Withdrawal of Inhaled Corticosteroids from COPD Patients with Mild or Moderate Airflow Limitation: Primary Care Feasibility Randomised Controlled Trial Reveals High Prevalence of Suspected Undiagnosed Asthma

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Abstract

Background

Inhaled corticosteroids (ICS) are frequently prescribedoutsideguidelines to COPD patients with mild or moderate airflow limitation and low exacerbation risk, despite little evidence of benefit and risk of adverse effects. This trial explored thefeasibilityof ICS withdrawalfrompatients with mild/moderate COPD in primary care.

Methods

Open, feasibility trial. Outcome measures included prevalence of suitable participants, sensitivity and specificity of their identification,their willingness to accept open randomisation to ICS withdrawal for up to 6 months or continuation with usual care.

Results

392 (13%) of 2967COPD patients from 20 practices (209,618 total population)identifiedas eligible for ICS withdrawalby algorithm electronic record search.Following individual record review, 243 (62%)deemedineligible because of (a)one severeor two moderate COPD exacerbations in previous year (86, 22%); (b)severe airflow limitation (65, 17%); (c) asthma (15, 4%); (d)other causes (77, 20%). Remainder (149)invited for assessment.61 attended and all agreed to randomisation to ICS withdrawal or usual care. At baseline assessment, 10 exhibitedairflow reversibility (forced expiratory volume ($FEV)_1$ reversibility>12% and 200ml) which was a safety exclusion criterion, 2 had suffered ≥2 moderate exacerbations in prior year,7 had severe airflow limitation,2 had normal spirometry.40 were randomised.During ensuing 6 months, 1 patient died and another was lost to follow-up. 18 (45%) of the 38 (10 withdrawal, 8 usual care) exhibited previously undocumented FEV_1variability consistent with asthma,supported bysignificant associations in ICS withdrawal group between FEV_1 variability andelevated fractional exhaled nitric oxide (p=0.04), atopic history (p=0.01), elevated symptom score (p=0.04),poorerquality of life (p=0.04).

Conclusion

Identifyingpatients with mild/moderate COPD suitable for ICS withdrawal was difficult because of poor recording of suitability criteria (undocumented exacerbations, unreliable lung function). Open, randomisation to ICS withdrawal or usual care was acceptableFollow-upretention at 6 months was excellent.Nearly 50% of participants with mild/moderate COPD and no previously recorded bronchodilator reversibility, demonstrated FEV_1 variability during follow-up. In patients with mild/moderate COPD considered suitable for ICS withdrawal in primary care, surveillance of variability should be undertaken over at least 6 months.

Trial registration

EudraCT Number: 2016-001876-31. Date registered: 5th August 2016.

Background

Therapy with higher-dosage inhaled corticosteroids (ICS)in combination with long-acting bronchodilators (LABA)reduces the risk of chronic obstructive pulmonary disease (COPD)exacerbations in patients with severe or very severe airflowlimitation (FEV_1<60% predicted).[1]This treatment is at the cost of increased risk of pneumoniaand fractures,[2,3]which add tothe financial burden for health services.[4]Many patients with a diagnosis ofCOPD and FEV_1>60% predicted are also prescribed these medications despite lack of evidence of benefit in randomised controlled trials.[5–7] Uncertainty about the effectiveness of ICS therapy in reducing the risk of COPD exacerbationshas led to interest in the impact of withdrawing this medication across the spectrum of COPD severity.[8,9]Withdrawal of ICS therapy in primary care from those COPD patients unlikely to benefit is acceptable in principle.[10]

International guidelines fail to clarify matters: according to the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[11] ICS therapy should be withdrawn from COPD patients if there are“equivocal effects on exacerbations/symptoms”, a “lack of response”,oran “incorrectoriginal indication forprescription”.Neither the magnitude of, nor the time scale over which these effects should be assessed are defined. Theguidelines of the European Respiratory Society(ERS) list theindications for ICS withdrawal, following exclusion of asthma, as:an absence of a history of a severe acute exacerbation of COPD (AECOPD) or less than two moderate exacerbations in a year or a baseline eosinophil count<300 cells/μL.[12]The ERS guidelines do not define the year in which exacerbations are noted as either the previous year or any year. The positive or negative predictive values of the eosinophil threshold of <300 cells/μLon a single occasion, whether or not a patient is using ICStherapy,have not been established.[13]In both guidelines the indications for withdrawal are based on authoritative consensus arising from evidence of association in post-hoc analyses of uneven quality.[14]

