Study protocol

Does the cost of inhaler devices affect therapy adherence and disease outcomes?

A historic cohort, Irish database evaluation of the role of inhaler device cost in maintenance therapy adherence and disease outcomes in patients with asthma and/or COPD

Date:
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TITLE	**Does the cost of inhaler devices affect therapy adherence and disease outcomes?**
Subtitle	A historic cohort, Irish database evaluation of the role of inhaler device cost in maintenance therapy adherence and disease outcomes in patients with asthma and/or COPD
Protocol version number	1.0
Study aims and objectives	The aim of the study is to investigate whether a raise in prescription costs affects maintenance therapy and disease outcomes in patients with asthma or COPD. The objectives are to characterise patients who pay prescription charges and those who do not (i.e. HSE medical card holders) in an Irish primary care population diagnosed with asthma or COPD and for both groups to assess whether maintenance therapy adherence and disease control is better in patients who do not pay prescription charges compared to those who do pay.
Country of study	Ireland
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Contents

1.0 Background

Asthma and chronic obstructive pulmonary disease (COPD) are, with a prevalence of 235 and 200 million respectively, two of the leading causes of morbidity and economic burden worldwide[1]. In the Republic of Ireland around 470,000 and 440,000 people are diagnosed with asthma[2] and COPD[3] respectively. A developed country is yearly spending 1-2 percent of their total health care expenditures on asthma which makes it an expensive condition. It is possible to lower the costs of emergency care by investing in prevention medication[4]. Also COPD as a serious and preventable disease is costly. The prevalence of this condition is increasing with age and with an ageing population, it is evident that the costs of this condition will rise as well[5].

A good compliance to maintenance medication in asthma and COPD is associated with significantly lower risk of hospitalization and reduced expenditures[6,7,8,9,10,11]. Research suggests that high prescription costs may have negative impacts on therapy adherence and disease outcomes across a range of chronic illnesses[12,13,14,15,16,17], though their effect in patients with chronic respiratory ailments is not well known yet[18,19,20]. Patients in the lowest income category showed a decrease in medication adherence for chronic conditions which may worsen disparities and adversely affect health[21,22], which is important to realise since COPD is inversely associated with socio-economic status[5,23,24].

In the Republic of Ireland, approximately 40% of patients have, based on their income, a Medical Card which provides them with subsidised prescriptions; the remainder pay considerable prescription charges[25,26]. From the 1st of December 2013, people with Medical Cards pay a €2.50 charge for medicines and other items that they get on prescription from pharmacies. The prescription charge is €2.50 for each item that is dispensed to a patient, up to a maximum of €25 per month, per person or family[27]. The Irish prescription charge system thus provides a unique opportunity to investigate the potential effects of prescription costs (as a proxy for inhaler device cost) on maintenance therapy adherence and disease outcomes in patients with asthma or COPD.

2.0 Study aim and objectives

2.1 Study aim

The aim of the study is to investigate whether a raise in prescription costs affects maintenance therapy and disease outcomes in patients with asthma or COPD.

2.2 Study objectives

- To characterise patients who pay prescription charges and those who do not (i.e. HSE medical card holders[*]) in an Irish primary care population diagnosed with asthma or COPD
- For patients with asthma, assess whether maintenance therapy adherence and disease outcomes (in terms of asthma control[†]) are better in patients who do not pay prescription charges compared to those who do pay
- For patients with COPD, assess whether maintenance therapy adherence and disease outcomes (in terms of moderate and severe exacerbation control[‡]) are better in patients who do not pay prescription charges compared to those who do pay

