Study protocol

Device Adherence Steering Group (DASG): Incidence of oral thrush in COPD patients prescribed ICS as part of ICS/LABA therapy

A historical cohort, UK database study in patients with COPD comparing the incidence of oral thrush in those prescribed ICS as part of fixed-dose combination ICS/LABA therapies, with that in patients prescribed long-acting bronchodilator therapies without ICS

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TITLE	Incidence of oral thrush in COPD patients prescribed ICS as part of ICS/LABA therapy
Subtitle	A historical cohort, UK database study in patients with COPD comparing the incidence of oral thrush in those prescribed ICS as part of fixed-dose combination ICS/LABA therapies, with that in patients prescribed long-acting bronchodilator therapies without ICS
Protocol version number	1.5
Medicinal product	Investigational products: fixed-dose combinations of inhaled corticosteroids and long-acting β_2 agonists (budesonide and formoterol fumarate dehydrate; fluticasone propionate and salmeterol xinafoate; beclometasone dipropionate and formoterol fumarate dehydrate) Comparators: long-acting β_2 agonists and long-acting muscarinic antagonists as single or combined bronchodilator therapy
Product code	NA
Marketing authorisation holder	NA
Marketing authorisation number	NA
Study aims and objectives	To investigate whether there is an association between FDC ICS/LABA use and oral thrush in patients with COPD, and whether this potential relationship is related to ICS drug and dose, and FDC inhaler device
Country of study	United Kingdom
Author / Research lead	Rafael Mares RiRL UK Ltd 5a Coles Lane Oakington Cambridge CB24 3BA United Kingdom

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1. Background

Oral thrush, also known as oral candidiasis, is one of the most commonly reported local side-effects associated with regular inhaled corticosteroid (ICS) use in patients with asthma.[1–6] There is, however, comparatively little information on real-world incidence rates of oral thrush in patients with chronic obstructive pulmonary disease (COPD) who are prescribed ICS, despite its widespread use as a maintenance therapy.[7,8] It is important that practitioners have a clear understanding of its potential side effects, particularly in cases where alternative treatments such as long-acting bronchodilators could also be prescribed as the preferred option.

ICS is almost exclusively (with a few country exceptions) licenced for use in COPD as part of a fixed-dose combination (FDC) with a long-acting β_2 agonist (LABA). Current COPD management guidelines recommend, broadly, the use of FDC ICS/LABA for patients with severe airflow limitation and/or at risk of severe exacerbations (i.e. in general those in groups C and D of the GOLD symptom/risk assessment).[7,8] For less severe patients (i.e. those in groups A and B of the GOLD symptom/risk assessment), long-acting bronchodilators alone or in combination are the recommended maintenance therapy.[7,8] Long-acting bronchodilators are also an option for more severe patients and may indeed be more appropriate for patients at risk of ICS-related side effects[9]. Recent studies, however, have found that ICS is being prescribed more frequently, particularly among less severe patients, than would be expected from current management guidelines.[10–12]

Whilst results from studies on ICS use in patients with asthma and from clinical trials in patients with COPD could suggest that oral thrush is likely to be a problem in real-world COPD patients,[1–5,13] precise incidence rates are currently unknown. Furthermore, if side effects do occur, the extent may be modulated by factors such as the ICS drug and dose in the FDC and the inhaler device type prescribed, which may largely determine the amount of drug deposited in the throat (a recognised contributing factor to oral thrush).[5,14] This is key information that practitioners need to consider when prescribing ICS therapies. To date, however, studies on FDC ICS/LABA use in patients with COPD have focused on a limited number of ICS drugs and inhaler devices, and the effect of ICS dose on the incidence of oral thrush has not been explicitly tested.

A comprehensive, real-world study, examining a range of drugs and devices commonly prescribed in primary care to patients with COPD, may help to assess the extent to which the incidence of oral thrush is attributable to ICS use as part of an FDC ICS/LABA; and whether oral thrush incidences differ across patients prescribed different ICS drugs, delivery devices and doses. Here, we present the protocol for a matched, historical cohort study to first, compare the incidence rates of oral thrush in patients with COPD who are prescribed ICS as part of an FDC ICS/LABA versus those prescribed long-acting bronchodilator therapy; and second, investigate the effect of ICS drug and dose, and FDC device on the incidence of oral thrush in patients prescribed FDC ICS/LABA.

2. Study aims and objectives

2.1. Study aims

The aim of the study is twofold: first, to investigate whether there is an association between ICS use as part of an FDC ICS/LABA and oral thrush in patients with COPD (Phase 1); and second, to assess whether this potential relationship between FDC ICS/LABA use and oral thrush is modulated by the ICS drug and dose within the prescribed FDC device (Phase 2).