Although withdrawal of ICS therapy fromCOPD patients labelled as suffering from mild or moderate airflow limitation might confer net clinical and financial benefits, there may existsubgroups of these patients in whom continuation of the therapy also confers net benefit. These latter patients may include those witheosinophilic COPD(blood eosinophil count ≥300 cells/μL) andthose with a missed diagnosisof asthma.[15,16]Eosinophilic COPD, proposed as evident in10-15% of the total COPD patient population,[16–18] may reflect co-existing COPD and asthma. These patients manifest greater bronchodilator reversibility, a better response to ICS therapy,elevatedfractional exhaled nitric oxide (FeNO)and are more likely to have a historyofasthma and/or atopy.[16,19]Among COPD patients with a high frequency of exacerbations, an elevatedblood eosinophil count has been associated with an improved response to ICS therapy although the quality of the evidence, derived from post-hoc analyses and observational studies, is inconsistent.[14,20]In the current studywe assessed the feasibility and acceptability of conducting an open randomised controlled trial of withdrawal of inhaled corticosteroids from patients with COPD and mild or moderate airflow limitationand low exacerbation history.

Methods

This was afeasibility trial for an open, randomised controlled clinical trial of withdrawal of ICS therapy from patients with COPD with mild or moderate airflow limitation.Set in primary care in the UK, the feasibility trial was conducted between 2017-2019.Analysis conformed to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for pilot and feasibility trials.[21,22]We have previously reported a qualitative study of the acceptability of the intervention and a study of the method of identifying and recruiting participants.[10,23]Ethical approval for the study was obtained from the National Research Ethics Service,London – London Bridge Committee (16/LO/1696 - IRAS 172251).

Study population, recruitment and randomisation

London (UK) general practices were recruited for the feasibility trial.From a previous study in London,[24] it was anticipated that the required sample would be obtained from at least 10 practices (see sample size calculation in statistical analysis below). Participating practicesconducted analgorithm-based digital search (supplementary data, figure S1) of their electronic patient records for possible eligible patients.Subsequent individual searches of these patients' recordsto confirm likely eligibility were required to confirm a recorded diagnosis of COPD, no recorded diagnosis of asthma, $FEV_1 \geq 50\%$ predicted, fewer than two moderate COPD exacerbations and no history of a severe exacerbation (hospital admission) in the previous year,and regular consumption of ICS therapy(>400mcg/day beclometasone dipropionate or equivalent). Likely eligible patients were invited to a clinical review at their ownpractice. The review wasconducted by a general practitioner (GP)member of the research team (THH) appointed as an honorary clinician in the general practice.The research GP conducted assessments of participants andmanaged prescribing decisions related to the research. Patients were provided in advance with written information and advised that, if suitable, they would be invited to take part in the feasibility trial.At clinical review,patients' histories were assessed; spirometry including bronchodilator reversibility(FEV_1 reversibility >15% and >400ml), as defined in the 2016 Global Initiative for Asthma (GINA) guidelines[25,26] was carried out; counselling about adherence to treatment was provided, and inhaler technique was checked.

Participant inclusion criteria were:age ≥45 years; recorded COPD diagnosis;forced expiratory volume/forced vital capacity (FEV_1/FVC) <0.7; $FEV_1 \geq 50\%$ predicted; current user of ICStherapy ≥400mcg/day beclometasonedipropionate or equivalent, alone or in combination with long-acting bronchodilator therapy,for at least the previous three months; no history of asthma; no evidence of bronchodilator reversibility;fewer than two moderate COPD exacerbations and no history of a severe exacerbation in the previous year;[27]and ICS prescription outside the GOLD guidelines.[11]Exclusion criteria were:active lung cancer; breathlessness due to heart disease; current severe mental illness including depression, psychosis, anxiety; current alcohol or drug dependence; continuous oral steroid use; deemed unsuitable by their GP.Participants provided informed consent. Randomisation with minimisation by age, gender and FEV_1 was carried out to test the acceptability of randomisation to potential participants,

allocation to withdrawal of ICS or usual care, and retention in the study.Randomisation was carried out independently by King's Clinical Trials Unit. All baseline and follow-up assessments were carried out by THH. Allocation was not concealed at assessment because the outcome of the study was feasibility and acceptability. Precise estimates for hypothesis testing were not made as the study was designed as a feasibility trial.