3.0 Study design

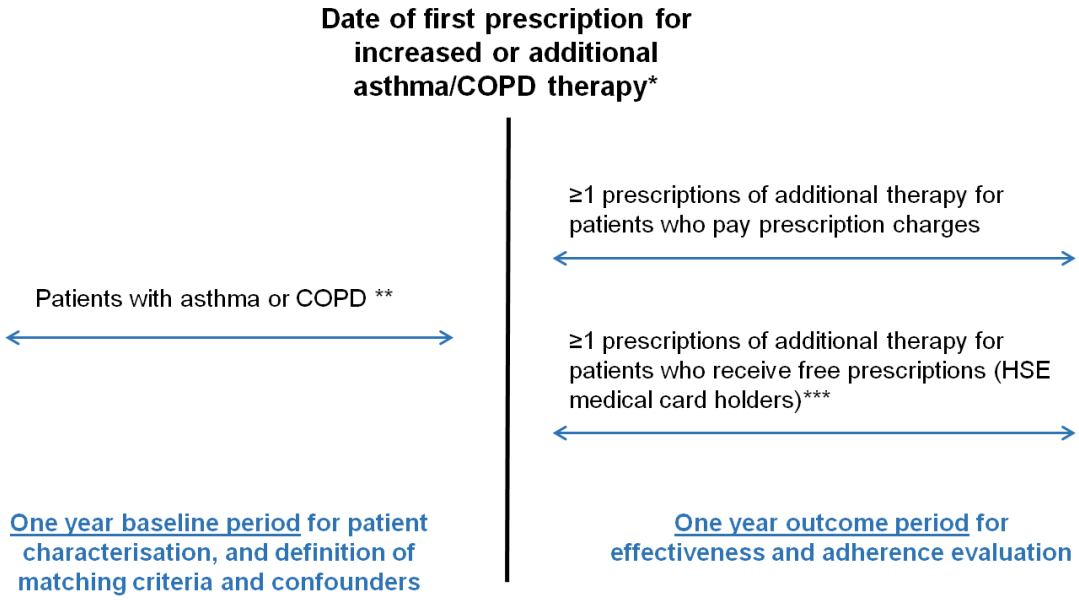
3.1 Study design

This study will be designed as a matched historic, cohort, database study consisting of a baseline period, an index prescription date (IPD) and an outcome period (Figure 1).

The baseline period is a 1-year period before index date and is intended for patient characterization and confounder definition. A patient will at least be prescribed a reliever therapy[§] during this year. The index date is defined as the date of first prescription for increased or additional asthma/COPD therapy[**]. The outcome period is 1-year period following index date and will be used to compare drug effectiveness and adherence

[*] A €0.50 prescription charge per item for Health Service Executive (HSE) medical card holders was introduced in 2010, and was increased to €2.50 as of 2013.
[†] Controlled asthma: absence of (a) asthma-related hospital admission, and A&E attendance, and out-patient department attendance; and (b) acute oral corticosteroid courses; and (c) antibiotics prescribed with lower respiratory consultation.
[‡] Moderate and severe COPD exacerbations: (a) acute oral corticosteroid course; or (b) antibiotics prescribed with a lower respiratory consultation; (c) coded admission to emergency department or hospital for COPD; or (d) recorded hospital admission on same day as a lower respiratory consultation (except when only lower respiratory code recorded was for a lung function test).
[§] Reliever therpay: SABA (short-acting beta2-agonist) and SAMA (short-acting muscarinic antagonist; for COPD only)
[**] LABA (long-acting beta2-agonist), LAMA (long-acting muscarinic antagonist; for COPD only), ICS (inhaled corticosteroids), or their combinations

evaluation. In this year patients will have 1 or more prescriptions of additional therapy and patients will be divided in a group who pay prescription charges and a group who receive free prescriptions*.



*LABA (long-acting beta2-agonist), LAMA (long-acting muscarinic antagonist; for COPD only), ICS (inhaled corticosteroids), or their combinations. |**Prescribed at least a reliever therapy: SABA (short-acting beta2-agonist) and SAMA (short-acting muscarinic antagonist; for COPD only). | ***A €0.50 prescription charge per item for Health Service Executive (HSE) medical card holders was introduced in 2010, and was increased to €2.50 as of 2013.

Figure 1 Study design

4.0 Study population

4.1 Inclusion and exclusion criteria

Patients will meet all the following inclusion criteria (Table 1).

Inclusion criteria
Diagnosis for asthma or COPD ever recorded*
For asthma: aged ≥ 18 years at the index date; for COPD: aged ≥ 40 years at the index date
At least 2 years of continuous practice data (1 year of baseline and 1 year of outcome data)
≥ 1 prescription for SABA, LABA or ICS prior to the index date (patients with COPD may alternatively be prescribed SAMA or LAMA)

*Subject to availability of data.

Table 1 Inclusion criteria

* Health Service Executive (HSE) medical card holders. A €0.50 prescription charge per item for HSE medical card holders was introduced in 2010, and was increased to €2.50 as of 2013.

Patients will not meet the following exclusion criteria (Table 2).

