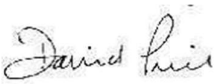
MAGNIFY: Statistical Analysis Plan

Study title: A pragmatic, cluster randomized trial evaluating the impact of an enhanced adherence package (dual bronchodilator+add-on+app) on time to treatment failure and other clinical outcomes in exacerbating COPD patients with poor adherence to mono or dual therapy over one year

Document history

Version number	Change	Date
1.0	n/a	31/10/24
2.0	• Inserted summary of changes since published protocol • Revised description of study population • Revised wording of secondary outcomes to better reflect analyses conducted • Removed adherence outcome • Revised description of exploratory outcome regarding healthcare resource utilisation outcome • Inserted justification for statistician not being blinded • Inserted description of confounding handling approach • Revised description of primary/secondary/exploratory analyses • Removed mention of propensity score weighting • Revised sensitivity analysis section • Inserted description of stratified analyses • Revised baseline characteristics and outcome tables	05/03/25
3.0	• Approach to matching simplified due to model convergence issues • Propensity score weighted analysis inserted as a sensitivity analysis to strengthen control of confounding by baseline characteristics. • Removed analysis of costs • Reduced list of healthcare resource utilisation outcomes • Inserted more granular category definitions for three baseline characteristics (blood eosinophil count, number of respiratory consultations and moderate/severe exacerbation count)	01/09/25

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1. Introduction

1.1. Study background

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease characterised by progressive airflow limitation. In the UK, approximately 3 million people have COPD and it costs the NHS £1-3 billion annually. Patients with COPD are often prescribed inhaled therapy to manage their symptoms, but non-adherence to these therapies is common, leading to poor clinical and economic outcomes. Electronic reminders and monitoring have been used in other diseases to improve medication adherence; studies in patients with asthma have reported improved adherence and clinical outcomes, but there is no solid RCT evidence regarding the impact of such interventions on clinical outcomes within the COPD population.

1.2. Study objectives

The aim of this study is to evaluate the impact of provision of indacaterol/glycopyrronium 110/50 µg (Ultibro® Breezhaler®)/add-on device/app (The package) on time to treatment failure and other clinical outcomes, in exacerbating COPD patients with evidence of poor adherence to treatment. Time to treatment failure is defined in Section 2.2.

The **primary outcome** is time to treatment failure during the 12-month trial period.

1.3. Study design

MAGNIFY is a multicentre, cluster randomised trial. GP practices (the unit of randomisation) recruited from England, Scotland, and Wales, will be randomly allocated to the intervention arm (adherence support arm [ASA]) or the control arm (routine care) of the trial.

1.4.Summary of changes made since published protocol

Since the MAGNIFY protocol manuscript was published in 2021, several modifications were required relating to patient identification and randomisation.

Much of the trial was conducted during the COVID pandemic, during which time face-to-face healthcare appointments were replaced with remote consultations wherever possible to encourage social distancing and reduce the spread of infections. Repeat prescriptions became increasingly automated for the same reason. EMR-based adherence data during the pandemic therefore likely overestimated patients' adherence, as it reflected the automated issuing of medication, which may not be commensurate with patient compliance

Due to low confidence in adherence status calculated from EMR prescription refills because of the COVID pandemic[1], clinical judgement in addition to EMR prescription re-fill data was used to determine intervention patients' clinical appropriateness for the adherence support device, based on healthcare practitioner discussion with patients during their COPD reviews. This change made the control group requirement for questionnaire data confirming they were non-adherent and willing to accept technology unnecessary as this would no longer identify comparable control group patients.

In light of the above, control patients were selected based on evidence of LABA/LAMA prescription within 30 days of an intervention patient being provided with the adherence technological support package, if they met the trial eligibility criteria regarding age, disease status and exacerbation history. Baseline adherence (based on EMR prescription data) was treated as a confounder in all analyses, to account for it not informing patient selection.

As a result of low confidence in EMR-based adherence data for a trial conducted largely during the COVID pandemic, as well as the difficulty of generating standardised formats of adherence data in baseline and follow-up periods, adherence was removed from the trial outcomes.

Since developing the trial protocol, there was a substantial increase in the proportion of patients with COPD who were prescribed triple therapy (ICS + LABA + LAMA). As triple therapy was an exclusion criterion for the trial, this change in prescription behaviour reduced the number of potentially eligible patients at each intervention arm practice. Funding limitations precluded extending the recruitment period or increasing the number of participating practices. To recruit the required number of patients in the intervention arm, the patient eligibility criteria were relaxed by removing the need for a recorded $FEV_1/FVC < 0.7$ and for patients to be current/former smokers.

