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Abstract

Low-dose oral theophylline combined with inhaled corticosteroids for people with chronic obstructive pulmonary disease and high risk of exacerbations: a RCT

Graham Devereux,[1]* Seonaidh Cotton,[2] Shona Fielding,[3] Nicola McMeekin,[4] Peter J Barnes,[5] Andy Briggs,[4] Graham Burns,[6] Rekha Chaudhuri,[7] Henry Chrystyn,[8] Lisa Davies,[9] Anthony De Soyza,[10] Simon Gompertz,[11] John Haughney,[7] Karen Innes,[2] Joanna Kaniewska,[2] Amanda Lee,[3] Alyn Morice,[12] John Norrie,[13] Anita Sullivan,[11] Andrew Wilson[14] and David Price[1,15]

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Background: Despite widespread use of therapies such as inhaled corticosteroids (ICSs), people with chronic obstructive pulmonary disease (COPD) continue to suffer, have reduced life expectancy and utilise considerable NHS resources. Laboratory investigations have demonstrated that at low plasma concentrations (1–5 mg/l) theophylline markedly enhances the anti-inflammatory effects of corticosteroids in COPD.

Objective: To determine the clinical effectiveness and cost-effectiveness of adding low-dose theophylline to a drug regimen containing ICSs in people with COPD at high risk of exacerbation.

Design: A multicentre, pragmatic, double-blind, randomised, placebo-controlled clinical trial.

Setting: The trial was conducted in 121 UK primary and secondary care sites.

Participants: People with COPD [i.e. who have a forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) of < 0.7] currently on a drug regimen including ICSs with a history of two or more exacerbations treated with antibiotics and/or oral corticosteroids (OCSs) in the previous year.

Interventions: Participants were randomised (1 : 1) to receive either low-dose theophylline or placebo for 1 year. The dose of theophylline (200 mg once or twice a day) was determined by ideal body weight and smoking status.

Primary outcome: The number of participant-reported exacerbations in the 1-year treatment period that were treated with antibiotics and/or OCSs.

Results: A total of 1578 people were randomised (60% from primary care): 791 to theophylline and 787 to placebo. There were 11 post-randomisation exclusions. Trial medication was prescribed to 1567 participants: 788 in the theophylline arm and 779 in the placebo arm. Participants in the trial arms were well balanced in terms of characteristics. The mean age was 68.4 [standard deviation (SD) 8.4] years, 54% were male, 32% smoked and mean FEV_1 was 51.7% (SD 20.0%) predicted. Primary outcome data were available for 98% of participants: 772 in the theophylline arm and 764 in the placebo arm. There were 1489 person-years of follow-up data. The mean number of exacerbations was 2.24 (SD 1.99) for participants allocated to theophylline and 2.23 (SD 1.97) for participants allocated to placebo [adjusted incidence rate ratio (IRR) 0.99, 95% confidence interval (CI) 0.91 to 1.08]. Low-dose theophylline had no significant effects on lung function (i.e. FEV_1), incidence of pneumonia, mortality, breathlessness or measures of quality of life or disease impact. Hospital admissions due to COPD exacerbation were less frequent with low-dose theophylline (adjusted IRR 0.72, 95% CI 0.55 to 0.94). However, 39 of the 51 excess hospital admissions in the placebo group were accounted for by 10 participants having three or more exacerbations. There were no differences in the reporting of theophylline side effects between the theophylline and placebo arms.

Limitations: A higher than expected percentage of participants (26%) ceased trial medication; this was balanced between the theophylline and placebo arms and mitigated by over-recruitment (n = 154 additional participants were recruited) and the high rate of follow-up. The limitation of not using documented exacerbations is addressed by evidence that patient recall is highly reliable and the results of a small within-trial validation study.

Conclusion: For people with COPD at high risk of exacerbation, the addition of low-dose oral theophylline to a drug regimen that includes ICSs confers no overall clinical or health economic benefit. This result was evident from the intention-to-treat and per-protocol analyses.

Future work: To promote consideration of the findings of this trial in national and international COPD guidelines.

Trial registration: Current Controlled Trials ISRCTN27066620.

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List of abbreviations

AE	adverse event
AR	adverse reaction
ASSET	Low-dose Theophylline as Anti-inflammatory Enhancer in Severe Chronic Obstructive Pulmonary Disease
ATS	American Thoracic Society
bd	twice a day
BMI	body mass index
BNF	*British National Formulary*
CAT	COPD Assessment Test
CHaRT	Centre for Healthcare Randomised Trials
CHSS	Chest Heart & Stroke Scotland
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CRN	Clinical Research Network
CSRI	Client Service Receipt Inventory
C_{ss}	steady-state concentration
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
EQ-5D-3L	EuroQoL-5 Dimensions, three-level version
ERS	European Respiratory Society
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GLM	generalised linear model
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	general practitioner
HARQ	Hull Airway Reflux Questionnaire
HDAC	histone deacetylase
HR	hazard ratio
HTA	Health Technology Assessment
IBW	ideal body weight
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroid
IL-8	interleukin 8
IQR	interquartile range
IRR	incidence rate ratio
ITT	intention to treat
LABA	long-acting β_2 agonist
LAMA	long-acting muscarinic antagonist
mMRC	modified Medical Research Council
MR	modified release
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OCS	oral corticosteroid
od	once daily
OR	odds ratio
PDE	phosphodiesterase
PI3K	phosphoinositide 3-kinase
PIC	participant identification centre
PIL	participant information leaflet
PPI	patient and public involvement
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
REC	Research Ethics Committee

RR	relative risk	SVC	slow vital capacity
SABA	short-acting β_2 agonist	TSC	Trial Steering Committee
SAE	serious adverse event	TWICS	Theophylline With Inhaled CorticoSteroid
SD	standard deviation		
SE	standard error		

Plain English summary

Chronic obstructive pulmonary disease (COPD) is a long-term lung disease that cannot be cured. The main symptom is shortness of breath on exertion. In the UK, about 1.2 million people have COPD. It is a major cause of death and costs the NHS > £1B a year. Sudden 'flare-ups' of symptoms often need emergency treatment, shorten life expectancy and reduce people's ability to get on with their lives.

Theophylline is a drug that has been around for decades. In the past, it was used in high doses to treat COPD by opening up airways. However, its benefits were limited and it often caused unpleasant side effects. High-dose theophylline has been replaced by drugs administered by inhalers, such as inhaled corticosteroids (ICSs). Recent work in the laboratory and in animal models suggests that, at low dose, theophylline could make ICSs work better in COPD with none of the side effects of high-dose theophylline.

The Theophylline With Inhaled CorticoSteroid (TWICS) trial tested whether or not adding low-dose theophylline reduces flare-ups in people with COPD taking ICSs. A total of 1578 people with COPD from 121 centres all over the UK took part. Participants were randomly divided into two groups: one group took low-dose theophylline and the other took dummy placebo pills. Participants were asked to attend visits at 6 and 12 months.

A total of 791 participants were prescribed low-dose theophylline and 787 were prescribed dummy placebo pills. Although not everyone took the tablets for a whole year, it was possible to count the number of flare-ups in 98% of those taking part. In total, there were 3430 flare-ups. On average, the people taking low-dose theophylline had 2.24 flare-ups and the people taking placebo had 2.23 flare-ups.

Overall, the trial showed that, for people with COPD, taking low-dose theophylline on top of steroid inhalers makes no real difference.

Scientific summary

Background

Chronic obstructive pulmonary disease (COPD) is an incurable lung disease characterised by airway inflammation and progressive airflow limitation; typical symptoms include slowly worsening shortness of breath on exertion, productive cough and wheeze. The progressive airflow limitation of COPD is associated with symptoms becoming increasingly worse, ill health, work absence, disability and premature mortality. In the UK, there are 1.2 million people with diagnosed COPD. It is the fifth leading cause of death, is also a leading cause of emergency hospital admission and costs the NHS in excess of £1B per year.

Acute deteriorations in symptoms, known as exacerbations, are an important clinical feature of COPD; many patients require treatment with antibiotics and/or corticosteroids and the severest exacerbations necessitate hospital admission. Exacerbations are associated with increased ill health and a poorer prognosis and are the most costly aspect of COPD for the NHS. Recent studies have identified a frequent COPD exacerbator (defined as two or more exacerbations in a year) phenotype. Such patients can be reliably identified by patient recall and are highly likely to exacerbate in subsequent years. Despite advances in management, there is still an unmet need for improved pharmacological treatment of COPD, particularly the prevention of exacerbations.

Oral theophylline has been used in the treatment of COPD for > 70 years. Conventionally, theophylline has been used as a bronchodilator; however, in order to achieve modest clinical effects, relatively high blood concentrations (of 10–20 mg/l) are required, which are also associated with a wide range of well-recognised side effects. The availability of more effective inhaled therapies as well as theophylline's narrow therapeutic index, its modest clinical effect and its side effect profile have resulted in current COPD guidelines relegating high-dose theophylline to third-line therapy, although in low- to middle-income countries it is often used earlier in clinical practice.

In recent years, molecular mechanisms contributing to the reduced corticosteroid sensitivity of the airway inflammation of COPD have been elucidated. In vitro and animal models have demonstrated that, at low plasma concentrations (of 1–5 mg/l), there is a marked synergistic effect between theophylline and corticosteroids, with theophylline inducing a 100- to 10,000-fold increase in the suppressive effect of corticosteroids on the release of pro-inflammatory mediators. A number of small exploratory studies of short duration have confirmed that, at low dose, theophylline increases the anti-inflammatory properties of inhaled corticosteroids (ICSs), as evidenced by molecular signatures. Two small, year-long, hospital-based placebo-controlled trials of low-dose theophylline in COPD have reported conflicting results. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) management strategy guideline [GOLD. *Global Strategy for the Diagnosis, Management and Prevention of COPD*. 2017. URL: https://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd (accessed March 2018)] highlights that the clinical relevance of low-dose theophylline has not been fully established and that clinical evidence on low-dose theophylline, particularly on exacerbations, is limited and contradictory.

The Theophylline With Inhaled CorticoSteroid (TWICS) trial was a pragmatic, double-blind, randomised, placebo-controlled clinical trial built on emerging evidence that low-dose (plasma concentration of 1–5 mg/l) theophylline may produce a beneficial synergistic effect in COPD by increasing the corticosteroid sensitivity of the airway inflammation underlying COPD and, as a consequence, reduce the rate of COPD exacerbation when used in conjunction with ICSs.

Objectives

The primary objective was to determine the clinical effectiveness and cost-effectiveness of adding low-dose theophylline to ICS therapy in patients with COPD and a history of two or more exacerbations treated with antibiotic and/or oral corticosteroids (OCSs) in the previous year. The primary clinical outcome was the number of exacerbations in the 1-year treatment period that required treatment with antibiotics and/or OCSs. The primary economic outcome was cost per QALY gained during the 1-year treatment period.

The secondary objectives were to compare the following outcomes between participants treated with low-dose theophylline and those treated with placebo:

- hospital admissions with a primary diagnosis of exacerbation of COPD
- total number of episodes of pneumonia
- total number of emergency hospital admissions
- lung function
- all-cause and respiratory mortality
- drug reactions and serious adverse events (SAEs)
- health-related quality of life
- disease-specific health status
- total inhaled corticosteroid dose/usage
- health-care utilisation
- modelled lifetime incremental cost per quality-adjusted life-year (QALY)
- time to first exacerbation (an additional secondary objective).

Methods

The TWICS trial was a pragmatic, double-blind randomised, placebo-controlled, UK multicentre clinical trial that compared the addition of low-dose theophylline to current COPD therapy that included ICS with the addition of placebo to current COPD therapy that included ICS for 52 weeks, in patients with COPD who had experienced two or more exacerbations in the previous year treated with OCSs and/or antibiotics. The aim was to recruit 1424 participants, with $\geq$ 50% being recruited from primary care.

Inclusion criteria

Participants were people with COPD likely to experience an exacerbation during the 52-week treatment period. The key inclusion criteria were:

- aged $\geq$ 40 years
- smoking history of > 10 pack-years
- predominant respiratory diagnosis of COPD [forced expiratory volume in 1 second (FEV_1)/forced vial capacity (FVC) of < 0.7]
- current use of ICS therapy
- patient report of two or more exacerbations treated with antibiotics and/or OCSs in the previous year.

Exclusion criteria

The key exclusion criteria are listed below. They include concomitant treatment with drugs with the potential to increase plasma theophylline concentration above the low-dose range of 1–5 mg/l:

- severe or unstable ischaemic heart disease
- a predominant respiratory disease other than COPD, including alpha-1-antitrypsin deficiency
- current use of drugs with the potential to increase plasma theophylline.

Participant identification and recruitment

Participants were identified and recruited from both primary and secondary care sites across the UK. Recruitment strategies differed between centres depending on local geographic and NHS organisational factors.

Randomisation/treatment allocation

Participants were randomised using an internet-based computerised randomisation system created and administered by the Centre for Healthcare Randomised Trials (CHaRT) in the University of Aberdeen. Participants were stratified by trial centre/area and recruitment setting (primary and secondary) and then randomised with equal probability to the intervention (low-dose theophylline) or control (placebo) arm.

Intervention

The treatment period was 52 weeks with either 200-mg tablets of Uniphyllin modified release (MR) (Napp Pharmaceuticals Ltd, Cambridge, UK) or a visually identical placebo. Dosing was based on pharmacokinetic modelling incorporating the major determinants of theophylline steady-state concentration, designed to achieve a steady-state plasma theophylline of 1–5 mg/l. The dosing of both the active and placebo drugs was determined by a participant's ideal body weight (IBW) and smoking status:

- 200 mg of Uniphyllin MR once daily (or one placebo once daily) for non-smoking participants, or participants who smoked but had an IBW of $\leq$ 60 kg
- 200 mg of Uniphyllin MR twice daily (or one placebo twice daily) for participants who smoked and had an IBW of > 60 kg.

All supplies of trial tablets were delivered to participants' homes, except for participants recruited in secondary care sites who received their initial 4-week supply from their local clinical trials pharmacy.

Data collection

Outcome data were collected by face-to-face assessments conducted at recruitment/baseline (week 0), 6 months (week 26) and 12 months (week 52). Participants unable to attend the 6- and 12-month assessments were followed up by telephone or home visit, or were sent the questionnaires to complete at home. The key data collected were:

- number of COPD exacerbations requiring antibiotics/OCSs (i.e. moderate/severe exacerbations)
- number of unscheduled hospital admissions
- health-related quality of life [measured using the EuroQol-5 Dimensions, three-level version (EQ-5D-3L)]
- disease-related health status [measured using the COPD Assessment Test (CAT)]

- modified Medical Research Council (mMRC) dyspnoea score
- post-bronchodilator spirometry (FEV_1, FVC)
- health-care utilisation
- adverse reactions and SAEs
- adherence, persistence with trial medication.

Sample size

The sample size was based on the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, which indicated that, in our trial population, the expected mean number of COPD exacerbations within 1 year would be 2.22 [standard deviation (SD) 1.86]. An estimated 669 participants were needed in each trial arm to detect a 15% reduction in COPD exacerbations (i.e. from a mean of 2.22 to 1.89) with 90% power at the 5% significance level. Allowing for 6% loss to follow-up, this was inflated to 712 participants in each trial arm, giving 1424 in total.

Statistical analysis

All analyses were prespecified in the statistical and health economic analysis plan approved in advance of analysis. All analyses were in accordance with the intention-to-treat (ITT) principle, with a per-protocol analysis performed as a sensitivity analysis. The per-protocol analysis excluded participants who were not compliant, with compliance being defined as taking $\geq 70\%$ of their expected doses of trial medication.

Results

Recruitment to the trial took place between 6 February 2014 and 31 August 2016. A total of 1578 people were randomised: 791 to theophylline and 787 to placebo. Participants were recruited in 121 trial sites (88 primary care and 33 secondary care); 941 (60%) participants were identified in primary care. There were 11 post-randomisation exclusions (theophylline, $n = 3$; placebo, $n = 8$). A total of 1567 participants were prescribed trial medication: 788 in the theophylline arm and 779 in the placebo arm. A higher proportion (26%) of participants than the expected 6% ceased their trial medication. To counteract this, recruitment continued beyond 1424 participants in the time available; therefore, the total number recruited was 1578.

The baseline characteristics of the participants allocated to theophylline and placebo were balanced: the mean age was 68.4 (SD 8.4) years, 54% were male, the mean body mass index (BMI) was 27.2 kg/m^2 (SD 6.1 kg/m^2), 31.7% smoked, 80% were using inhaled corticosteroids (ICSs)/long-acting β_2-agonists (LABAs)/long-acting muscarinic antagonists (LAMAs), the mean FEV_1 was 51.7% (SD 20.0%) predicted, 13.6% had very severe airflow obstruction (i.e. FEV_1 of $< 30\%$ predicted), 37.7% had severe airflow obstruction (i.e. FEV_1 of 30–50% predicted), 39.6% had moderate airflow obstruction (i.e. FEV_1 of 50–80% predicted) and 9.2% had mild airflow obstruction (FEV_1 of $> 80\%$ predicted). The mean number of participants reporting exacerbations in the previous year was 3.6 (SD 2.2). CAT scores indicated that COPD had a high impact on participants' lives: the mean CAT score was 22.6 (SD 7.7)] and the mean EQ-5D-3L utility score was 0.63 (SD 0.28).

Intention-to-treat analysis

Primary outcomes

For the ITT analysis, primary outcome data were available for 98% of participants: 772 in the theophylline arm and 764 in the placebo arm. There were 1489 person-years of follow-up data. In total, there were 3430 exacerbations (theophylline; $n = 1727$; placebo, $n = 1703$), the mean number of exacerbations in

participants allocated to theophylline was 2.24 (SD 1.99) and for participants allocated to placebo it was 2.23 (SD 1.97) [unadjusted incidence rate ratio (IRR) 1.00, 95% confidence interval (CI) 0.92 to 1.09; adjusted IRR 0.99, 95% CI 0.91 to 1.08].

As there was no statistically significant difference in the exacerbation rate between treatment arms, the economic analysis was limited to a within-trial analysis. There was a significant difference in unadjusted mean total costs (£452, 95% CI £133 to £771), which were higher in the placebo arm than in the theophylline arm. This was driven by a significant difference in exacerbation costs between arms of £447 (95% CI £186 to £709). This difference was a result of higher costs in the placebo arm for hospitalisations. After adjusting mean costs for baseline characteristics, there was no significant difference between arms in either exacerbation or total costs, although total costs were £222 (95% CI –£27 to £472) higher in the placebo arm.

Adjusted mean QALYs were 0.621 [standard error (SE) 0.006] in the theophylline arm and 0.616 (SE 0.007) in the placebo arm; there was no significant difference between arms. Overall, theophylline dominates placebo, with lower costs and higher QALYs. However, this result is not significant and care should be taken when interpreting it.

Secondary outcomes

There were 319 severe COPD exacerbations treated in hospital: 134 in the theophylline arm and 185 in the placebo arm. The mean number of severe COPD exacerbations treated in hospital was 0.17 (SD 0.49) in the theophylline arm and 0.24 (SD 0.66) in the placebo arm (unadjusted IRR 0.72, 95% CI 0.55 to 0.95; adjusted IRR 0.72, 95% CI 0.55 to 0.94). However, 39 of the 51 excess hospital admissions in the placebo group were accounted for by 10 participants having three or more exacerbations. Low-dose theophylline had no significant effect on non-COPD-related hospital admissions (adjusted IRR 0.99, 95% CI 0.71 to 1.38), episodes of pneumonia (incidence 1.5%, unadjusted IRR 1.55, 95% CI 0.67 to 3.62), FEV_1% predicted (adjusted mean difference –0.56, 95% CI –2.42 to 1.30), CAT score (adjusted marginal mean difference 0.01, 95% CI –0.65 to 0.68), mMRC dyspnoea score [adjusted odds ratio (OR) 1.20, 95% CI 0.88 to 1.63], total mortality (which was 2.5% in the theophylline arm and 1.8% in the placebo arm; $p = 0.400$) or COPD-/respiratory-related mortality (which was 0.9% in the theophylline arm and 1.1% in the placebo arm; $p = 0.762$).

Low-dose theophylline was not associated with a significant increase in adverse reactions (ARs) or SAEs: the percentage of participants reporting ARs was 48.1% in the theophylline arm and 43.9% in the placebo arm ($p = 0.116$), the total number of ARs was 883 in the theophylline arm and 818 in the placebo arm and the percentage of participants reporting SAEs was 13.2% in the theophylline arm and 14.0% in the placebo arm ($p = 0.616$). There were no differences in the profiles of ARs or SAEs between the theophylline and placebo arms.