Exclusion criteria
Any other chronic respiratory disease other than asthma and COPD at any time

Table 2 Exclusion criteria

4.2 Data source

The database that will be used will be provided by Dermot Ryan and Sean Higgins. This will involve extraction of anonymised, patient level diagnostic, clinical and prescribing information in several practices in Ireland. The extraction and use of the data will be subject to local ethical guidance.

5.0 Study variables and study outcomes

5.1 Demographic and baseline variables

For each patient, the following characteristics will be collected to assess baseline differences between the study cohorts (free versus paid prescriptions), and to identify potential matching criteria and confounders for the outcome analyses*.

- Demographic characteristics, including:
  - Age at IPD
  - Sex
  - Body mass index (BMI) calculated as weight/height^2 and categorised in standard categories of “underweight” (<18.5), “normal weight” (≥18.5 and <25), “overweight” (≥25 and <30) and “obese” (≥30). Height and weight will be the height and weight measurements taken closest to IPD
  - Smoking status recorded closest to IPD, if available patients will be classified as “current smokers”, “ex-smokers” and “non-smokers”
- Important, potentially confounding comorbidities and co-medication, including:
  - Gastroesophageal reflux disease (GERD)
  - Rhinitis
  - Oral thrush
  - Eczema
  - Hypertension
  - Ischaemic heart disease (IHD)
  - Charlson Comorbidity Index (CCI) score

* Subject to availability of data

- Prescription of non-steroidal anti-inflammatory drugs (NSAIDs) in the year prior to IPD
- Prescription of beta blockers in the year prior to IPD

• Measures of asthma/COPD severity, including:
- Acute oral corticosteroid courses, defined as:
  - all courses that are definitely not maintenance therapy, and/or
  - all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
  - all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

  where "maintenance therapy" is defined as: daily dosing instructions of <=10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.
- Antibiotics prescribed with lower respiratory consultation*
- Severe exacerbations for patients with asthma, defined as (based on the American Thoracic Society and European Respiratory Society Position Statement[28]) an occurrence† of the following:
  1. Asthma-related‡:
     a. Hospital admissions OR
     b. A&E attendance; OR
  2. An acute course of oral corticosteroids.
- Moderate/severe exacerbations for patients with COPD, defined as an occurence*** of the following:
  1. COPD-related†††:
     a. Unscheduled hospital admission OR
     b. A&E attendance; OR
  2. An acute course of oral corticosteroids; OR
  3. Antibiotics prescribed with lower respiratory consultation§§.
- Respiratory therapies usage in the year prior to the index date
- SABA reliever usage in the year prior to the index date

* **Lower Respiratory Consultations -** consist of the following:
- Lower Respiratory read codes (including Asthma, COPD and LRTI read codes);
- Asthma/COPD review codes excluding any monitoring letter codes;
- Lung function and/or asthma monitoring

† Where ≥1 oral steroid course / hospitalisation occurs within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

‡ **Asthma or COPD-Related Hospitalisations:** consists of either a definite Asthma or COPD Emergency Attendance or a definite Asthma or COPD Hospital Admission; OR a generic hospitalisation read code which has been recorded on the same day as a Lower Respiratory Consultation; excluding where the only lower respiratory code recorded on that day was for a lung function test.

5.2 Primary outcome

The primary outcome of this study will be adherence to asthma or COPD therapy evaluated in terms of percentage of refill rate of inhaler devices for maintainence therapy over a 1 year period whereby refill rate will be calculated from total pack days (consisting of the number of actuations per pack per day). A refill rate of 80% or more will be used as a cut-off for good adherence.

$$\text{Number days per pack} = \frac{\text{Number of actuations per pack}}{\text{Number of actuations per day}}$$

$$\text{Total Pack Days} = \Sigma\ (\text{Number days per pack})$$

$$\text{Refill rate \% over 1 year} = \frac{\text{Total Pack Days}}{365} * 100$$

$$\text{Refill rate \% over 1 year} = \frac{\frac{\text{Number of actuations per pack}}{\text{Number of actuations per day}}}{365} * 100$$

5.3 Secondary and exploratory outcomes

For patients with asthma the secondary outcome of this study will be disease outcome evaluated in terms of:

- Risk-domain asthma control (RDAC)
- Severe exacerbations
- Acute respiratory events
- SABA reliever usage

Whereby:

- Risk-domain asthma control will be defined as:
  Controlled: absence of the following:
  1. Asthma-related:
     a. Hospital admission AND
     b. A&E attendance, AND
     c. Out-patient department attendance; AND
  2. Acute use of oral corticosteroids; AND

3. Antibiotics prescribed with lower respiratory consultation.

Uncontrolled: all others.