Intervention

Participants allocated to the intervention arm were instructed aboutICS withdrawal while continuingall other current COPD treatment. Control arm participants were instructed to continue on all current COPD treatment. Withdrawal of ICS therapy followed the London Borough of Lambeth Clinical Commissioning Group'sstep-down inhaler guide for COPD (supplementary data, figure S2).[28]Participants in the ICS withdrawal group were telephoned at 2, 4, and 6 weeks after baseline to check on the progress of withdrawal and to assess and record symptoms or events of concern. Each wasinvited for assessment at their GP's surgery at 3 and 6 months after baseline. The baseline measures,except for bronchodilator reversibility testing, were repeated at each assessment. Reports of disease exacerbations were verified by checking the electronic patient records. A moderate exacerbation of COPD was defined as treatment with antibiotics and/or oral corticosteroids in the community and a severe exacerbation as admission to hospital.[29]

Outcome measures and assessment intervals

At baseline, participants completed a questionnaire of demographic and medical details including age, sex, smoking status and pack-year history, evidence of clinical type 1 allergy(hayfever, seasonal or perennial rhinitis, eczema, past severe allergic reaction, or specific allergies), current medication and exacerbation frequency in the previous year.At baseline, 3 and 6 months, the following assessments were carried out:spirometry according to the American Thoracic Society(ATS)/ERS guidance;[30]COPD-specific quality of life with the Chronic Obstructive Pulmonary Disease Assessment Test (CAT)[31] and the Chronic Respiratory Questionnaire Self-Administered Standardised(CRQ-SAS).[32]ACAT score of ≥10 points indicates high symptom burden.[33]The minimum clinically important difference (MCID)in CAT is a score change of ≥2.[31,34]The CRQ-SAS consists of four domain scores: dyspnoea, fatigue, emotional functioning and mastery.[32] The MCID for the CRQ-SAS is a change of ≥0.5 per domain. Participants also completed the Hospital Anxiety and Depression Scale (HADS).A score of ≥11 in either domain suggests the presence of anxiety or depression.[35]

Blood was taken for eosinophil count (absolute cells/ml), and periostinconcentration (ng/ml).Samples were transported within two hours to the local National Health Service hospital pathology laboratory. Eosinophil analysis was carried out within six hours. Samples for periostin were taken into biochemistry tubes, centrifuged and stored at -28°C for batch analysis following the6-month assessment. FeNO levels were assessed with a Circassia NIOX Vero hand-held electrochemical analyser,as recommended by the ERS.[36] Participants were seated, without nose-clip, advised to inhale to their total lung capacity through

the mouthpiece, then exhale, maintaining an appropriate and constant expiratory flow rate by following an animated interface on the analyzer.[36] A FeNO level <25 ppb was considered normal and ≥25 ppb was considered elevated as recommended by the ATS.[37] Each FeNO assessment was repeated three times and a mean reading recorded.

Statistical analysis

The sample size for the feasibility trial was based on anestimation of the prevalence of patients who would deem it acceptable to be randomised to withdraw or continue their ICS therapy. We assumed that 90% of patients who had expressed interest in participating would find randomisation acceptable. At least 75 patients would have given 95% confidence of being within ±7% of the true figure of acceptability if the proportion who found randomisation acceptable was 90%. Data were analysed using SPSS version 27 (IBM, Chicago, USA). Conformity ofthe continuous/parametric outcome measures with a parametric distribution was verified using the Shapiro-Wilk normality test.Parametricallydistributed data are presented as the mean ± standard deviation (SD), and skewed data as the median and interquartile range (IQR). Group comparisons between ICS withdrawal and usual care groups of normally distributed data were analysed using the independent samples t-test. For skewed data, group comparisons were calculated using the Mann-Whitney U test. Categorical variables were compared using the Chi^2 test.

Results

Twenty general practices, with a total patient population of 209,618,took part.A summary of COPD characteristics identified by digital search algorithm in participating practicesis shown in Table 1. Records of the 392 (13.2%) COPD patients identified by the digital searchalgorithmwere reviewed individually (Figure 1). Inconsistencies in diagnosis and exacerbation recording were common.[38] Repeat prescriptions of antibiotics and prednisolone (rescue packs) were often provided without associated evidence of an exacerbation.243 (62%) of the 392 patients identified by the algorithm were ineligible for the trial (Figure 1). 149 eligible patients were invited for clinical review.[23]61 patients attended the review.21 were excluded as a result of characteristics identified at the review, absent from their electronic records. 10 exhibited evidence suggestive of asthma (FEV_1 reversibility >15% and 400ml), 2 had suffered two or more moderate COPD exacerbations in the prior year, 7 had severe airflow limitation and 2 had normal spirometry. 40 were eligible andagreed to be randomisedto withdrawal of ICS therapy or continuation ofusual care.None of these 40 participants demonstrated FEV_1reversibility defined as>15% and >400ml or as>12% and >200ml in the GINA guidelines of 2016[25,26] and 2021[39]respectively, following bronchodilatation. One patient died during the study of an unrelated cause. One patient defaulted from further follow-up after three months.