2.2. Study objectives

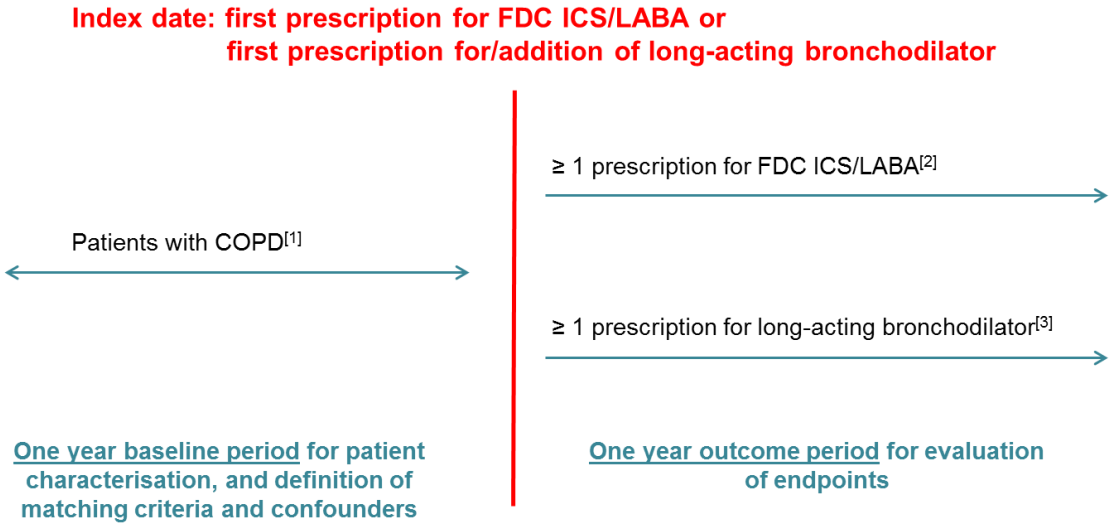
1. The first objective (Phase 1) is to assess whether patients with COPD who are prescribed ICS as part of an FDC ICS/LABA have a higher incidence of oral thrush than those prescribed long-acting bronchodilator therapies without ICS
2. The second objective (Phase 2) is to assess whether the incidence of oral thrush in patients with COPD who are prescribed FDC ICS/LABA is dependent on:
    - ICS drug and FDC inhaler device
    - ICS dose within the FDC

3. Study design

3.1. Study design

This will be a historical, matched cohort study, consisting of a one-year baseline period prior to a first prescription for either an FDC ICS/LABA or long-acting bronchodilator therapy (for Phase 1 only),* followed by a one-year outcome period (see Figure 1; further details below). One-year time periods for baseline and outcome were deemed necessary to record any measurable changes in variables, and also to allow for seasonal changes in respiratory disease and its related conditions.

Figure 1. Study design



[1] Includes patients with no prescriptions for reliever/maintenance therapy or with ≥ 1 prescription for SABA (short-acting β_2 agonist) and/or SAMA (short-acting muscarinic antagonist), and those with ≥ 1 prescription for LAMA (long-acting muscarinic antagonist) or LABA (long-acting β_2 agonist). | [2] Includes **Symbicort® DPI**: budesonide and formoterol fumarate dehydrate; **Seretide® DPI/pMDI**: fluticasone propionate and salmeterol xinafoate; **Fostair® DPI/pMDI**: beclometasone dipropionate and formoterol fumarate dehydrate (note that Seretide pMDI is not currently licensed for COPD management in the UK) | [3] Refers to LABA, LAMA and their combination. Patients may be included more than once with different prescriptions and prescription dates (e.g. a first prescription for LABA and the addition of LAMA on a different date), but only unique patients will be included in the endpoint analysis after matching (see section 6.5).

* Phase 2 will focus only on a subset of patients receiving a first prescription for FDC ICS/LABA at the index date. Further details in section 4.2 below.

4. Study population

4.1. Inclusion and exclusion criteria

The study will include patients that fulfil all of the criteria listed in Table 1 below.

Table 1. Inclusion criteria

Quality and Outcomes Framework coded diagnosis for COPD[†] ever recorded
Aged ≥ 40 years at first prescription (i.e. index date) for FDC ICS/LABA[‡], or first prescription for or addition of long-acting bronchodilator[§]
At least 2 years of continuous practice data (1 year of baseline and 1 year of outcome data)
≥ 2 prescriptions for FDC ICS/LABA[‡] or long-acting bronchodilator[§] during the outcome period (including the index date prescription)

Patients will be excluded if they meet any of the criteria listed in Table 2 below.

Table 2. Exclusion criteria

≥ 1 prescription for ICS during the baseline period
≥ 1 prescription for LABA/LAMA during the baseline period
Maintenance course for oral corticosteroids[**] during the baseline period
Evidence of any chronic respiratory disease other than COPD, asthma and bronchiectasis (diagnostic code ever recorded)

[†] COPD diagnosis confirmed by post bronchodilator spirometry, such that the ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) is less than 0.7.