- An acute respiratory event will be defined as an occurrence of the following:
  1. Asthma-related:
     a. Hospital admissions OR
     b. A&E attendance; OR
  2. An acute course of oral corticosteroids; OR
  3. Antibiotics prescribed with lower respiratory consultation.

- SABA reliever usage will be defined as:

  Average daily SABA dosage during outcome year, calculated as average number of puffs per day over the year multiplied by strength (in mcg);

$$\frac{Number\ of\ inhalers * doses\ per\ inhaler}{365} * strength \text{ in } \mu g$$

For patients with COPD the secondary outcome of this study will be disease outcome evaluated in terms of:

- Moderate and severe COPD exacerbation rate
- SABA reliever usage

For patients with COPD the exploratory outcomes of this study will be COPD-related hospitalisation rate (number of hospitalisations in the outcome period) and severe exacerbation rate (number of exacerbations in the outcome period) as these will likely be underpowered.

6.0 Statistical analysis

6.1 General methods

All statistical analyses will be conducted using SAS 9.3 (SAS Institute, UK) and/or SPSS Statistics 22 (IBM SPSS Statistics, UK). Statistically significant results will be defined as $p < 0.05$ and trends as $0.05 \leq p < 0.10$.

6.2 Power calculation

The study will be powered on the primary outcome, adherence to maintenance therapy. With an expected clinically significant difference set at ***15%***, a two group Chi-square test with a 0.050 two-sided significance level will have 90% power to detect the difference between a group 1 proportion of 0.500 and a group 2 proportion of 0.650 (odds ratio of 1.857) when the sample size in each group is 227.

OR

The study will be powered on the primary outcome, adherence to maintenance therapy. With an expected clinically significant difference set at ***25%***, a two group Chi-square test with a 0.050 two-sided significance level will have 90% power to detect the difference between a group 1 proportion of 0.500 and a group 2 proportion of 0.750 (odds ratio of 3.000) when the sample size in each group is 77.

6.3 Data preparation

Prior to the extended statistical analysis, an exploratory analysis of all variables will be carried out for data validation and to identify potential outliers. Skewed data will be transformed and heavily skewed data will be categorised. The exploratory analysis will also help to investigate possible baseline differences between the two treatment groups in order to evaluate whether the variables can be used for matching.

6.4 Summary statistics

Summary statistics will be produced for all baseline and outcome variables including:

1. For variables measured on the interval/ratio scale:
    - Sample size (n)
    - Percentage (%) non-missing
    - Mean
    - Standard deviation (SD)
    - Median
    - Inter-quartile range (IQR; 25th and 75th percentiles)
2. For categorical variables:
    - Sample size (n)
    - Range (if applicable)
    - Count and percentage (%) per category (distribution)

Unadjusted outcomes will be compared using Chi-square tests for unmatched data or conditional logistic regressions for matched data.

6.5 Matching

The matching criteria and matching ratio will be determined once the baseline data are examined. Patients may be matched on demographic characterisation, and baseline respiratory therapies and measures of disease severity to minimise confounding of outcomes. Matching variables and categories will be selected based on clinical relevance and on evaluation of baseline differences between the cohorts (t-test, Mann-Whitney U test, Chi-square test; $p<0.05$)

6.6 Statistical tests

The below table summarises the statistical tests that may be used in the analysis.