TABLE 1. COPD characteristics of patients in participant practices

Practice characteristics	Participant practices(n = 20)
Population (mean/practice)	209,628(10,081)
Patients with diagnosis of COPD (%)	2967 (1.42%)
COPD patients with spirometry recorded - %	1999 (67.4%)
COPD patients with FEV_1≥45% in past year	839 (28.3%)
COPD patients taking higher dosage ICS - %	485 (16.35%)
COPD patients with: **Diagnosis of COPD +** **No record FEV_1<45% in past year** **Taking higher dosage ICS +** **No history of asthma**	- - **392 (13.2%)**
COPD patients with: **Diagnosis of COPD +** **FEV_1≥45% in past year,** **Taking higher dosage ICS +** **No history of asthma**	161 (19.2%)

Baseline characteristics of participants

There were no significant differences in the baseline characteristics of the participants allocated tothe ICS withdrawal and usual care arms (*Table2*). All participants were using a combination of inhaled LABA, inhaled long-acting muscarinic antagonist (LAMA) and ICS therapy on entry to the trial.

TABLE 2. Characteristics of participants at baseline

	All participants n=40	ICS withdrawal n=20	Usual care n=20
Age (years): mean (SD)*	70.10 (±9.22)	71.07 (±8.33)	69.19 (±10.16)
Male sex, n (%)†	20 (50%)	10 (50%)	10 (50%)
BMI (kg/m^2) : mean (SD)*	26.40 (±5.29)	26.09 (±5.55)	26.72 (±5.15)
Tobacco Exposure (Pack Years) : mean (SD)*	33.47 (±20.79)	29.83 (±17.96)	37.11 (±23.20)
AECOPD in prior year: mean (SD)*	0.48 (±0.51)	0.50 (±0.51)	0.45 (±0.51)
History of Atopy, n (%)†	65%	75%	55%
FEV_1 (L): mean (SD)*	1.86 (±0.53)	1.82 (±0.45)	1.90 (±0.61)
FEV_1 % predicted: mean (SD)*	73.16 (±13.73)	73.53 (±14.12)	72.79 (±13.70)
FEV_1/FVC: mean (SD)*	0.64 (±0.08)	0.65 (±0.07)	0.62 (±0.09)
Currently on LABA+LAMA+ICS (%)†	100%	100%	100%
CAT score: mean (SD)*	15.76 (±7.54)	17.84 (±6.87)	13.68 (±7.79)
CRQ dyspnoea score: median (IQR)**	5.33 (4.25-6.48)	5.25 (4.60-6.50)	5.60 (4.00-6.35)
CRQ fatigue score: mean (SD)*	4.11 (±1.42)	4.04 (±1.15)	4.18 (±1.69)
CRQ emotional functioning score: mean (SD)*	4.80 (±1.25)	4.81 (±1.06)	4.79 (±1.44)
CRQ mastery score: median (IQR)**	5.63 (4.69-6.56)	5.25 (4.25-6.50)	5.75 (5.00-6.75)
HADS anxiety score: mean (SD)*	6.29 (±3.59)	6.42 (±3.32)	6.16 (±3.93)
HADS depression score: median (IQR)**	4.00 (1.50-5.50)	4.00 (1.00-6.00)	3.50 (1.75-5.75)
Blood eosinophil count ≥300 cells/μL (%)†	8 (20%)	2 (10%)	6 (30%)
Blood eosinophil count (cells/μL): median (IQR)**	200 (100-220)	200 (100-200)	200 (100-300)
FeNO concentration ≥25ppb (%)†	11 (28%)	5 (25%)	6 (30%)
FeNO concentration (ppb): median (IQR)**	15 (9-25)	14 (8-20)	17 (12-26)
Blood periostin concentration (ng/ml): median (IQR)**	27.45 (19.99-60.00)	29.33 (22.53-60.00)	26.06 (16.14-60.00)

inhaled corticosteroids; *t-test; ** Mann-Whitney U-test, †Chi-squared test. SD: standard deviation. IQR: Interquartile range. BMI: Body Mass Index. CAT score: COPD Assessment Test. FEV_1: Post-bronchodilatation Forced Expiratory Volume in 1 second. FVC: Post-bronchodilatation Forced Expiratory Volume. AECOPD: acute exacerbations in COPD. FeNO: Fractional Exhaled Nitric Oxide. CRQ dyspnoea: Chronic Respiratory Disease Questionnaire Self-Administered Standardized Dyspnoea score. LABA: long-acting beta-agonist. LAMA: long-acting muscarinic antagonist. ICS: inhaled corticosteroid. HADS: Hospital Anxiety and Depression Scale. AECOPD: moderate exacerbation of COPD (max of 1 for inclusion in trial).