The published protocol defined the primary outcome of treatment failure as a composite outcome of four components: moderate/severe exacerbation; prescription of triple therapy; prescription of additional chronic therapy for COPD; respiratory-cause mortality. Occurrence of any component would be defined as treatment failure. Due to the challenge of accurately establishing cause of death from EMR data, and following advice from the steering committee, the component of respiratory-related mortality was replaced with all-cause mortality. Secondly, the component regarding prescription of triple therapy was modified to step up to ICS therapy, to capture a broader range of therapy changes i.e. patients moving to ICS/LABA or triple therapy (LABA/LAMA/ICS), rather than triple therapy alone.

Sensitivity analyses were proposed to assess the impact of selected definitions of the primary outcome (treatment failure) and the index date for control patients. For the treatment failure composite outcome, the sensitivity analysis proposed using a modified definition whereby step up to triple therapy was replaced with step up to any therapy. In light of the revised primary outcome definition described above, this analysis was no longer relevant. Sensitivity analyses regarding the index date for

control patients were justifiable, to explore the impact of using patient-level rather than practice-level index dates, as the protocol specified that the same index date would be used for all control patients from a single practice. However, the control patient selection used for the final analysis (described earlier in this section) rendered the sensitivity analyses unnecessary, as controls were matched based on individual patients' LABA/LAMA prescription dates.

In version 1.0 of the SAP, to maximise the number of controls, we specified matching "with replacement" whereby different episodes in the same individual were allowed to be a control for multiple treated patients. However, this led to model convergence issues for some outcomes when accounting for clustering by patient nested within practice. We have simplified the matching process in version 2.1 of the SAP to avoid these issues. The current approach (described in Section 1.5) was previously specified as a sensitivity analysis. The revised control patient selection did not have any impact on the analysis findings.

In version 1.0 of the SAP, it was proposed to address the potential for confounding through adjustment for three pre-specified covariates (see Section 2.3.4). To assess the robustness of the main trial analyses to confounding from a broader panel of baseline characteristics, we have added a propensity score weighted analysis of primary and secondary outcomes as a sensitivity analysis (see Section 2.3.8).

We have removed the analysis of costs from the exploratory outcomes due to concerns over the calculation and interpretation of the data in the context of the COVID pandemic.

1.5.Study time periods

Baseline

In the ASA group, the baseline from which outcomes will be assessed for each patient, is defined as the date of provision of the package following cluster-randomisation of the site. Patients in the control group will be matched on the basis of a LABA/LAMA prescription date within 30 days of the date of provision of the package in the ASA group. The baseline date for control patients will be the LABA/LAMA prescription date. Up to 2 matched control patient observations will be identified for each patient in the ASA group using matching without replacement.

Study period

Outcome data will be assessed in the 12 months (365 days) after baseline for both treatment groups.

1.6.Sample size and power

The sample size was calculated based on existing electronic medical record data from over 670 GP practices within the Optimum Patient Care Research Database (OPCRD). In total, 5555 patients in the OPCRD were identified as meeting the study suitability criteria. Of these, 3010 had outcome data available for 365 days and a further 2530 had a treatment failure within this outcome period.

For the primary endpoint of time to treatment failure, assuming that the median time to treatment failure in control arm is 90 days (estimated based on the above OPCRD dataset) and based on a clinically meaningful increase of 20% (in line with (Chapman et al. 2013) in the ASA arm (i.e. 108 days), we calculated that 82 practices per arm are required (total 164). This equates to a hazard in the control group of 0.0077 per day and 0.0064 in the intervention group, giving a hazard ratio of 0.83 (comparing these two rates, assuming an exponential distribution truncated at 365 days). Under the null

hypothesis, 477 events of treatment failure would be expected in each group; under the alternative hypothesis, a combined total of 951 events would be expected. The sample size calculation assumed that approximately 50% of suitable patients would accept the add-on device and app technology (on average 17 suitable patients were identified at 200 practices that would qualify as suitable for the study; of the suitable patients, it was estimated that an average of 8 would accept provision of the technology). This total sample size of 1312 patients will provide adequate power (80%), based on 5% level of significance and Intraclass Correlation Coefficient (ICC) of 0.038. To allow for a practice drop-out rate of approximately 6%, 88 practices per arm will be enrolled.

