1991. He is a founder member of the Italian Cochrane Centre. He has been involved since 1996 in creating a NHS Centre devoted to the transfer of information, guideline production and implementation at national and local level and teaching of evidence-based medicine.
His main areas of interest are defining new formats to synthesise available information on benefits and risks of drugs, better ways to present methodology and findings of RCTs, research findings transfer and implementation and Ethics Commitee.

Publ. 1: Fuccio L, Minardi ME, Zagari RM, Grilli D, Magrini N, Bazzoli F. Meta-analysis: duration of first-line proton-pump inhibitor based triple therapy for Helicobacter pylori eradication. Ann Intern Med 2007; 147(8):553-562.

Publ. 2: Formoso G, Menna A, Voci C, Violante A, and Magrini N. Do coxibs reduce prescription of gastroprotective agents? Results of a record linkage study. Cost Eff Resour Alloc. 2006; 4:4

Publ. 3: Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer TT, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490

Unit code 2

First Name: CARLO	*Last Name: ZOCCHETTI*	*Gender: M*	*Year of birth: 1952*
Tipo Istituzione: Struttura pubblica sanitaria (es. Regione,Ospedale,ASL)			
Institution: REGIONE LOMBARDIA - DIREZIONE GENERALE SANITA'		*Unit: DIREZIONE GENERALE SANITÀ - REGIONE LOMBARDIA, STRUTTURA OSSERVATORIO EPIDEMIOLOGICO E SISTEMI DI REMUNERAZIONE*	
Address: VIA POLA, 9-11 - MILANO (MI)			
Tel: 02-6765.3277	*Fax: 02-3936097*	*Email: carlo_zocchetti@regione.lombardia.it*	*Web Site: WWW.SANITA.REGIONE.LOMBARDIA.IT*

Curriculum: Education:

° 1978 Electronic Engineer, Polytechnic University, Milan
° 1982 Specialization in Biostatistics, University of Milan (a three year post graduate course)
° Participation in many international intensive (1 week) or summer (2-3 weeks) courses on epidemiology and biostatistics (particularly on methods of study design and analysis)

Present position:

° Head: Epidemiologic Observatory Office, Lombardy Region Health Directorate
° Editorial Board of "La Medicina del Lavoro"
° Consultant in Occupational and Environmental Health

Teaching duties:

° Professor of Epidemiology, Postgraduate School of Biostatistics, University of Milan
° Member of the faculty of "Master in Epidemiology" organized by Associazione Italiana di Epidemiologia
° Many short courses (1 week, or two), mainly for The Biometric Society, Italian Region, on regression models in epidemiology and epidemiologic methods in occupational/environmental epidemiology

Scientific interests and research:

° Statistical methods in occupational/environmental epidemiology, with emphasis on regression models
° Design and analysis of epidemiologic studies (including software packages), with emphasis on cohort studies
° Analysis of geographical distribution of diseases, with emphasis on cancer
° Risk assessment (with emphasis on occupational risks)
° Evaluation of health needs/demands in general populations
° Analysis of patient discharge sheets, with emphasis on epidemiologic evaluations.

Publications:

Dr. Carlo Zocchetti is author (or co-author) of about one hundred and sixty scientific papers (or books chapters) on statistics and epidemiology (more than 40 published on international Journals or books, more than 60 referenced in "Medline").

Publ. 1: Dragani A.T., Zocchetti C. (2008) Occupational exposure to vinyl chloride and risk of hepatocellular carcinoma. Cancer Causes Control 19: 1193-1200

Publ. 2: Consonni D., Pesatori A.C., Zocchetti C., Sindaco R., Cavalieri D'Oro L., Rubagotti M., Bertazzi P.A. (2008) Mortality in a Population Exposed to Dioxin after the Seveso, Italy, Accident in 1976: 25 Years of Follow-Up. Am J Epidemiol 167: 847-858

Publ. 3: Gabriele S., Cislaghi C., Costantini F., Innocenti F., Lepore V., Tediosi F., Valerio M., Zocchetti C. (2006) Demographic factors and health expenditure profiles by age: the case of Italy. ENEPRI Research Report n. 18, May 2006

