FINAL STUDY REPORT (FSR)

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1. General data

1.1 Title page

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

Acronyms: OUTPUL study

Drug tested:

R03AC Selective beta-2-adrenoreceptor agonists

R03AH Combinations of adrenergics

R03AK Adrenergics and other drugs for obstructive airway diseases

R03BA Glucocorticoids (inhaled)

R03BB Anticholinergics

Type of study:

Epidemiological study based on health information system databases at population levels in three Italian regions.

Date of contract:

16/6/2010

Date of Ethic Committee approval:

10/9/2010

Period covered:

cohort enrolment period: 2006-2009

follow-up: up to 2011

1.2 Study Administration and Investigators

Name and affiliation of principal investigator:

Nera Agabiti, ASL RME, Roma

Name, affiliation and role in the study of all other investigators:

ASL Roma E, Roma

Ursula Kirchmayer collaboration in study design, interpretation of results, drafting papers

Mirko Di Martino collaboration in study design, analysis. interpretation of results, drafting papers

Silvia Cascini collaboration in study design, data management, analysis, interpretation of results, drafting papers

Valeria Belleudi collaboration in study design, data management, analysis. interpretation of results, drafting papers

Luigi Pinnarelli collaboration in study design and drafting papers

Eliana Ferroni collaboration in study design and drafting papers

Danilo Fusco collaboration in study design, interpretation of results, drafting papers

Marina Davoli collaboration in study design, interpretation of results, drafting papers

Agenzia Sanitaria e Servizi Sociali Emilia Romagna, Bologna

Nicola Magrini collaboration in study design, interpretation of results, drafting papers

Anna Maria Marata collaboration in study design, interpretation of results, drafting papers

Oreste Capelli collaboration in study design, interpretation of results

Giulio Formoso collaboration in study design, interpretation of results, drafting papers

Claudio Voci collaboration in study design, data management, interpretation of results

Direzione Generale Sanità Lombardia, Milano

Carlo Zocchetti collaboration in study design, providing data

Università Cattolica S.Cuore – Fisiopatologia Respiratoria, Complesso Integrato Columbus Roma

Riccardo Pistelli collaboration in study design, interpretation of results, drafting papers

Vittoria Colamesta collaboration in study design and literature review

Maria Rosaria Castriotti collaboration in the study on quality of data

Erminia Lo Greco collaboration in the study on quality of data

Collaboration with Elisabetta Patorno *Division of Pharmacoepidemiology, Brigham and Women's Hospital and Harvard Medical School, Boston*

1.3 Table of Contents

1.4 List of Abbreviations and Definition of Terms

AT = As-Treated
AMI = acute myocardial infarction
ATC = Anatomical Therapeutic Chemical (classification system)
COPD = chronic obstructive pulmonary disease
CRE = comparative effectiveness research
CV = cardiovascular
DEP = Dipartimento di Epidemiologia ASL RME
ER = Emilia Romagna
FEV_1 = maximun expiratory flow in one second
FSR = final study report
HIS = health information systems
HR = Hazard Ratio
ICD-9-CM = International Classification of Diseases, 9^{th} Revision, Clinical Modification
ICS = inhaled corticosteroids
ITT = Intention-to-treat
LABA = long acting beta 2 agonists
LB = long acting bronchodilators
MPR= medication possession ratio
n.a. = not applicable
OR= Odds Ratio
RCT = randomized controlled trial
TORCH = Towards a Revolution in COPD Health
Tio = tiotropium

2. Synopsis

Study 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.