The ICC was calculated in the OPCRD dataset of 2530 patients from 508 practices, using a one-way random effects analysis of variance model, with the model fit in Stata V14 (Stata Corp, College Station, Tx, USA) using the 'loneway' command specifying 'failure time' as the dependent variable, and practice ID as the independent variable (Donner 1986)

1.7.Study population

Patients in the intervention arm will be identified as potentially eligible using EMR data, if they are aged ≥40 years, have a COPD diagnosis, have ≥2 exacerbations in the last 2 years or 2 years preceding March 2020, have been prescribed maintenance inhaled COPD therapy in the last 12 months, do not have an unresolved asthma diagnosis with an inhaled corticosteroid (ICS) prescription in the last 12 months and, have 2 years' valid EMR data. Pharmacists will be reminded of guideline recommendations for use of LABA/LAMA therapy in COPD patients. Following pharmacist review, patients deemed to be clinically suitable and poorly adherent to inhaled therapy (according to EMR, self-report or clinical judgement), will be offered the technological support package. Patients accepting the technological support package (i.e. agreeing to use the add-on device and mobile app, and to be prescribed Ultibro® Breezhaler® if not already using it) will be included in the study.

Patients from control arm practices will be included in the study if they are matched to intervention patients based on LABA/LAMA prescription date and are aged ≥40 years, have a COPD diagnosis, have ≥2 exacerbations in the last 2 years or 2 years preceding March 2020, are prescribed maintenance inhaled COPD therapy in the last 12 months, do not have an unresolved asthma diagnosis with an inhaled corticosteroid (ICS) prescription in the last 12 months and, have 2 years' valid EMR data.

In cluster trials, there is the potential for baseline imbalance and confounding when patients are recruited after the randomization of clusters. To assess the robustness of the main trial analyses, a sensitivity analysis will be performed using propensity score weighting methods[2]. Patients in both arms will be weighted according to their propensity score to ensure comparability between treatment groups. Overlap weights will be used which emphasize the target population with the most overlap in observed characteristics between treatment arms (see Section 2.3.8 for details).

1.8.Statistical analysis plan (SAP)

1.8.1. SAP objective

The objective of this SAP is to describe the statistical analyses to be carried out for the MAGNIFY study. The SAP is based on protocol version 5.1 (6th May 2022). Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary and any changes to the SAP documented under version control.

1.8.2. General principles

Categorical variables will be described with number and % in each category. Continuous variables will be described with mean and standard deviation (SD) or median and inter-quartile range (IQR) depending on the distribution. The amount of missing data will be provided for each variable.

1.8.3. Abbreviations

Abbreviation	Term
A&E	Accident and Emergency
ASA	Adherence Support Arm
COPD	Chronic Obstructive Pulmonary Disease
EMR	Electronic medical records
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GP	General Practitioner
ICS	Inhaled corticosteroid
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
NHS	National Health Service
OCS	Oral corticosteroid
OPC	Optimum Patient Care
OPCRD	Optimum Patient Care Research Database
OPRI	Observational Pragmatic Research International
PI	Principal Investigator
RCT	Randomized Controlled Trial
REC	Research Ethics Committee
The Package	Ultibro+add-on device+app
UK	United Kingdom

1.8.4. Software

All analyses will be conducted using STATA version 14 or later, or the current version of R (at the time of writing, version 2022.02.0). Anonymised data will be stored electronically on a locally hosted secure server, with access limited to those who require it.

2. Analysis

2.1. Analysis populations

All primary effectiveness analysis will be carried out on the intention to treat population. All patients who meet the inclusion criteria and either accept new technology (ASA patients) or are matched to ASA patients, will be analysed according to the treatment group that their GP practice was randomised to.

2.2. Effectiveness outcomes

2.2.1. Primary outcome

The primary outcome is time to treatment failure in the 12 months after initiation of intervention. Treatment failure is defined as the first occurrence of either: (i) a moderate/severe exacerbation, (ii) prescription of ICS, (iii) prescription of additional maintenance COPD therapy or, (iv) all-cause death. Patients will be censored due to moving practice or reaching 12 months without treatment failure.

Moderate/severe exacerbations are defined as an EMR-recorded acute oral corticosteroid prescription or, antibiotics prescribed with evidence of a lower respiratory consultation on the same day or, respiratory-related hospital attendance/admission or, respiratory-related A&E attendance. Additional maintenance COPD therapies include: Theophylline or other methylxanthines, long-term oral corticosteroid, PDE4 inhibitors (e.g. roflumilast), long-term macrolides (e.g. azithromycin), mucolytics (e.g. carbocysteine, N-acetylcysteine) or, any other long-term respiratory medication prescribed for COPD.