[‡] Includes Symbicort®, Seretide® and for Phase 1 only, Fostair®.

[§] For Phase 1 only, and refers to LABA (long-acting $beta_2$-agonist), LAMA (long-acting muscarinic antagonist), and their combination.

[**] Refers to prescriptions for Prednisolone with daily dosing instructions of ≤ 10 mg, or prescriptions for 1 mg or 2.5 mg Prednisolone tablets where daily dosing instructions are not available.

4.2. Study cohorts

Phase 1 will focus on two cohorts of patients with COPD, namely

- Patients prescribed FDC ICS/LABA at the index date, including the following drugs/devices:
  - **Symbicort®** (budesonide and formoterol fumarate dehydrate) via dry powder inhaler (DPI; Turbohaler®)
  - **Seretide®** (fluticasone propionate and salmeterol xinafoate) via DPI (Accuhaler®) and pressurised metered dose inhaler (pMDI; Evohaler®)
  - **Fostair®** (beclometasone dipropionate and formoterol fumarate dehydrate) via DPI (NEXThaler®) and pMDI
- Patients prescribed long-acting bronchodilator at the index date: LABA, LAMA or their combination††

Phase 2 will focus on three subgroups of patients within the FDC ICS/LABA cohort described above, namely‡‡

- Patients prescribed **Symbicort®** (budesonide and formoterol fumarate dehydrate) via DPI (Turbohaler®)
- Patients prescribed **Seretide®** (fluticasone propionate and salmeterol xinafoate) via DPI (Accuhaler®)
- Patients prescribed **Seretide®** (fluticasone propionate and salmeterol xinafoate) via pMDI (Evohaler®) with and without a spacer device

4.3. Data source

Data for this study will be obtained from the Optimum Patient Care Research Database (OPCRD; http://optimumpatientcare.org/). The OPCRD is a quality controlled, primary care

†† Patients may be included more than once with different first prescriptions and prescription dates (e.g. a first prescription for LABA, followed by a prescription for LABA/LAMA on a different date) if they satisfy the inclusion and exclusion criteria. However, only unique patients will be included in the endpoint analysis after matching (see section 6.5).

‡‡ Patients prescribed Fostair® will be excluded from Phase 2 due to the expected low number of patients.

research database with a focus on respiratory disease, and contains anonymous routine recorded patient data from over 500 UK general practices.

The OPCRD has been approved by the Trent Multi Centre Research Ethics Committee for use within clinical research, and all applications to use the database must be reviewed by the independent Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (http://www.optimumpatientcare.org/Html_Docs/adept.html). OPCRD data are used in clinical, epidemiological and pharmaceutical research in both the private and academic sectors (see http://www.optimumpatientcare.org/OPCRD.html for a list of recent publications).

5. Study variables

5.1. Primary endpoint

Incidence of oral thrush, defined as the proportion of patients with a diagnosis and/or prescribed medication for treating oral thrush[§§] within the outcome period.

5.2. Baseline demographic and clinical variables

For each phase of the study, patient demographics, comorbidities and respiratory-related clinical measures and prescribed therapies recorded by a general practitioner at or prior to the index date, will be summarised for each cohort/subgroup (i.e. for Phase 1, FDC ICS/LABA and long-acting bronchodilator cohorts; for Phase 2, Symbicort® and Seretide® subgroups). Baseline summaries will be used to assess differences between the cohorts/subgroups and potential matching criteria, and to identify confounders for the endpoint analysis (details in section 6). The following baseline measures will be assessed (see definitions in section 5.2.1):[***]

[§§] See Tables 5 and 6 in Appendix 1 for the list of terms and corresponding Read codes that will be used to identify oral thrush diagnosis and antifungal drugs.

[***] A full list of the Read codes used to identify the baseline clinical variables used in this study will be provided via the following link: https://app.smartsheet.com/b/home

- Demographic characteristics including age, sex, body mass index (BMI) and smoking status closest to the index date
- Important, potentially confounding comorbidities and co-medications, including diagnoses of oral thrush, severe anaemia, poor immune system, hypertension and pneumonia; prescriptions for nasal corticosteroids and antibiotic courses; and Charlson Comorbidity Index (CCI) score during the baseline period; and diagnoses of diabetes, cardiovascular disease, ischaemic heart disease, osteoporosis, eczema, rhinitis, gastroesophageal reflux disease and asthma prior to the index date
- Measures of COPD severity and respiratory-related therapies including moderate/severe exacerbations, acute courses of oral corticosteroids and short-acting β_2 agonist (SABA) reliever usage in the baseline period; and FEV_1, mMRC score and GOLD group closest to the index date