Principal Investigator: Nera Agabiti

Study center location: multicentre study - Lazio, Lombardia, Emilia Romagna (ER)

Study period: 2006-2011

Name of active ingredient(s): Selective beta-2-adrenoreceptor agonists, Combinations of adrenergics, Adrenergics and other drugs for obstructive airway diseases, Glucocorticoids (inhaled), Anticholinergics

Cohort enrolment: 2006-2009

Follow-up: up to 2011

Objectives of study: to assess effectiveness and safety of inhaled drugs in COPD patients

Methods: Retrospective study based on Health Information Systems (HIS). From hospital information systems databases of three regions (Lazio, Lombardia, ER) a cohort of people (45+ years of age) discharged after exacerbation of COPD were enrolled by using a standardized ICD-9-CM code based algorithm. Socio-demographic characteristics (i.e. gender, age), confounders (i.e. comorbidities) and outcomes (both effectiveness and safety outcomes) were derived from health information systems (HIS) of each participating region following standardized algorithms and procedures. Exposure to studied drugs was measured analysing data from the regional Drug Registers. Overall, more than 72.000 people were studied. Multivariate models - logistic regression (OR, 95% CI) or Cox proportional hazard models (HR, 95 % CI) - were applied in the different studies (see below).

Comparisons were made between drug users and non users (=control group), as follows:

1. inhaled long-acting beta-2-agonists

Users: patients using one of the following ATCs:
1.inhaled beta 2 agonists
R03AC12 salmeterol
R02AC13 formoterol
R03AK03 fenoterol plus ipratropium bromide
R03AK06 salmeterol plus fluticason
R03AK07 formoterol plus beclometason
R03AK07 formoterol plus budesonid

2. inhaled long-acting anticholinergics
Users: patients using one of the following ATCs:
R03BB04 tiotropium bromide

3. inhaled corticosteroids
Users: patients using drugs belonging to the ATC:
R03BA inhaled Glucocorticoids

R03AK04 salbutamol plus beclometason
R03AK04 salbutamol plus flunisolid
R03AK06 salmeterol plus fluticason
R03AK07 formoterol plus beclometason
R03AK07 formoterol plus budesonid

Results

Six "*epidemiological studies*" were performed: 1 of them was published in COPD Journal 2013, 1 has been already submitted to an international journal, 3 had an internal peer review and are ready to be submitted, 1 is in preparation.

As the first step, a study to describe the use of inhaled drugs and its determinants was performed (***see Appendices Paper A***). To evaluate *effectiveness* and *safety*, appropriate study designs and idoneous analytical approaches were chosen in order to deal with specific research questions on the different inhaled drugs under study. Starting from the initial COPD population under study (over 72.000), criteria for inclusion/exclusion of people, and consequently numbers, varied in the specific studies depending on the research question and on the adopted strategy of analysis. Particular attention was paid to overcome biases that arise in observational studies like this. Intention-to-treat (ITT) and As-Treated (AT) based on censoring at switching approaches were applied in 3 cohort studies (***see Appendices Papers B, C, D)***. A nested-control design was applied in one study (***see Appendices Paper E***). Finally, a time-dependent analysis was performed to measure the relationship between drug exposure and long-term outcomes (***see Appendices Materials F8***). Multivariate models (Logistic regression or Cox proportional hazard models) were applied to take confounders into account. Propensity score adjustment was used. Sensitivity analyses were also run to confirm the robustness of the results.

Results are described in detail in the ***Appendices***.

A summary is presented in Table1.

Table 1

	Research question	**Study design / other details on methods**	**Population (n)**	**Drug under study**	**Outcomes**	**Main results**	**Appendices (ref)**
1	Limited information exists on the patterns of use of COPD therapy in routine care.	Retrospective cohort	11.452 (Lazio)	Inhaled beta 2 agonists, anticholinergic, corticosteroids	Adherence to guidelines (two years follow up)	Only 34.8% received long-acting bronchodilators continuously. The MPR was greater than 75% in 19.6% of cases. Among the determinants of not receiving long-acting bronchodilators continuously, older age and comorbidities played an important role.	Paper A (published)
2	In clinical practice tiotropium is	Retrospective new user	68.795 (Lazio, ER,	Inhaled LABA, tiotropium, ICS	Incidence of COPD moderate and	In the intention-to-treat analysis the multivariate	Paper B (submitted)

