

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 Pulmonary Disease (COPD) - a cohort study based on health information systems in three Italian regions.

A study protocol's (hi)story

*In 2009, the Department of Epidemiology of the Lazio Regional Health Service applied for funding of a **multicenter Italian observational study** through a public call issued by the **Italian Medicines Agency** and received a positive reply.*

*In **April 2010**, the Department of Epidemiology of the Lazio Regional Health Service became a **member of ENCePP** .*

*In **June 2010** we **applied for inclusion of the study in the ENCePP register**.*

*On **June 16th 2010**, the **contract** for funding by the **Italian Medicines Agency** was signed.*

*At the **end of August 2010**, we received the confirmation of **inclusion of our study into the ENCePP register** and the award of the **ENCePP study seal**.*



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Press release

October 1st, 2010

European Medicines Agency awards first 'ENCePP study' seal for post-marketing study

New seal awarded to transparent, independent observational study in patients with chronic obstructive pulmonary disease.

The European Medicine Agency and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) have awarded the first 'ENCePP study' seal to an observational study investigating the "[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 Pulmonary Disease \(COPD\)](#)".

How did we get there?

Dipartimento di Epidemiologia
del Servizio Sanitario Regionale
Regione Lazio





EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



European Network of Centres for
Pharmacoepidemiology and
Pharmacovigilance

London, 7 May 2010
EMA/489873/2008

The ENCePP Code of Conduct

FOR SCIENTIFIC INDEPENDENCE AND TRANSPARENCY IN THE CONDUCT OF
PHARMACOEPIDEMIOLOGICAL AND PHARMACOVIGILANCE STUDIES



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



European Network of Centres for
Pharmacoepidemiology and
Pharmacovigilance

London, 19 March 2010
Doc.Ref. EMEA/540136/2009

Checklist of Methodological Standards for ENCePP Study Protocols

As adopted by the ENCePP Steering Group on 19/03/2010

Data entry form

Please fill in this **form** for the purposes of registering your study in the electronic ENCePP register of studies.

Once completed the form should be sent via e-mail to: ENCePP_Studies@ema.europa.eu

Investigators wishing to apply for the "ENCePP seal" are reminded of their obligation to submit also the original signed **declaration** and **checklists** to the ENCePP Secretariat (c/o EMA, 7 Westferry Circus, London E14 4HB, United Kingdom) before the study commences.

A copy of the study protocol should also be submitted at this stage, either electronically (preferably as PDF file) or by post.

[* mandatory information; of note It is mandatory to answer ALL labelled questions]

Section 1: Administrative Information

1. Study Identification

Official title*:	free text
Study title acronym:	free text
Study type*:	[multiple options possible]



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



London, 19 March 2010
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Checklist of Methodological Standards for ENCePP Study Protocols

As adopted by the ENCePP Steering Group on 19/03/2010

The purpose of the checklist is to improve the quality of studies by stimulating consideration of important epidemiological principles for designing a pharmacoepidemiological (PE) or pharmacovigilance (PV) study and writing a study protocol. The checklist is intended to promote quality of such studies, not their uniformity. ENCePP welcomes innovative designs and new methods of research. However, it is possible that some of the questions below do not apply to such innovations, in which case, the answer 'N/A' (Not Applicable) can be checked. **Please fill the 'Comments' field included at each section in situations where a listed question does not apply or where your answer is "No". This will help ENCePP keep the *Checklist of Methodological Standards for ENCePP Study Protocols* in line with the developments in science and methodology.**

Section 1: Research question

	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
1.1.1. Why the study is conducted (e.g. to answer an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
1.1.2 The objectives of the study	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
1.2 Does the formulation of the research question specify:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
1.2.1 Target population (or relevant subgroup) (i.e. population or subgroup to whom the study results are intended to be generalised)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
1.2.2 Hypotheses to be tested (if appropriate, otherwise statement that there is no <i>a priori</i> hypothesis)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

Doc Ref: EMA/540136/2008

Data entry form

Section 1: Administrative Information

1. Study identification

Official 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 Pulmonary Disease (COPD) - a cohort study based on health information systems in three Italian regions.

Study type*: Observational study

Brief description of the study: Objectives: to measure long-term outcomes and adverse events of inhaled drugs in COPD patients; to compare effectiveness of the different drugs (mono- and polytherapy) in terms of long-term survival or exacerbations; to compare incidence of side effects of inhaled therapy among users vs non-users. Design: patients discharged with COPD in 2006-07 will be enrolled from the Hospital Information Systems (HIS) and record linkage performed with mortality, hospital, emergency and drug claims data to define exposure (ICS, LABA, and anticholinergics), potential confounders, and to measure outcomes over 4 years. Outcomes: all-cause, respiratory and cardiovascular mortality, incidence of adverse events, and COPD exacerbations. Cox-proportional-hazard models will be applied to compare outcomes in users vs non-users of exposure to different drug groups (mono-/polytherapy). Sensitivity analyses will take into account different subgroup susceptibility or different definitions of chronic exposure.