5.2.1. Baseline variable definitions and categories

- Smoking status, closest to the index date: non-smoker, current smoker and ex-smoker
- BMI, closest to the index date: defined as the ratio of weight (kg) to squared height (m^2), and categorised as 'underweight' (< 18.5 kg/m^2), 'normal weight' (≥ 18.5 kg/m^2 and < 25 kg/m^2), 'overweight' (≥ 25 kg/m^2 and < 30 kg/m^2) and 'obese' (≥ 30 kg/m^2)
- CCI score, calculated for the baseline period: a weighted index that takes into account the number and seriousness of comorbid diseases to estimate the risk of death from comorbid diseases[15]
- Respiratory-related therapies, in the year prior to the index date:
    - Short-acting β_2 agonist (SABA) and/or short-acting muscarinic antagonist (SAMA)
    - Long-acting β_2 agonist (LABA)
    - Long-acting muscarinic antagonist (LAMA)

- Moderate/severe COPD exacerbations, defined as the occurrence of any of the following:[†††]
    - Acute course of oral corticosteroids[‡‡‡]
    - Antibiotics prescribed with a lower respiratory consultation[§§§]
    - COPD-related, unscheduled hospital admission / emergency department attendance (i.e. severe exacerbation)[****]
- SABA reliever usage, in the year prior to the index date: average daily dose in µg/day calculated as

  ([Count of inhalers x doses in pack] / 365) x µg strength

- FEV_1, closest to the index date: refers to the forced expiratory volume in 1 second, expressed as a percentage of the predicted normal value
- mMRC score, closest to the index date: refers to the modified British Medical Research Council questionnaire for assessing the severity of breathlessness, graded from 0, lowest score of breathlessness, to 4, highest score of breathlessness.[7] Both routine medical practice recorded and patient questionnaire mMRC scores will be used, with the most recent score taking precedence

[†††] Where > 1 oral corticosteroid courses / hospitalisations / antibiotic prescriptions occurred within 2 weeks of each other, they will be considered to be the result of the same exacerbation (and only counted once).

[‡‡‡] Defined as any of the following: (a) courses that are definitely not maintenance therapy (defined as prescriptions for Prednisolone with daily dosing instructions of ≤ 10 mg, and for 1 mg or 2.5 mg Prednisolone tablets where daily dosing instructions are not available); (b) courses where dosing instructions suggest exacerbation treatment (e.g. 6-1 reducing, or 30 mg as directed); and (c) courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

[§§§] Identified by Read codes for any of the following: (a) lower respiratory diagnosis (including asthma, COPD and lower respiratory tract infection codes); (b) asthma/COPD review codes excluding any monitoring letter codes; (c) lung function and/or asthma monitoring codes; and (d) any additional respiratory examinations, referrals, chest x-rays, or events.

[****] Identified by Read codes for any of the following: (a) definite COPD emergency attendance or definite COPD hospital admission; (b) generic hospitalisation code which has been recorded on the same day as a lower respiratory consultation (see footnote above, refers to (a) - (c) only and excluding those where the lower respiratory code was for a lung function test only).

- GOLD group, closest to the index date: based on 2014 GOLD guidelines:[7]
    - A = low risk, less symptoms: mMRC of ≤ 1; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations)
    - B = low risk, more symptoms: mMRC of ≥ 2; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations)
    - C = high risk, less symptoms: mMRC of ≤ 1; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation)
    - D = high risk, more symptoms: mMRC of ≥ 2; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation)

6. Statistical analysis

6.1. Software

The study will be conducted using R statistical software (R Foundation for Statistical Computing, Austria), SPSS Statistics 22 (IBM SPSS Statistics, UK) and SAS 9.3 (SAS Institute, UK).

6.2. Significance testing

Statistically significant results will be defined as those where $p < 0.05$ and trends, where $0.05 \leq p < 0.10$.

6.3. Power calculation

The study will be powered for Phase 1 on the primary endpoint: incidence of oral thrush. The sample size required for 90% power to reject the null hypothesis that there is no difference between the study cohorts (i.e. FDC ICS/LABA vs long-acting bronchodilator) in the proportion of patients with a diagnosis and/or medication for oral thrush in the outcome period, is 360 patients in each of the cohorts†††† (i.e. for 1:1 patient matching). The calculation was made assuming that a difference in proportions of 0.05 (π_1 = 0.020 and π_2 =

†††† Calculated using a two-group Chi-squared test with a 0.05 two-sided significance level.

0.070; odds ratio of 3.688) will be statistically significant, based on the results from a similar study by Calverley et al. (2007) in patients with COPD. Calverley et al. (2007) showed that the rate per year of reports of candidiasis associated with corticosteroid use was 0.07 in patients that were prescribed salmeterol and fluticasone propionate vs 0.02 in those prescribed salmeterol alone.[13]

6.4. Data preparation and baseline characterisation

Data will be prepared for analysis by investigating outliers, type and reason for missing data, and categorising skewed data if appropriate.