	commonly used in addition to Long-Acting β2-agonists (LABA) and/or Inhaled Corticosteroids (ICS), however the benefits remain debatable.	design "as treated approach" and "intention to treat approach" were both tested Propensity score adjustment	Lombardia)		severe exacerbations in one year follow up	adjusted HR for overall exacerbation was 1.02 (0.89-1.16) for triple vs. double therapy. Similar HRs were observed when severe and moderate exacerbations were considered separately: 1.08 (0.91-1.28) and 0.92 (0.76-1.12) respectively.	
3	Evidence regarding tiotropium safety is conflicting.	Retrospective new user design "as treated approach" and "intention to treat approach" were both tested Propensity score adjustment	33.891(Lazio, ER, Lombardia)	Tiotropium, LABA	One year mortality	The adjusted HR for Tio only compared to LABA only was 1.08 (95% CI: 0.95-1.23) at the ITT analysis and 1.00 (95% CI: 0.93-1.09) at the AT analysis.	Paper C (to be submitted)
4	The benefit of combination therapy with ICS plus LABA on survival is still debated.	Retrospective new user design "as treated approach" and "intention to treat approach" were both tested Propensity score adjustment	18.615 (Lazio, ER, Lombardia)	ICS, LABA	Two-years mortality	Crude mortality rates were 110 and 143 cases per 1000 person-years in the LB plus ICS and LB alone groups, respectively, the crude rate ratio was 0.77 (95% CI: 0.66 – 0.90). Adding ICS to LB significantly reduced mortality. The adjusted hazard ratio was 0.84 (95% CI: 0.72 – 0.98). Greater effect in those with history of previous exacerbations (HR 0.63, 95% CI: 0.44 – 0.90)	Paper D (to be submitted)
5	Is ICS treatment, with or without LBs, associated with an increased	Nested case control study	19288 (Lazio)	ICS, other inhaled drugs	Hospitalizations for community acquired pneumonia	Current use is associated with more than two fold (RR=2.34, 95%CI 1.99-2.73). In the past users there was an increase of 29%	Paper E (to be submitted)

	risk of pneumonia ?				Five year follow up	(RR=1.29, 95%CI 1.10-1.51).	
6	Whether adherence to guidelines is associated with better survival is not clearly known	Cohort study new user design Time dependent analysis	12.793 (Lazio, ER)	ICS, LABA, Tio	Cardiovascular and respiratory mortality Five year follow up	Overall mortality in five years 19% (respiratory mortality 28% cardiovascular mortality 72%). High level of adherence to appropriate drugs is associated with a reduced risk of mortality (RR 0.69, 95% CI 0.55-0.86)	F.8 (in preparation)

Conclusion

This large observational multicentre study is the first one in Italy to address the issue of *effectiveness* and *safety* of inhaled drugs for COPD patients using data from HIS. The real-life picture of inhaled drug use in COPD patients gives insight into the adherence to clinical guidelines on drug therapy. Large numbers, long-term follow up, and sophisticated analytical procedures provided a large amount of information in the field of COPD management and therapy in the real-world setting in Italy. Results from the observational studies performed in the context of OUTPUL contribute to the ongoing debate on *effectiveness* and *safety* of inhaled drugs in COPD, mostly supported by the findings from RCTs. The development and implementation of various analytical strategies to compare *effectiveness* and *safety* of inhaled drugs, according to the most updated scientific literature, is one of the strengths of the OUTPUL study. Moreover, this work offered a special opportunity for sharing experience and collaboration between researchers who reached a good level of harmony and enthusiasm together.

Date of report: 16/7/2014

3 Ethics

3.1 Independent Ethics Committee (IEC)

The protocol was approved from the IEC (Independent Ethics Committee) on 10/9/2010.

No amendments were made.