Per-protocol analysis

Primary outcome

Of the 1578 participants randomised, 1567 were prescribed trial medication, of whom 31 were missing some primary outcome data: 16 in the theophylline arm and 15 in the placebo arm. Adherence/compliance was < 70% for 356 participants: 181 (23.4%) in the theophylline arm and 175 (22.9%) in the placebo arm ($p = 0.802$). The reasons given by participants for ceasing trial medication and the numbers reporting each reason were the same in the theophylline and placebo arms.

For the per-protocol analysis, primary outcome data were available for 1180 (75%) participants, 591 in the theophylline arm and 589 in the placebo arm; there were 1146 person-years of follow-up data. There were 2556 exacerbations: 1298 in the theophylline arm and 1258 in the placebo arm. The mean number of exacerbations in participants allocated to theophylline was 2.20 (SD 1.96), and in participants allocated to placebo it was 2.14 (SD 1.92) (unadjusted IRR 1.02, 95% CI 0.92 to 1.13; adjusted IRR 1.00, 95% CI 0.91 to 1.10).

Secondary outcomes

There were 218 severe COPD exacerbations treated in hospital: 92 in the theophylline arm and 126 in the placebo arm. The mean number of severe COPD exacerbations treated in hospital was 0.16 (SD 0.45) in the theophylline arm and 0.21 (SD 0.61) in the placebo arm (adjusted IRR 0.70, 95% CI 0.50 to 0.97). For the other secondary outcomes, the per-protocol analysis did not differ significantly from the results of the ITT analysis.

Conclusions

This is the first pragmatic, double-blind, randomised, placebo-controlled trial to assess the effectiveness of adding low-dose theophylline to a drug regimen containing ICSs in people with COPD at high risk of exacerbation. The analyses demonstrated that, overall, low-dose theophylline has no clinical or health economic benefit.

Implications for health care

This is the largest trial of low-dose theophylline in COPD to date. National and international COPD guidelines will need to consider the findings of this trial when making recommendations on the treatment of COPD and the prevention of COPD exacerbations.

Recommendations for research

A further study investigating the clinical effectiveness and cost-effectiveness of low-dose theophylline in reducing severe COPD exacerbations requiring admission to hospital needs careful consideration. Such a study would necessarily be very large.

Trial registration

This trial is registered as ISRCTN27066620.

Funding

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Chapter 1 Introduction

Chronic obstructive pulmonary disease (COPD) is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as:

> *a common preventable and treatable disease characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.*
>
> *Global Strategy for the Diagnosis, Management and Prevention of COPD.[1] Reproduced with permission from GOLD. © GOLD 2017*

People with COPD typically present with breathlessness on exertion, a productive cough and wheeze. COPD is usually diagnosed from the age of 40 years onwards and prevalence increases with age.[2] In Westernised countries, COPD is predominantly (80–90%) caused by cigarette smoking,[3] but outdoor air pollution and occupational exposure to dusts, vapours and fumes can be significant contributory factors.[4,5] COPD is closely associated with social deprivation, and makes a major contribution to health inequalities in the UK.[6] The progressive airflow limitation of COPD is associated with increasing disability, work absence, long-term morbidity, common physical and psychological comorbidities and premature mortality. People with COPD are more likely to have associated comorbidities,[7] including ischaemic heart disease,[8] hypertension,[9] heart failure,[10,11] diabetes mellitus,[12] osteoporosis,[13] depression[14] and lung cancer,[15] which increase morbidity and complicate the management of COPD.[7]

Acute deteriorations in symptoms, known as exacerbations, are an important clinical feature of COPD. These are usually precipitated by viral/bacterial infection and/or air pollution and are characterised by increasing breathlessness and/or cough, sputum expectoration and malaise. Many exacerbations are severe enough for patients to seek medical help, which usually takes the form of antibiotics and/or corticosteroids from their general practitioner (GP); more severe exacerbations frequently necessitate admission to hospital for more intensive treatment. Exacerbations are associated with accelerated rate of lung function decline,[16] reduced physical activity,[17] reduced quality of life (QoL),[18] increased mortality[19] and increased risk of comorbidities such as acute myocardial infarction and stroke.[20]

The observational Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study of 2138 COPD patients shed light on factors that influence COPD exacerbations.[21] This study identified a frequent exacerbator (defined as two or more exacerbations in a year) phenotype that affects ≈25% of COPD patients. Patients with this phenotype have an 84% chance of at least one exacerbation in the subsequent year; moreover, this frequent exacerbator phenotype is stable for at least 3 years and can be reliably identified by patient recall. This has been supported by further work demonstrating that the strongest predictor for exacerbations is the number of exacerbations in the preceding year.[22] Frequent exacerbators account for a disproportionate amount of the annual NHS spend on COPD.

The burden of chronic obstructive pulmonary disease on individuals and the NHS

Chronic obstructive pulmonary disease is a major personal and public health burden.[23,24] Data from 591 UK general practices comprising The Health Improvement Network (THIN) indicate that the prevalence of diagnosed COPD in the UK increased from ≈991,000 in 2004 to 1.2 million in 2012.[2] COPD is the fifth leading cause of death in the UK, accounting for ≈5% of all deaths (≈30,000 deaths in 2014). More than 80% of COPD patients, irrespective of disease severity, report a reduced QoL.[24–26] Comorbidities are an important feature of COPD, contributing to ill health and treatment burden. It has been estimated that, in the UK, 33% of people with COPD have hypertension, 19% have ischaemic heart disease, 18% have

depression, 11% have diabetes mellitus and 6% have heart failure.[23] Over 50% of people currently diagnosed with COPD in the UK are < 65 years of age, and 24 million working days are lost each year as a result of COPD, with £3.8B per year being lost through reduced productivity.[23]

Chronic obstructive pulmonary disease costs the NHS > £1B per year. In 2001, average annual NHS direct costs were £819 (> £1300 in severe COPD) for each COPD patient; 60% of this was accounted for by exacerbations and 19% was due to drug costs.[27] The Hospital Episode Statistics database shows that emergency hospital admissions for exacerbations of COPD in the UK have steadily increased as a percentage of all admissions, from 0.5% in 1991 to 1% in 2000 and to 1.5% in 2008/9.[28] In 2008/9, COPD exacerbations resulted in 164,000 hospital admissions in the UK, with an average length of stay of 7.8 days, accounting for 1.3 million bed-days.[28] COPD is the second leading cause of emergency admission to hospital in the UK and is one of the most costly inpatient conditions treated by the NHS.[23,24] At least 10% of emergency admissions to hospital are as a consequence of COPD, and this proportion is even greater during winter. Approximately 25% of patients who have been diagnosed as having COPD are admitted to hospital at some point, and ≈15% of COPD patients are admitted each year.[23,24] Over 30% of patients admitted to hospital with an exacerbation of COPD are re-admitted within 30 days, and an average of 12% of COPD patients die in the year following admission to hospital.[19]

Despite advances in management that have led to the current National Institute for Health and Care Excellence (NICE) COPD guidelines,[24] there is still an unmet need for improved pharmacological treatment of COPD, particularly the prevention of exacerbations.

Standard chronic obstructive pulmonary disease therapy

Standard COPD therapy remains suboptimal. At the time when the Theophylline With Inhaled CorticoSteroid (TWICS) trial was conceived, most international COPD management guidelines recommended the use of inhaled corticosteroids (ICSs) – usually in combination with inhaled long-acting β_2-agonists (LABAs), known as ICS/LABA – to reduce COPD exacerbation rates and to improve lung function and QoL.[1,24] Although more recent guidelines advocate the use of LABAs in combination with long-acting muscarinic antagonists (LAMAs), ICS/LABA and ICS/LABA/LAMA combinations remain major therapeutic options and continue to be used very widely in the treatment of COPD.[29,30] However, when compared with the marked responses observed in asthma, ICSs in COPD fail to fully suppress airway inflammation and patients continue to have exacerbations despite high ICS doses. Furthermore, little or no positive impact of ICS on mortality or disease progression is evident[31,32] and concerns have been raised about long-term sequelae of high-dose ICS use in COPD.[33,34] A relative insensitivity of COPD airway inflammation to the anti-inflammatory effects of high-dose ICS has been demonstrated in induced sputum and airway biopsies of people with COPD.[35–37]

In recent years, molecular mechanisms contributing to the reduced corticosteroid sensitivity of COPD have been elucidated. The chronic airway inflammation of COPD is driven by expression of multiple inflammatory genes regulated by acetylation of core histones, which open up the chromatin structure, allowing transcription factors and ribonucleic acid (RNA) polymerase II to bind to deoxyribonucleic acid (DNA), enabling gene transcription and increased synthesis of inflammatory proteins.[38] In COPD, there is increased acetylation of core histones associated with the promoter regions of inflammatory genes, with the degree of acetylation being positively associated with disease severity.[39] Histone acetylation is reversed by histone deacetylase (HDAC) enzymes. Corticosteroids appear to work by reversing histone acetylation through the recruitment of a specific HDAC called HDAC2,[38,40,41] thereby switching off activated inflammatory genes. In people with COPD, increased histone acetylation appears to be a consequence of markedly reduced HDAC2 activity/expression in airways, lung tissue and alveolar macrophages.[39] It has been shown that the oxidative stress of COPD activates the enzyme phosphoinositide 3-kinase (PI3K)-δ, which then phosphorylates downstream kinases, resulting in the phosphorylation and inactivation of HDAC2.[41,42] The critical role played by reduced HDAC2 in the corticosteroid resistance of COPD is demonstrated by the finding that the corticosteroid resistance of COPD bronchoalveolar macrophages is completely reversed by overexpressing HDAC2 (using a plasmid vector) to levels seen in control patients without COPD.[40]

Low-dose theophylline may have synergistic anti-inflammatory effects with corticosteroids

Oral theophylline has been used in the treatment of COPD for > 70 years, but usually at doses required to achieve relatively high blood concentrations (10–20 mg/l). It has been observed that the reduced HDAC2 activity of COPD can be reversed in a dose-dependent manner by low doses of theophylline; moreover, low-dose theophylline reduces corticosteroid insensitivity in COPD such that there is a marked synergistic interaction between theophylline and corticosteroids in suppressing the release of inflammatory mediators from alveolar macrophages from COPD patients. This in vitro work has shown that at (low) concentrations of 1–5 mg/l theophylline increases HDAC2 activity (sixfold) but at (high) concentrations of over ≈10 mg/l theophylline inhibits rather than stimulates HDAC2 activity.[43,44] These studies show that at concentrations of 1–5 mg/l, there is a marked synergistic effect between theophylline and corticosteroids, with theophylline inducing a 100- to 10,000-fold increase in the suppressive effect of corticosteroids on the release of pro-inflammatory mediators. Such an increase in corticosteroid potency is worthy of clinical interest, particularly if associated with reduced exacerbation rate. An explanation for the ability of low-dose (i.e. 1–5 mg/l) theophylline to increase HDAC activity has been described: it specifically inhibits the enzyme PI3K-δ with consequent restoration of HDAC2 activity to normal in COPD macrophages, rendering them steroid responsive. In mice exposed to cigarette smoke,[42] steroid-resistant lung inflammation has also been found to be reduced by low-dose theophylline when given together with steroids. Similarly, rats exposed to cigarette smoke were found to have markedly decreased lung HDAC2 expression, and that reduced HDAC2 expression was correlated with increased lung destruction index.[45] The increased lung destruction index was restored to normal with ICS treatment in combination with low- (but not high-) dose theophylline. It was concluded that low-dose theophylline might provide protection from cigarette smoke damage and improve the anti-inflammatory effects of steroids by increasing HDAC2 activity.

In human peripheral blood mononuclear cells, corticosteroid insensitivity and reduced HDAC2 activity after oxidative stress have been shown to be reversed with low concentrations of theophylline.[46] In a study of human alveolar macrophages extracted from resected lung samples, the addition of hydrogen peroxide reduced HDAC expression and was associated with an increase in interleukin 8 (IL-8) and matrix metalloproteinase-9 (MMP-9) release.[47] The addition of low-dose theophylline restored HDAC expression to levels above that observed with LABA, ICS and ICS/LABA.

These basic research studies suggest that low-dose (i.e. 1–5 mg/l) theophylline could increase HDAC activity and hence reduce corticosteroid resistance in COPD patients, thereby enabling ICS to switch off inflammation and potentially reduce exacerbation rates more effectively. This is supported by findings from two small randomised controlled trials (RCTs) and a population-based health administration database study. The first RCT in 35 patients with acute COPD exacerbations found that low-dose theophylline increased responsiveness to corticosteroids as measured by increased HDAC activity and further reduced concentrations of pro-inflammatory mediators in induced sputum compared with ICSs alone.[48] In the second small ($n = 30$) pilot RCT of COPD patients, the combination of low-dose theophylline with high-dose ICSs was associated with increased HDAC activity, improved lung function and reduced sputum inflammatory cells and mediators, whereas either drug alone was ineffective.[49] A Canadian health administration database study of 36,492 COPD patients reported that treatment with theophylline alone or in combination with ICS was more protective against exacerbations than treatment with LABA or ICS/LABA [relative risk (RR) 0.89, 95% confidence interval (CI) 0.87 to 0.92].[50]

More recent studies, however, have not replicated the results of earlier studies. Fexer *et al.*[51] used data from a German ambulatory COPD management programme and closely matched 1496 COPD patients commenced on theophylline with 1496 COPD patients not commenced on theophylline. The use of theophylline was associated with an increased likelihood of exacerbation [hazard ratio (HR) 1.41, 95% CI 1.24 to 1.60] and hospital admission (HR 1.61, 95% CI 1.29 to 2.01). Although it was concluded that theophylline is associated with an increased incidence of exacerbations and hospitalisations, it should be noted that this study did not identify those patients on low-dose theophylline.[51] The Spanish Low-dose Theophylline as Anti-inflammatory Enhancer in Severe Chronic Obstructive Pulmonary Disease (ASSET) trial

recruited patients with COPD while hospitalised for a COPD exacerbation and randomised to low-dose theophylline (100 mg twice a day) or matched placebo in addition to usual ICS/LABA treatment.[52] In total, 70 patients were randomised (theophylline, *n* = 36; placebo, *n* = 34) and 46 completed the year of treatment (theophylline, *n* = 23; placebo, *n* = 23). The addition of theophylline had no effect on the COPD exacerbation rate or plasma/sputum concentrations of HDAC and inflammatory mediators. It should be noted that the study was small and designed to detect a 50% reduction in exacerbations.

Conventionally, oral theophylline has been used as a bronchodilator in COPD; however, to achieve modest clinical effects, relatively high blood concentrations (of 10–20 mg/l) are required. The bronchodilator effect of high-dose theophylline is the consequence of inhibition of phosphodiesterase (PDE) and the consequent relaxation of airway smooth muscle. However, non-specific inhibition of PDE by theophylline is also associated with a wide range of well-recognised side effects that may occur within the conventional therapeutic range of plasma theophylline, namely nausea, gastrointestinal upset, headaches, insomnia, seizures, cardiac arrhythmias and malaise. Theophylline toxicity is dose related, and this is an issue with conventional theophylline use because the therapeutic ratio of theophylline is small and most of the beneficial bronchodilator effect occurs when near-toxic doses are given.[53] Theophylline is metabolised by cytochrome P450 mixed function oxidase; as a consequence, theophylline use is further complicated by significant drug interactions with drugs commonly prescribed to people with COPD, for example clarithromycin or ciprofloxacin.[54] The narrow therapeutic index, modest clinical effect and side effect profile of theophylline, together with drug interactions, the need for blood concentration monitoring and the availability of more effective inhaled therapies, have resulted in current COPD guidelines relegating high-dose theophylline to third-line therapy.[1]

The TWICS trial was a pragmatic, double-blind, randomised, placebo-controlled clinical trial that was built on emerging evidence that low-dose (i.e. 1–5 mg/l) theophylline may produce a beneficial synergistic effect in COPD by increasing the corticosteroid sensitivity of the airway inflammation underlying COPD and, as a consequence, reduce the rate of COPD exacerbation when used in conjunction with ICSs.

Hypothesis

The hypothesis being tested was that the addition of low-dose theophylline to ICS therapy in COPD reduces the risk of COPD exacerbation requiring treatment with antibiotics and/or oral corticosteroids (OCSs) during the year of treatment, delivers QoL improvements and is cost-effective.

Objectives

The primary objective of the trial was to determine the clinical effectiveness and cost-effectiveness of adding low-dose theophylline to ICS therapy in patients with COPD and a history of two or more exacerbations treated with antibiotics and/or OCSs in the previous year in relation to the number of exacerbations in the 1-year treatment period requiring therapy with antibiotics and/or OCSs.

The secondary objectives were to compare the following outcomes between participants treated with low-dose theophylline and those treated with placebo:

- hospital admissions with a primary diagnosis of exacerbation of COPD
- total number of episodes of pneumonia
- total number of emergency hospital admissions
- lung function
- all-cause and respiratory mortality
- drug reactions and serious adverse events (SAEs)
- health-related QoL
- disease-specific health status

- total ICS dose/usage
- health-care utilisation
- incremental cost per exacerbation avoided
- lifetime cost-effectiveness based on extrapolation modelling
- modelled lifetime incremental cost per quality-adjusted life-year (QALY).

An additional secondary objective was the time to the first exacerbation of COPD.

Outcomes

Primary outcomes

The primary outcome was the total number of exacerbations of COPD necessitating changes in management (minimum management change: use of OCSs and/or antibiotics) during the 1-year treatment period, as reported by the participant.

The primary economic outcome was cost per QALY gained during the 1-year treatment period.

Secondary outcomes

- Total number of COPD exacerbations requiring hospital admission.
- Total number of episodes of pneumonia.
- Total number of emergency hospital admissions (all causes).
- Lung function [forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC)] post bronchodilator, measured using spirometry performed to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards.
- All-cause and respiratory mortality.
- Serious adverse events and adverse reactions (ARs).
- Total dose of ICS.
- Utilisation of primary or secondary health care for respiratory events.
- Disease-specific health status measured using the COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnoea scale.
- Generic health-related QoL measured using the EuroQoL-5 Dimensions, three-level version (EQ-5D-3L) index.
- Modelled lifetime incremental cost per QALY.

An additional secondary outcome was the time to the first exacerbation of COPD.

Chapter 2 Methods/design

Trial design

The trial protocol has been published in an open-access journal.[55]

The TWICS trial was a pragmatic, double-blind, randomised, placebo-controlled, parallel-arm, UK multicentre clinical trial that compared the addition of low-dose theophylline or placebo for 52 weeks with current COPD therapy that included ICSs in patients with COPD who had experienced two or more exacerbations of COPD in the previous year treated with OCSs and/or antibiotics. The aim was to recruit 1424 participants, with at least 50% recruited in primary care. The trial was approved by Scotland A Research Ethics Committee (REC) (reference number 13/SS/0081) and the Medicines and Healthcare products Regulatory Agency (MHRA) (EudraCT 2013-001490-25, Clinical Trial Authorisation 21583/0218/001). All participants provided written informed consent, which included consent to inform a participant's GP of involvement in the trial and consent to pass on a participant's name and address to a third-party distributer that delivered the trial drug to participants' homes. *Figure 1* provides a schematic representation of the trial design and schedule. Face-to-face trial assessments were carried out at recruitment/baseline and at 6 and 12 months, as shown in *Figure 2*.

The trial was registered on 19 September 2013 as ISRCTN27066620.

Participants

Inclusion criteria

The participants in the TWICS trial were people with COPD who were likely to experience an exacerbation during the 52-week treatment period as evidenced by two or more exacerbations of COPD in the previous

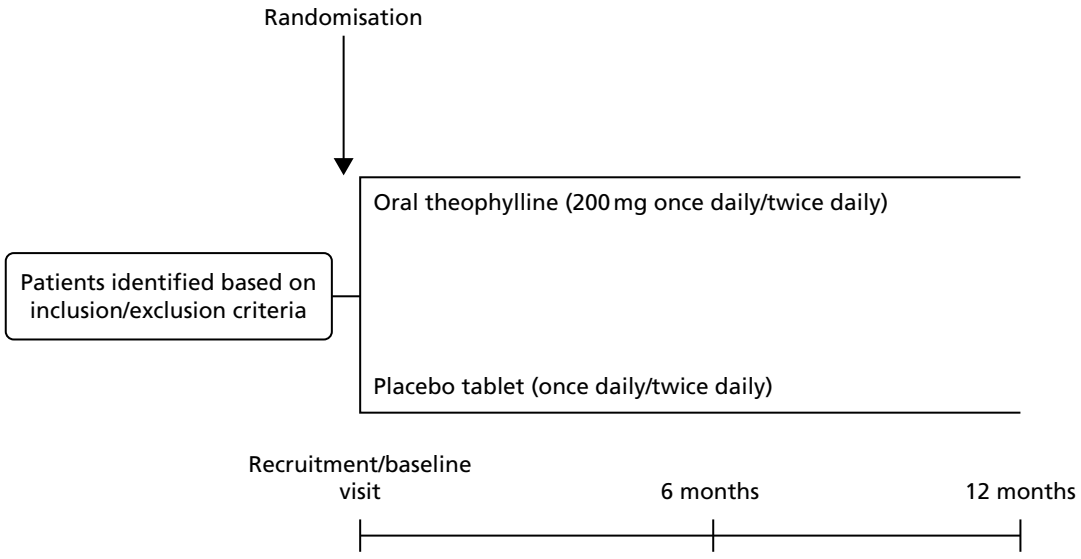

FIGURE 1 Trial design.