Summary statistics will be presented for each cohort (see Appendix 2 for a sample summary table), as appropriate for each variable:

- Variables measured on the interval or ratio scale: n and % of non-missing data; mean (standard deviation) and median (inter-quartile range)
- Categorical variables: n (%) of non-missing data; n (%) per category

Baseline differences between the two cohorts will be evaluated prior to matching (see below) using t-tests, Mann-Whitney U tests or Pearson's Chi-squared tests, as described in Table 3.

Table 3. Statistical tests for baseline data comparisons

Statistical test	Data type	Distribution	Groups
t-test	interval or ratio scale	normal	2
Mann-Whitney U test	interval or ratio scale	not normal	2
Chi-squared test	categorical	n/a	≥ 2

6.5. Matching

Phase 1: Unique patients from each cohort (i.e. FDC ICS/LABA vs long-acting bronchodilator) will be matched (1:1 matching) on demographics and baseline clinical measures and medications that are likely to have a direct impact on the incidence of oral thrush (i.e. potentially confounding variables in the analysis of the primary endpoint), including:

- Age (+/- 5 years)
- Smoking status (non-smoker / current smoker / ex-smoker)
- Baseline moderate/severe exacerbations (0-1 / ≥ 2)
- Baseline COPD therapy (none or reliever / LAMA [+/- reliever] / LABA [+/- reliever])

- Baseline use of nasal corticosteroids (yes / no)
- Baseline diagnosis/medication for oral thrush (yes / no)
- Baseline diagnosis/medication for diabetes (yes / no)

Phase 2: Patients will be matched using two-way matching (1:1 matching) for each of the three subgroups (i.e. Symbicort®, Seretide® DPI and Seretide® pMDI). As described for Phase 1, patients will be matched on demographic and baseline clinical measures and medications that are likely to have a direct impact on the incidence of oral thrush (as listed above). The three two-way matchings required for Phase 2 will be performed using all eligible patients included in the larger, unmatched FDC ICS/LABA cohort.

Baseline differences between cohorts/subgroups (assessed as described above) will also be taken into account when selecting the matching variables for each phase of the study.

6.6. Analysis of study endpoint

For both phases of the study, all two-way comparisons of the primary endpoint between the cohorts/subgroups will be analysed using conditional logistic regression. Results will be reported as both:

- Number (and percentage) of patients who, in the year after the index prescription date had a diagnosis and/or drug prescribed for oral thrush (yes/no)
- Odds ratios (OR) with 95% confidence intervals (CI), unadjusted and adjusted for baseline predictors/confounders

Confounders will be defined as baseline variables:

- With residual differences between the cohorts/subgroups after matching (conditional logistic regression, $p < 0.10$); or
- Predictive of the endpoint (full multivariable model, $p \leq 0.05$)

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

In addition to baseline confounders, the use of a spacer device in the outcome period will also be included as a potential confounder of the endpoint analysis.

Phase 2: The potential **impact of ICS drug and FDC inhaler device** on the incidence of oral thrush, will be investigated via three two-way comparisons:

- Symbicort® vs Seretide® DPI
- Symbicort® vs Seretide® pMDI (+/- spacer)
- Seretide® DPI vs Seretide® pMDI (+/- spacer)

To investigate the potential **impact of ICS dose** on the incidence of oral thrush, the average daily ICS dose (in fluticasone propionate equivalents‡‡‡‡) consumed over the outcome period will be included as a predictor in all Phase 2 endpoint analyses. Patients will be categorised as follows (to be confirmed):§§§§

- Low dose: < 500 µg/day
- Moderate dose: 500 – 999 µg/day
- High dose: ≥ 1000 µg/day

7. Regulatory and ethical compliance

This study was designed, and shall be implemented and reported in accordance with the criteria of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Once a final version of the protocol is reviewed and agreed upon by the advisory group, formal ethics and research management approval of this study protocol will be obtained from the ADEPT Committee, which verifies the scientific and ethical soundness of all research using OPC data. A final version of this protocol will then be registered with www.encepp.eu.

‡‡‡‡ Half the dose of fluticasone propionate in micrograms (µg) is equivalent to a given dose of budesonide (2:1 dose ratio).[16]

§§§§ Low, moderate and high fluticasone dose categories as reported in previous studies in patients with COPD.[17] ICS dose may also be analysed as a continuous variable, depending on the distribution of the data.

8. Data dissemination

Initial results will be first presented and discussed at the DASG meeting in May 2015, and followed shortly after with presentations in poster and/or oral format at appropriate thoracic conferences. A manuscript containing more detailed results and methodology will be submitted to a journal specialising in respiratory medicine.