3.2 Ethical Conduct of the Study

The study was conducted in accordance with the Declaration of Helsinki and its amendments.

3.3 Subject / Patient Informed Consent

n.a.

4 Investigational Plan

n.a.

5 Study Assessments (including efficacy and safety variables)

n.a.

6 Data Quality Assurance

In order to assess the quality of the diagnosis reported in the discharge abstract records (which is the basis for the identification of the study population), we performed a re-abstract study to investigate the agreement between medical charts and discharge electronic abstracts. A random sample of all COPD patients included in the OUTPUL study and resident in Rome was selected. A total of 441 medical charts were examined by two expert and trained physicians. The overall agreement between the two sources of data for the diagnosis was good (confirmation rate: 87%). Details are reported in the ***Appendices Materials F.5***.

7 Data Management Procedures

On the basis of a regional law, the Department of Epidemiology ASL RME E is in charge for the management and analysis of the Regional HIS for epidemiological purposes. Data from HIS (hospital discharges, emergency admissions, drugs, co-payment exemptions, mortality) are collected through standardized procedures and periodically updated. Coding procedures are based on International Classification of Disease ICD-9-CM (hospital, emergency), ICD-9 (mortality) and ATC classification (drug). Completeness and quality are also systematically checked. Each record is anonymous.; a unique code allows for linkage between databases. Deterministic record linkage procedures are performed to link different datasets. Softwares used are: ORACLE, SAS, STATA.

8 Statistical Considerations

The analyses performed on behalf of the OUTPUL study was intended to simulate as far as possible the trial approach in an observational setting, following the experiences reported in the scientific literature. The whole population of discharged COPD patients in the three regions was enrolled (no sampling). For each treatment in study, comparison was made between users of the treatment versus non-users. Different approaches were applied in order to answer different research questions. Procedures of risk adjustment were applied, including the propensity score adjustment. Details on the adopted strategies of analysis, on procedures to limit bias and on sensitivity analyses are described in the papers (***see Appendices***).

9 Changes in the Conduct of the Study or Planned Analysis

n.a.

10 Results

Research question n. 1: Even if compliance to guidelines and drug adherence play a central role in the treatment of COPD, limited information exists on the patterns of use of COPD therapy in routine care.

What this study adds

We identified a cohort of patients discharged from hospital with diagnosis of COPD between 2006 and 2008 in the Lazio region. Patients were observed for a two-year follow-up period, starting from the day of discharge. Follow-up was segmented in six-month periods, in order to dynamically evaluate prescription patterns of Long-Acting Beta-Agonists (LABA), tiotropium, and inhaled corticosteroids. Patients with prescriptions for LABA and/or tiotropium in each of the six-month periods were defined as "continuously treated with long-acting bronchodilators". The degree of drug treatment coverage was measured through the Medication Possession Ratio (MPR). Logistic regression was performed to identify determinants of not receiving long-acting bronchodilators continuously.

A total of 11,452 patients diagnosed with COPD were enrolled. Only 34.8% received long-acting bronchodilators continuously. The MPR was greater than 75% in 19.6% of cases. Among the determinants of not receiving long-acting bronchodilators continuously, older age and comorbidities played an important role. (***see Appendices - Paper A***)

Research question n. 2: In clinical practice tiotropium is commonly used in addition to Long-Acting β2-agonists (LABA) and/or Inhaled Corticosteroids (ICS), however the benefits remain debatable. We assessed the effect of tiotropium in reducing COPD-exacerbations when combined with LABA/ICS.

What this study adds

This new user cohort study was based on administrative data from three Italian regions. We identified adults hospitalized for COPD in 2006-2009 who received a new prescription of LABA/ICS. Based on the date of the first prescription, we classified patients according to whether tiotropium was also prescribed (triple therapy), following them for 1 year. With both intention-to-treat and as-treated approaches, we compared the risk of severe and moderate exacerbations between patients with triple or double therapy. Multivariate and propensity score-adjusted hazard ratios (HRs, 95%CI) were calculated by Cox regression models.