2.2.2. Secondary outcomes

- The rate of exacerbations over the 12-month trial period (based on electronic medical records)
- Time to first moderate/severe exacerbation over the 12-month trial period (based on electronic medical records)

2.2.3. Exploratory outcomes

- Respiratory-related healthcare resource utilisation. Resource utilisation will be calculated per 1,000 patient-years, based on OPCRD data for the number of:
    - Moderate/severe COPD exacerbations
    - Respiratory-related primary care consultations
    - Respiratory-related outpatient visits/hospital admissions/A&E attendances
- ASA package acceptance rate, defined as the percentage of patients among those offered The Package at ASA sites who accepted provision of The Package.

2.3. Analysis

2.3.1. General principles

Statistical analyses will be according to the intention to treat principle. All analyses will be governed by this comprehensive SAP, which will be agreed by the sponsor, independent steering committee and funder prior to any analyses being undertaken. There will be no formal interim analyses undertaken. Unless pre-specified, a 5% two-sided significance level will be used to denote statistical significance

throughout. Any estimates calculated will be presented alongside their 95% confidence intervals. It was not possible to blind the statistician conducting the analysis to group allocation because of the matching process that needed to be undertaken to identify eligible control patients, and the associated decision about the ratio of control to intervention arm observations.

2.3.2. Data description

Baseline characteristics will be reported as summary statistics by treatment group. Binary and categorical variables will be presented as count and percentage, while continuous variables will be presented as mean and standard deviation (if normally distributed) or median and interquartile range (if non-normally distributed). The standardised mean difference of each baseline characteristic will be assessed to determine potential confounders, which will inform the propensity score weighting process.

2.3.3. Missing data

A CONSORT flow diagram will describe the flow of trial participants, withdrawals and post-randomisation exclusions.

a. **Missing baseline data:** As this is obtained directly from EMR it is anticipated that missing baseline data will be minimal. Missing baseline data will be reported in the form of the count and percentage (n [%]) by variable and by randomised group. If necessary, we will deal with missing data using the methods recommended by White and Thompson (2005)[3]: Given the potential for EMR data to be missing not at random (MNAR), the missing indicator method will be adopted as the preferred approach.
b. **Missing/censored primary outcome data:** In the absence of codes indicating death or leaving the participating practice, patients with no EMR-recorded treatment failure will be assumed to be event free at the end of the 12-month trial period, and will be censored at 365 days for analysis purposes.
c. **Missing/censored secondary/exploratory outcome data:** In the absence of codes indicating death or leaving the participating practice, patients with no EMR-recorded data for a secondary/exploratory outcome will be censored at 365 days for analysis purposes.

2.3.4. Confounding handling approach

Due to concerns regarding the potential impact of overadjustment of treatment effects, three pre-specified confounders were used (age, baseline exacerbation rate, and baseline adherence to inhaled therapy). Adherence will be included as a confounder, as this will not be accounted for in the selection of control patients.

2.3.5. Analysis for primary outcome

Time to treatment failure will be determined at the individual patient level, with standard errors adjusted for clustering of patients within the same practice. The primary comparison of study arms will be based on the intention-to-treat principle including all patients identified as suitable and accepting of new technology. A time-to-event analysis will be performed to analyse the association between intervention and time to first outcome event (treatment failure) with censoring at loss to follow-up or end of study-defined follow-up period (365 days). Kaplan-Meier curves will be used to

describe and compare event-free survival over time. Cox regression, with random effects (gamma distribution) for the practice and fixed effects for the stratification factors used in the randomisation algorithm, will be performed with time to the first event as the outcome variable to estimate Hazard Ratios (HR). The analysis will include adjustment for age, baseline exacerbation rate and baseline adherence to inhaled therapy. The proportional hazard assumption will be evaluated visually by means of a log-log plot of survival. If the assumptions of proportional hazards are not met, or cannot be addressed using stratification or time-interaction effects, then the results will be presented using the restricted mean survival time at an appropriate time point.

2.3.6. Analysis for secondary outcomes

Secondary outcomes will be analysed in the primary (ITT) population, using the same samples described above. Negative binomial regression will be used to compare rate of exacerbations over the 12-month trial period, and Cox regression will be used to compare time to first exacerbation. Both analyses will include random effects for the practice and fixed effects for the stratification factors used in the randomisation algorithm, as well as time in study to account for potential drop-out. All models will include adjustment for age, baseline exacerbation rate and baseline adherence to inhaled therapy. Level of significance will be set at 5% for both endpoints.