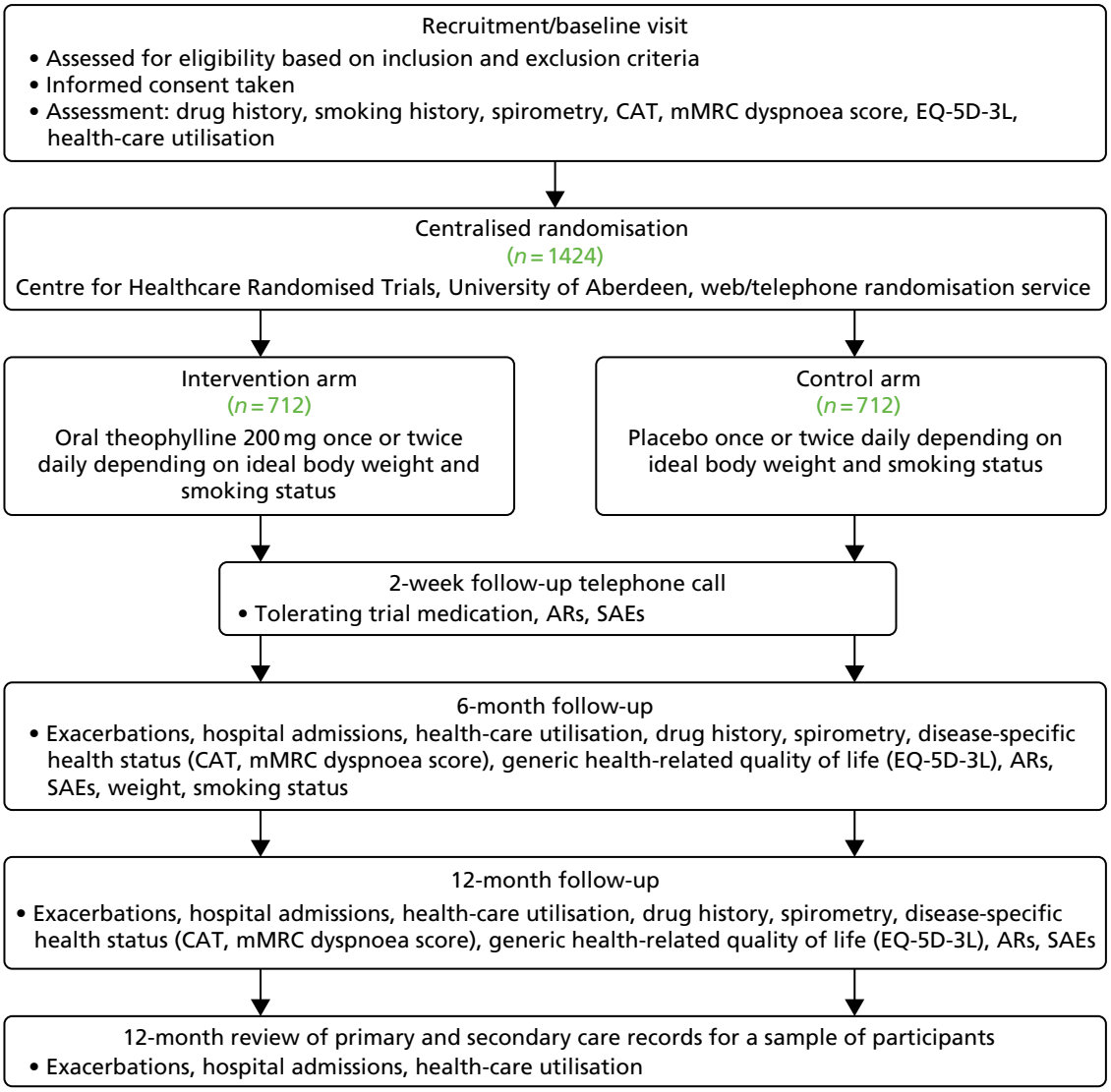

FIGURE 2 Flow diagram of trial schedule.

year treated with OCSs or antibiotics. Participants had to meet all of the following inclusion criteria, which are typical of studies of people with COPD with exacerbations as the primary end point:

- aged ≥ 40 years
- a smoking history of ≥ 10 pack-years
- an established predominant respiratory diagnosis of COPD (GOLD/NICE guideline definition: post bronchodilator FEV_1/FVC of < 0.7)[1,2]
- current use of ICS therapy at the baseline/recruitment visit
- a history of at least two exacerbations requiring treatment with antibiotics and/or OCS use in the previous year, based on patient report
- clinically stable with no COPD exacerbation for at least the previous 4 weeks
- able to swallow trial medication
- able and willing to give informed consent to participate
- able and willing to participate in the trial procedures, undergo spirometric assessment and complete the trial questionnaire.

Potential participants with COPD who did not fulfil the lung function criterion of FEV_1/FVC of < 0.7 at the recruitment/baseline visit were asked to complete a slow vital capacity (SVC) manoeuvre, and FEV_1/SVC of < 0.7 was accepted as evidence of airflow obstruction. Historical evidence of FEV_1/FVC of < 0.7 was deemed acceptable for those participants who did not achieve FEV_1/FVC of < 0.7 or FEV_1/SVC of < 0.7 or who were unable to complete spirometry at the recruitment/baseline assessment. Eligibility for inclusion was confirmed by a medically qualified person.

Exclusion criteria

The exclusion criteria for the TWICS trial were typical of studies of people with COPD but also included criteria specific for theophylline, notably concomitant treatment with drugs that were likely to increase plasma theophylline concentration above the low-dose range of 1–5 mg/l. Potential participants were excluded if they fulfilled any of the following criteria:

- severe or unstable ischaemic heart disease
- a predominant respiratory disease other than COPD
- any other significant disease/disorder that, in the investigator's opinion, put the patient at risk because of trial participation, or might influence the results of the trial or the patient's ability to participate in the trial
- previous allocation of a randomisation code in the trial or current participation in another interventional study [Clinical Trial of an Investigational Medicinal Product (CTIMP) or non-CTIMP]
- women who were pregnant or breastfeeding, or were planning a pregnancy during the trial period
- current medication includes theophylline
- known or suspected intolerance to theophylline
- current use of drugs known to interact with theophylline and/or increase plasma theophylline[54] –
    - antimicrobials: aciclovir, clarithromycin, ciprofloxacin, erythromycin, fluconazole, ketoconazole, levofloxacin and norfloxacin
    - cardiovascular drugs: diltiazem, mexiletine, pentoxifylline and verapamil
    - neurological drugs: bupropion, disulfiram, fluvoxamine and lithium
    - hormonal drugs: medroxyprogesterone and oestrogens
    - immunological drugs: methotrexate, peginterferon alpha and tacrolimus
    - miscellaneous: cimetidine, deferasirox, febuxostat, roflumilast and thiabendazole.

Patients with COPD as a consequence of alpha-1-antitrypsin deficiency were excluded; however, short- or long-term use of azithromycin[56] or use of topical oestrogens or aciclovir were not exclusion criteria.

Identification

Potential participants were recruited from both primary and secondary care sites across the UK. To ensure generalisability, the intention was that the majority of participants (> 50%) would be recruited from primary care. Recruitment strategies differed between centres depending on local geographic and NHS organisational factors.

Primary care and other community-based services

In England, recruitment from general practices was conducted in conjunction with the National Institute for Health Research (NIHR) Clinical Research Network (CRN) at the national and local levels. Practices could participate as independent research sites or as participant identification centres (PICs) for secondary care or other primary care research sites.

In general practices, the local CRN/collaborating recruitment site/trial office liaised directly with practice staff who performed database searches (based on search criteria including the use of inhaled preparations containing corticosteroids, a record of one exacerbation treated with OCSs in the previous year and the

use of interacting medications) to identify potential participants. Potentially suitable patients were sent an invitation letter and a participant information leaflet (PIL). For general practices acting as independent research sites, interested potential participants were invited to contact the practice-based trial team for more information and to arrange a recruitment visit. For general practices acting as PICs, interested potential participants were invited to contact the local trial team at the associated secondary or primary care research site for more information and to arrange a recruitment visit. All invitation material, consent forms, trial case report forms and participant-completed questionnaires can be found on the project web page at www.journalslibrary.nihr.ac.uk/programmes/hta/115815/#/ (accessed 23 April 2019).

In Scotland, the Scottish Primary Care Research Network mirrored the role undertaken by the English CRN by identifying potential participants in primary care, with interested patients being invited to make contact with a local trial team based in secondary care.

Potential participants were also identified from other community COPD services, such as pulmonary rehabilitation, COPD community matrons, smoking cessation services and integrated/intermediate care services for patients with COPD. Potentially suitable participants identified by these services were sent an invitation letter and a PIL, and if interested, participants were asked to contact the local trial team (usually in secondary care) for more information and to arrange a recruitment visit.

Secondary care

Potential participants were also identified from patients attending (or who had previously attended) respiratory outpatient appointments or who had been inpatients at the hospitals of the individual recruiting centres. Potentially suitable patients were sent an invitation letter and a PIL from a member of their hospital care team (usually their consultant). Interested patients were invited to contact the local hospital-based trial team for more information and to arrange a recruitment visit.

Recruitment/baseline visit

At the recruitment visit, a participant's eligibility was confirmed by a medically qualified doctor and fully informed consent was recorded in writing. Baseline data (see *Data collection*) were also collected.

Randomisation/treatment allocation

Participants were randomised, usually by a research nurse, using a computerised randomisation system available as both an interactive voice response telephone system and an internet-based application; the internet application was used for all randomisations within the trial. The randomisation service was created and administered by the Centre for Healthcare Randomised Trials (CHaRT) in the University of Aberdeen. Consenting participants were stratified by trial centre (for participants recruited in secondary care) or area (for participants recruited in primary care) and by where the participant had been identified (primary or secondary care) and then randomised with equal probability to the intervention (low-dose theophylline) and control (placebo) arms.

The random allocation sequence for the TWICS trial was generated using permuted blocks. This provided randomly generated blocks of entries of varying sizes permuted for each combination of trial centre/area and where the participant had been identified (primary or secondary care). Each entry was assigned a treatment according to a randomly generated sequence utilising block sizes of two or four. Each treatment option was assigned an equal number of times within each block, ensuring that the total number of entries assigned to each treatment remained balanced. The sequence of blocks was also random, so it was not possible for anyone to determine the next treatment to be allocated based on previous allocations made during the randomisation process.

It was possible to randomise a participant only if the relevant eligibility criteria had been met. In addition to trial centre/area and where the participant had been identified (primary or secondary care), sex, height, weight, smoking status (and, for smokers, number of cigarettes per day) and date of birth were captured during the randomisation process to calculate the correct dosage of trial medication for that participant and assign an appropriate drug pack.

With this information captured, the randomisation process assigned a trial number (i.e. a participant identification), allocated a treatment and assigned a drug pack. The user/caller was notified of the trial number and drug pack either on screen or during the randomisation telephone call. The allocated treatment remained blinded throughout, with neither the user/caller nor the participant (or anyone involved in the participant's care or the assessment of outcomes) made aware of the allocation. All of the data captured or assigned were saved to a secure database.

The random permuted blocks that defined how treatments were allocated to participants were created by the CHaRT programming team during the system development process. The system built to utilise these permuted blocks was tested by a run of simulated randomisations that allowed the outcomes to be cross-checked and validated. Before the randomisation system went 'live', enough blocks were created to ensure that entries existed for the maximum expected number of participants across the maximum expected number of trial centres/areas. However, the randomisation system was flexible enough to allow the option to add further permuted blocks to the list if more were required during the lifetime of the trial. In such circumstances, randomly generated sequences in blocks of two and four continued to be utilised.

Intervention

The active intervention was 200-mg tablets of Uniphyllin modified release (MR) taken once or twice a day for 52 weeks. The placebo was manufactured to be visually identical, and was also taken once or twice a day for 52 weeks. The packaging and labelling of active and placebo interventions were identical. The intervention was for 52 weeks of therapy. The 200-mg tablets of Uniphyllin MR and placebo were supplied by Napp Pharmaceuticals Ltd (Cambridge, UK). Napp Pharmaceuticals Ltd is the holder of the marketing authorisation for 200-mg tablets of Uniphyllin MR (marketing authorisation number: PL 16950/0066–0068). Uniphyllin Continus 200 mg, 300 mg and 400 mg is licensed for the treatment and prophylaxis of bronchospasm associated with COPD, asthma and chronic bronchitis; consequently, theophylline was administered within licensed indication.[54] Placebo tablets were manufactured by Mundipharma Research Ltd (Cambridge, UK).

Dosage

The pre-clinical studies outlined in *Chapter 1* demonstrate the critical importance of plasma theophylline concentration, with plasma concentrations of 1–5 mg/l having the maximal effect in reducing corticosteroid insensitivity, whereas at concentrations of > 10 mg/l theophylline is inhibitory, augmenting corticosteroid insensitivity. Theophylline dosing in the TWICS trial was based on pharmacokinetic modelling[57–66] of theophylline, incorporating the major determinants of theophylline steady-state concentration (C_{ss}) [i.e. weight, smoking status and clearance of theophylline (i.e. low, normal, high)], and was designed to achieve a C_{ss} plasma theophylline of 1–5 mg/l, and to certainly be < 10 mg/l (> 10 mg is the concentration associated with high-dose theophylline, possible side effects and augmentation of corticosteroid insensitivity). For full details, see *Appendix 1*.

The dosing of both the interventional arm (200-mg tablets of Uniphyllin MR) and the control arm (placebo tablets) was determined by a participant's ideal body weight (IBW) and self-reported smoking status:

- A dose of 200 mg of theophylline MR (one tablet) once daily (or one placebo once daily) was taken by participants who did not smoke, or participants who smoked but had an IBW of ≤ 60 kg.
- A dose of 200 mg of theophylline MR (one tablet) twice daily (or one placebo twice daily) was taken by participants who smoked and had an IBW of > 60 kg.

Ideal body weight was used unless a participant's actual weight was lower than the ideal body weight; in such cases, actual body weight was used to determine dose.

Ideal body weight was calculated using the following standard equations:[67]

$$\text{IBW female} = 45 + [0.9\ (\text{height in cm} - 152)]\ \text{kg}, \quad (1)$$

$$\text{IBW male} = 50 + [0.9\ (\text{height in cm} - 152)]\ \text{kg}. \quad (2)$$

For the calculation of dose, to be classed as a 'non-smoker' at recruitment, a participant must have abstained from smoking for ≥ 12 weeks. Participants who had given up smoking recently (< 12 weeks ago) were classed as smokers.

Protocol-defined changes in dose during the treatment period

Table 1 summarises changes in dose during the treatment period based on changes in smoking status or weight.

Changes in smoking status

Changes in smoking status are known to influence the pharmacokinetics of theophylline (smokers clear the drug more rapidly). Self-reported smoking status was checked at every contact and participants were advised, in writing and verbally, to contact their trial team if their smoking status changed during the treatment period. Participants who stopped smoking during the treatment period were reclassified as 'non-smokers' if they abstained from smoking for ≥ 12 weeks. Smoking participants whose IBW (and actual body weight) was > 60 kg and who stopped smoking had their dose reduced to 200 mg once daily (od) (one tablet once a day); those with an IBW of ≤ 60 kg maintained their 200 mg od dose. Participants who started smoking during the treatment period were reclassified as 'smokers' when they had smoked for ≥ 12 weeks. Non-smoking participants whose IBW (and actual body weight) was > 60 kg and who started smoking had their dose increased to 200 mg twice a day (bd) (one tablet twice a day).

TABLE 1 Protocol-defined changes in dose during the trial

Characteristics at baseline				Changes to smoking during follow-up		Changes to weight during follow-up	
IBW (kg)	ABW (kg)	Smoking status	Initial dose	Change to smoking status	Dose change	Change to weight	Dose change
> 60	> 60	Smoker	bd	Stop smoking	Reduce to od	Lose; ABW now ≤ 60 kg	Reduce to od
> 60	≤ 60	Smoker	od	Stop smoking	No change	Gain; ABW now > 60 kg	Increase to bd
≤ 60	> 60	Smoker	od	Stop smoking	No change	Lose; ABW now ≤ 60 kg	No change
						Gain	No change
≤ 60	≤ 60	Smoker	od	Stop smoking	No change	Gain	No change
> 60	> 60	Non-smoker	od	Start smoking	Increase to bd	Lose; ABW now ≤ 60 kg	No change
						Gain	No change
> 60	≤ 60	Non-smoker	od	Start smoking	No change	Gain	No change
≤ 60	> 60	Non-smoker	od	Start smoking	No change	Lose; ABW now ≤ 60 kg	No change
						Gain	No change
< 60	≤ 60	Non-smoker	od	Start smoking	No change	Gain	No change

ABW, actual body weight; bd twice a day; od, once daily.

Changes in weight

Changes in weight are known to influence the pharmacokinetics of theophylline. Participants who smoked and had an IBW of > 60 kg but an actual body weight of ≤ 60 kg had their dose reduced to 200 mg od. Participants who smoked and had an IBW of > 60 kg but whose actual body weight increased to > 60 kg had their dose increased to 200 mg bd.

Changes in concomitant medication

When informed of their patient's participation in the trial, GPs were advised to manage their patient for exacerbations as per normal clinical practice but to assume that the participant was taking low-dose theophylline. GPs were advised to avoid, whenever possible, prescribing drugs that were likely to increase plasma theophylline concentrations; they were provided with a list of such drugs. In the event that drugs known to increase theophylline concentration had to be prescribed for ≤ 3 weeks, GPs/participants were asked to suspend the trial medication and recommence it after the course of the interacting drug had been completed, for example prescription of clarithromycin for an exacerbation of COPD. If the interacting drug was to be prescribed for > 3 weeks, GPs/participants were asked to discontinue the trial medication but remain in the trial, and were followed up in accordance with the trial protocol.

Participants were asked to carry a trial card and to show this to anyone prescribing medication for them. This advised the prescriber to assume that the participant was taking low-dose theophylline and included a link to the list of drugs that may increase plasma theophylline concentrations.

Theophylline in the form of intravenous aminophylline is sometimes used in the treatment of severe acute exacerbations of COPD in the hospital setting. It was anticipated that, during the trial, some participants would be hospitalised with life-threatening exacerbations of COPD and that the treating physician may wish to use intravenous aminophylline. The commonly used clinical protocol for intravenous aminophylline was established during the era of high-dose oral theophylline, when patients would be prescribed oral theophylline aiming for a plasma concentration of 10–20 mg/l and a loading dose of aminophylline would raise plasma theophylline concentrations to toxic concentrations (i.e. > 20 mg/l). For a patient not established on oral theophylline, the intravenous protocol comprises a bolus of intravenous aminophylline (usually 250 mg, or 5 mg/kg) followed by a maintenance dose (0.5 mg/kg/hour). For a patient established on oral theophylline, the bolus dose is omitted (because of concerns regarding toxicity) and a maintenance infusion (0.5 mg/kg/hour) is commenced. In the era of high-dose theophylline, it was critical to establish if a patient was taking oral theophylline before a physician started a patient on intravenous aminophylline.

Pharmacokinetic modelling of the low-dose theophylline dosing regimen demonstrated that a 250-mg (or 5 mg/kg if a participant's weight was < 50 kg) loading dose of aminophylline could be administered to trial participants and their plasma theophylline would remain within the therapeutic high-dose bronchodilating concentration of 10–20 mg/l (see *Appendix 1*). As per guideline recommendations for plasma theophylline monitoring,[24] we advised that plasma theophylline be measured 24 hours after commencing intravenous aminophylline (allocation status would not be discernible from such a concentration). The trial drug was discontinued during intravenous aminophylline therapy, but restarted after discontinuation of intravenous aminophylline therapy.

The advice regarding use of intravenous aminophylline was summarised on a participant's trial card. In reality, no treating physician contacted the trial team with concerns about intravenous aminophylline.

Supply of trial medication

Each participant received their first bottle of 4 weeks of trial medication (or placebo) from a participating clinical trials pharmacy. For secondary care sites, this was usually the clinical trials pharmacy based at that secondary care site. For participants recruited in primary care study sites, the first bottle of medication was dispensed from the clinical trials pharmacy in NHS Grampian and couriered to a participant's address.