We identified 5717 new users of LABA/ICS and 31.9% initiated triple therapy. A high probability of exacerbation was associated with previous COPD hospitalization, respiratory failure, and use of systemic corticosteroids or xanthines. In the intention-to-treat analysis the multivariate adjusted HR for overall exacerbation was 1.02 (0.89-1.16) for triple vs. double therapy. Similar HRs were observed when severe and moderate exacerbations were considered separately: 1.08 (0.91-1.28) and 0.92 (0.76-1.12) respectively. The propensity score adjustment produced similar results. Same findings were seen with the as-treated analysis. (***see Appendices - Paper B***)

Research question n. 3: Long-acting bronchodilators, i.e. beta-2-agonists (LABA) and tiotropium (Tio) are commonly used in COPD treatment. Choice of a specific agent is based on effectiveness and safety. Evidence yields controversial results with respect to mortality. The present study compared 1-year mortality associated to treatment Tio versus LABA.

What this study adds

A population based cohort study using data from Italian health information systems was performed. Patients aged 45+ years, discharged with COPD diagnosis in 2006-2009 were identified. Through record linkage with drug claims, patients who received a first prescription of LABA or Tio within 6 months after discharge were enrolled. The main analysis was restricted to naïve users (no prior use of either LABA or Tio). We used "intention to treat" (ITT) and "as treated" (AT) approaches. We followed patients for a maximum of twelve months. Hazard ratios (HR) were calculated by Cox regression including quintiles of propensity score. In sensitivity analysis patients receiving Tio+LABA combination were included in the Tio group.
Among the 33891 enrollees, 28% were exposed to Tio, 56% to LABA, 16% to both. Overall mean age was 74 years and the mortality rate was 108/1000 person-years (py) at the ITT analysis and 115/1000 py at the AT analysis.. The adjusted HR for Tio only compared to LABA only was 1.08 (95% CI: 0.95-1.23) at the ITT analysis and 1.00 (95% CI: 0.93-1.09) at the AT analysis. Results were robust in sensitivity analysis.
In this real-world study use of Tio was not associated with an increased risk of 1-year mortality compared to LABA. (***see Appendices - Paper C***)

Research question n. 4: Although the TORCH (Towards a Revolution in COPD Health) trial showed a modest mortality benefit with ICS plus LABA combination, meta-analyses suggested that they may only reduce mortality when compared to placebo or ICS alone but, according to a recent meta-analysis, not to LABA alone. Therefore, no definitive conclusions can be drawn. The objective of this study is to analyze, in a real world setting, whether adding ICS to LB therapy reduces mortality in severe COPD patients.

What this study adds
Among the 18.615 adults enrolled, crude mortality rates were 110 and 143 cases per 1000 person-years in the LB plus ICS and LB alone groups, respectively, the crude rate ratio was 0.77 (95% CI: 0.66 – 0.90). Adding ICS to LB significantly reduced mortality. The adjusted hazard ratio was 0.84 (95% CI: 0.72 – 0.98; p-value: 0.027). (***see Appendices - Paper D***)

Research question n. 5: Is ICS treatment, with or without LBs, associated with an increased risk of pneumonia among patients discharged with a COPD diagnosis?

What this study adds
This study included 19.288 patients with COPD, 45% were men and aged 75.5 (±9.9) years at enrolment admission. The average duration of follow up was 3.4 (±2.1) years. During follow up 3111 subject were hospitalized for pneumonia (cases), corresponding to a pneumonia rate of 4.7 per 100 person-years. Current use is associated with more than two fold (RR=2.34, 95%CI 1.99-2.73). In the past users there was an increase of 29% (RR=1.29, 95%CI 1.10-1.51). (***see Appendices- Paper E***)

Research question n. 6: Limited data exist on the effect of adherence to guidelines on prognosis in stable COPD patients.