2.3.7. Analysis for exploratory outcomes

Respiratory-related healthcare resource utilization and costs will be analysed in the primary population, using a linear mixed model to compare the parameters between the two arms. Analysis will be performed on an intention-to-treat basis.

2.3.8. Sensitivity analyses

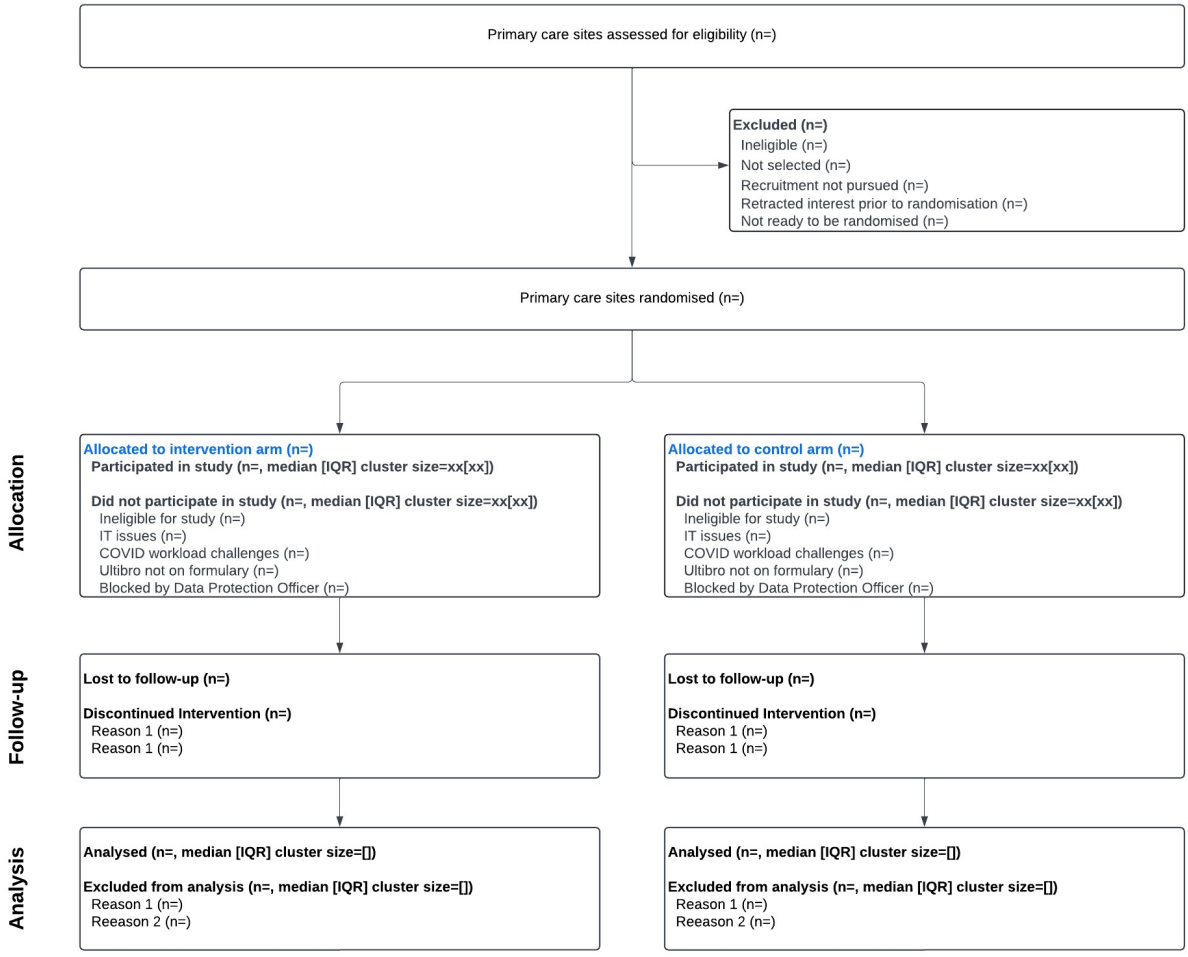
A sensitivity analysis using propensity score weighting (with overlap weights) will be conducted to avoid confounding due to differences in baseline characteristics between intervention and control groups. Propensity scores will be calculated using a logistic regression model based on relevant baseline patient characteristics including age, sex, BMI, smoking status, baseline exacerbations, baseline adherence, time since COPD diagnosis, QRISK, mMRC, individual comorbidities, most recent FEV1, prior minimum FEV1/FVC ratio, highest blood eosinophil count (prior 5 years), baseline number of respiratory consultations, prior vaccination, baseline use of SABA therapy, prior COPD maintenance therapy and type of inhaler. The criterion for achieving covariate balance will be a Standardised Mean Difference <0.1.