Each participant also received two further supplies of six bottles (each bottle being a 4-week supply). These supplies were dispatched to participants by a third party (AndersonBrecon, Hereford, UK) and delivered to participants' addresses via a courier. These shipments were made around weeks 3 and 27 to enable continuity of supply. Receipt of trial medication to a participant's home address was confirmed by signature on receipt.

Data collection

Baseline, outcome and safety data were collected by face-to-face assessments conducted at recruitment/baseline (week 0), 6 months (week 26) and 12 months (week 52). Participants were telephoned 2 weeks after starting the trial medication to ensure that they were tolerating the medication. The schedule for data collection in the trial is outlined in *Table 2*. If a participant was unable to attend a scheduled follow-up assessment visit because of an acute illness, for example exacerbation of COPD, or other reasons, the visit was postponed and the participant was assessed within 4 weeks of the scheduled assessment visit. Participants unable to attend a face-to-face assessment at 6 and 12 months were followed up by telephone or home visit, or were sent the questionnaires to complete at home.

The following data were collected.

Demographic and clinical data

Demographic, contact, clinical history and, if necessary, clinical examination data were captured at the recruitment visit.

TABLE 2 Schedule of trial assessments

Assessment	Time point				
	Recruitment	2 weeks (telephone)	Month 6 (face to face)	Month 12 (face to face)	Post-study GP records
Assessment of eligibility criteria	✓				
Written informed consent	✓				
Demographic data; contact details	✓				
Clinical history	✓				
Drug history	✓		✓	✓	
Smoking status	✓	✓	✓	✓	
Height	✓				
Weight	✓		✓	✓	
Total number of COPD exacerbations requiring OCSs/antibiotics			✓	✓	✓
Hospital admissions			✓	✓	✓
Health-related quality of life	✓		✓	✓	
Disease-related health status (CAT, mMRC dyspnoea, HARQ)	✓		✓	✓	
Post-bronchodilator lung function	✓		✓	✓	
AEs/drug reactions		✓	✓	✓	
Health-care utilisation	✓		✓	✓	
Patient compliance			✓	✓	

AE, adverse event; HARQ, Hull Airway Reflux Questionnaire.

Drug history

Regular use of prescription drugs was recorded at recruitment and at the 6- and 12-month assessments. ICS use was checked at recruitment and at 6 and 12 months. Many participants brought their repeat prescription list with them to the assessments. Participants were asked how many times a day they used their ICS preparation and the dose.

Smoking history

Smoking history (i.e. age commenced, age ceased and average number of cigarettes smoked per day) and current smoking status were recorded at recruitment, and pack-year consumption was computed. At the 6- and 12-month assessments, current smoking status was recorded.

Height and weight

Height was measured using clinic stadiometers at baseline. Weight was assessed using clinic scales at recruitment and at the 6- and 12-month assessments.

Number of chronic obstructive pulmonary disease exacerbations

The primary outcome measure of the total number of COPD exacerbations requiring antibiotics/OCSs while on trial medication was ascertained at the 6- and 12-month assessments. Participants were encouraged to record any exacerbations in a space provided on the outer packaging (carton) used to ship medication or on the participant follow-up card, and to bring this to their follow-up assessments. If follow-up at 12 months could not be completed, GPs were contacted and asked to provide information on the number of exacerbations experienced by the participant in the treatment period, and whether or not these resulted in hospital admission.

The ATS/ERS guideline definition of COPD exacerbation was used: a worsening of a patient's dyspnoea, cough or sputum beyond day-to-day variability sufficient to warrant a change in management.[55,68] The minimum management change was treatment with antibiotics or OCSs. A minimum of 2 weeks between consecutive hospitalisations or the start of a new therapy was necessary to consider events as separate. A modified ATS/ERS operational classification of exacerbation severity was used for each exacerbation:[68]

- level I – increased use of a short-acting β_2 agonist (SABA) (mild)
- level II – use of OCSs or antibiotics (moderate)
- level III – care by services to prevent hospitalisation (moderate)
- level IV – admitted to hospital (severe).

An exercise to validate patient-reported exacerbations was carried out (see *Appendix 2*).

Hospital admissions

The number of unscheduled hospital admissions while on trial medication was ascertained at the 6- and 12-month assessments. Emergency admissions consequent on COPD were also identified. Participants were encouraged to record any hospital admissions in the space provided on the outer packaging (carton) used to ship medication or on the participant follow-up card, and to bring this to their follow-up assessments. If follow-up at 12 months could not be completed, participants' GP or hospital records were checked to ascertain the number of hospital admissions during the treatment period.

Health-related quality of life

Health-related quality-of-life data were captured at recruitment and at the 6- and 12-month assessments by questionnaire using the EQ-5D-3L index,[69,70] which has been used widely in studies of COPD. The completed instrument can be translated into quality-of-life utilities suitable for calculation of QALYs through the published UK tariffs.[71]

Disease-related health status

Disease-related health status was ascertained at recruitment and at the 6- and 12-month assessments by participant completion of the CAT.[71–74] CAT is an eight-item unidimensional measure of the impact of COPD on a patient's health. CAT has a scoring interval of 0–40, with 0–5 being the norm for healthy non-smokers and > 30 being indicative of a very high impact of COPD on quality of life.[72] CAT is reliable and responsive, correlates very closely with the St George's Respiratory Questionnaire and is preferred because it provides a more comprehensive assessment of the symptomatic impact of COPD and is shorter and, thus, easier to complete.[72–74]

Participants were also asked to grade their breathlessness using the mMRC dyspnoea scale at recruitment and at the 6- and 12-month assessments.[75] The mMRC dyspnoea scale has been in use for many years to grade the effect of breathlessness on daily activities. The mMRC dyspnoea scale is a single question that assesses breathlessness related to activities; the scoring interval is 0–4, with 0 being 'not troubled by breathlessness except on strenuous exercise' and 4 being 'too breathless to leave the house, or breathless when dressing or undressing'. The mMRC score has been validated against walking test performance and other metrics of COPD health status, for example the St George's Respiratory Questionnaire.[76]

In self-selected recruitment centres, the Hull Airway Reflux Questionnaire (HARQ) was completed by participants at recruitment and at 6 and 12 months. HARQ was used to assess symptoms not elucidated by CAT or the mMRC dyspnoea scale. HARQ is a validated, self-administered questionnaire that is responsive to treatment effects.[77]

Post-bronchodilator lung function

Lung function was measured at recruitment and at 6 and 12 months using spirometry performed to ATS/ERS standards.[78] Spirometry is a routine part of the clinical assessment of people with COPD. Post-bronchodilator (LABA within 8 hours, SABA within 2 hours) FEV_1 and FVC were measured. If necessary, lung function was measured 15 minutes after administration of a participant's own SABA. The European Coal and Steel Community predictive equations were used to compute predicted values for FEV_1 and FVC.[79] When spirometry was contraindicated, or participants were not able to complete spirometry, it was omitted.

Health-care utilisation

Health-care utilisation during the previous 6 months was ascertained at recruitment and at the 6- and 12-month assessments using a modified version of the Client Service Receipt Inventory (CSRI).[80] CSRI is a research questionnaire for retrospectively collecting cost-related information about a participant's use of health and social care services.

Adverse reactions and serious adverse events

This trial complied with the UK NHS Health Research Authority guidelines for reporting adverse events (AEs).[81] ARs and SAEs occurring during the 12-month follow-up period were ascertained at the 2-week telephone call and at the 6- and 12-month assessments. Participants were notified of recognised ARs and encouraged to contact their local trial centre if they experienced these.

Hospitalisations for treatment planned prior to randomisation and hospitalisations for elective treatment of pre-existing conditions were not considered, recorded or reported as SAEs. Complications occurring during such hospitalisation were also not considered, recorded or reported as SAEs, unless there was a possibility that the complication arose because of the trial medication (i.e. a possible AR). Exacerbations of COPD, pneumonia or hospital admissions as a consequence of exacerbations of COPD or pneumonia were not considered, recorded or reported as AEs or SAEs because they were primary and secondary outcomes for the trial.

Serious adverse events were assessed as to whether or not the SAE was likely to be related to the treatment using the following definitions:

- unrelated – when an event is not considered to be related to the trial drug
- possibly – although a relationship to the trial drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
- probably – the temporal relationship and absence of a more likely explanation suggest that the event could be related to the trial drug
- definitely – the known effects of the trial drug or its therapeutic class, or based on challenge testing, suggest that the trial drug is the most likely cause.

The reference safety information used to assess whether or not the event was expected was section 4.8 of the Summary of Product Characteristics for theophylline.[54]

Compliance

Compliance/adherence and persistence with trial medication were assessed at the 6- and 12-month assessments. Participants were asked to return empty drug bottles and unused medication; compliance was calculated by pill counting.[82] Participants were deemed to be compliant if they had taken ≥ 70% of the expected doses.

Participant withdrawal

Participants who withdrew from treatment (e.g. because of unacceptable side effects, or because they were prescribed a contraindicated medicine for > 3 weeks) but who agreed to remain in the trial for follow-up were followed up at 6 and 12 months. Those who did not want to attend for clinical follow-up at 6 and 12 months could be followed up by telephone or home visit, or could opt to receive questionnaires at home. Participants who wanted to withdraw from trial follow-up could continue to contribute follow-up data by agreeing to have data extracted from their primary and secondary care medical records.

Sample size

The sample size of 1424 was estimated on the basis of the ECLIPSE study reporting the frequency of COPD exacerbations in 2138 patients.[21] For patients identical to the target population (who in a 1-year period have had at least two self-reported COPD exacerbations requiring antibiotics or OCSs), the mean number of COPD exacerbations within 1 year was 2.22 (SD 1.86).[21] Given a similar rate in the placebo arm, 669 participants were needed in each arm of the trial to detect a clinically important reduction in COPD exacerbations of 15% (i.e. from a mean of 2.22 to 1.89) with 90% power at the two-sided 5% significance level. Allowing for 6% loss to follow-up,[83] this was inflated to 712 participants in each trial arm, giving 1424 in total.

The sample size of 1424 included a 6% loss to follow-up based on a Cochrane Review of oral theophylline in COPD.[83] During the present trial, a higher proportion of participants than expected ceased their trial medication (although most were not lost to follow-up). With the appropriate REC and regulatory approvals, recruitment continued beyond 1424 in the time available, with the total number recruited being 1578 to counteract this loss of person-years on medication. Recruitment ended in August 2016.

Statistical analysis

All analyses were prespecified in the statistical analysis plan, which was approved by both the Trial Steering Committee (TSC) and the Data Monitoring Committee (DMC) in advance of analysis. The statistical analysis

plan can be found on the project web page at www.journalslibrary.nihr.ac.uk/programmes/hta/115815/#/ (accessed 23 April 2019). Unless prespecified, a 5% two-sided significance level was used to denote statistical significance throughout and estimates are presented alongside their 95% CIs. No adjustments were made for multiple testing. All analyses were conducted in accordance with the intention-to-treat (ITT) principle, with a per-protocol analysis performed as a sensitivity analysis. The per-protocol analysis excluded participants who were not compliant, with compliance being defined as taking $\geq$ 70% of their expected doses of trial medication. All analyses were undertaken in Stata® version 14 (StataCorp LP, College Station, TX, USA).

Categorical variables are described with number and percentage in each category. Continuous variables are described with mean and SD if normally distributed and median and interquartile range (IQR) if skewed. The number of missing data is reported for each variable.

Primary outcome

The primary outcome (i.e. the number of COPD exacerbations requiring antibiotics and/or OCSs in the 12-month treatment period following randomisation) was compared between randomised groups using a generalised linear model (GLM) with log-link function, overdispersion parameter and length of time in trial as an offset. The estimated treatment effect is presented as unadjusted rate ratio followed by adjusted rate ratio for a set of prespecified baseline variables. The adjustment variables were centre (as a random effect), where the participant was identified (primary or secondary care), age (in years) centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, number of COPD exacerbations in the previous year, treatment with LAMA/LABA or a combination, and treatment with long-term antibiotics. Participants who did not provide a full 12 months of follow-up information were included to the point at which they were lost to follow-up, with their time in the trial utilised in the offset variable.

Secondary outcomes

The total number of COPD exacerbations requiring hospital admission and the total number of emergency admissions (all causes) were analysed in the same way as the primary outcome. Occurrence of pneumonia during follow-up was analysed with a mixed-effects logit model. QoL measures (i.e. CAT, EQ-5D-3L, HARQ) and lung function (i.e. FEV_1 and FVC) measured at baseline and at the 6- and 12-month follow-ups were compared between groups using a mixed-effects model unadjusted and adjusted for the same prespecified covariate set as described for the primary outcome. Fixed effects included visit number and treatment, with participant and participant–visit interaction fitted as random effects. A treatment–visit interaction was included to assess the differential treatment effect on rate of change in outcome. An autoregressive [AR(1)] correlation structure was used throughout. All participants in the ITT population were included in the analysis and missing outcome data were assumed to be missing at random. Breathlessness as measured by the mMRC dyspnoea scale was analysed using a mixed-effects GLM using a logit link function. All-cause mortality rate and COPD-related mortality and time to first exacerbation were compared between randomised groups using Kaplan–Meier survival curves and Cox regression for adjustment. Total dose of ICS at the end of follow-up and change in total daily dose from baseline were calculated and compared between randomised groups using an independent-samples *t*-test and linear regression for adjustment. The proportion of participants changing medication during the follow-up period was compared using a chi-squared test.

Sensitivity analyses

To assess the impact of death on the treatment effect for the primary outcome, the total number of exacerbations and the number of exacerbations requiring hospital admission, we undertook a sensitivity analysis excluding those participants who died during the trial period. A sensitivity analysis for QoL and lung function was also undertaken by repeating the mixed-effects models on only those participants who survived until the 12-month follow-up.

Prespecified subgroup analysis

The analysis for the primary outcome was repeated for a number of subgroups. The subgroups were age (< 60, 60–69, ≥ 70 years), sex, body mass index (BMI) (< 18.5, ≥ 18.5–< 25, ≥ 25 kg/m^2), smoking status at recruitment (ex-/current smoker), baseline treatment for COPD [triple therapy (ICS/LAMA/LABA), double therapy (ICS/LAMA or ICS/LABA) or single therapy (ICS only)], GOLD stage (I or II, III, IV), number of exacerbations in the 12 months prior to recruitment (2, 3 or 4, ≥ 5), taking OCSs at recruitment (yes/no) and dose of inhaled ICS at recruitment (1600 or ≥ 1600 µg per day of beclomethasone equivalents). A subgroup analysis was undertaken by the addition of a treatment–covariate interaction term and using the 'lincom' command in Stata to obtain group-specific estimates. We report observed mean (SD) exacerbations in each subgroup by treatment group, the treatment effect [incidence rate ratio (IRR) and 99% CIs] along with the *p*-value for the interaction term. We used 99% CIs because of the exploratory nature of the subgroup analysis.

Health economics

Resource use

Health-care resource utilisation during the previous 6 months was collected at the 6- and 12-month assessments using a modified version of the CSRI.[84] The CSRI is a research questionnaire for retrospectively collecting cost-related information about a participant's use of health and social care services. The main resources whose use was collected during the follow-up period were as follows:

- theophylline intervention
- costs of exacerbation treatment; this was broken down into two groups of costs – (1) the location of the treatment, 'home', 'care by services to prevent hospitalisation' and 'admitted to hospital' and (2) the treatment cost of the exacerbations, including medication
- cost of COPD maintenance medications
- other health service use (including inpatient, outpatient and primary care use); none of these included exacerbation costs
- non-COPD emergency hospital admissions
- regular medication.

Baseline resource use was collected for current use of COPD maintenance treatment and regular medication. For calculating baseline resource use and costs, we have assumed use to be for the 6 months prior to baseline. The number of exacerbations needing treatment in the previous 12 months and the number of exacerbations resulting in hospitalisation in the previous 12 months were also collected.

Unit costs

All resource use was valued in Great British pounds (GBP) and indexed to 2016, using the Health Service Cost Index[85] to adjust if necessary.

- Medication costs were obtained from the *British National Formulary* (BNF).[86]
- For exacerbations, non-COPD emergency admissions, inpatient stays, outpatient attendances and primary care, costs were obtained from *NHS Reference Costs 2015 to 2016*,[87] Information Services Division (ISD),[88] Personal Social Services Research Unit (PSSRU),[85] the BNF[86] and papers by Oostenbrink *et al.*[89] and Scott *et al.*[90]

The total cost per participant was calculated by assigning unit costs to resource use for each participant. Total mean costs were calculated using a GLM with a gamma family and clustering for centre number. After multiple imputation, total costs were adjusted for baseline characteristics using standard regression methods, to account for any differences in cost-related variables at baseline.[91]

Unit costs and their sources are presented in *Table 3*.

TABLE 3 Unit costs and sources

Resource	Unit	Unit cost (£)	Source
Intervention			
Theophylline	200 mg od	0.05	BNF[86]
	200 mg bd	0.11	BNF[86]
Exacerbation treatment			
Oxygen	Per day	19	Oostenbrink *et al.*[89]
Medication	Daily dose	Various	BNF[86]
Inpatient costs			
Ward stay (elective)	Bed-day	362	*NHS Reference Costs 2015 to 2016* (elective excess bed-day unit cost)[87]
Ward stay (non-elective)	Bed-day	298	*NHS Reference Costs 2015 to 2016* (non-elective excess bed-day unit cost)[87]
COPD-related ward stay	Bed-day	262	*NHS Reference Costs 2015 to 2016* (weighted average of COPD hospital stays DZ65)[87]
Long stay on ward	Day	133	PSSRU (not-for-profit care home fee: mean £931 per week)[85]
Outpatient costs			
Day case	Day	521	ISD costs book (day cases, all specialties)[88]
Outpatient appointment	Appointment	177	*NHS Reference Costs 2015 to 2016* (total outpatient attendances unit cost)[87]
Primary care costs			
Emergency GP visit	Per contact	86	Based on Scott *et al.*[90] for out-of-hours home visit
Routine GP visit	Per contact	31	PSSRU (including direct care staff costs, without qualifications, 9.22 minutes)[85]
Community/district nurse	Per contact	38	*NHS Reference Costs 2015 to 2016* (Community Health Services – N02AF – district nurse)[87]
Hospital at home team	Per contact	84	*NHS Reference Costs 2015 to 2016* (Community Health Services – N08AF – specialist nursing asthma and respiratory nursing liaison)[87]
GP telephone	Per contact	23.43	PSSRU (including direct care staff costs, without qualification costs, 7.1 minutes)[85]
GP home visit	Per contact	77.22	PSSRU (including direct care staff costs, without qualification costs, 11.4 minutes visit plus 12 minutes of travelling time)[85]
Blood test	Per contact	14.42	ISD costs book[88] (laboratory services, haematology plus practice nurse appointment, PSSRU 2016[85])
Dental service	Per contact	77	*NHS Reference Costs 2015 to 2016* (general dental service attendance)[87]
Hearing aid clinic	Per contact	53	*NHS Reference Costs 2015 to 2016* (audiology)[87]
Occupational therapist	Per contact	79	*NHS Reference Costs 2015 to 2016* (occupational therapist)[87]
Diabetic nurse	Per contact	71	*NHS Reference Costs 2015 to 2016* (specialist nursing, diabetic)[87]
Cardiac nurse	Per contact	81	*NHS Reference Costs 2015 to 2016* (specialist nursing, cardiac)[87]
Long-term condition nurse/community matron	Per contact	89	*NHS Reference Costs 2015 to 2016* (active case management)[87]
Paramedic	Per contact	181	*NHS Reference Costs 2015 to 2016* (ambulance, see, treat, refer)[87]
Chiropodist/community clinic/endoscopy	Per contact	60	*NHS Reference Costs 2015 to 2016* (mean of community health services, no separate chiropodist or community clinic cost)[87]
Physiotherapist	Per contact	49	*NHS Reference Costs 2015 to 2016* (physiotherapist)[87]

TABLE 3 Unit costs and sources (*continued*)

Resource	Unit	Unit cost (£)	Source
Podiatrist	Per contact	40	*NHS Reference Costs 2015 to 2016* (podiatrist)[87]
Practice nurse	Per contact	9.42	PSSRU (practice nurse, 15.5 minutes per contact)[85]
Speech therapist	Per contact	88	*NHS Reference Costs 2015 to 2016* (speech and language therapist)[87]
Nurse telephone call	Per contact	6.10	PSSRU (nurse-led triage)[85]
Treatment room nurse	Per contact	27	*NHS Reference Costs 2015 to 2016* (specialist nursing, treatment room)[87]
Urine sample/sputum test	Per contact	10.28	ISD costs book[88] (clinical chemistry, plus practice nurse appointment, PSSRU[85])
Dietitian	Per contact	81	*NHS Reference Costs 2015 to 2016* (dietitian)[87]
Influenza vaccination	Per contact	14.67	BNF[86] plus practice nurse appointment, PSSRU 2016[85]
Early support discharge	Per contact	124	*NHS Reference Costs 2015 to 2016* (crisis response and early discharge services)[87]
Diagnostic imaging	Per contact	37.3	*NHS Reference Costs 2015 to 2016* (total outpatient attendances, diagnostic imaging)[87]
Optometry	Per contact	79.19	*NHS Reference Costs 2015 to 2016* (total outpatient attendances, optometry)[87]
Health-care assistant	Per contact	6.20	PSSRU 2016 (band 3 nurse, 15.5 minutes)[85]
Talking matters	Per contact	24.06	PSSRU 2009/10 (counselling services in primary care, telephone consultation 29.7 minutes)[92]
Community psychiatric nurse/stroke nurse	Per contact	77	*NHS Reference Costs 2015 to 2016* (other specialist nursing)[87]
Counselling	Per contact	78.27	PSSRU 2009/10 (counselling services in primary care, consultation 96.6 minutes)[92]
Breast care nurse	Per contact	59	*NHS Reference Costs 2015 to 2016* (beast care nursing)[87]
Community mental health team	Per contact	121	*NHS Reference Costs 2015 to 2016* (other mental health specialist team)[87]
Pulmonary rehabilitation	Per contact	78	*NHS Reference Costs 2015 to 2016* (other single condition community rehabilitation teams)[87]
Emergency costs			
Ambulance	Per attendance	236	*NHS Reference Costs 2015 to 2016* (see, treat convey)[87]
Accident and emergency attendance	Per attendance	138	*NHS Reference Costs 2015 to 2016* (emergency medicine average unit cost)[87]

ISD, Information Services Division.