Characteristics at baseline of all participants, participants allocated to withdrawal from ICS and those allocated to usual care, and outcome of comparisons (Mann-Whitney U or t-test or Chi-squared test) between withdrawal and usual care groups

Acceptability of the trial design, randomisation, and measurements undertaken

The processes of randomisation to withdrawal of ICS therapy or usual care, and the withdrawal of ICS therapy itself were acceptable to participants (*Table 3*). All participants either agreed or strongly agreed that the process of randomisation to ICS withdrawal or usual care was acceptable, as were the tests they undertook during each assessment. Theinstructions on ICS withdrawal (for participants in the withdrawal arm), and follow-up telephone calls during ICS withdrawal were found helpful. Of patients withdrawn from ICS therapy, similar numbers reported feeling “better” or “worse”.

Table 3. Acceptability of randomisation and of withdrawal of ICS therapy among participants

Acceptability assessment questions	Strongly agree	Agree	Disagree	Strongly disagree	Not available
All participants					
I was pleased to have a COPD check as part of the trial (n=37)	30 (81%)	7 (19%)	0	0	0
Allocation at random at the start of the trial to continue or to stop my steroid inhaler was acceptable to me (n=38)	29 (76%)	9 (24%)	0	0	0
I found the tests (blood test, breathing test, questionnaires) at each appointment acceptable (n=38)	28 (74%)	10 (26%)	0	0	0
Taking part in this research took up too much of my time (n=38)	0	0	0	24 (63%)	14 (37%)
ICS withdrawal participants only					
I understand the reasons why this trial is being done (n=19)	9 (47%)	10 (53%)	0	0	0
The research team answered my questions satisfactorily (n=19)	10 (53%)	9 (47%)	0	0	0
The telephone calls from the research team to check how I found the withdrawal of my inhaler were helpful (n=19)	12 (63%)	7 (37%)	0	0	0
The instructions on how to reduce the dose of my steroid inhaler were clear (n=19)	10 (53%)	9 (47%)	0	0	0
Stopping my steroid inhaler has made me feel better (n=19)	3 (16%)	6 (32%)	6 (32%)	3 (16%)	1 (4%)
Stopping my steroid inhaler has made me feel worse (n=19)	2 (11%)	5 (26%)	11 (58%)	1 (5%)	0

Measurements at baseline and at 3 and 6 months

38 participants were followed up at 3 and 6 months (*Figure 1*). Four participants in the ICS withdrawal group resumed ICS therapy use after their 3-month review of whom three resumed ICS therapy on medical advicefollowing deterioration of symptoms on objective testing and reductions of 15-36% in their FEV_1 measurements, and one asked to restart despite no change in FEV_1 or other measures. No significant differences between the ICS withdrawal group and the usual care group were seen in any measures at 3- or 6-month reviews (*Table 4*).There was no evidence of reduction in FEV_1, quality of life, breathlessness measures, blood eosinophil count, FeNO, or blood periostinconcentration at 3 or 6 months after

withdrawal of ICS therapyby intention-to-treat analyses.There was no difference in rate of exacerbations between the ICS withdrawal and usual care groups.An eosinophilic COPD subgroup did not emerge from the cohort. There was no evidence of severe adverse events related to withdrawal of ICS therapy.

Table 4 Comparison of withdrawal and usual care groups at 3 and 6 months.