Test	Use
Chi-square (χ^2) test	Tests for the association between 2 categorical variables (data presented in contingency tables).
Mann Whitney U test	Nonparametric test to compare the distribution of variables measured on the interval / ratio scale across 2 groups when the variable is not normally distributed.
t test	Parametric test to compare the means of variables measured on the interval / ratio scale across 2 groups when the variable is normally distributed.
Logistic regression model	Used to examine the impact of predictors on the odds of a certain event/outcome
Conditional Logistic Regression Model	Used to examine the impact of predictors on the odds of a certain event/outcome in a matched analysis.
Odds ratio (OR)	Measure of effect size when the outcome measure is binary (it is the ratio of 2 odds, for example: the odds of disease in patients exposed and unexposed to a factor). Estimated using logistic regression.
Ordinal Logistic regression model	Used to examine the impact of predictors on the odds of levels of an ordinal variable having higher / lower ordered values.
Conditional Ordinal Logistic Regression Model	Used to examine the impact of predictors on the odds of levels of an ordinal variable having higher / lower ordered values in a matched analysis.
Poisson Regression	A form of generalized linear model used to relate one or more predictors to the log of the expected rate of event. Used to model count data such as number of exacerbations.
Conditional Poisson Regression	A form of generalized linear model used to relate one or more predictors to the log of the expected rate of event in a matched analysis. Used to model count data such as number of exacerbations.

Rate Ratio	A test for the equality of two Poisson means. This is done by investigating procedures for comparing two independent Poisson variates that are observed over unequal sampling frames.

Table 3 Statistical tests

6.7 Analysis of study outcomes

6.7.1 Primary outcome

The numbers and percentages of patients with a good adherence to their prescribed maintenance therapy (refill rate >80% over 1 year: yes/no) in the year after the index prescription date will be reported for both patients with free and paid prescriptions. A Chi square test, or conditional logistic regression in case groups require matching, will be used to compare the adherence between the groups and *p*-values will be reported.

6.7.2 Secondary outcomes

For patients with asthma the numbers and percentages of patients who:

- achieved controlled asthma (risk-domain asthma control: yes/no)
- experienced none, 1, 2 or 3+ severe exacerbations
- experienced none, 1, 2 or 3+ acute respiratory events

in the year after the index prescription date will be reported. Chi square tests, or conditional logistic regression in case treatment groups require matching, will be used to compare between the groups and a p-value will be reported.

For patients with COPD the numbers and percentages of patients who:

- experienced none, 1, 2 or 3+ moderate and severe exacerbations
- experienced none, 1, 2 or 3+ severe exacerbations (hospitalisations)

in the year after the index prescription date will be reported. Chi square tests, or conditional logistic regression in case treatment groups require matching, will be used to compare between the groups and a p-value will be reported.

For patients with asthma or CPOD SABA reliever usage (µg/day) will be categorised (high/medium/low) as appropriate to the data and numbers. Percentages of each category in the year after the index prescription date will be reported. Chi square tests, or conditional logistic regression in case treatment groups require matching, will be used to compare between the groups and a p-value will be reported.

The exacerbation rate in the outcome period will be compared between cohorts. A Poisson regression model will be used to obtain an estimate of relative exacerbation rates. The model will use a robust estimator of the covariance matrix for more conservative confidence interval estimates. If treatment groups require matching, a conditional Poisson regression model will be used instead, using empirical standard errors (for more conservative confidence interval estimations) and adjustments will be made for potential baseline confounders.

For SABA usage, the adjusted odds of being in a higher SABA/adherence category will be compared between (matched) cohorts using (conditional) ordinal logistic regression models

Rate ratio and 95% confidence interval will be reported both before and after having adjusted for baseline predictors/confounders. Residual baseline variables that will be significantly different or show a trend ($p < 0.10$) towards a difference using conditional logistic regression after matching* will be included as potential confounding factors. In addition, baseline variables that are found to be predictive ($p < 0.05$) of the outcome through multivariate analysis will also be considered as potential confounders.

Potential confounders will be checked for collinearity using Spearman's correlation coefficients for linear relationships ($\rho>0.3$), plots and univariate logistic regressions for non-linear relationships

Multivariable analyses will be carried out using the full dataset to identify baseline variables that are predictive ($p < 0.05$) of outcomes. These will be considered as potential confounders when modelling the outcome variables.

Superiority of outcomes in patients receiving free prescriptions compared to those who pay for prescriptions will be assessed as follows:

- The adjusted upper limit of the 95% confidence interval (CI) will be calculated for the difference in proportions (free vs paid prescriptions) of outcomes
- Based on previous studies[29,30] and expert advice, superiority in therapy adherence (free vs paid prescriptions) may be satisfied when the difference between cohorts is greater than or equal to either 15% or 25% (*TBC*)
- Thus, differences of greater than or equal to either 15% or 25% in the upper limit of 95% CIs will be considered clinically significant (*TBC*)

* If deemed necessary after exploring baseline data

7.0 Regulatory and ethical compliance

Data extraction and use will be subject to local Irish ethics. This study was designed and shall be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu

8.0 Data dissemination TBC!

Initial results will be presented in poster and/or oral format at appropriate thoracic/health economic conferences. At least one manuscript containing more detailed results and methodology will be submitted to a journal specialising in respiratory medicine. Submission for publications will be made as soon as the analyses are completed and the results are verified.