Health outcomes

The economic outcome used was the QALY, a combination of quality and quantity of life. The QoL measure was generated using completed EQ-5D-3L questionnaires. Participants completed the questionnaire at baseline and at 6 months and 12 months.

Patient-reported health-related QoL obtained from EQ-5D-3L questionnaires was valued in terms of utilities (on a scale from –0.59 to 1, where 1 is full health) using a standard UK value set,[71] which were converted into QALYs using standard area under the curve methods; patient utility measurements from each follow-up point were weighted by the time interval between follow-up points. Discrete changes in utility values between follow-up time points were assumed to be linear. After multiple imputation, QALYs were adjusted for baseline characteristics using standard regression methods.

Analysis

The total cost per participant in each intervention was summed and divided by the number of participants in each arm to calculate the total mean cost per participant in each arm, along with the difference in means and a 95% CI.

The mean number of QALYs per participant for each intervention was calculated by summing all participants' QALYs and dividing by the number of participants in that intervention arm. The differences in the means were also calculated, along with a 95% CI.

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in mean costs by the difference in mean QALYs. The NICE threshold of £20,000 to £30,000 per QALY was used when judging whether or not the intervention was cost-effective.[93]

Withdrawn participants were included in the analysis; the total time they spent in the trial was used to adjust total costs and QALYs using regression methods.

To explore the uncertainty around the cost and QALY differences and the resulting ICER, a non-parametric bootstrapping technique was employed with 1000 iterations. The results are presented (see *Figures 7–10*) using a cost-effectiveness plane, showing all 1000 incremental cost-effectiveness pairs, and a cost-effectiveness acceptability curve.

The analysis was carried out using Stata version 14.

Missing data

There was a small amount of multivariate missingness in collected resource data.

Resource use data were not available for some exacerbations because this was not reported by participants or because only limited data were available from GP or hospital records. Missing resource use data on exacerbations were dealt with as follows:

- For exacerbations with missing length of exacerbation data, the length was assumed to be the mean length of exacerbation specific to that treatment arm.
- For exacerbations missing a marker to indicate the location of treatment, this was assumed to be at home, as most locations of treatments were at home (> 80%).
- For exacerbations treated in hospital, missing lengths of stay were assumed to be the length of exacerbation.
- For exacerbations missing treatment costs, a mean cost of treatment, specific to that treatment arm, was assumed.

At a resource use level, there were small numbers of missing data, which were dealt with as follows:

- If the length of stay data were missing for emergency hospital admissions, these were imputed using the mean length of stay specific to that treatment arm.
- If participants had no observations completed to indicate the duration of a COPD maintenance treatment, it was assumed that the treatment duration was the 6 months prior to the date on which the information about the COPD maintenance treatment was collected.
- If a participant indicated that they had received a COPD maintenance treatment but no medication details were available, a mean cost, specific to that treatment arm, was imputed for that specific maintenance medication.
- If resource use data were missing for inpatient, outpatient and primary care service use, the participant was assumed not to have used the resource in question.

Complete cases were analysed initially and multiple imputation was used to explore the effect of missing data on the analysis.

The multiple imputation technique used was multiple imputation by chained equations. Multiple imputation assumes that data are missing at random; missing data may depend on observed data.

Assumptions

The following assumptions were made in the health economics analysis: a complete case is defined as a case with data covering resource use for the 12-month follow-up period. In a small number of participants, there was no 6-month data collection; however, the 12-month data collection covered resource use for the whole of the 12-month follow-up period.

Patient and public involvement

A person with COPD was an independent voting member of the TSC. Initially, this was a patient from the Aberdeen Chest Clinic who was nominated by Chest Heart & Stroke Scotland (CHSS) as part of its Voices Scotland initiative. In 2015, this person had to resign from the TSC because of ill health and was replaced by another patient, who is living with COPD, from the Aberdeen Chest Clinic.

Early versions of the trial protocol and PILs were reviewed by a representative from the British Lung Foundation–North Region and by a person who lives with COPD and attends the chest clinic at the Freeman Hospital, Newcastle. They both attended the trial initiation meeting, purposely held in Newcastle in February 2013, and contributed suggestions and changes to the final trial design that were reflected in the protocol and PIL.

The TWICS trial was publicised in 2014 by a press release that included supportive quotations from the British Lung Foundation and CHSS. This publicity resulted in members of the public with COPD volunteering to participate; with their permission, their details were passed on to their local TWICS trial site.

We anticipate that the patient and public involvement (PPI) member of the TSC will comment on the results letter to be sent to trial participants. It is also anticipated that the publication of the trial results will be co-ordinated with press releases from the participating academic/NHS institutions, the British Lung Foundation and CHSS. Members of the trial team will be participating in local public engagement with research activities.

Protocol amendments

There were seven protocol amendments, which are summarised in *Table 4*.

Trial oversight

A TSC, with independent members, including PPI members, oversaw the conduct and progress of the trial. An independent DMC oversaw the safety of participants in the trial.

Breaches

Breaches of trial protocol or good clinical practice were recorded and reported to the sponsor. A summary of breaches is included in *Appendix 3*. Participants who were the subject of a breach remained in the ITT population, the safety population and the per-protocol population (if compliance criteria were met).

TABLE 4 Summary of protocol amendments

Version number, date	Summary of amendments
Version 2, 20 June 2013	Version initially approved by the REC
Version 3, 5 August 2013	To incorporate clarification of the definition of smoker and non-smoker as required by the MHRA
Version 4, 5 February 2014	• To add episodes of pneumonia as a secondary outcome and to confirm that pneumonia will not be classified as an AE or SAE within the trial • To clarify that, in addition to the trial intervention, participants will receive 'usual NHS care' in the treatment of COPD rather than guideline-compliant care • To clarify that patients with alpha-1-antitrypsin deficiency and COPD should be excluded
Version 5, 2 July 2014	• To clarify when spirometry may be contraindicated • To update the version of the SmPC appended to the protocol • To include the definition of the source data
Version 6, 4 August 2014	• To list additional potential avenues for identification of eligible patients (including smoking cessation clinics, community spirometry clinics and other services for patients with COPD) • To confirm that participants with limited mobility or who live some distance from the trial site can be recruited during a home visit
Version 7, 11 August 2015	• To update the telephone number for the switchboard at Aberdeen Royal Infirmary (for emergency unblinding) • To describe how cases in which medications that potentially interact with theophylline are prescribed to trial participants are documented within the trial
Version 8, 19 May 2016	To amend the protocol to allow for over-recruitment
Version 9, 14 April 2017	• To describe how requests for unblinding made by participants (or their GPs) at the end of their 12-month follow-up should be handled • To revise the planned validation exercise in relation to participant-reported exacerbations

MHRA, Medicines and Healthcare products Regulatory Agency; SmPC, Summary of Product Characteristics.

Chapter 3 Baseline characteristics

Recruitment

Participants were recruited to the trial between February 2014 and August 2016. During this 31-month period, 141 UK sites were opened to recruitment. Once opened, some sites ($n = 20$) failed to recruit any participants to the trial. Reasons for this included staff changeover, lack of eligible patients, competing priorities, practice closure and eligible patients who did not agree to take part.

In total, 1578 participants were recruited from 121 sites (*Table 5*). A detailed summary of recruitment, by site, is given in *Appendix 4*. In summary, across 33 secondary care sites, 1101 participants were recruited, and, across 88 primary care sites, 477 participants were recruited. Of those recruited in secondary care, 464 were identified in primary care. Overall, 59.6% of participants were identified in primary care.

The initial funding included a 24-month recruitment period. Delays in manufacturing and packaging the trial medication led to the projected recruitment being reprofiled across 21 months. After ≈6 months of recruitment, it became clear that we were unlikely to meet the recruitment target within 21 months. To address this, several measures were successfully implemented: 'second'- and 'third'-wave sites were opened earlier than planned; additional primary and secondary care sites were identified and a rolling programme of opening these sites was established; a 6-month extension to recruitment was granted by the funder; and additional recruitment time was accommodated within the existing funding. In the 31-month recruitment period we were granted approval to over-recruit beyond the original target of 1424 participants. The justification for this was the higher than anticipated numbers of participants who ceased taking the trial medication (see *Chapter 4*, *Treatment adherence/compliance*).

Figure 3 shows the original recruitment targets, the reprofiled recruitment targets (to accommodate the delay in manufacturing/packaging), the revised recruitment targets (after the extension to recruitment was granted) and the actual recruitment.

Post-randomisation exclusions

Eleven participants were recruited in error and were then excluded. None of these participants took any dose of trial medication and all are excluded from all trial analyses. Reasons for these post-randomisation exclusions are given in *Table 6*.

Sixteen participants who were recruited into the TWICS trial were subsequently noted to be ineligible for the trial at the point of recruitment. All 16 participants had taken at least one dose of trial medication and were retained in the follow-up and included in the trial analyses. Seven of these were taking a form of diltiazem at recruitment, and were identified during a review of all baseline medication recorded for participants. Diltiazem can cause a slight increase in serum theophylline concentration; however, any effect

TABLE 5 Summary of recruitment

Recruitment site based in	Participants identified in	Number of participants
Secondary care	Secondary care	637
Secondary care	Primary care	464
Primary care	Primary care	477

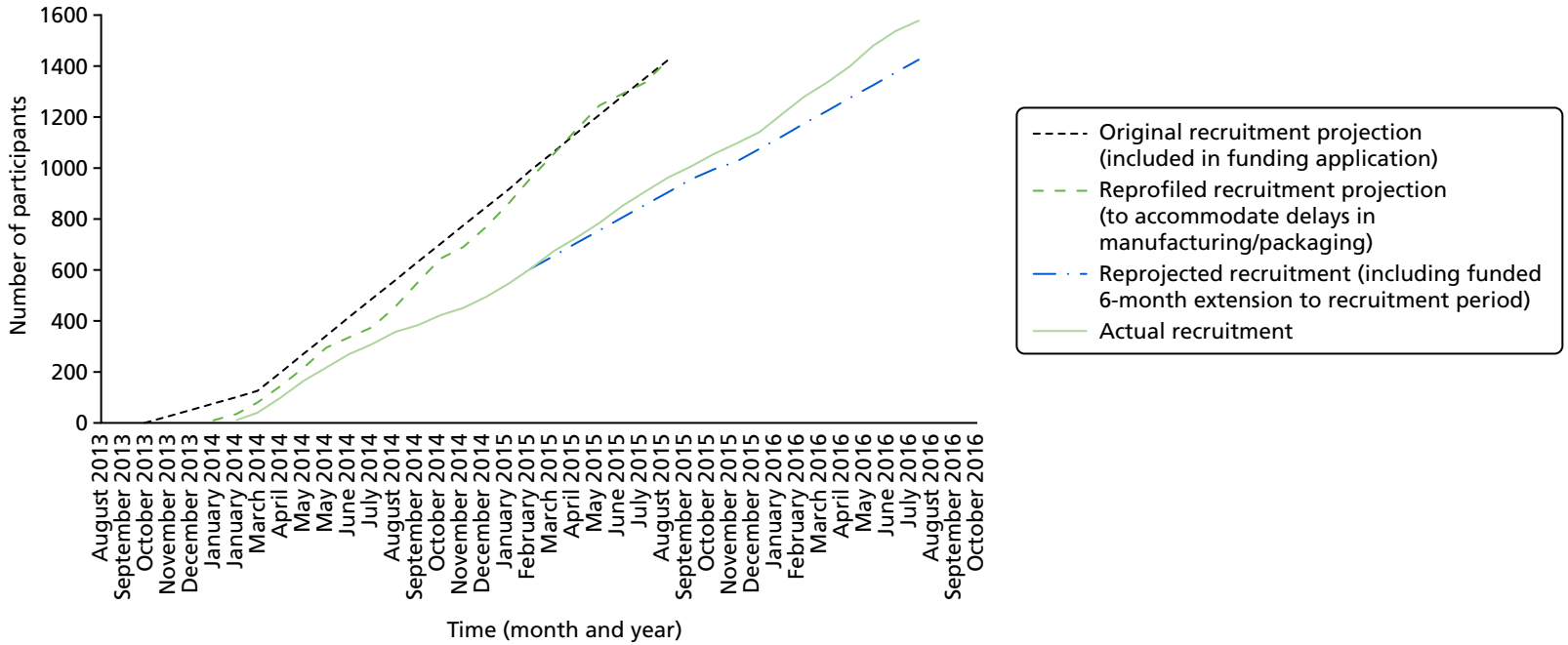

FIGURE 3 Recruitment.

TABLE 6 Reasons for post-randomisation exclusions

Overarching reason	Specific reason
Concomitant medications	Already taking a form of theophylline (*n* = 1)
	Concomitant prescription of diltiazem (*n* = 2)
	Concomitant prescription of methotrexate (*n* = 1)
	Not currently prescribed ICS (*n* = 1)
COPD diagnosis	Diagnosed with right middle lobe collapse, not COPD (*n* = 1)
	COPD diagnosis disputed by consultant (*n* = 1)
	Fewer than two exacerbations in the previous year (*n* = 3)
Spirometry	Did not fulfil spirometric criterion for the trial (*n* = 1)

is usually clinically insignificant.[94] One of these participants took the trial medication for ≈10 days but stopped because they experienced symptoms considered likely to be related to theophylline. A further participant experienced some symptoms that may have been side effects related to the trial medication and stopped after ≈4 months. One further participant experienced some symptoms that may have been side effects related to the trial medication but did not cease taking the trial medication.

In this same review, a further five participants were noted to have been taking a contraindicated medication at baseline. Three participants were noted to be taking a form of oestrogen. Serum theophylline concentration is slightly increased by concomitant oestrogen but no toxicity has been reported.[94] Two participants who were co-prescribed oestrogen continued to take the trial medication through their 12-month follow-up with no ARs. The third participant experienced symptoms (thought to be related to theophylline) and stopped taking the trial medication after 14 days. One participant was noted to have been taking febuxostat at recruitment. They had taken the trial medication through their 12-month follow-up and experienced symptoms that may have been side effects related to the trial medication. High-dose febuxostat has been reported to possibly increase serum theophylline.[94] One participant was noted to have been taking roflumilast at recruitment. Although roflumilast has no reported effect on serum theophylline concentrations, the two drugs act through phosphodiesterase enzymes,[94] albeit theophylline is a phosphodiesterase inhibitor at serum concentrations of 10–20 mg/l when used at 'high-dose' levels. This participant had taken trial medication throughout their 12-month follow-up without any ARs.

Three participants were taking a form of theophylline at recruitment. In two cases, this was noted only after the participant had completed their 12-month follow-up (and the participants had taken the trial medication throughout their 12-month follow-up). In the third case, this was noted after the participant had taken the trial medication for 8 days; the trial medication was then stopped. In all three cases, no ARs relating to the trial medication were noted.

One participant was recruited into the TWICS trial when they were already participating in another CTIMP for an unrelated condition. The participant did not disclose this at the time of recruitment and it was not clearly documented in their hospital notes. No interaction between the TWICS trial medication and the medication used in the other trial is likely. The participant continued to take the trial medication for ≈11 months, at which point the participant ceased taking the trial medication as a result of a non-related throat problem.

Baseline characteristics

Baseline characteristics are presented for the 1567 included participants (after exclusion of the 11 post-randomisation exclusions). The theophylline and placebo groups were well balanced in terms of demographic and disease characteristics at baseline.

The mean age of participants was 68.4 years (SD 8.4 years) (*Table 7*). Just over half of the participants (53.8%) were male. Approximately one-third (31.7%) were current smokers; the remainder were ex-smokers. The median number of pack-years smoked was 42 (IQR 27.7–56.0 pack-years). The mean BMI was 27.2 kg/m^2 (SD 6.1 kg/m^2).

The median number of participant-reported exacerbations in the 12 months prior to recruitment was 3 (IQR 2–4) and the mean number of exacerbations was 3.6 (SD 2.2) (*Table 8*). The majority of participants (79.9%) were prescribed the 'triple therapy' combination of ICS, LABA and LAMA at baseline. Almost one-fifth (16.7%) were prescribed ICS and LABA. The remainder were prescribed ICS only (2.0%) or ICS and LAMA (1.5%).

Comorbidities, as reported by participants, were relatively common. Almost one-fifth of participants (18.3%) had a concurrent diagnosis of asthma. Four per cent of participants reported a diagnosis of bronchiectasis. Just over one-third of participants (38.2%) reported a diagnosis of hypertension. Thirteen per cent reported ischaemic heart disease and 6.7% reported a previous cerebrovascular event. Almost one-third (28.0%) reported anxiety or depression in the previous 5 years. Eleven per cent had a diagnosis of diabetes mellitus and 12.8% had a diagnosis of osteoporosis.

Measurement of lung function at baseline revealed that the mean FEV_1 was 51.7% (SD 20.0%) predicted. Using the GOLD classification,[1] 13.6% were classified as having very severe COPD, 37.7% as having severe COPD, 39.6% as having moderate COPD and 9.2% as having mild COPD.