Measure	3 months			6 months		
	Withdrawal n=19	Usual care n=19	p-value	Withdrawal n=19	Usual care n=19	p-value
FEV_1 % predicted: mean (SD)*	70.95 (±18.22)	73.94 (±15.13)	0.59	72.00 (±16.59)	71.63 (±12.63)	0.94
CAT score: mean (SD)*	18.90 (±7.56)	15.24 (±7.64)	0.16	17.16 (±6.78)	16.42 (±9.28)	0.78
CRQ dyspnoea score: median (IQR)**	5.25 (4.40-6.00)	5.80 (4.68-7.00)	0.23	5.40 (5.00-6.20)	6.00 (4.80-6.60)	0.40
CRQ fatigue score: mean (SD)*	3.67 (±1.32)	4.18 (±1.69)	0.32	4.29 (±1.28)	4.44 (±1.65)	0.76
CRQ emotional functioning score: mean (SD)*	4.81 (±1.21)	4.84 (±1.43)	0.94	5.41 (±1.04)	4.81 (±1.67)	0.20
CRQ mastery score: median (IQR)**	5.00 (4.00-5.50)	5.63 (4.81-6.75)	0.06	5.50 (4.00-6.00)	5.75 (4.50-6.75)	0.43
HADS anxiety score: mean (SD)*	5.74 (±3.59)	5.28 (±4.32)	0.73	5.21 (±3.66)	5.47 (±5.05)	0.86
HADS depression score: median (IQR)**	5.00 (1.00-5.00)	5.50 (2.00-7.00)	0.59	4.00 (1.00-5.00)	3.00 (1.00-8.00)	0.99
Blood eosinophil count(cells/µL): median (IQR)**	200(110-300)	300(200-300)	0.31	200(200-300)	200 (190-370)	0.40
FeNO (ppb): median (IQR)**	17.00 (8.50-26.00)	14.00 (9.00-17.00)	0.20	19.00 (13.00-35.50)	13.00 (10.00-18.50)	0.09
Blood periostin concentration (ng/ml): median (IQR)**	28.43 (6.30-60.00)	35.85 (21.96-60.00)	0.27	30.28 (27.03-60.00)	34.02 (24.77-60.00)	0.92

*t-test; ** Mann-Whitney U-test. FEV_1: forced expiratory volume in first second; SD: standard deviation; IQR: interquartile range; CAT: COPD assessment test; FeNO: fractional exhaled nitric oxide. CRQ-SAS: Chronic Respiratory Disease Questionnaire Self-Administered Standardized Dyspnoea, Fatigue, Emotional functioning, Mastery scores. HADS: Hospital Anxiety and Depression Scale.

Lung function, quality of life, breathlessness, blood eosinophil count, fractional exhaled nitric oxide and blood periostin concentration (Mann-Whitney U or t-test)

Variability in FEV_1 (>12% and 200ml) was observed at 3 or 6 months after baseline assessment in 18 (45%) participants, 10 in the ICS withdrawal group and 8 in the usual care group. Exploratory post-hoc analysis (supplementary data, figure S3) identified that, at 3 months after withdrawal of ICS, those patients demonstrating significant variability of the FEV_1following withdrawal of ICS therapy were more likely to report a history of atopy (p=0.01)(Chi-squared test), have elevated FeNO (≥25ppb)(p=0.04) (Mann-Whitney U test), toreport an elevated symptom burden (increase of ≥+2 in CAT score) (p=0.04)(t-test), and to report a significant deterioration in quality of life (decrease of ≥0.5 in CRQ-SAS fatigue domain score) (p=0.04)(t-test). They recorded a deterioration (decrease)in the CRQ-SAS dyspnoea domain score (p=0.04)(Mann-Whitney U test), although this did not reach the threshold for the MCID. These associations were not present at 6 months (except in the case of FeNO), by which time 4 of the patients in the ICS withdrawal group had recommenced ICS therapy as noted above.

Discussion

We have demonstrated that identification of patients with COPD and mild or moderate airflow limitation suitable for a trial of withdrawal of ICS is feasible by suitable screening of primary care records. Eligible patients were happy to be randomised to withdraw ICS therapy under supervision or to continue with usual care. There was high compliance with withdrawal and no indication of associated significant adverse effects, including psychological problems such as withdrawal anxiety, at least for the 6-month period in which they were followed.

Our trial also highlights two major, potential pitfalls with this process which can be avoided with suitable planning. The first pitfall relates to the complexity of identifying, from the patients' medical records, those with indications for continued prescription of ICS therapy. As many as 22% of our patients had a record of exacerbations of COPD, while a further 17% manifested severe airways obstruction, not readily identifiable by an electronic search algorithm. The second pitfall was that almost 50% of our study participants, regardless of whether they continued or discontinued existing ICS therapy, manifestedvariability of FEV_1suggesting benefit from maintaining ICS use according to the current GINA guideline.[39]This was despite the absence of any previous evidence of FEV_1 variability, whether spontaneous or in response to bronchodilators, or any previous history of asthmain their medical records at entryto the trial. In patients with FEV_1 variability, the suspicion of asthma was reinforced, albeit from an unpowered, exploratory analysis, by a history of atopy, elevated FeNO in the exhaled breath and deterioration of symptoms and quality of life after discontinuing ICS therapy. In such patients the suspicion of asthma should be formally explored. These are important considerations when estimating the numbers of patients to be screened, and the screening protocol when identifying patients with true mild/moderate COPD for future clinical trials. In the current trial, these lower-than-expected numbers of recruitable patients reduced the precision of the estimates of biomarkers and outcome measures.