9.0 Steering Committee

A scientific advisory committee consisting of both UK and international experts will be constituted to guarantee scientific soundness of the study and also to follow up on the progress of the appropriate conduct of the study. The members of the scientific advisory committee will be involved in reviewing the data and preparation of the reports.
It is likely that the members of the Steering Committee will be drawn from the following list of DASG members:

- Richard Ahrens
- Leif Bjermer
- Sinthia Bosnic-Anticevich
- Sidney Braman
- Henry Chrystyn
- Richard Costello
- Richard Dekhuijzen
- Myrna Dolovich
- Monica Fletcher
- Beth Laube
- Federico Lavorini
- Marc Miravitlles
- Alberto Papi
- David Price

- Cindy Rand
- Roberto Rodríguez-Roisin
- Dermot Ryan
- Omar Usmani
- Bernard Vrijens

10.0 Research team

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Study sponsor:

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11.0 Timelines

Action	***Timeline***
Protocol final definition	*1 week*
Data extraction	*4-6 weeks*
Matched baseline analysis (stage I)	*7 weeks*
Baseline report writing	*2 weeks*
Outcome analysis (stage II)	*4 weeks*
Final report writing	*2 weeks*
First draft of paper	*8-12 weeks from final report*

12.0 APPENDIX

12.1 Appendix 1: Definitions

- Exacerbation definition based on the ATS/ERS Position Statement – sensitivity definition

  An exacerbation is defined as an occurrence of the following:

  1. Asthma-related:
     a. Hospital admissions OR
     b. A&E attendance; OR
  2. An acute course of oral steroids with lower respiratory consultation.

- Moderate/Severe Exacerbations – sensitivity definition

  Where an exacerbation is defined as an occurrence of:

  1. COPD-related: Unscheduled hospital admission / A&E attendance; OR
  2. An acute course of oral steroids with lower respiratory consultation**Error! Bookmark not defined.**; OR
  3. Antibiotics prescribed with lower respiratory consultation.

- Acute oral steroid use associated with asthma exacerbation treatment will be defined as:
  - all courses that are definitely not maintenance therapy, and/or
  - all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
  - all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

  where “maintenance therapy” is defined as: daily dosing instructions of <=10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.

- Lower Respiratory Consultations - consist of the following:
  - Lower Respiratory Read codes (including Asthma, COPD and LRTI Read codes);
  - Asthma/COPD review codes excl. any monitoring letter codes;
  - Lung function and/or asthma monitoring

- Risk-domain asthma control will be defined as:

Controlled: absence of the following:

1. Asthma-related:
    a. Hospital admission AND
    b. A&E attendance, AND
    c. Out-patient department attendance; AND
2. Acute use of oral corticosteroids; AND
3. Antibiotics prescribed with lower respiratory consultation.

Uncontrolled: all others.

- An acute respiratory event will be defined as an occurrence of the following:
    1. Asthma-related:
        a. Hospital admissions OR
        b. A&E attendance; OR
    2. An acute course of oral corticosteroids; OR
    3. Antibiotics prescribed with lower respiratory consultation.

12.2 Appendix 2: Mock baseline results tables

		Free prescription	Paid prescription	*p* value*
Age (years)	N (% non-missing)	x (x)	x (x)	x
	Mean (SD)	x (x)	x (x)	
	Median (IQR)	x (x, x)	x (x, x)	
Sex	Male n (%)	x (x)	x (x)	x
	Female n (%)	x (x)	x (x)	
	Total n (%)	x (x)	x (x)	
BMI (categorised)	Underweight n (%)	x (x)	x (x)	x
	Normal weight n (%)	x (x)	x (x)	
	Overweight n (%)	x (x)	x (x)	
	Obese n (%)	x (x)	x (x)	
	Total n (%)	x (x)	x (x)	
Smoking status (closest to IPD)	Non-smokers n (%)	x (x)	x (x)	x
	Current smokers n (%)	x (x)	x (x)	
	Ex-smokers n (%)	x (x)	x (x)	
	Total n (%)	x (x)	x (x)	
* *p* values will be calculated using the following tests: chi square test for categorical variables; Mann Whitney U test / t test for variables measured on the interval scale OR conditional logistic regression in case of matched cohorts				