TABLE 7 Baseline sociodemographic characteristics

Characteristics	Trial arm		Overall
	Theophylline	Placebo	
Sex (*N*, *n*, %)			
Male	788, 425, 53.9	779, 418, 53.7	1567, 843, 53.8
Female	788, 363, 46.1	779, 361, 46.3	1567, 724, 46.2
Age (*n*, mean, SD)	788, 68.3, 8.2	779, 68.5, 8.6	1567, 68.4, 8.4
Smoking status (*N*, *n*, %)			
Current smoker	788, 247, 31.3	779, 249, 32.0	1567, 496, 31.7
Ex-smoker	788, 541, 68.7	779, 530, 68.0	1567, 1071, 68.3
Pack-years (*n*, mean, SD)	785, 47.0, 26.3	775, 47.1, 30.6	1560, 47.1, 28.5
Pack years (*n*, median, IQR)	785, 43.0, 28.5–57.0	775, 41.0, 27.0–55.0	1560, 42.0, 27.7–56.0
BMI (*n*, mean, SD)	788, 27.1, 6.2	779, 27.3, 6.0	1567, 27.2, 6.1
BMI group (*N*, *n*, %)			
Underweight	788, 37, 4.7	779, 38, 4.9	1567, 75, 4.8
Normal	788, 285, 36.2	779, 246, 31.6	1567, 531, 33.9
Overweight	788, 252, 32.0	779, 266, 34.1	1567, 518, 33.1
Obese	788, 214, 27.2	779, 229, 29.4	1567, 443, 28.3

TABLE 8 Baseline clinical characteristics

Characteristics	Trial arm		Overall
	Theophylline	Placebo	
Exacerbations in the previous 12 months			
n, mean, SD	785, 3.6, 2.2	773, 3.5, 2.1	1558, 3.6, 2.2
n, median, IQR	785, 3, 2–4	773, 3, 2–4	1558, 3, 2–4
Exacerbations requiring hospitalisation in the previous 12 months			
n, mean, SD	784, 0.4, 0.8	773, 0.4, 1.0	1557, 0.4, 0.9
n, median, IQR	784, 0, 0–1	773, 0, 0–0	1557, 0, 0–0
GOLD 2011 category (*N*, *n*, %)			
C: two or more exacerbations in the previous year, mMRC dyspnoea score of 0–1 and CAT score of < 10	779, 37, 4.7	768, 45, 5.9	1547, 82, 5.3
D: two or more exacerbations in the previous year, mMRC dyspnoea score of ≥ 2 and CAT score of ≥ 10	779, 742, 95.3	768, 723, 94.1	1547, 1465, 94.7
FEV_1% predicted (*n*, mean, SD)	785, 51.3, 20.1	771, 52.2, 19.8	1556, 51.7, 20.0
FEV_1% predicted category (*N*, *n*, %)			
≥ 80% (GOLD mild)	785, 70, 8.9	771, 73, 9.5	1556, 143, 9.2
50–79.9% (GOLD moderate)	785, 308, 39.2	771, 308, 39.9	1556, 616, 39.6
30–49.9% (GOLD severe)	785, 291, 37.1	771, 295, 38.3	1556, 586, 37.7
0–29.9% (GOLD very severe)	785, 116, 14.8	771, 95, 12.3	1556, 211, 13.6
FVC% predicted (*n*, mean, SD)	783, 84.3, 22.3	770, 86.2, 23.4	1553, 85.2, 22.8
FEV_1/FVC ratio (*n*, mean, SD)	783, 49.0, 19.7	770, 48.5, 14.1	1553, 48.8, 17.1
***Current treatment for COPD* (N, n, %)**			
ICS			
ICS only	788, 14, 1.8	779, 17, 2.2	1567, 31, 2.0
ICS/LABA	788, 136, 17.3	779, 125, 16.0	1567, 261, 16.7
ICS/LAMA	788, 13, 1.6	779, 10, 1.3	1567, 23, 1.5
ICS/LABA/LAMA	788, 625, 79.3	779, 627, 80.5	1567, 1252, 79.9
Oral mucolytic use	784, 201, 25.6	771, 197, 25.6	1555, 398, 25.6
Long-term antibiotic use	784, 51, 6.5	771, 48, 6.2	1555, 99, 6.4
***Comorbidities* (N, n, %)**			
Asthma	782, 138, 17.6	772, 147, 19.0	1554, 285, 18.3
Bronchiectasis	782, 41, 5.2	770, 27, 3.5	1552, 68, 4.4
Ischaemic heart disease	781, 111, 14.2	771, 96, 12.5	1552, 207, 13.3
Hypertension	782, 317, 40.5	772, 277, 35.9	1554, 594, 38.2
Diabetes mellitus	782, 83, 10.6	772, 93, 12.0	1554, 176, 11.3
Osteoporosis	783, 109, 13.9	771, 90, 11.7	1554, 199, 12.8
Anxiety/depression treated in the previous 5 years	782, 222, 28.4	772, 213, 27.6	1554, 435, 28.0
Cerebrovascular event	783, 46, 5.9	772, 58, 7.5	1555, 104, 6.7

The mean score on the CAT was 22.6 (SD 7.7), indicating that, overall, COPD was having a high impact on the lives of participants (*Table 9*). Considering the cut-off points used to interpret the scores derived from the CAT, COPD was having a low impact on the lives of 5.3% of participants, a medium impact on the lives of 29.9% of participants, a high impact on the lives of 44.4% of participants and a very high impact on the lives of 20.4% of participants.

The mean EQ-5D-3L utility score was 0.63 (SD 0.28). The mMRC dyspnoea score revealed that 7.1% of participants were too breathless to leave the house, 27.6% had to stop for breath after walking ≈100 m, 31.5% walked more slowly than contemporaries on level ground because of breathlessness, 28.3% became short of breath when hurrying or walking up a slight hill and only 5.5% of participants were not troubled by breathlessness except on strenuous exercise.

A comparison of the participants recruited in primary and secondary care indicated that those identified in secondary care were slightly younger, were more likely to be ex-smokers and had experienced a greater number of exacerbations in the previous 12 months. Furthermore, a higher proportion of those identified in secondary care had more severe COPD, were on triple (ICS/LAMA/LABA) therapy and long-term antibiotic use, and had a significantly greater prevalence of comorbidities, such as bronchiectasis, ischaemic heart disease and osteoporosis (see *Appendix 5, Table 35*). Participants recruited in secondary care had a higher CAT score and a slightly lower QoL.

TABLE 9 Baseline patient-reported symptoms and QoL

Symptoms and QoL	Trial arm		Overall
	Theophylline	Placebo	
Degree of breathlessness (mMRC dyspnoea)[75] [*N*, *n* (%)]			
Not troubled by breathlessness except on strenuous exercise	783, 35 (4.5)	772, 50 (6.5)	1555, 85 (5.5)
Short of breath when hurrying or walking up a slight hill	783, 216 (27.6)	772, 224 (29.0)	1555, 440 (28.3)
Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace	783, 251 (32.1)	772, 239 (31.0)	1555, 490 (31.5)
Stops for breath after walking ≈100 m or after a few minutes on level ground	783, 225 (28.7)	772, 204 (26.4)	1555, 429 (27.6)
Too breathless to leave the house, or breathless when dressing or undressing	783, 56 (7.2)	772, 55 (7.1)	1555, 111 (7.1)
CAT [*N*, mean (SD)]	780, 22.8 (7.5)	771, 22.3 (7.9)	1551, 22.6 (7.7)
CAT group [*N*, *n* (%)]			
Low (score of 0–9)	780, 37 (4.7)	771, 45 (5.8)	1551, 82 (5.3)
Medium (score of 10–19)	780, 219 (28.1)	771, 244 (31.6)	1551, 463 (29.9)
High (score of 20–29)	780, 361 (46.3)	771, 328 (42.5)	1551, 689 (44.4)
Very high (score of 30–40)	780, 163 (20.9)	771, 154 (20.0)	1551, 317 (20.4)
EQ-5D-3L utility [*N*, mean (SD)]	785, 0.62 (0.28)	772, 0.63 (0.28)	1557, 0.63 (0.28)
EQ-5D-3L VAS [*N*, mean (SD)]	785, 59.6 (19.0)	770, 60.8 (19.1)	1555, 60.2 (19.1)

VAS, visual analogue scale.

Chapter 4 Clinical effectiveness

Clinical effectiveness of low-dose theophylline compared with placebo

In this chapter, we report the results of people with COPD being treated for 1 year with low-dose theophylline compared with placebo. A total of 1578 participants were randomised to theophylline or placebo; 11 post-randomisation exclusions resulted in 1567 participants being eligible to initiate trial medication and for whom baseline characteristics have been reported (see *Chapter 3*). Follow-up data were unavailable for 31 (2%) participants (theophylline, $n = 16$; placebo, $n = 15$); therefore, the results presented for the ITT analysis are based on 1536 participants (theophylline, $n = 772$; placebo, $n = 764$). *Figure 4* shows the Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the ITT analysis. In total there were 1489 person-years of follow-up data: 747 person-years in the theophylline group and 742 person-years in the placebo group (*Table 10*).

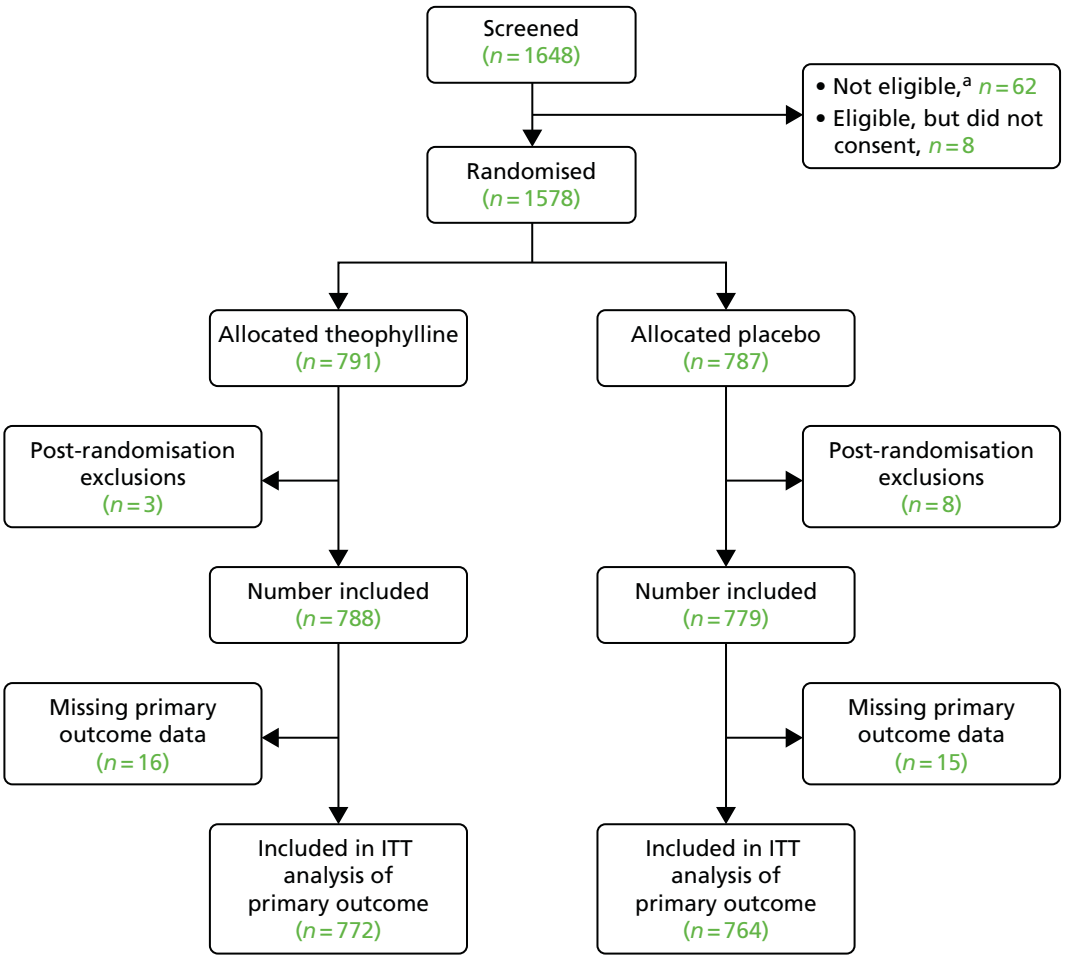

FIGURE 4 The CONSORT flow diagram for the ITT analysis. a, Reasons for ineligibility were as follows: 16 did not meet the inclusion criteria for established COPD diagnosis or had a predominant respiratory disease other than COPD, 10 had not had two exacerbations in the previous year, seven did not meet the smoking history criteria, seven were taking contraindicated medication, three were not currently using ICSs, one was not clinically stable, two were participating in another clinical trial, one was currently taking theophylline, one had known or suspected hypersensitivity to theophylline, one was pregnant, two had severe heart disease and 11 did not meet two or more of the inclusion criteria.

TABLE 10 Exacerbation outcomes (ITT analysis)

Exacerbations	Trial arm		Adjusted or unadjusted	Estimate	95% CI	*p*-value
	Theophylline	Placebo				
Primary outcome: exacerbations						
Total number included in analysis	772	764				
Person-years of follow-up	747.5	742.1				
Number with at least one exacerbation	633	609				
Number of exacerbations						
Total	1727	1703				
Mean	2.24	2.23	Unadjusted IRR	1.00	0.92 to 1.09	0.965
SD	1.99	1.97	Adjusted IRR[a]	0.99	0.91 to 1.08	0.840
Exacerbations requiring hospital treatment						
Total number included in analysis	772	764				
Person-years of follow-up	747.5	742.1				
Number with at least one exacerbation	106	130				
Number of exacerbations						
Total	134	185				
Mean	0.17	0.24	Unadjusted IRR	0.72	0.55 to 0.95	0.021
SD	0.49	0.66	Adjusted IRR[a]	0.72	0.55 to 0.94	0.017
Time to first exacerbation (from randomisation)						
Total number included in analysis[b]	756	753				
Number with at least one exacerbation	617	598				
% with at least one exacerbation	81.6	79.4				
Median time to first exacerbation (days)	219	227	Unadjusted HR	1.03	0.92 to 1.14	0.652
25th percentile [time to first exacerbation (days)]	132	116	Adjusted HR[a]	1.01	0.90 to 1.13	0.895
75th percentile [time to first exacerbation (days)]	334	337				

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.
b Number in analysis differs to primary outcome as exacerbation onset date was unavailable for 27 participants.
Note
The secondary outcome is the total number of exacerbations of COPD resulting in hospital admission.

Intention-to-treat analysis

Primary outcome: total number of exacerbations of chronic obstructive pulmonary disease necessitating a change in management

In total, 633 out of 772 (82.0%) participants allocated to theophylline had at least one exacerbation, with 1727 exacerbations in the group overall. Among participants allocated to placebo, 609 out of 764 (79.7%) had at least one exacerbation and there were 1703 exacerbations in the group overall. The mean number of exacerbations per participant was 2.24 (SD 1.99) in those allocated to low-dose theophylline and 2.23 (SD 1.97) in those allocated to placebo. The adjusted IRR for exacerbation was 0.99 (95% CI 0.91 to 1.08), indicating no difference in the exacerbation rate during the 12-month follow-up period between those on low-dose theophylline and those on placebo (see *Table 10*).

The primary outcome was exacerbation treated with antibiotics and/or OCSs, but we also conducted analyses relating treatment with low-dose theophylline to differing levels of treatment for COPD exacerbations, that is antibiotics only, OCSs only or antibiotics and OCSs (see *Appendix 5, Table 39*). In the adjusted model, for exacerbations treated with antibiotics only, the IRR was 0.94 (95% CI 0.78 to 1.14); for exacerbations treated with OCSs only, the IRR was 0.88 (95% CI 0.62 to 1.25); and for exacerbations treated with antibiotics and OCSs, the IRR was 1.02 (95% CI 0.92 to 1.14).

Among participants allocated to low-dose theophylline, 106 (13.7%) had at least one exacerbation requiring hospital admission, with a total of 134 hospital admissions in the group. Among participants allocated to placebo, 130 (17.0%) had at least one exacerbation requiring hospital admission, and there were 185 admissions in total. A comparison of the proportion of participants with at least one exacerbation requiring hospital admission was not significant at the 5% level (13.7% in the theophylline arm vs. 17.0% in the placebo arm; $p = 0.074$). In the adjusted model, the IRR for exacerbations of COPD requiring hospital treatment was 0.72 (95% CI 0.55 to 0.94), suggesting that low-dose theophylline resulted in a reduction in the number of exacerbations requiring hospital admission when compared with placebo (see *Table 10*). However, further exploration of the data showed that, in the theophylline group, only three participants had three or more exacerbations necessitating treatment in hospital (12 exacerbations in total), compared with 13 participants in the placebo group having three or more exacerbations necessitating hospital treatment (51 exacerbations in total). Therefore, a small excess of participants ($n = 10$) allocated to placebo who had three or more exacerbations requiring treatment in hospital accounted for 39 of the 51 excess admissions in the placebo group (*Table 11*).

TABLE 11 Number of exacerbations requiring hospital admission

Number of exacerbations requiring hospital admission	Trial arm, *n* (%)	
	Theophylline	Placebo
0	666 (86)	634 (83)
1	84 (11)	100 (13)
2	19 (2)	17 (2)
3	0 (0)	5 (1)
4	3 (< 1)	5 (1)
5	0 (0)	2 (< 1)
6	0 (0)	1 (< 1)
Total (*n*)	772	784

Secondary outcomes

Time to first exacerbation

The date of onset of the first exacerbation after commencing trial medication was not available for 27 of the 1242 participants who had at least one exacerbation; therefore, this analysis was based on 1509 participants in the ITT population [294 who had no exacerbation and 1215 (80.5%) who had an exacerbation]. Of the 756 participants allocated to theophylline, 617 (81.6%) had at least one exacerbation, with a median time to first exacerbation of 219 days (7.2 months) after randomisation. In the placebo group, 598 out of 753 (79.4%) participants had at least one exacerbation, with a median time to first exacerbation of 227 days (7.5 months). In a Cox regression analysis, the adjusted HR for the time to first exacerbation was 1.01 (95% CI 0.90 to 1.13), suggesting no significant difference between the treatment groups in terms of the time to first exacerbation (from point of randomisation) during the 12-month follow-up period (see *Table 10*).

Total number of emergency hospital admissions (including those not related to chronic obstructive pulmonary disease)

Hospital admission data were available for 1517 of the 1536 participants in the ITT population (theophylline, $n = 762$; placebo, $n = 755$). A similar proportion of participants had at least one hospital admission for non-COPD-related causes. Among the participants allocated to low-dose theophylline, this proportion was 10.4% (79/762); among those allocated to placebo, it was 12.2% (92/755). In total, there were 116 hospital admissions among participants allocated to theophylline and 119 among those allocated to placebo. The adjusted IRR was 0.99 (95% CI 0.71 to 1.38), suggesting no significant difference in the rate of emergency (unscheduled) hospital admissions between the groups (*Table 12*).

Mortality (all cause and respiratory related)

There were 33 deaths (from all causes) during the 12-month follow-up period: 19 (2.5%) in the low-dose theophylline group and 14 (1.8%) in the placebo group. Respiratory-related disease accounted for seven deaths in theophylline group and eight deaths in the placebo group. Relative to the placebo group, the adjusted HR for death from all causes in the theophylline group was 1.38 (95% CI 0.69 to 2.76), and for respiratory-related causes it was 0.85 (95% CI 0.30 to 2.40). Therefore, there was no evidence of a significant difference between treatment groups for mortality outcomes (see *Table 12*).

Total number of episodes of pneumonia

In total, there were 23 episodes of pneumonia reported during the follow-up: 14 in participants allocated to theophylline and nine in participants allocated to placebo (1.8% in the theophylline arm vs. 1.2% in the placebo arm). The proportion of admissions for pneumonia was not found to significantly differ between treatment groups ($p = 0.307$). The unadjusted odds ratio (OR) was 1.55 (95% CI 0.67 to 3.62); however, in the light of the small event counts, no adjustments were made (see *Table 12*).

Total dose of inhaled corticosteroids

The total daily dose of ICSs at baseline was available for 1532 of the 1536 members of the ITT population (two missing from each treatment group). The mean total daily beclomethasone-equivalent ICS dose at baseline was 1662 µg (SD 677 µg) in those allocated to theophylline and 1680 µg (SD 691 µg) in those allocated to placebo. During the 12-month follow-up, 215 participants changed their medication: 104 (13.5%) theophylline participants and 111 (14.6%) placebo participants ($p = 0.550$). The mean total daily beclomethasone-equivalent dose at the end of follow-up was 1606 µg (SD 694 µg) in those allocated to theophylline and 1622 µg (SD 714 µg) in those allocated to placebo, resulting in an adjusted difference of –12.4 µg per day (95% CI –81.4 to 56.6 µg) for theophylline compared with placebo (see *Table 12*). This lower dose at the end of follow-up in those taking theophylline was not significantly different from the dose for those taking placebo. Both groups showed a slight reduction in total daily dose from baseline to end of follow-up, but a comparison of the adjusted mean dose change between treatment groups was not significant ($p = 0.852$).

TABLE 12 Secondary clinical outcomes (ITT analysis)

Secondary outcome	Trial arm		Adjusted or unadjusted	Estimate	95% CI	*p*-value
	Theophylline	Placebo				
Emergency hospital admissions (non-COPD)						
Total number included in analysis	762	755				
Number with one or more emergency hospital admissions	79	92				
Total number of admissions	116	119				
Mean admission rate	0.15	0.16	Unadjusted IRR	0.96	0.69 to 1.35	0.830
SD admission rate	0.56	0.47	Adjusted IRR[a]	0.99	0.71 to 1.38	0.952
All-cause mortality						
Total number included in analysis	772	764				
Number deceased within 12 months	19	14	Unadjusted HR	1.35	0.68 to 2.69	0.398
Percentage deceased within 12 months	2.5	1.8	Adjusted HR[a]	1.38	0.69 to 2.76	0.369
COPD-/respiratory-related mortality						
Total number included in analysis	772	764				
Number deceased within 12 months	7	8	Unadjusted HR	0.87	0.31 to 2.39	0.785
Percentage deceased within 12 months	0.9	1.0	Adjusted HR[a]	0.85	0.30 to 2.40	0.762
Pneumonia						
Total number included in analysis	772	764				
Number with pneumonia	14	9	Unadjusted OR	1.55	0.67 to 3.62	0.307
Percentage with pneumonia	1.8	1.2				
Total daily dose of ICSs						
Total number included in analysis	770	762				
Number who changed medication from baseline	104	111				
Mean daily dose of ICS at end of follow-up (µg)	1606	1622	Unadjusted mean difference	–16.3	–86.8 to 54.2	0.650
SD daily dose of ICS at end of follow-up (µg)	694	714	Adjusted mean difference[a]	–12.4	–81.5 to 56.6	0.724
Change in daily ICS dose from baseline						
Total number included in analysis	770	762				
Mean change in daily ICS dose from baseline (µg)	–57	–58	Unadjusted mean difference	1.4	–36.5 to 39.2	0.943
SD change in daily ICS dose from baseline (µg)	346	408	Adjusted mean difference[a]	3.6	–34.1 to 41.3	0.852

OR, odds ratio.