2.3.9. Stratified analyses

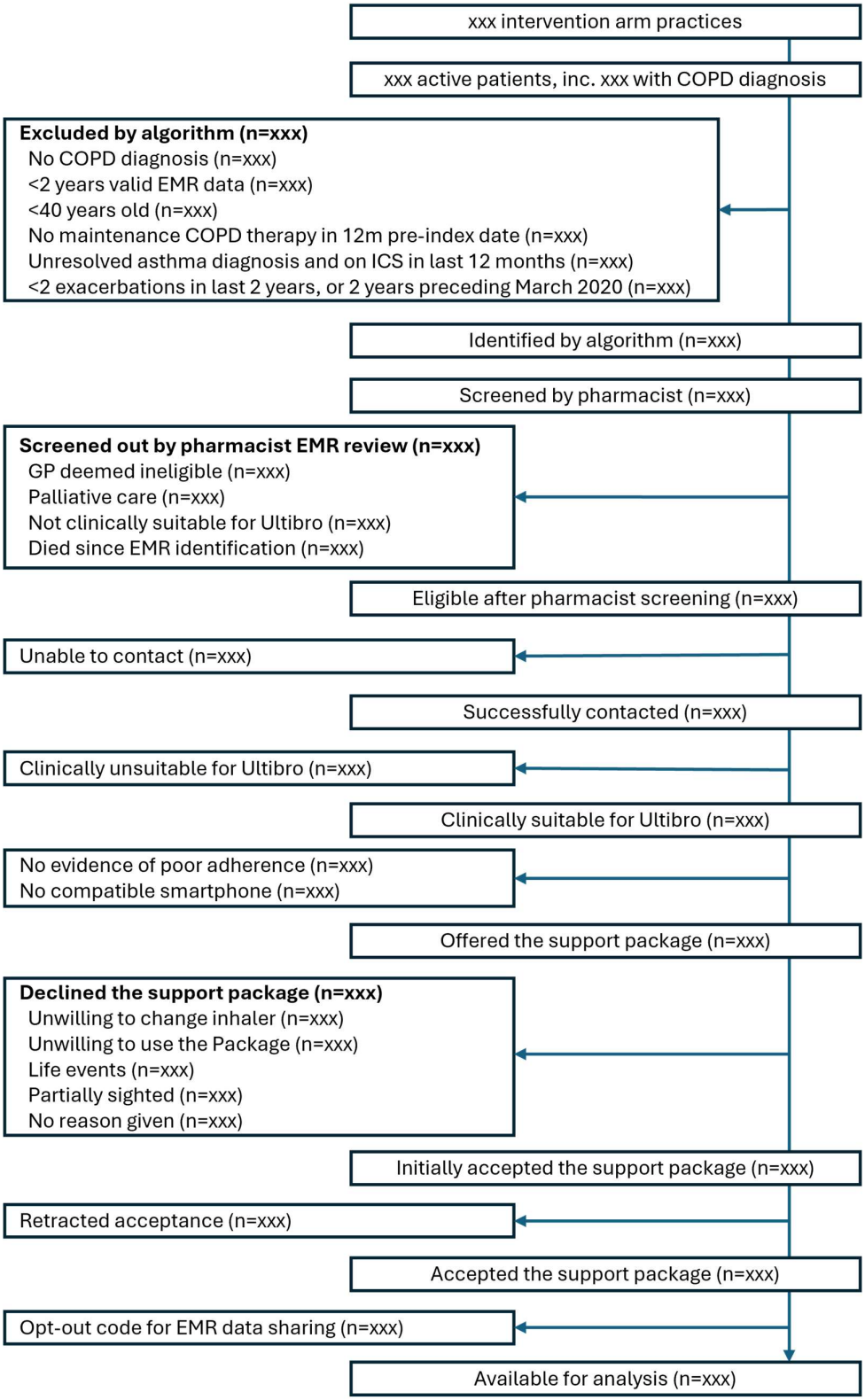
Should the primary analysis identify a statistically significant intervention effect, analyses of the primary outcome (time to treatment failure) and main secondary outcome (rate of moderate/severe exacerbations) will be repeated, stratified by pre-specified baseline characteristics. Treatment effects will be reported by age (<70 years, ≥70 years), FEV_1 (<50%, 50-79%, ≥80%), FEV_1/FVC ratio (<0.7, ≥0.7), number of baseline exacerbations (0, ≥1) and, Cambridge multimorbidity score (<3, ≥3).