Was this study originally requested by a regulator? *

Yes

Country of Regulator:

Italy

Data entry form

Section 1: Administrative Information

2. Research centres and Investigator details

Coordinating study entity*

Is the coordinating study entity registered in the ENCePP inventory of research centres?*

Yes

Name of Centre*:

[Department of Epidemiology Lazio Region, Italy](#)

Details of (Primary) lead investigator*

Title*

Dr

Last name*

Agabiti

First name*

Nera

Address line 1*

Via S. Costanza, 53

City*

Roma

Postcode

00198

Country*

Italy

Phone number*

39-06-83060402

Fax number

39-06-83060374

Email address*

agabiti@asplazio.it

Data entry form

Section 1: Administrative Information

Is this study being carried out with the collaboration of a research network? *

No

Other centre(s) where this study is being conducted*

How many centres in total are involved in this study?

4

Name of Centre(s) registered with ENCePP: [CeVEAS](#)

Name(s) of other participating centre(s), Location:

Epidemiologic Observatory of the Health Directorate of the Lombardy region, Milan, Italy

Respiratory Physiology Unit in the Columbus Hospital, Catholic University, Rome, Italy

Countries in which this study is being conducted

National study

Country:

Italy

Data entry form

Section 1: Administrative Information

3. Study timelines: initial administrative steps, progress reports and final report

Study timeline	Planned	Actual
Date when funding contract was signed*	01/06/2010	dd/mm/yyyy
Start date of data collection*	15/09/2010	dd/mm/yyyy
Start date of data analysis	01/01/2012	dd/mm/yyyy
Date of interim report, if expected	31/12/2011	dd/mm/yyyy
Date of final study report*	01/06/2013	dd/mm/yyyy

4. Source of funding:

Please provide estimates of the percentage of funding by source for this study*

Government body	Name(s):	AIFA - Italian Medicines Agency	approximate % funding:	50 %
Other	Name(s):	participating study centres	approximate % funding:	50 %

5. Contact details for enquiries

Scientific Enquiries*

Use the same details of (Primary) lead investigator

Public Enquiries*

Use the same details of (Primary) lead investigator

100% public funding

Data entry form

Section 2: Targets of the study

6. Study drug(s) information

Study drug information *

Substance class

R03 DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

Data Entry Form: Electronic ENCePP Register of Studies

Name of class(es) or ATC H02AB Glucocorticoids (oral)

code(s):

J01 Antibacterials for systemic use

7. Medical conditions to be studied

Medical condition *

Chronic Obstructive Pulmonary Disease (COPD)

Data entry form

Section 2: Targets of the study

8. Population under study

Population under study*

Adults (46-64 years)

Adults (65-75 years)

Adults (76 years and older)

Sex*

Male

Female

9. Number of patients

Estimated total number of subjects*:

40000

**100% routinely collected data
from health information
systems**

10. Source of data

Type of data source*

Administrative database, e.g. claims database

Pharmacy dispensing records

Name of data source:

Please enter the short name of either a registered data source within ENCePP or external data source

[Mortality Information System \(MIS\)](#)

[Hospital Information System \(HIS\)](#)

[Healthcare Emergency Information System \(HEIS\)](#)

[Drug dispense registry \(PHARM\)](#)

Data entry form

Section 3: Methodological aspects

11. Scope of the study

What is the scope of the study? And which is the primary scope? *

Primary scope

Risk assessment

Effectiveness evaluation

Background: Evidence based treatments in COPD

Smoking cessation
Oxygen therapy



Benefits in terms
of mortality

Farmacological therapy with
inhalant drugs



Benefits in terms of
quality of life
(symptoms,
exacerbations,
pulmonary function)

Controversial evidence on the benefits of
inhalant drugs on long term mortality and the
occurrence of adverse events

Data entry form

Section 3: Methodological aspects

12. Main objective(s)

Which is the main objective of the study? *

To measure long-term outcomes and adverse events of inhaled drugs in the study cohort over a 4-year follow up period; to compare effectiveness of the different drugs (both "monotherapy" and "combined therapy") in terms of long-term survival or exacerbations; to compare the incidence of side effects of inhaled therapy (ICS, LABA and anticholinergics) among users versus non users

Are there primary outcomes? *

Yes Mortality (All causes, respiratory causes, cardiovascular causes)