What this study adds
We performed a cohort study including 12.783 patients discharged after COPD in Lazio and in ER. We applied a new user design and a time-dependent analytical approach to take the variation over a 5-year-follow up period in various individual characteristics and drug use into account. Overall mortality was 19% (respiratory mortality 28% , cardiovascular mortality 72%). High

level of adherence to appropriate drugs was associated with a reduced risk of mortality (RR 0.69, 95% CI 0.55-0.86). A paper on this topic is in preparation. (***see Appendices – Materials F8***)

Research question n. 7: There is an ongoing debate on cardiovascular safety of tiotropium in COPD patients.

What we aim to investigate starting from the OUTPUL study experience to the selection of a "new studied population"

While working on behalf of OUTPUL study, we considered to take advantage of the multicentric collaboration to analyse a cohort of "*tiotropium users*", that is a different from the OUTPUL study population ("*COPD patient discharged from hospital and followed up*"). The objective was to measure the effect of tiotropium on cardiovascular outcomes in the overall exposed population. For this analysis we used Lazio and ER datasets. A total of 371.416 individuals who used tiotropium were identified in the period 2006-2011 from the Drug Registers of the two regions. All-cause mortality and/or cardiovascular (CV) hospital admissions occurred in 28%. CV mortality and/or CV hospitalizations in 19%. Lower rates (range: 4.3-6.7%) were observed for specific CV hospitalizations (heart failure, AMI, angina, arrhythmia). The rationale and preliminary results were presented during the final conference held in Rome on 13th June, 2014. ***(see Appendices – Materials F.11)***

11 Discussion and Overall Conclusions

The OUTPUL study is the first large multicentre observational study in Italy to address the *effectiveness* and *safety* of inhaled drugs for COPD patients using data from HIS. A population of over 72.000 COPD patients was enrolled in the period 2006-2009 from three Italian regions using HIS databases according to standardized procedures. This study contributes to the Italian experience in Comparative Effectiveness Research (CRE) on drugs for: 1) specific results on the *effectiveness* and *safety* of inhaled drugs from a large population-based epidemiological study; 2) development and implementation of various analytical strategies to compare *effectiveness* and *safety* of inhaled drugs, according to the most updated scientific literature; 3) special opportunity for collaboration and knowledge transfer between researchers at national and international level to be promoted for future research.

The OUTPUL study contributes to the knowledge in the field of COPD. The real-life picture of inhaled drug use in COPD patients gives insight into the adherence to clinical guidelines on drug therapy in stable COPD. Large numbers, long follow up periods to measure outcomes, and sophisticated analytical procedures provided a large amount of information on COPD management and therapy in the real-world setting in Italy. Results from the observational studies on behalf of OUTPUL add evidence to the ongoing debate on *effectiveness* and *safety* of inhaled drugs in COPD, mostly supported by the findings from RCTs. Moreover, the large effort to overcome biases of observational studies by implementing complex analytical methodologies, according to the most updated scientific literature, is one of the strengths of the OUTPUL study.

Many open questions still exist on *effectiveness* and *safety* of inhaled drugs in stable COPD patients. Besides the evidence of ICS/LABA combination on quality of life, functional respiratory capacity and symptoms, the long- term effect on survival is still debated. Adverse events of both ICS and anticholinergics need to be clearly demonstrated and a controversy is still ongoing.

To deal with specific research questions, the OUTPUL study produced different "epidemiological studies" which gave a wide picture of the COPD management in Italy and on

real-life *effectiveness* and *safety* of inhaled drugs. First, in clinical practice, the COPD pharmacotherapy is not consistent with clinical guidelines. Second, tiotropium in addition to LABA/ICS did not reduce one-year risk of COPD exacerbations when compared with LABA/ICS alone. Third, we did not find differences in 1-year mortality comparing tiotropium to long-acting beta-2-agonists. Fourth, adding ICS to LB significantly reduced mortality (16% reduction); the effect was more pronounced (37%) in those patients with a history of previous COPD exacerbations. Fifth, we found that current ICS use is strongly associated with increased risk of pneumonia. Sixth, high level of adherence to appropriate drugs is associated with a reduced risk of mortality over a five-year follow up period.