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, the number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

Lung function (% predicted forced expiratory volume in 1 second and forced vital capacity)

In the ITT analysis, lung function was found to be similar between the treatment groups with mean % predicted FEV_1 (FEV_1%) at the end of the 12-month follow-up of 51.5% (SD 20.4%) for participants allocated to low-dose theophylline ($n = 533$) and 52.1% (SD 21.7%) for participants allocated to placebo ($n = 489$). The overall difference in FEV_1% predicted (across the 12-month period) was –0.56% (95% CI –2.42% to 1.30%) between the groups. A similar pattern was observed for % predicted FVC, with an overall significant difference of –0.28% (95% CI –2.33% to 1.76%) (*Table 13*).

TABLE 13 Lung function (ITT analysis)

Outcome	Trial arm		Adjusted or unadjusted	Overall mean difference	95% CI	*p*-value
	Theophylline	Placebo				
% predicted FEV_1						
Baseline						
Total (*n*)	769	757				
Mean	51.2	52.3				
SD	20.1	19.8				
6 months						
Total (*n*)	553	539				
Mean	52.2	53.2				
SD	20.5	20.9				
12 months						
Total (*n*)	533	489				
Mean	51.5	52.1	Unadjusted	–0.57	–2.51 to 1.36	0.561
SD	20.4	21.7	Adjusted[a]	–0.56	–2.42 to 1.30	0.555
% predicted FVC						
Baseline						
Total (*n*)	767	756				
Mean	84.3	86.3				
SD	22.3	23.4				
6 months						
Total (*n*)	548	535				
Mean	83.8	84.5				
SD	22.8	24.7				
12 months						
Total (*n*)	525	486				
Mean	83.1	82.3	Unadjusted	–0.37	–2.50 to 1.75	0.732
SD	23.8	25.3	Adjusted[a]	–0.28	–2.33 to 1.76	0.788

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, the number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

Modified Medical Research Council dyspnoea scale

Table 14 details the responses to the mMRC breathlessness scale at baseline and at 6 and 12 months for each treatment group. The proportions of participants in each category are relatively similar in both groups at each time point. The overall adjusted OR (*Table 15*) from the mixed-effects ordinal logistic regression for theophylline relative to placebo is 1.20 (95% CI 0.88 to 1.63), indicating a slight increase in odds of higher mMRC score in theophylline participants than in the placebo participants, but the increase is not significant.

TABLE 14 The mMRC dyspnoea scale (ITT analysis)

	Trial arm	
mMRC category	Theophylline	Placebo
***Baseline* (N, n, %)**		
Not troubled by breathlessness except on strenuous exercise	767, 35, 4.6	757, 50, 6.6
Short of breath when hurrying or walking up a slight hill	767, 211, 27.5	757, 218, 28.8
Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace	767, 248, 32.3	757, 235, 31.0
Stops for breath after walking about 100 m or after a few minutes on level ground	767, 219, 28.6	757, 201, 26.6
Too breathless to leave house, or breathless when dressing/undressing	767, 54, 7.0	757, 53, 7.0
***6 months* (N, n, %)**		
Not troubled by breathlessness except on strenuous exercise	676, 42, 6.2	655, 51, 7.8
Short of breath when hurrying or walking up a slight hill	676, 209, 30.9	655, 189, 28.9
Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace	676, 197, 29.1	655, 179, 27.3
Stops for breath after walking about 100 m or after a few minutes on level ground	676, 178, 26.3	655, 186, 28.4
Too breathless to leave house, or breathless when dressing/undressing	676, 50, 7.4	655, 50, 7.6
***12 months* (N, n, %)**		
Not troubled by breathlessness except on strenuous exercise	631, 38, 6.0	615, 52, 8.5
Short of breath when hurrying or walking up a slight hill	631, 186, 29.5	615, 158, 25.7
Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace	631, 174, 27.6	615, 182, 29.6
Stops for breath after walking about 100 m or after a few minutes on level ground	631, 178, 28.2	615, 167, 27.2
Too breathless to leave house, or breathless when dressing/undressing	631, 55, 8.7	615, 56, 9.1

TABLE 15 The ORs for the mMRC dyspnoea scale (ITT analysis)

OR	Estimate	95% CI	*p*-value
Unadjusted OR	1.27	0.91 to 1.76	0.157
Adjusted OR[a]	1.20	0.88 to 1.63	0.244

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, the number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

The COPD Assessment Test

The CAT scores were very similar between groups at baseline (*Table 16*) and remained similar throughout the 12-month treatment period, with a mean score of 21.4 (SD 8.2) for participants allocated to low-dose theophylline ($n = 633$) and 21.4 (SD 8.6) for participants allocated to placebo ($n = 615$). A comparison of the profile of the CAT scores across the three time points (i.e. 0, 6 and 12 months) showed an adjusted difference of 0.01 (95% CI –0.65 to 0.68), suggesting no significant difference between the groups of the impact of COPD on the participants' lives.

TABLE 16 Participant-reported outcomes (ITT analysis)

Outcome	Trial arm		Adjusted or unadjusted	Overall mean difference	95% CI	*p*-value
	Theophylline	Placebo				
CAT score						
Baseline						
Total (*n*)	764	756				
Mean	22.7	22.3				
SD	7.5	7.9				
6 months						
Total (*n*)	675	657				
Mean	21.3	21.1				
SD	8.1	8.3				
12 months						
Total (*n*)	633	615				
Mean	21.4	21.4	Unadjusted	0.13	–0.59 to 0.85	0.715
SD	8.2	8.6	Adjusted[a]	0.01	–0.65 to 0.68	0.975
HARQ score						
Baseline						
Total (*n*)	199	203				
Mean	24.9	25.8				
SD	16.0	14.8				
6 months						
Total (*n*)	191	188				
Mean	21.9	22.9				
SD	15.1	15.7				
12 months						
Total (*n*)	184	172				
Mean	24.1	24.2	Unadjusted	–0.85	–3.34 to 1.64	0.504
SD	15.7	15.9	Adjusted[a]	–1.10	–3.46 to 1.26	0.359

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, the number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

Hull Airways Reflux Questionnaire

The HARQ assesses respiratory symptoms associated with airway reflux, and was completed by a subset of participants. Participants for whom HARQ data were available were more likely to be female and younger than those who had no HARQ data (see *Appendix 5, Table 37*). Data were available for 199 (26.0%) participants allocated to theophylline and 203 (26.9%) allocated to placebo at baseline. The HARQ scores were very similar between treatment groups throughout the trial and at the 12-month follow-up; for participants allocated to low-dose theophylline, the mean HARQ score was 24.1 (SD 15.7), based on 184 participants, and for those allocated to placebo, it was 24.2 (SD 15.9), based on 172 participants. A comparison of the profiles of HARQ scores across the three time points (i.e. 0, 6 and 12 months) revealed an adjusted difference of –1.10 (95% CI –3.46 to 1.26), suggesting no significant difference between the groups in reflux-associated respiratory symptoms measured by the HARQ (see *Table 15*).

Safety outcomes (safety population)

The safety population comprised all participants who were randomised and included in the trial ($n = 1567$) and initiated their trial medication. Five out of 788 (0.6%) participants allocated theophylline did not initiate medication; 9 out of 779 (1.2%) participants in the placebo group did not initiate placebo. The safety population consisted of 1553 (99.1%) participants (theophylline, $n = 783$; placebo, $n = 770$).

Serious adverse events

Overall, 211 (13.6%) participants had at least one SAE, 103 (out of 783, 13.2%) in the low-dose theophylline group and 108 (out of 770, 14.0%) in the placebo group. A total of 276 SAEs were reported in individuals in the safety population. These were balanced between the treatment groups, with 141 in participants allocated to theophylline and 135 in placebo participants. SAEs were classified using System Organ Classes (SOCs).[95] *Table 17* details, for each SOC code and for each treatment group, the number of participants experiencing at least one SAE of that code, and the total number of SAEs of that SOC code. No significant differences were observed in the SAE profile of the two treatment groups. The most common SAE SOC code was for 'cardiac disorders' [2.8% (2.3% in the theophylline arm and 3.4% in the placebo arm)]. SAEs with a coding of 'respiratory, thoracic and mediastinal' occurred in 2.5% of participants (2.3% in the theophylline arm and 2.7% in the placebo arm). A borderline significantly higher proportion of participants in the theophylline group (2.7%) reported a gastrointestinal SAE than in the placebo group (1.3%) ($p = 0.051$). No pregnancies were reported. Line listings are provided in *Appendix 6*.

Adverse reactions

Information on adverse reactions was available for 1408 participants (theophylline, $n = 709$; placebo, $n = 699$), with 648 (46%) suffering at least one AR (theophylline, $n = 341$; placebo; $n = 307$). There were 1701 ARs in total: 883 in those allocated to low-dose theophylline and 818 in those allocated placebo. *Table 18* presents these ARs in more detail, with total number available for analysis for each AR, number of participants with at least one AR of that type and the percentage in each group. The five most common ARs were nausea (10.9% in the theophylline arm and 8.0% in the placebo arm; $p = 0.059$), insomnia (9.3% in the theophylline arm and 8.9% in the placebo arm; $p = 0.790$), dizziness (8.1% in the theophylline arm and 9.6% in the placebo arm; $p = 0.290$), gastro-oesophageal reflux (9.4% in the theophylline arm and 7.5% in the placebo arm; $p = 0.217$) and headache (9.0% in the theophylline arm and 7.7% in the placebo arm; $p = 0.383$). In addition, the proportion reporting tachycardia was slightly higher in the placebo group (3.5%) than in the theophylline group (1.9%) ($p = 0.058$). There were no other observed significant differences in ARs between treatment groups.

TABLE 17 Serious adverse events (ITT analysis)

SAE	Trial arm		*p*-value
	Theophylline	Placebo	
Total number included in analysis	783	770	
All SAEs			
Number of participants with at least one SAE	103	108	
Percentage of participants with at least one SAE	13.2	14.0	0.616
Total number of SAEs	141	135	
Infection and infestations			
Number of participants with at least one SAE of this type	13	9	
Percentage of participants with at least one SAE of this type	1.7	1.2	0.413
Total number of SAEs of this type	13	9	
Neoplasms: benign, malignant and unspecified			
Number of participants with at least one SAE of this type	17	11	
Percentage of participants with at least one SAE of this type	2.2	1.4	0.272
Total number of SAEs of this type	18	11	
Blood and lymphatic system disorders			
Number of participants with at least one SAE of this type	0	2	
Percentage of participants with at least one SAE of this type	0	0.3	
Total number of SAEs of this type	0	2	
Immune system disorders			
Number of participants with at least one SAE of this type	0	0	
Percentage of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Endocrine disorders			
Number of participants with at least one SAE of this type	0	0	
Percentage of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Metabolism and nutrition disorders			
Number of participants with at least one SAE of this type	1	0	
Percentage of participants with at least one SAE of this type	0.1	0	
Total number of SAEs of this type	2	0	
Nervous system disorders			
Number of participants with at least one SAE of this type	11	7	
Percentage of participants with at least one SAE of this type	1.4	0.9	0.361
Total number of SAEs of this type	13	7	
Psychiatric disorders			
Number of participants with at least one SAE of this type	1	2	
Percentage of participants with at least one SAE of this type	0.1	0.3	
Total number of SAEs of this type	1	3	

TABLE 17 Serious adverse events (ITT analysis) (*continued*)

SAE	Trial arm		*p*-value
	Theophylline	Placebo	
Eye disorders			
Number of participants with at least one SAE of this type	0	0	
Percentage of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Ear and labyrinth disorders			
Number of participants with at least one SAE of this type	0	0	
Percentage of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Cardiac disorders			
Number of participants with at least one SAE of this type	18	26	
Percentage of participants with at least one SAE of this type	2.3	3.4	0.201
Total number of SAEs of this type	21	29	
Vascular disorders			
Number of participants with at least one SAE of this type	5	6	
Percentage of participants with at least one SAE of this type	0.6	0.8	
Total number of SAEs of this type	6	6	
Respiratory, thoracic and mediastinal disorders			
Number of participants with at least one SAE of this type	18	21	
Percentage of participants with at least one SAE of this type	2.3	2.7	0.590
Total number of SAEs of this type	19	22	
Hepatobiliary disorders			
Number of participants with at least one SAE of this type	2	4	
Percentage of participants with at least one SAE of this type	0.3	0.5	
Total number of SAEs of this type	2	4	
Gastrointestinal disorders			
Number of participants with at least one SAE of this type	21	10	
Percentage of participants with at least one SAE of this type	2.7	1.3	0.051
Total number of SAEs of this type	22	12	
Skin and subcutaneous tissue disorders			
Number of participants with at least one SAE of this type	1	0	
Percentage of participants with at least one SAE of this type	0.1	0	
Total number of SAEs of this type	1	0	
Musculoskeletal and connective tissue disorders			
Number of participants with at least one SAE of this type	5	9	
Percentage of participants with at least one SAE of this type	0.6	1.2	
Total number of SAEs of this type	5	11	

continued

TABLE 17 Serious adverse events (ITT analysis) (*continued*)

SAE	Trial arm		*p*-value
	Theophylline	Placebo	
Renal and urinary disorders			
Number of participants with at least one SAE of this type	6	4	
Percentage of participants with at least one SAE of this type	0.8	0.5	
Total number of SAEs of this type	6	4	
Pregnancy, puerperium and perinatal conditions			
Number of participants with at least one SAE of this type	0	0	
Percentage of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Reproductive system and breast disorders			
Number of participants with at least one SAE of this type	0	0	
Percentage of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Congenital, familial and genetic disorders			
Number of participants with at least one SAE of this type	0	0	
Percentage of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
General disorders and administration site disorders			
Number of participants with at least one SAE of this type	0	0	
Percentage of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Investigations			
Number of participants with at least one SAE of this type	0	2	
Percentage of participants with at least one SAE of this type	0	0.3	
Total number of SAEs of this type	0	2	
Injury, poisoning and procedural complications			
Number of participants with at least one SAE of this type	9	13	
Percentage of participants with at least one SAE of this type	1.1	1.7	0.369
Total number of SAEs of this type	11	13	
Surgical and medical procedures			
Number of participants with at least one SAE of this type	1	0	
Percentage of participants with at least one SAE of this type	0.1	0	
Total number of SAEs of this type	1	0	
Social circumstances			
Number of participants with at least one SAE of this type	0	0	
Percentage of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	

TABLE 18 Adverse reactions (ITT analysis)

AR	Trial arm		*p*-value
	Theophylline	Placebo	
Any AR			
Number included in analysis	709	699	
Number with at least one AR	341	307	
Percentage with at least one AR	48.1	43.9	0.116
Total number of ARs	883	818	
Anaphylactic/anaphylactoid reaction			
Number included in analysis	692	679	
Number with at least one AR of this type	0	1	
Percentage with at least one AR of this type	0.0	0.1	
Hypersensitivity			
Number included in analysis	692	679	
Number with at least one AR of this type	5	5	
Percentage with at least one AR of this type	0.7	0.7	> 0.999
Nausea			
Number included in analysis	695	679	
Number with at least one AR of this type	76	54	
Percentage with at least one AR of this type	10.9	8.0	0.059
Reflux			
Number included in analysis	693	678	
Number with at least one AR of this type	65	51	
Percentage with at least one AR of this type	9.4	7.5	0.217
Diarrhoea			
Number included in analysis	693	680	
Number with at least one AR of this type	53	46	
Percentage with at least one AR of this type	7.6	6.8	0.527
Abdominal pain			
Number included in analysis	692	679	
Number with at least one AR of this type	42	34	
Percentage with at least one AR of this type	6.1	5.0	0.390
Gastric irritation			
Number included in analysis	691	679	
Number with at least one AR of this type	38	28	
Percentage with at least one AR of this type	5.5	4.1	0.235
Vomiting			
Number included in analysis	693	678	
Number with at least one AR of this type	28	22	
Percentage with at least one AR of this type	4.0	3.2	0.432

continued

TABLE 18 Adverse reactions (ITT analysis) (*continued*)

AR	Trial arm		*p*-value
	Theophylline	Placebo	
Palpitations			
Number included in analysis	690	678	
Number with at least one AR of this type	29	26	
Percentage with at least one AR of this type	4.2	3.8	0.729
Tachycardia			
Number included in analysis	691	678	
Number with at least one AR of this type	13	24	
Percentage with at least one AR of this type	1.9	3.5	0.058
Insomnia			
Number included in analysis	691	678	
Number with at least one AR of this type	64	60	
Percentage with at least one AR of this type	9.3	8.9	0.790
Anxiety			
Number included in analysis	691	679	
Number with at least one AR of this type	52	42	
Percentage with at least one AR of this type	7.5	6.2	0.327
Rash			
Number included in analysis	691	679	
Number with at least one AR of this type	35	27	
Percentage with at least one AR of this type	5.1	4.0	0.332
Pruritus			
Number included in analysis	692	679	
Number with at least one AR of this type	51	63	
Percentage with at least one AR of this type	7.4	9.3	0.201
Tremor			
Number included in analysis	691	678	
Number with at least one AR of this type	34	38	
Percentage with at least one AR of this type	4.9	5.6	0.571
Headache			
Number included in analysis	691	678	
Number with at least one AR of this type	62	52	
Percentage with at least one AR of this type	9.0	7.7	0.383
Dizziness			
Number included in analysis	691	678	
Number with at least one AR of this type	56	66	
Percentage with at least one AR of this type	8.1	9.7	0.290

TABLE 18 Adverse reactions (ITT analysis) (*continued*)

AR	Trial arm		*p*-value
	Theophylline	Placebo	
Agitation			
Number included in analysis	691	679	
Number with at least one AR of this type	22	18	
Percentage with at least one AR of this type	3.2	2.6	0.558
Convulsions			
Number included in analysis	691	678	
Number with at least one AR of this type	2	4	
Percentage with at least one AR of this type	0.3	0.6	0.448
Hyperuricemia			
Number included in analysis	691	678	
Number with at least one AR of this type	9	7	
Percentage with at least one AR of this type	1.3	1.0	0.803
Diuresis			
Number included in analysis	691	678	
Number with at least one AR of this type	49	48	
Percentage with at least one AR of this type	7.1	7.1	0.993
Urinary retention			
Number included in analysis	691	677	
Number with at least one AR of this type	16	15	
Percentage with at least one AR of this type	2.3	2.2	0.901
Other			
Number included in analysis	691	677	
Number with at least one AR of this type	82	86	
Percentage with at least one AR of this type	11.9	12.7	0.638

Subgroup analysis (intention to treat)

Appendix 5, *Table 40* details the results of the subgroup analysis for the prespecified subgroups. Given the exploratory nature of the analyses, we present 99% CIs. *Figure 5* displays this information, alongside the *p*-values for the interaction in the adjusted model. There was no evidence at the 1% level of statistical significance that any effect of low-dose theophylline differed between subgroups of age, sex, smoking status, BMI, COPD treatments, exacerbation history, COPD severity, baseline ICS dose or use of maintenance OCSs.