Unit code 3

First Name: RICCARDO	*Last Name: PISTELLI*	*Gender: M*	*Year of birth: 1949*
Tipo Istituzione: Università pubblica (compresi policlinici)			
Institution: COMPLESSO INTEGRATO COLUMBUS (CIC) DI ROMA		*Unit: UNIVERSITÀ CATTOLICA DEL SACRO CUORE, SERVIZIO FISIOPATOLOGIA RESPIRATORIA, COMPLESSO INTEGRATO COLUMBUS*	
Address: L.GO MOSCATI 31/33 - ROMA (RM)			
Tel: 06 3503779	*Fax: 06 3503779*	*Email: pneumologia@h-columbus.it*	*Web Site:*

Curriculum: Riccardo Pistelli (RP) graduated as MD in 1973, he is a specialist in respiratory and cardiovascular medicine. RP has a position of researcher in the Catholic University in Rome and chairs the Respiratory Physiology Unit in the Columbus Hospital.
RP spent the most of time during the last thirty years working in the Catholic University and some time in foreign countries. The longest period of work outside Italy was in Cambridge (UK) in the period 1984-86, when he worked as Senior Registrar in the Respiratory Physiology Department directed by Prof TW Higgenbottam.
RP collaborates with many public institutions in Italy among which it is worth to remember: National Research Council in Pisa, National Institute of Health in Rome, Regional Health Authority of Lazio in Rome, National Olympic Committee in Rome, and National Authority for Energy and Ambient in Rome. RP works also as expert in biometrics in some collaboration between the Catholic University and private and public institutions.
RP is member of the European Respiratory Society (member of the council), American Thoracic Society, Italian Society of Respiratory Medicine (chair of the study group Epidemiology and member of the council), Italian Society of Respiratory Medicine in Geriatrics (member of the council). RP is associated editor of the International Journal of Tuberculosis and Lung Diseases and the International Journal of Sport Medicine and Physical Fitness and acts as referee for many international journals in the field of respiratory medicine and epidemiology.
RP is author or co-author of more than 150 papers published in national and international journals on many topics of respiratory medicine.
RP teaches "Respiratory Clinical Physiology" in the School of Specialisation in Respiratory Medicine and "Respiratory Medicine" in the School of Economics and in the School of Medicine of the Catholic University in Rome.

Publ. 1: Sunyer J, Pistelli R, Plana E, Andreani M, Baldari F, Kolz M, Koenig W, Pekkanen J, Peters A, Forastiere F.
Systemic inflammation, genetic susceptibility and lung function.
Eur Respir J. 2008 Jul;32(1):92-7. Epub 2008 Apr 2.

Publ. 2: Lagorio S, Forastiere F, Pistelli R, Iavarone I, Michelozzi P, Fano V, Marconi A, Ziemacki G, Ostro BD.
Air pollution and lung function among susceptible adult subjects: a panel study.
Environ Health. 2006 May 5;5:11.

Publ. 3: Pistelli R, Lange P, Miller DL.
Determinants of prognosis of COPD in the elderly: mucus hypersecretion, infections, cardiovascular comorbidity.
Eur Respir J Suppl. 2003 May;40:10s-14s. Review.

D3. LIST THE INVESTIGATORS IN CHARGE OF THE UNITS DEDICATED TO DATA ANALYSIS AND TO THE GCP MONITORING OF THE STUDY (when applicable)

nº	Unit(s) dedicated to:	a) data analysis/ b) GCP monitoring

D4. DISCLOSURE OF INTEREST

		If yes, please specify
Member of a Steering Committee or of an Advisory Board	***No***	
Principal investigator	***No***	
Consultant	***No***	
Financial contribution received (more than 50,000 €)	***No***	
Other	***No***	
I do hereby declare that I do not have any other direct or indirect interests in the pharmaceutical companies working in the field of the proposed study than those listed above.	***Yes***	

ANNEX

Chiuso il 24/02/2009 16:02

Allegati 1 ANNEX - details methodology