The clearest indication for ICS therapy in COPD patients is reduction of exacerbation risk. In the absence of epidemiological or trial evidence of a causal relationship between ICS therapy and reduction of

exacerbation risk in COPD patients with mild or moderate airflow limitation, our feasibility data suggest that the co-primary outcomes in future trials of withdrawal of ICS therapy from these patients would be best based on a combination of FEV_1 and respiratory specific quality of life. Our data also provide evidence upon which sample size estimates can be made for these primary outcomes. Our confidence in the analysis of association carried out in this trial is limited by the low number of participants.

Practically, and paradoxically, current guidelines may confound the decision to withdraw ICS therapy from those mild/moderate patients with confirmed COPD in whom the benefit/risk ratio of continued therapy is likely to be unfavourable. For example, the GOLD guidelines recommend commencement or withdrawal of ICS treatment for these patientsaccording to whether they have evidence of "≥2 moderate exacerbations or ≥1 severe exacerbation in a year".[11]It is readily apparent that this could easily result in the prescription ofICS therapy either continuously or alternating on and off annually. This situation is further exacerbated by the arbitrary definition of an "exacerbation" in contemporary international guidelines,[27]a moderate exacerbation for example being defined as an *ad hoc* decision by the attending physician to prescribe antibiotics or oral corticosteroids.

The finding of previously undetected airflow variability, suggestive of asthma, in roughly half of the patients identified from their records as suffering from mild/moderate COPDrepresents another significant challenge to primary care clinicians when attempting to withdraw ICS therapy from these patients. Participants with mild asthma and near normal lung function at the time of testing may exhibit "irreversible" airways obstruction on some occasions, as noted in the GINA guidelines.[39]The accuracy of "one off" testing of bronchodilator reversibility for the diagnosis of asthma in patients with borderline airways obstruction is limited.[40,41]Ideally, confirmation of asthma should come from evidence of clear, sustained peak flow variability or a positive methacholine (PC20) challenge.[42]Our data provide preliminary evidence that, in the absence of availability of bronchial hyperresponsiveness testing in primary care, regular monitoring of lung function and symptom burden by the patient and their physician, possibly supplemented by FeNO measurement in the months following ICS withdrawal may be a useful adjunct in identifying those patients who may benefit from ICS therapy. If the diagnosis of asthma is rejected, the potential role of ICS therapy reverts to being primarily governed by the history of COPD exacerbations.[23]

Consistent with our present findings, undiagnosed asthmain many COPD clinical trials and observational studies is suggested by the presence of bronchodilator reversibility in their participants.[43,44]Bronchodilator reversibility was found in 42% of participants in the ISOLDE trial,[44] 54% in the UPLIFT trial[45]and 24% in the ECLIPSE observational study.[46]It was most prevalent in patients with GOLD stage II disease. In a cross-sectional study in primary care,10% of COPD patients had evidence of reversibility of airflow limitation.[43]Reversibility of airflow limitation with a confirmed clinical diagnosis of asthma is an indication for ICS as a first line treatment.[39]

Conclusion

This feasibility trial has demonstrated the practicability and acceptability of the withdrawal of ICS therapy from patients with mild/moderate COPD in primary care. It has highlighted the pitfalls (particularly the complexity and inaccuracy of existing records of lung function and exacerbations and the prevalence ofreversibility in airflow limitation) and provided data that will support recruitment planning and powering of future studies to examine the impact of ICS withdrawal in patients with COPD in primary care.

Abbreviations

COPD: Chronic obstructive pulmonary disease

ICS: Inhaled corticosteroids

RCT: Randomised controlled trial

LABA: Long-acting beta-agonist

LAMA: Long-acting muscarinic antagonist

$FEV_{1:}$ forced expiratory volume

GOLD: Global Initiative for Chronic Obstructive Lung Disease

ERS: European Respiratory Society

AECOPD: Acute exacerbation of COPD

FeNO: fractional exhaled nitric oxide

CONSORT: Consolidated Standards of Reporting Trials

GP: General Practitioner

GINA: Global Initiative for Asthma

FVC: forced vital capacity

ATS: American Thoracic Society

CAT: Chronic Obstructive Pulmonary Disease Assessment Test

CRQ-SAS: Chronic Respiratory Questionnaire Self-Administered Standardised

MCID: minimum clinically important difference

HADS: Hospital Anxiety and Depression Scale

SD: standard deviation

IQR: interquartile range

PC20: positive methacholine

BMI: Body Mass Index

Declarations

Ethics approval and consent to participate

Ethics approval and consent was obtained for this study. Approved by the London Bridge Research Ethics Committee of the NHS Health Research Authority (REC reference: 16/LO/1696).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during this study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests

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Authors' contributions

THH, PW, CC, NH, PM, MT devised the study. THH, PW, GG undertook practice and patient recruitment. THH, PW, GG, CC undertook the analysis. All authors contributed to the write up of the final manuscript. PW provided the original idea for the study. All authors read and approved the final manuscript.