9. Advisory group

The steering committee for this study includes the following DASG members:

- Sinthia Bosnic-Anticevich
- Leif Bjermer
- Henry Chrystyn
- Richard Dekhuijzen
- Monica Fletcher
- Alberto Papi
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11. Timeline

Table 4. Study timeline

Action	Timeline
Data extraction	1 week
Phase 1: Unmatched baseline analysis	1 week
Phase 1: Matching and matched baseline analysis	2 weeks
Phase 1: Outcome analysis/preliminary results (*to be presented at the 20 May 2015 DASG meeting*)	3 weeks
Phase 2: Unmatched baseline analysis	2 weeks
Phase 2: Matching and matched baseline analysis	3 weeks
Phase 2: Outcome analysis	3 weeks
Final report writing	4 weeks (TBC)
First draft of paper	6-8 weeks from final report

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13. Appendix 1: Oral thrush diagnosis and antifungal codes

Table 5. Oral thrush diagnosis codes

Read code version	Code	Term ID	Term details
3	AB20.	YE0PG	Candidiasis: [oral and oesophagus] or [pharyngeal]
2	AB20.	00CIt	Candidiasis of mouth and oesophagus
2	AB20.	12CIv	Thrush of mouth and oesophagus
2	AB20.	15CIy	Oral moniliasis
3	AB200	Y21Hy	Moniliasis of mouth
3	AB200	Y21I2	Oral thrush
3	AB200	Y71po	Candidiasis of mouth
3	AB200	Y71pp	Oral moniliasis
3	AB200	Y71pq	Oral candidiasis
2	AB200	00CIz	Candidiasis of mouth
3	AB201	Y301F	Oesophageal candidiasis
3	AB201	Y301H	Oesophageal thrush
3	AB201	YM0iQ	Candidiasis of oesophagus
2	AB201	00CJ1	Candidiasis of oesophagus
2	AB202	00CJ2	Candida angular cheilitis
3	AB20z	Y71ph	Candidiasis of mouth and oesophagus NOS
2	AB20z	00CJ3	Candidiasis of mouth and oesophagus NOS
3	X00mS	Y02VK	Acute pharyngeal candidiasis
3	X00mU	Y02VY	Chronic pharyngeal candidiasis
3	X20RT	YaYm6	Acute oral pseudomembraneous candidiasis
3	X20RU	YaYm7	Acute oral atrophic candidiasis
3	X20RV	YaYm8	Oral erythematous candidiasis
3	X20RW	Ya4Dz	Chronic hyperplastic candidiasis
3	X20RX	Ya4E0	Familial chronic mucocutaneous candidiasis
3	X70Qf	Y71ps	Pharyngeal candidiasis
3	X70Qf	Y71pt	Pharyngeal thrush
3	X70Qi	Ya4E1	Candidiasis of trachea
3	X70Qz	Ya4EE	Familial chronic mucocutaneous candidiasis - late onset type
3	XE0SG	Y71pe	Candidiasis of mouth and oesophagus
3	XE0SG	Y71pf	Thrush of mouth and oesophagus

Non-specific candidiasis codes (to be used in combination with medication codes)			
3	AB2..	Y71pd	Candidiasis
3	AyuE5	YMA6I	[X]Candidiasis, unspecified
3	AB2..	Y71pc	Thrush
3	AB2..	Y71pb	Moniliasis

Diagnosis codes taken from the NHS Clinical Terminolagy Browser, versions 2 and 3, and revised by an expert clinical adviser.

Table 6. Drug codes for antifungals used in the treatment of oral thrush

Read code version	Code	Term ID	Term details
3	eh11.	y02U1	Fungilin 100mg tablet
2	eh12.	00RtT	FUNGILIN 100mg/mL sugar free suspension
3	eh12.	y02U2	Fungilin 100mg/mL s/f suspension
3	eh1x.	y02U5	Amphotericin 100mg tablet
2	eh1y.	00Rte	AMPHOTERICIN 100mg/mL sugar free suspension
3	eh1y.	y02U6	Amphotericin 100mg/mL s/f suspension
2	lc1..	00UUc	AMPHOTERICIN [OROPHARYNGEAL]
3	lc1..	y00pv	Amphotericin [oropharyngeal]
2	lc11.	00UUd	*FUNGILIN 10mg lozenges
3	lc11.	y037R	Fungilin 10mg lozenge
2	lc12.	00UUe	FUNGILIN 100mg/mL suspension 12mL
3	lc12.	y00pw	Fungilin 100mg/mL suspension 12mL
2	lc1y.	00UUf	*AMPHOTERICIN 10mg lozenges
3	lc1y.	y037S	Amphotericin 10mg lozenge
2	lc1z.	00UUg	AMPHOTERICIN 100mg/mL suspension
3	lc1z.	y00px	Amphotericin 100mg/mL suspension
3	x01IS	y045r	Oral amphotericin
2	eh8b.	00RuZ	DIFLUCAN 50mg/5mL suspension 35mL
3	eh8b.	y07BM	Diflucan 50mg/5mL suspension 35mL
2	eh8c.	00Rua	DIFLUCAN 200mg/5mL suspension 35mL
3	eh8c.	y07BN	Diflucan 200mg/5mL suspension 35mL
2	eh8d.	00Rub	FLUCONAZOLE 50mg/5mL suspension
3	eh8d.	y02Ut	Fluconazole 50mg/5mL oral suspension