3. Tables

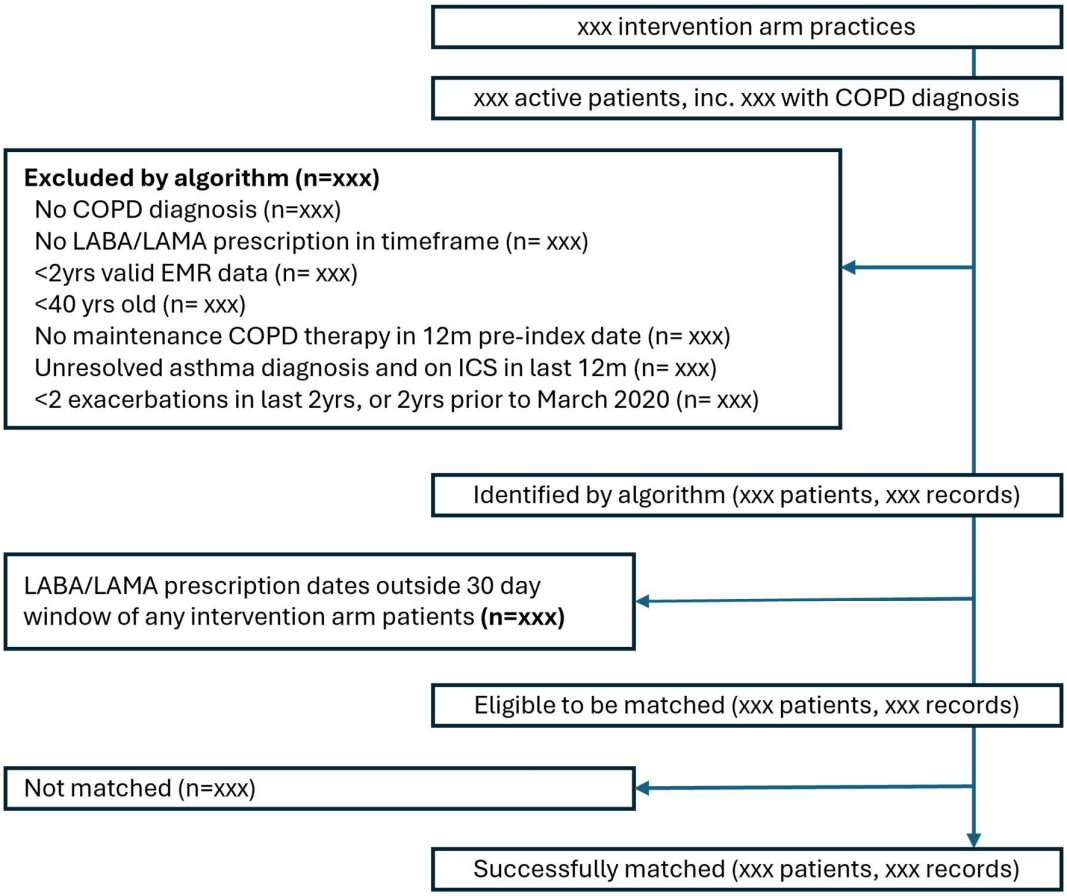
3.1. Practice flow diagram



3.2.Intervention patient flow diagram



3.3.Control patient flow diagram



3.4.Baseline characteristics

	Intervention group (n=xxx)	Control group (n=xxx)
Age in years; mean (SD)		
Age in years; n (%) 40 – 49 50 – 59 60 – 69 70 – 79 ≥80		
Sex; n (%) male		
Ethnicity; n (%) White – British, Irish, other Asian/Asian British Black/Black British Middle Eastern/Middle Eastern British Mixed race Other ethnic group Unknown/Prefer Not to Say Missing		
Smoking status; n (%) Current Ex Missing		
BMI (most recent); n (%) Underweight (<18.5) Normal weight (18.5-24) Overweight (25-29) Obese (≥30) Missing		
Blood eosinophil count (within 2yrs of index date); mean (SD) count 10^9/L		
Blood eosinophil count (within 5yrs of index date); mean (SD) count 10^9/L		
Blood eosinophil count (highest recorded within 5yrs of index date); n (%) <100 cells/µl 100 – 199 cells/µl 200 - 299 cells/µl ≥300 cells/µl None recorded in period		
CAT score; mean (SD) Missing; n (%)		
mMRC; n (%) grade 2-4* Missing; n (%)		
No. respiratory consults in 24m pre-index date; n (%) 0 1 2-3 4-9*		