Are there secondary outcomes? *

Yes 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

Adverse cardio- and cerebrovascular events

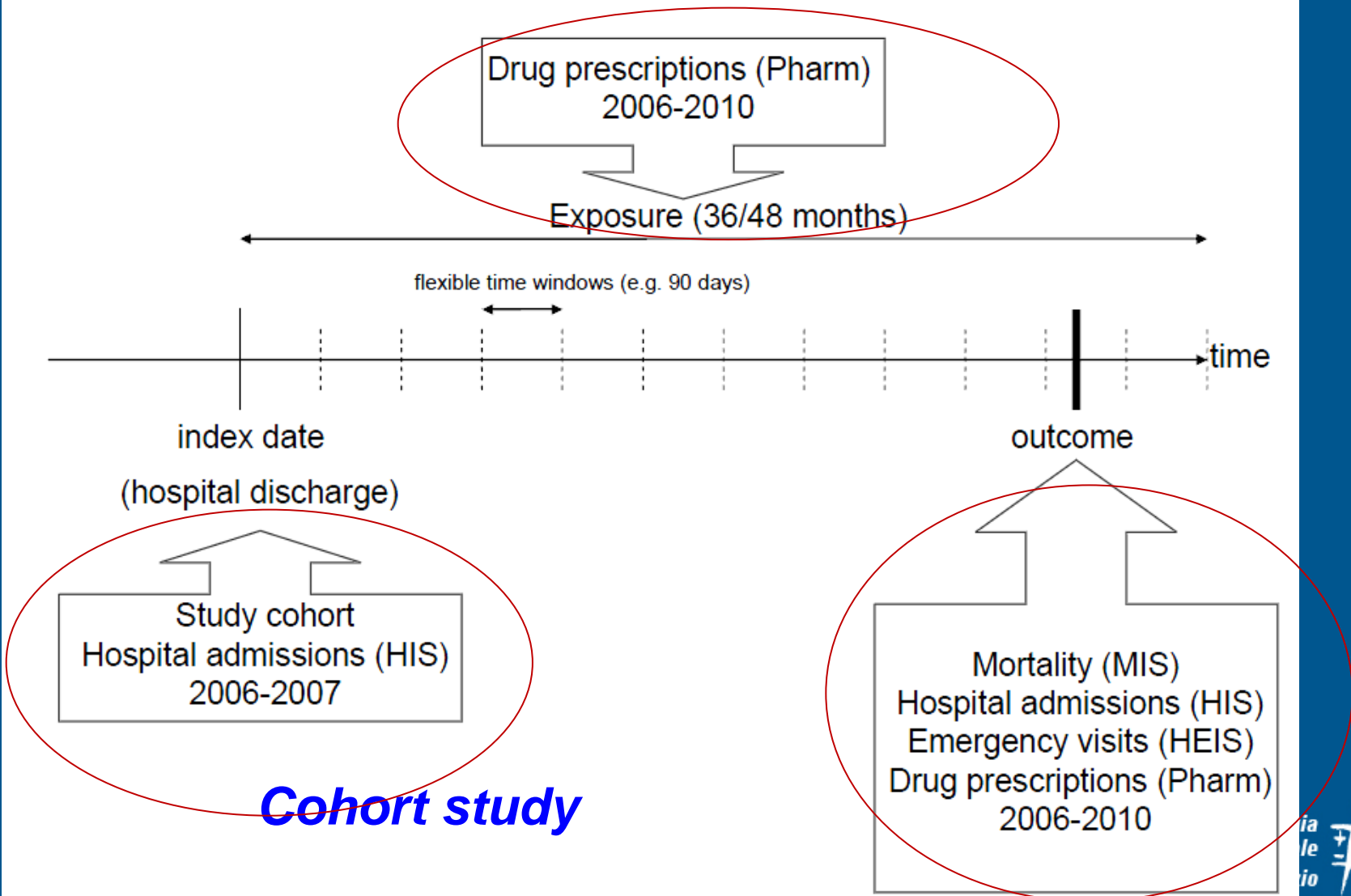
Pneumonia

Osteoporotic fractures

13. Study design

14. Follow-up of patients

PART A - Study design: Figure 1 – overview of the study design



Data entry form

Section 3: Methodological aspects

15. Data analysis plan

Please provide a brief summary of the analysis method*

Cox proportional hazard models will be applied to compare outcomes in users vs non-users of exposure to different drug groups (mono-/polytherapy). Sensitivity analyses will take into account different subgroup susceptibility or different definitions of chronic exposure.

Section 4: ENCePP Seal and relevant documents

16. ENCePP seal

Are you requesting the ENCePP seal for this study? *

Yes

17. Full protocol

If requesting the ENCePP seal, please send electronic copy to ENCePP Secretariat prior to the start of the study (encepp_studies@ema.europa.eu). * for ENCePP studies

Please be aware that the protocol will be made public when the study ends.

Would you like to make the protocol public now? * for ENCePP studies

Yes, I wish to make the protocol public now

18. Study results

If final report already available, please send electronic copy to ENCePP Secretariat for its publication on the website (encepp_studies@ema.europa.eu) * for ENCePP studies

If final report already available, please list the 5 most relevant publications using data from your study for the last five calendar years. * for ENCePP studies

19. Other relevant information

Conflict(s) of interest of investigator(s)* for ENCePP studies

I am sending a detailed description to the ENCePP Secretariat as a separate file to be made publicly available on the website

Composition of Steering Group and Observers* for ENCePP studies

I am sending a detailed description to the ENCePP Secretariat as a separate file to be made publicly available on the website

Other documents

I am sending the following additional document(s) to the ENCePP Secretariat as a separate file to be made publicly available on the website

Document name: ANNEX ENCePP.pdf

Description: details relating to the study protocol



Thank you!