2	eh8e.	00Ruc	FLUCONAZOLE 200mg/5mL suspension
3	eh8e.	y02Uu	Fluconazole 200mg/5mL oral suspension
3	x025n	y02Ur	Diflucan 50mg/5mL oral suspension
3	x025o	y02Us	Diflucan 200mg/5mL oral suspension
2	eh94.	00Ruo	ITRACONAZOLE 10mg/mL sugar free oral solution
3	eh94.	y09p8	Itraconazole 10mg/mL s/f oral solution
2	eh95.	00Rup	SPORANOX 10mg/mL sugar free oral solution 150mL
3	eh95.	y09pB	Sporanox 10mg/mL s/f oral solution 150mL
3	x03h5	y09p9	Sporanox 10mg/mL s/f oral solution
3	x03h5	y0AAj	Sporanox 10mg/mL oral liquid
3	eh51.	y02US	Daktarin 250mg tablet
2	eh5x.	00Ru9	MICONAZOLE 25mg/ml oral gel
3	eh5x.	y02UU	Miconazole 25mg/mL oral gel
3	eh5y.	y02UV	Miconazole 250mg tablet
2	lc4..	00UUn	MICONAZOLE [OROPHARYNGEAL]
3	lc4..	y00q1	Miconazole [oropharyngeal]
2	lc41.	00UUo	*DAKTARIN oral gel 40g
3	lc41.	y00q2	Daktarin oral gel 40g
2	lc42.	00UUp	DAKTARIN oral gel 80g
3	lc42.	y00q3	Daktarin oral gel 80g
2	lc43.	00UUq	DAKTARIN oral gel 15g
3	lc43.	y00q4	Daktarin oral gel 15g
2	lc44.	00UUr	DUMICOAT 50mg/g dental lacquer
3	lc44.	y081B	Dumicoat 50mg/g dental lacquer
2	lc45.	00UUs	MICONAZOLE 50mg/g dental lacquer
3	lc45.	y081A	Miconazole 50mg/g dental lacquer
2	lc46.	00UUt	LORAMYC 50mg muco-adhesive buccal tablets
3	lc46.	y0IN2	LORAMYC 50mg muco-adhesive buccal tablets
2	lc4y.	00UUu	MICONAZOLE 50mg muco-adhesive buccal tablets
3	lc4y.	y0IN3	MICONAZOLE 50mg muco-adhesive buccal tablets
2	lc4z.	00UUv	MICONAZOLE 25mg/ml oral gel
3	x00Xm	y03Ui	Daktarin 25mg/mL oral gel
3	x01Im	y045g	Oral miconazole
2	eh7..	00RuF	NYSTATIN [SYSTEMIC]

2	eh71.	00RuG	NYSTATIN 100,000units/mL suspension
3	eh71.	y02UZ	Nystatin 100,000units/mL oral suspension
2	eh72.	00RuH	*NYSTAN 500,000units tablets
3	eh72.	y02Ua	Nystan 500,000units tablet
2	eh73.	00RuI	NYSTAN 100,000units/mL suspension
3	eh73.	y02Ub	Nystan 100,000units/mL oral suspension
2	eh74.	00RuJ	NYSTAN GF LF SF 100,000units/mL suspension
3	eh74.	y02Uc	Nystan 100,000units/mL s/f g/f l/f oral suspension
2	eh75.	00RuK	NYSTATIN-DOME 100,000units/mL suspension
3	eh75.	y02Ud	Nystatin Dome 100,000units/mL oral suspension
2	eh76.	00RuL	*NYSTATIN 500,000units tablets
3	eh76.	y02Ue	Nystatin 500,000units tablet
2	eh77.	00RuM	NYSTATIN 100,000units/mL sugar free suspension
3	eh77.	y02Uf	Nystatin GF/LF/SF 100,000units/mL suspension
2	eh78.	00RuN	NYSTAMONT 100,000units/mL sugar free oral suspension
3	eh78.	y08Xs	Nystamont 100,000units/mL s/f suspension
2	lc6..	00UV1	NYSTATIN [MOUTH]
3	lc6..	y00qA	Nystatin [mouth]
2	lc61.	00UV2	NYSTATIN 100,000units/mL mixture
3	lc61.	y00qB	Nystatin 100,000units/mL mixture
2	lc62.	00UV3	*NYSTAN 100,000units pastilles
3	lc62.	y037W	Nystan 100,000units pastille
2	lc63.	00UV4	NYSTAN 100,000units/mL suspension 30mL
3	lc63.	y00qC	Nystan 100,000units/mL suspension 30mL
2	lc64.	00UV5	*NYSTAN SF suspension 24mL
3	lc64.	y00qD	Nystan sf suspension 24mL
2	lc65.	00UV6	NYSTATIN-DOME 100,000units/mL suspension 30mL
3	lc65.	y00qE	Nystatin Dome 100,000units/mL suspension 30mL
2	lc66.	00UV7	NYSTAMONT 100,000units/mL sugar free oral suspension 30mL
3	lc66.	y08Xt	Nystamont 100,000units/mL sugar free oral suspension 30mL
2	lc67.	00UV8	INFESTAT 100,000units suspension 30mL
3	lc67.	y09ji	Infestat 100,000units/mL suspension 30mL