Table 4 Baseline characteristics

		Free prescription	Paid prescription	*p* value*
GERD	Yes n (%)	x (x)	x (x)	x
	No n (%)	x (x)	x (x)	
	Total n (%)	x (x)	x (x)	
Rhinitis	Yes n (%)	x (x)	x (x)	x
	No n (%)	x (x)	x (x)	
	Total n (%)	x (x)	x (x)	
Oral thrush	Yes n (%)	x (x)	x (x)	x
	No n (%)	x (x)	x (x)	
	Total n (%)	x (x)	x (x)	
Eczema	Yes n (%)	x (x)	x (x)	x
	No n (%)	x (x)	x (x)	
	Total n (%)	x (x)	x (x)	
Hypertension	Yes n (%)	x (x)	x (x)	x
	No n (%)	x (x)	x (x)	
	Total n (%)	x (x)	x (x)	
IHD	Yes n (%)	x (x)	x (x)	x
	No n (%)	x (x)	x (x)	
	Total n (%)	x (x)	x (x)	
CCI Score	0 n (%)	x (x)	x (x)	x
	1-4 n (%)	x (x)	x (x)	
	5+ n	x (x)	x (x)	
	Total n (%)	x (x)	x (x)	
Prescription of	Yes n (%)	x (x)	x (x)	

NSAID in the year prior to IPD	No n (%)	x (x)	x (x)	x
	Total n (%)	x (x)	x (x)	
Prescription of beta blockers in the year prior to IPD	Yes n (%)	x (x)	x (x)	x
	No n (%)	x (x)	x (x)	
	Total n (%)	x (x)	x (x)	
* *p* values will be calculated using the following tests: chi square test for categorical variables OR conditional logistic regression in case of matched cohorts				

Table 5 Comorbidities and co-medication

		Free prescription	Paid prescription	*p* value*
Acute Oral Corticosteroid Prescriptions (categorised)	0 n (%) 1 n (%) 2+ n (%)	x (x) x (x) x (x)	x (x) x (x) x (x)	x
	Total n (%)	x (x)	x (x)	
Antibiotics prescription with evidence of respiratory review (categorised)	0 n (%) 1+ n (%)	x (x) x (x)	x (x) x (x)	x
	Total n (%)	x (x)	x (x)	
Severe Exacerbations (categorised)	0 n (%) 1 n (%) 2+ n (%)	x (x) x (x) x (x)	x (x) x (x) x (x)	x
	Total n (%)	x (x)	x (x)	
Severe Exacerbations (count)	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x
Respiratory therapie usage in the year prior to IPD	?	?	?	
SABA reliever usage in the year prior to IPD	?	?	?	
* *p* values will be calculated using the following tests: chi square test for categorical variables OR conditional logistic regression in case of matched cohorts				

Table 6 Measures of severity of asthma

		Free prescription	Paid prescription	*p* value*
Acute Oral Corticosteroid Prescriptions (categorised)	0 n (%) 1 n (%) 2+ n (%)	x (x) x (x) x (x)	x (x) x (x) x (x)	x
	Total n (%)	x (x)	x (x)	
Antibiotics prescription with evidence of respiratory review (categorised)	0 n (%) 1+ n (%)	x (x) x (x)	x (x) x (x)	x
	Total n (%)	x (x)	x (x)	
Moderate/Severe Exacerbations (categorised)	0 n (%) 1 n (%) 2+ n (%)	x (x) x (x) x (x)	x (x) x (x) x (x)	x
	Total n (%)	x (x)	x (x)	
Moderate/Severe	N (% non-	x (x)	x (x)	x

Exacerbations (count)	missing) Mean (SD) Median (IQR)	 x (x) x (x, x)	 x (x) x (x, x)	
Respiratory therapie usage in the year prior to IPD	?	?	?	
SABA reliever usage in the year prior to IPD	?	?	?	
* *p* values will be calculated using the following tests: chi square test for categorical variables OR conditional logistic regression in case of matched cohorts				

Table 7 Measures of severity of COPD

12.3 Appendix 3: Mock outcome results tables

13.0 References

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