The results of the OUTPUL study have been presented and discussed during Scientific Conferences at national and at international levels in the last years. Six papers have been prepared: 1 of them has been published in COPD Journal 2013, 1 has been already submitted to an international journal, 3 had an internal peer review and are ready to be submitted, 1 is in preparation.

Findings from studies like this can have an important impact on public health and on the management of patients with chronic diseases in current clinical practice. Moreover, the collaboration and the experience shared in the contest of the OUTPUL study constitutes an important input for future research on CRE in Italy.

12 Tables, Figures and Graphs

See the single papers in the ***Appendices***

13 Reference

See the single papers in the ***Appendices***

14 Appendices

Papers (n=5)

A - Di Martino M, Agabiti N, Bauleo L, Kirchmayer U, Cascini S, Pistelli R, Colamesta V, Patorno E, Pinnarelli L, Fusco D, Perucci CA, Davoli M on behalf of OUTPUL Study Group. Use patterns of long-acting bronchodilators in routine COPD care: the OUTPUL study. COPD 2013;11: 414-23.

B - Ferroni E, Belleudi V, Agabiti N, Di Martino M, Cascini S, Kirchmayer U, Pistelli R, Patorno E, Pinnarelli L, Formoso G, Fusco D, Davoli M, Perucci CA on behalf of the OUTPUL study group. Role of tiotropium in reducing exacerbations of chronic obstructive pulmonary disease when combined with long-acting β2-agonists and inhaled corticosteroids. (submitted)

C - Kirchmayer U, Cascini S, Agabiti N, Di Martino M, Formoso G, Voci C, Pistelli R, Patorno E, Davoli M on behalf of the OUTPUL study group. One-year mortality associated with COPD treatment - a comparison of tiotropium and long-acting beta2-agonists in three Italian regions: results from the OUTPUL study. (to be submitted)

D - Di Martino M, Cascini S, Agabiti N, Bauleo L, Kirchmayer U, Fusco D, Pinnarelli L, Belleudi V, Voci C, Pistelli R, Patorno E, Davoli M on behalf of the OUTPUL Study Group. The effect on total mortality of adding inhaled corticosteroids to long-acting bronchodilators for COPD: a real practice analysis in Italy. (to be submitted)

E - Cascini S, Agabiti N, Di Martino M, Kirchmayer U, Belleudi V, Davoli M on behalf of the OUTPUL Study Group. Inhaled corticosteroid use in COPD patients and the risk of pneumonia in the Lazio region. (to be submitted)

Materials from the Final Conference held in Rome 16/6/2014 (n=12)

F.1- Brochure

F.2 - Introduction *Riccardo Pistelli*

F.3 - The OUTPUL study: overview *Nera Agabiti*

F.4 - Sources of data and study population *Silvia Cascini, Claudio Voci, Lisa Bauleo*

F.5 - Quality of data *Lisa Bauleo*

F.6 - Use of inhaled drugs in COPD patients *Mirko Di Martino*

F.7 -Adding inhaled corticosteroids to long-acting bronchodilators for COPD: effect on total mortality *Mirko Di Martino*

F.8 - Adherence to inhaled drugs and cause-specific long term mortality *Valeria Belleudi*

F.9 - Inhaled corticosteroids and the risk of pneumonia *Silvia Cascini*

F.10 - Tiotropium and one year mortality *Ursula Kirchmayer*

F.11- Cardiovascular adverse events among tiotropium users *Giulio Formoso, Silvia Cascini*

F. 12 - Triple therapy and the risk of exacerbation *Eliana Ferroni*