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Monitoring

The study was a Controlled Trial of an Investigational Medicinal Product, subject to monitoring by the Medicines and Healthcare Products Regulation Authority CTA 14523/0267/001-0003.

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Figures

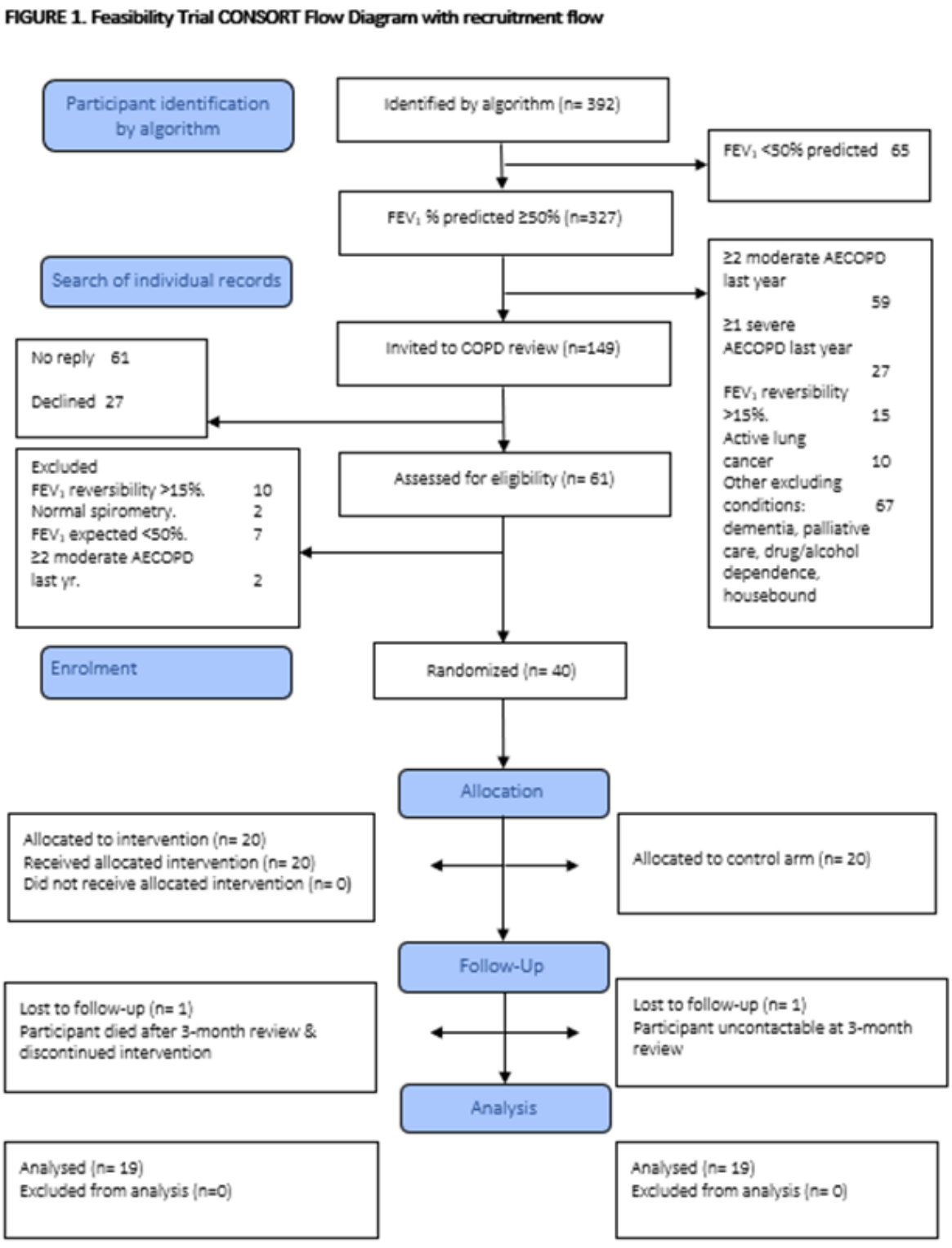

Figure 1

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