2	lc6v.	00UV9	NYSTATIN 100,000units/mL suspension
2	lc6w.	00UVA	NYSTATIN 100,000units pastilles
3	lc6w.	y037X	Nystatin 100,000units pastille
2	lc6x.	00UVB	NYSTATIN S/F granules for suspension 24mL
3	lc6x.	y00qF	Nystatin s/f granules for suspension 24mL
3	x01IZ	y0465	Oral nystatin
3	x03do	y09jh	Infestat 100,000units/mL suspension
3	ehdz.	y0Gy0	Posaconazole 40mg/mL oral suspension
3	ehd1.	y0Gy1	Noxafil 40mg/mL oral suspension

Drug codes taken from the NHS Clinical Terminolagy Browser, versions 2 and 3, and revised by an expert clinical adviser.

14. Appendix 2: Sample baseline and endpoint tables

Table 7. Sample baseline characterisation table (for Phase 1)

		FDC ICS/LABA	LABA and/or LAMA	p-value
Age (years)	mean (SD)			
Age (categorised)	40 - 60, n (%)			
	61 - 80, n (%)			
	> 80, n (%)			
Sex	male, n (%)			
BMI (closest to index date; categorised)	non-missing, n (%)			
	underweight, n (%)			
	normal weight, n (%)			
	overweight, n (%)			
	obese, n (%)			
Smoking status (closest to index date)	non-missing, n (%)			
	non-smoker, n (%)			
	current smoker, n (%)			
	ex-smoker, n (%)			
FEV_1 % predicted (closest to index date)	non-missing, n (%)			
	median (IQR)			
FEV_1 % predicted (categorised)	< 30 (very severe), n (%)			
	30 - 49 (severe), n (%)			
	50 - 79 (moderate), n (%)			
	≥ 80 (mild), n (%)			
mMRC score (closest to index date; categorised)	non-missing, n (%)			
	0-1, n (%)			
	≥ 2, n (%)			
COPD exacerbations	median (IQR)			
COPD exacerbations (categorised)	0, n (%)			
	1, n (%)			
	2, n (%)			
	≥ 3, n (%)			
GOLD group (closest to index date)	non-missing, n (%)			
	A, n (%)			
	B, n (%)			
	C, n (%)			
	D, n (%)			
Acute oral corticosteroid courses (during baseline period)	0, n (%)			
	1, n (%)			
	2, n (%)			
	≥ 3, n (%)			

Antibiotic prescriptions (during baseline period)	0, n (%)			
	1, n (%)			
	2, n (%)			
	≥ 3, n (%)			
COPD therapy (during baseline period)	None, n (%)			
	SABA (+/- SAMA), n (%)			
	LABA, n (%)			
	LAMA, n (%)			
SABA inhaler usage (µg per day, during baseline period)	0, n (%)			
	≤ 200, n (%)			
	> 200, n (%)			
Oral thrush (during baseline period)	n (%)			
Severe anaemia (during baseline period)	n (%)			
Immunodeficiency (during baseline period)	n (%)			
Hypertension (during baseline period)	n (%)			
Diabetes (prior to index date)	n (%)			
Cardiovascular disease (prior to index date)	n (%)			
IHD (prior to index date)	n (%)			
Osteoporosis (prior to index date)	n (%)			
Eczema (prior to index date)	n (%)			
Rhinitis (prior to index date)	n (%)			
GERD (prior to index date)	n (%)			
Asthma (prior to index date)	n (%)			
CCI score (for baseline period; categorised)	0, n (%)			
	1 - 4, n (%)			
	5 - 9, n (%)			
	≥ 10, n (%)			
Nasal corticosteroids (during baseline period)	n (%)			

Index date refers to the date of first prescription for FDC ICS/LABA or long-acting bronchodilator (LABA and/or LAMA). | Baseline period refers to the year before the index date. | See variable definitions in section 5.2.1.

Table 8. Sample endpoint table (for Phase 1)

		FDC ICS/LABA	LABA and/or LAMA	p-value
Incidence of oral thrush	mean (SD)			
	median (IQR)			
Unadjusted odds ratio (95% CI) for oral thrush diagnosis/medication				
Adjusted odds ratio (95% CI) for oral thrush diagnosis/medication				