10 or more*		
Moderate/severe exacerbations in 24m pre-index date n (%) 0 1 2 3 4 5 or more		
No. rescue inhaler prescriptions in 12m pre-index, mean (SD) SABA SAMA		
No. SABA prescriptions in 24m pre-index; n (%) 0-4 5-9 10-14 15 or more*		
Major cardiac ever, n (%) New diagnosis for heart failure Myocardial Infarction Stroke		
QRISK 3 score; mean (SD)		
Spirometry values ever recorded, n (%)		
FEV1 % predicted (most recent prior to index date); mean (SD)		
FEV1/FVC ratio; mean (SD) Missing; n (%)		
Inhaled therapy at index date; n (%) ICS LABA LAMA LABA/LAMA LABA/ICS LAMA/ICS LABA/LAMA/ICS		
Other medication; n (%) Statin ACE inhibitor Angiotensin receptor blocker Calcium channel blocker Beta blocker Atypical antipsychotic Mineralocorticoid receptor antagonist Anticoagulant Antiplatelet Antidiabetic Macrolide Mucolytics		
Vaccination in 12m pre-index; n (%) Pneumococcal		

Influenza Covid-19		
Clinically diagnosed comorbidities (ever), n (%) *Potentially steroid related* Diabetes mellitus type 1 or 2 Osteoporosis Hypertension Chronic kidney disease Depression/Anxiety Obesity Resolved asthma *Other* OSA GERD Rhinitis Dementia Atrial fibrillation Angina Ischemic heart disease Dyslipidemia Peripheral arterial disease Cancer in last 5 years Epilepsy Constipation Rheumatoid arthritis Hearing loss Irritable bowel syndrome Alcohol problems Lupus Migraine Erectile dysfunction Nasal polyps Parkinson's disease Sleep disorder Lung cancer		
Cumulative comorbidities[†]; n (%) 0 1-2 3-4* 5 or more*		
Cambridge multimorbidity score; mean (SD)		
Care home residence; n (%) yes		
Time since COPD diagnosis; mean (SD) years		
Blood pressure in 12m pre-index; mean (SD) Systolic Diastolic		
	Intervention group (n=xxx)	Control group (n=xxx)
Total patient list size; n (%) ≥11314 patients(median for the UK) <11314 patients (median for the UK)		

Index of Multiple Deprivation rank; n (%) ≥12242 (median for the UK) <12242 (median for the UK)		
Proportion of COPD patients with a spirometry-confirmed diagnosis who are receiving treatment; n (%) ≥89.1% (median for the UK) <89.1% (median for the UK)		

* identified as an important covariate in synthetic control analysis

† tally of following: type 1 or 2 diabetes, OSA, IHD, chronic kidney disease, rhinitis, GERD, osteoporosis, anxiety/depression, dementia

3.5.Outcome data

	Intervention group (n=xxx)	Control group (n=xxx)	Test; p value	Effect size (95% CI)
Primary outcomes				
Time to treatment failure[†] (days); median (IQR)				*[Hazard ratio]*
Secondary outcomes				
Rate of exacerbations over the 12-month trial period; mean (SD)				*[Incidence rate ratio]*
Time to first moderate/severe exacerbation during 12-month trial period; n (%)				*[Odds ratio]*
Exploratory outcomes				
Healthcare resource utilisation (per patient/per year); mean (SD)				*[Mean difference]*
ASA package acceptance rate; n (%)		n/a	n/a	n/a

[†] first occurrence of: moderate/severe exacerbation (acute oral corticosteroid prescription or, antibiotics prescribed with evidence of a lower respiratory consultation on the same day or, respiratory-related hospital attendance/admission or, respiratory-related A&E attendance), prescription of ICS, prescription of additional maintenance therapy for COPD (Theophylline or other methylxanthines, long-term oral corticosteroid, PDE4 inhibitors, long-term macrolides, mucolytics or, any other long-term respiratory medication prescribed for COPD) or, all-cause death

References

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2. Leyrat, C., Caille, A., Donner, A. & Giraudeau, B. Propensity scores used for analysis of cluster randomized trials with selection bias: a simulation study. *Stat Med* **32**, 3357–3372 (2013).

3. White, I. R. & Thompson, S. G. Adjusting for partially missing baseline measurements in randomized trials. *Stat Med* **24**, 993–1007 (2005).