Treatment adherence/compliance

Adherence/compliance was defined as having taken ≥ 70% of expected doses of trial tablets. In the ITT population (n = 1536), 1180 (76.8%) participants fulfilled the definition of adherent/compliant (and made up the per-protocol population). In the theophylline-allocated group, 181 out of 772 (23.4%) participants were classed as non-adherent/non-compliant; three of these never initiated treatment, 171 were non-persistent with (i.e. ceased) trial medication and seven persisted with trial medication but from returned

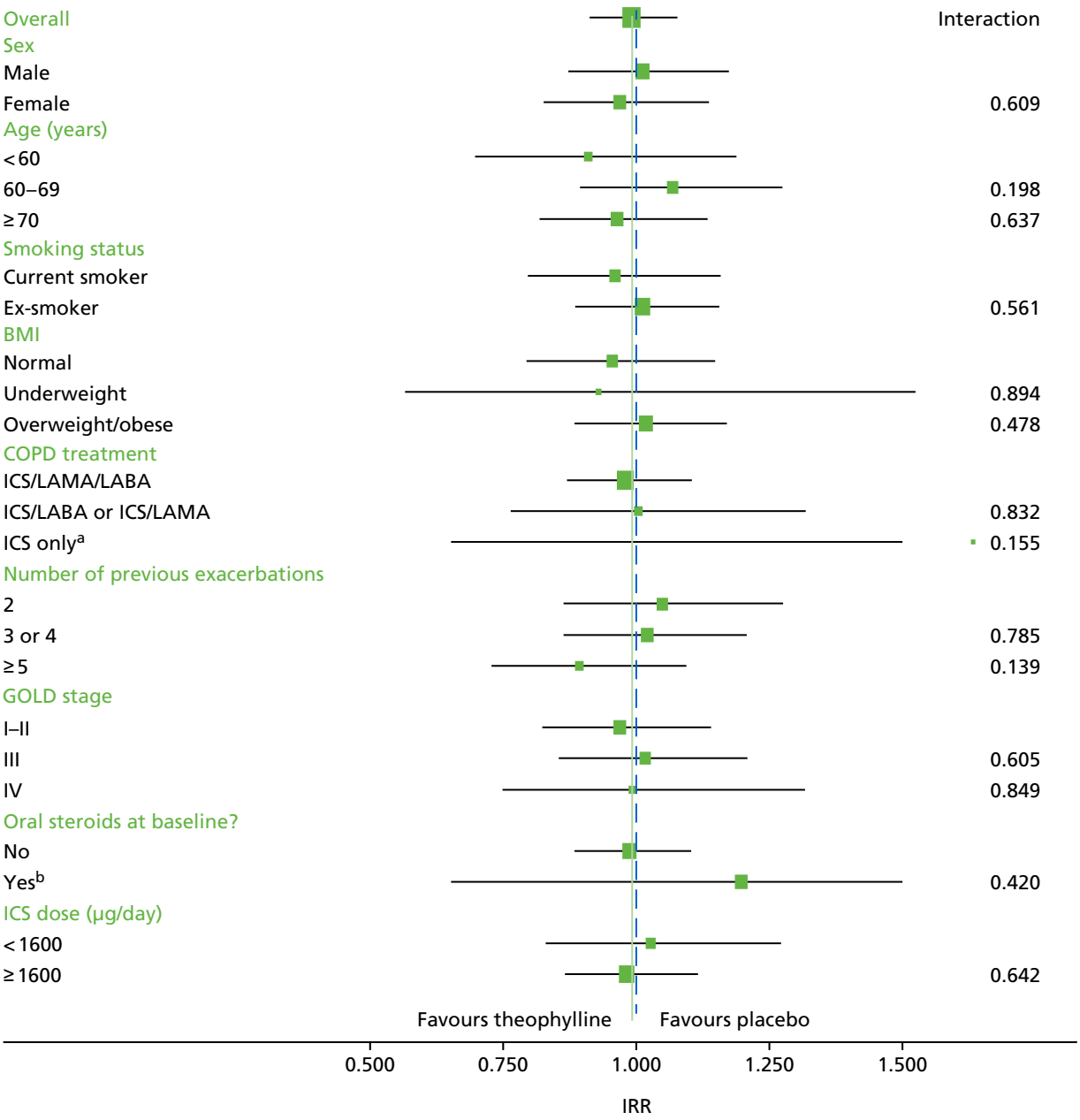

FIGURE 5 Forest plot of estimates from the subgroups. Vertical dashed line represents no effect (IRR = 1), vertical solid line indicates the overall treatment effect for exacerbation (IRR = 0.992). a, Upper limit of CI truncated to 1.5, actual value is 4.09; b, upper limit of CI truncated to 1.5, actual limit is 2.20.

medication it was evident that they were non-adherent/non-compliant (*Table 19*). In addition, 32 out of 591 low-dose theophylline participants fulfilled the adherent/compliant definition despite not persisting with the trial medication, usually very late in the treatment period (*Table 20*). In the placebo group, 175 out of 764 (22.9%) participants were classed as non-adherent/non-compliant; six never initiated medication, 159 were non-persistent with trial medication and 10 persisted with trial medication but medication returns demonstrated poor implementation (see *Table 19*). A further 34 participants were non-persistent with medication but fulfilled the definition of adherent/compliant because they ceased trial medication late into the treatment period (see *Table 20*). In summary, the per-protocol population comprises 1180 participants (591 from the theophylline arm and 589 from the placebo arm) and there were 1146 person-years of follow-up data (see *Table 19*). A comparison of the proportion who were non-adherent/non-compliant (23.4% in the theophylline arm vs. 22.9% in the placebo arm) was not significant ($p = 0.802$). In total, 203 out of 772 participants in the theophylline arm were non-persistent with medication, compared with 193 out of 764 in the placebo arm (unadjusted IRR 1.05, 95% CI 0.84 to 1.32).

TABLE 19 Compliance information

Compliance	Trial arm (*n*)	
	Theophylline	Placebo
Total	772	764
Not adherent/compliant (took < 70% of doses)[a]	181	175
Did not start medication (non-initiation)	3	6
Actively ceased medication (non-persistence)	171	159
Did not cease (persistent), but adherence/compliance was < 70%	7	10
Compliant (≥ 70%)	591	589

a Unadjusted IRR 1.03, 95% CI 0.81 to 1.31; $p = 0.802$.

TABLE 20 Reasons for stopping medication (of those who started)

Stopping medication	Trial arm (*n*)	
	Theophylline	Placebo
Total	772	764
Did not start medication (non-initiation)	3	6
Actively ceased medication (non-persistent)	171	159
Adherent/compliant but ceased medication (non-persistent)	32	34
Total ceasing medication (who started) (non-persistent)[a]	203	193
Reason for stopping medication		
Infections: and infestations	2	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7	2
Psychiatric disorders	2	4
Nervous system disorders	19	15
Ear and labyrinth disorders	3	3
Cardiac disorders	7	6
Vascular disorders	1	1
Respiratory, thoracic and mediastinal disorders	10	19
Gastrointestinal disorders	46	32
Hepatobiliary disorders	0	1
Skin and subcutaneous tissue disorders	9	7
Musculoskeletal and connective tissue disorders	4	8
Renal and urinary disorders	5	1
Injury, poisoning and procedural complications	1	1
Surgical and medical procedures	19	21
Social circumstances	15	14
Participant felt no benefit	25	21
No reason given	28	36

a Unadjusted IRR 1.05, 95% CI 0.84 to 1.32; $p = 0.676$.

Reasons for stopping medication

Table 20 presents the reasons for stopping medication among the ITT population by SOC code. The most common reason for stopping medication was gastrointestinal disorders (theophylline, $n = 46$; placebo, $n = 32$), followed by surgical and medical procedures (theophylline, $n = 19$; placebo, $n = 21$). Although the surgical and medical procedures group included some participants who had discontinued ICSs containing inhalers, the majority of this group comprised participants advised to discontinue the trial drug by a clinician after presenting with a wide range of illnesses. In total, 46 participants discontinued the trial medication because they felt no benefit (theophylline, $n = 25$; placebo, $n = 21$), and in 64 cases no reason was given (theophylline, $n = 28$; placebo, $n = 36$), with a further 29 ceasing for social circumstances (theophylline, $n = 15$; placebo, $n = 14$). There were no obvious differences between the two treatment groups in the reasons why trial medication was discontinued, but no formal statistical testing was undertaken.

Per-protocol analysis

The per-protocol population comprised the 1180 participants of the ITT population who met the trial definition of adherence with the trial medication. The per-protocol analysis comprised 591 participants allocated to low-dose theophylline and 589 allocated to placebo (*Figure 6*).

Primary outcome: total number of exacerbations of chronic obstructive pulmonary disease necessitating a change in management

In the per-protocol population, 591 theophylline-allocated participants had a mean of 2.20 (SD 1.96) exacerbations, compared with a mean of 2.14 (SD 1.92) exacerbations among the 589 placebo participants. There were 1298 exacerbations in the theophylline group and 1258 in placebo group. The adjusted IRR for COPD exacerbation was 1.00 (95% CI 0.91 to 1.10), indicating no difference in the exacerbation rate during the 12-month follow-up period for those on low-dose theophylline compared with those receiving placebo who were adherent/compliant with the trial medication (*Table 21*).

Secondary outcomes

Total number of exacerbations of chronic obstructive pulmonary disease resulting in hospital admission

In the per-protocol population, 76 out of 591 (13%) participants allocated to theophylline had at least one COPD exacerbation necessitating hospital admission; there were 92 admissions in the group overall. Among participants allocated to placebo, 88 out of 589 (15%) had at least one admission and there were 126 admissions overall. The mean number of COPD exacerbations necessitating hospital admission was 0.16 (SD 0.45) among the 591 compliant participants in the theophylline group and 0.21 (SD 0.61) among the 589 compliant participants in the placebo group. In the adjusted model, the IRR for COPD exacerbations necessitating hospital admission was 0.70 (95% CI 0.50 to 0.97), suggesting a significant reduction in the number of exacerbations necessitating hospital admission in the low-dose theophylline group compared with the placebo group (see *Table 21*).

Time to first exacerbation

The information for the time to first exacerbation was missing for 19 of the 1180 per-protocol participants; therefore, this analysis was based on 1161 participants. Among participants allocated to theophylline, 468 out of 578 (81.0%) had at least one exacerbation, with a median time to first exacerbation of 221 days (7.3 months) after randomisation. In the placebo group, 459 out of 583 (78.7%) participants had at least one exacerbation, with a median time to first exacerbation of 232 days (7.7 months). In a Cox regression analysis, the adjusted HR for time to first exacerbation was 1.02 (95% CI 0.90 to 1.16), suggesting no

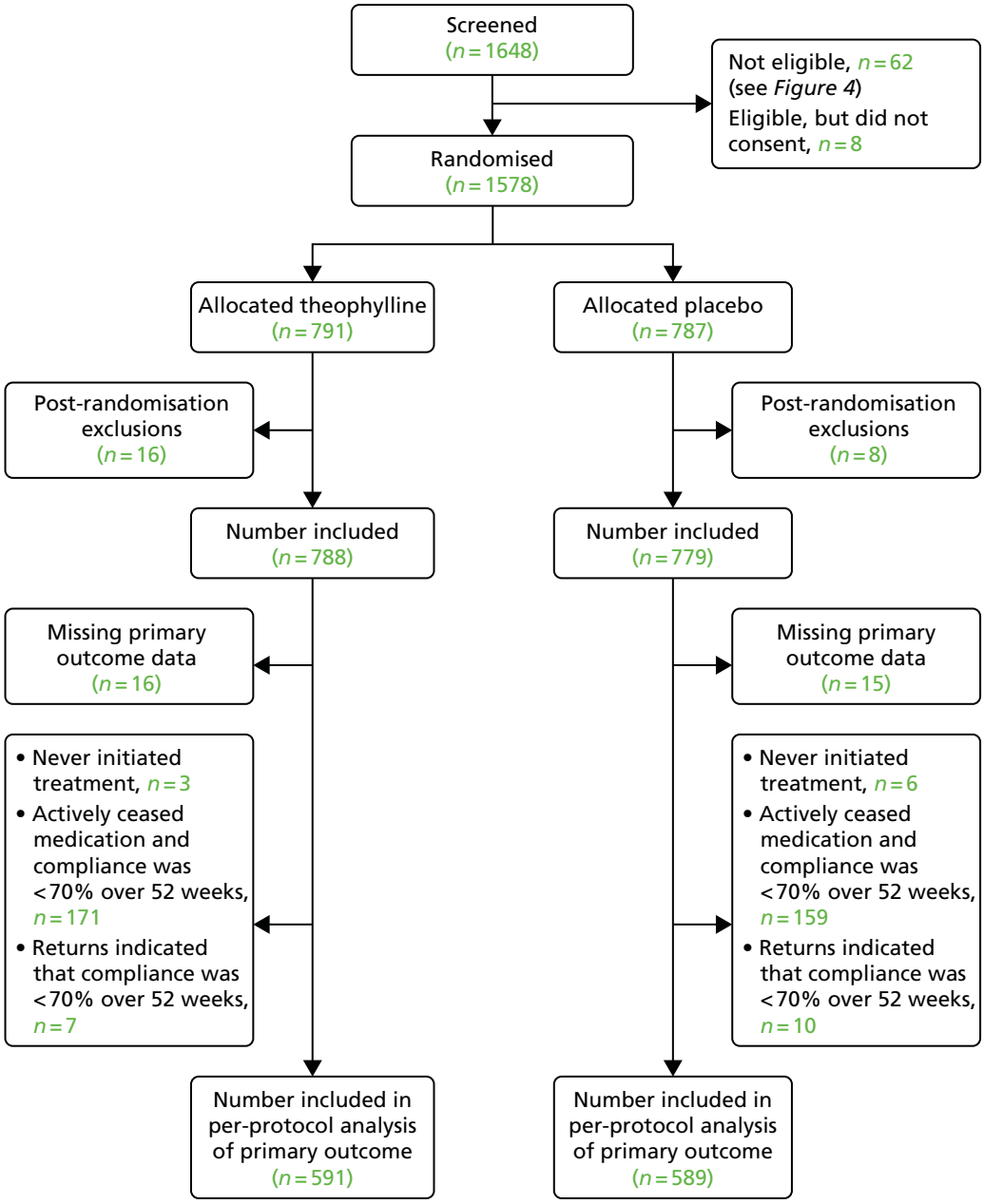

FIGURE 6 The CONSORT flow diagram for the per-protocol analysis.

difference between the treatment groups in terms of time to first exacerbation (from point of randomisation) during the 12-month follow-up period (see *Table 21*).

Total number of emergency hospital admissions (non-chronic obstructive pulmonary disease related)

Hospital admission data were available for 1176 out of 1180 participants in the per-protocol population. Overall, 111 participants had at least one admission (theophylline, $n = 45$; placebo, $n = 66$), with 66 admissions in the theophylline group and 85 admissions in the placebo group. The adjusted IRR for admission was 0.82 (95% CI 0.54 to 1.24), suggesting no significant difference in the rate of non-COPD-related emergency hospital admissions between participants compliant with low-dose theophylline and those compliant with placebo (*Table 22*).

TABLE 21 Exacerbation outcomes (per-protocol analysis)

Exacerbations	Trial arm		Adjusted or unadjusted	Estimate	95% CI	*p*-value
	Theophylline	Placebo				
Primary outcome: exacerbations						
Total number included in analysis	591	589				
Person-years of follow-up	572.8	573.8				
Number with at least one exacerbation	481	465				
Total number of exacerbations	1298	1258				
Mean number of exacerbations	2.20	2.14	Unadjusted IRR	1.02	0.92 to 1.13	0.664
SD (number of exacerbations)	1.96	1.92	Adjusted IRR[a]	1.00	0.91 to 1.10	0.934
Exacerbations requiring hospital admission						
Total number included in analysis	591	589				
Number with at least one exacerbation	76	88				
Total number of exacerbations	92	126				
Mean number of exacerbations	0.16	0.21	Unadjusted IRR	0.74	0.53 to 1.03	0.072
SD (number of exacerbations)	0.45	0.61	Adjusted IRR[a]	0.70	0.50 to 0.97	0.031
Time to first exacerbation (from randomisation)						
Total number included in analysis[b]	578	583				
Number with at least one exacerbation	468	459				
Percentage with at least one exacerbation	81.0	78.7				
Median time to first exacerbation (days)	221	232	Unadjusted HR	1.04	0.91 to 1.18	0.576
25th percentile [time to first exacerbation (days)]	132	126	Adjusted HR[a]	1.02	0.90 to 1.16	0.733
75th percentile [time to first exacerbation (days)]	341	339				

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.
b Number included is reduced because the date of onset of first exacerbation was missing for 19 participants.

Mortality (all cause and respiratory related)

There were 22 deaths (from all causes) during the 12-month follow-up period in the per-protocol population: 13 (2.2%) in participants taking theophylline and nine (1.5%) in participants taking placebo. These deaths were respiratory related in five cases in each of the theophylline and placebo groups. The unadjusted HR for deaths from all causes was 1.45 (95% CI 0.62 to 3.38); for deaths from respiratory-related causes, the HR was 1.00 (95% CI 0.29 to 3.46) for theophylline relative to placebo (see *Table 22*). Therefore, there was no evidence of a significant difference between treatment groups for mortality outcomes in the per-protocol population. No adjustments were made because of small event counts.

TABLE 22 Secondary clinical outcomes (per-protocol analysis)

Non-COPD-related hospital admissions	Trial arm		Adjusted or unadjusted	Estimate	95% CI	*p*-value
	Theophylline	Placebo				
Emergency hospital admissions (non-COPD related)						
Total number included in analysis	587	589				
Number with at least one emergency hospital admission	45	66				
Total admissions	66	85				
Mean admission rate	0.11	0.14	Unadjusted IRR	0.77	0.51 to 1.17	0.220
SD admission rate	0.49	0.45	Adjusted IRR[a]	0.82	0.54 to 1.24	0.351
All-cause mortality						
Total number included in analysis	591	589				
Number deceased within 12 months	13	9	Unadjusted HR	1.45	0.62 to 3.38	0.394
% deceased within 12 months	2.2	1.5				
Respiratory related mortality						
Total number included in analysis	591	589				
Number deceased within 12 months	5	5	Unadjusted HR	1.00	0.29 to 3.46	0.998
Percentage deceased within 12 months	0.9	0.9				
Pneumonia						
Total number included in analysis	591	589				
Number with pneumonia	9	5	Unadjusted OR	1.81	0.60 to 5.44	0.291
Percentage with pneumonia	1.5	0.9				
Total daily dose ICS						
Total number included in analysis	589	588				
Number changed medication from baseline	78	93				
Mean ICS daily dose at end of follow-up (μg)	1617	1605	Unadjusted mean difference	12.2	–67.6 to 92.1	0.764
SD (ICS daily dose at end of follow-up) (μg)	693	704	Adjusted mean difference[a]	12.5	–65.9 to 90.9	0.754
Change in daily ICS dose from baseline						
Total number included in analysis	589	588				
Mean change in daily ICS dose from baseline (μg)	–62	–60	Unadjusted mean difference	–1.60	–45.4 to 42.3	0.943
SD (change in daily ICS dose from baseline) (μg)	347	417	Adjusted mean difference[a]	–0.58	–44.3 to 43.1	0.979

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

Total number of episodes of pneumonia

There were 14 episodes of pneumonia: nine (out of 591, 1.5%) among low-dose theophylline-adherent/compliant participants and five (out of 589, 0.9%) among placebo-compliant participants. The unadjusted IRR was 1.81 (95% CI 0.60 to 5.44) and no adjustments were made because of small event counts (see *Table 22*).

Total dose of inhaled corticosteroids

The total daily dose of ICS at baseline was available for 1176 of the 1180 members of the per-protocol population. During the 12-month follow-up, 171 participants changed their medication: 78 (13.2%) theophylline participants and 93 (15.8%) placebo participants ($p = 0.210$). The mean total daily beclomethasone-equivalent dose at the end of follow-up was 1617 µg (SD 693 µg) in those allocated to theophylline and 1605 µg (SD 704 µg) in those allocated to placebo, resulting in an adjusted daily beclomethasone-equivalent difference of 12.5 µg (95% CI –65.9 to 90.9 µg) between theophylline and placebo (see *Table 22*); this difference was not significantly different. Both groups showed a slight reduction in total daily dose from baseline to end of follow-up, but a comparison of the adjusted mean dose change between treatment groups revealed that the difference was not significant ($p = 0.979$).

Lung function (% predicted forced expiratory volume in 1 second and forced vital capacity)

In the per-protocol analysis, lung function profile was similar in both treatment groups. The mean % predicted FEV_1 at the end of the 12-month follow-up period was slightly lower in the compliant/adherent theophylline group than in the placebo group [51.3% (SD 20.3%) ($n = 455$) vs. 52.6% (SD 21.8%) ($n = 432$)], giving an overall difference between the groups of –1.33% (95% CI –3.47% to 0.80%) (*Table 23*). A similar pattern was observed for % predicted FVC, with an overall difference of –0.65% (95% CI –2.96% to 1.67%). This was a larger reduction than that observed in the ITT analysis, but remained non-significant.

Modified Medical Research Council dyspnoea scale

Tables 24 and *25* detail the responses to the mMRC dyspnoea scale at baseline, 6 months and 12 months for each treatment group in the per-protocol population. In the unadjusted model, the OR for higher mMRC dyspnoea score in theophylline participants compared with placebo participants is 1.54 (95% CI 1.05 to 2.26); the adjusted OR is 1.39 (95% CI 0.97 to 1.98).

The COPD Assessment Test

The CAT scores were very similar between treatment groups at baseline (*Table 26*) and remained similar through to 12 months, with a mean score of 21.0 (SD 8.2) for theophylline-adherent/compliant participants ($n = 534$) and 20.9 (SD 8.7) for placebo participants ($n = 527$) in the per-protocol population. A comparison of the profile of the CAT scores across the three time points (0, 6 and 12 months) showed an adjusted difference of 0.29 (95% CI –0.45 to 1.04), suggesting that the impact of COPD on participants' lives did not significantly different between the groups of the per-protocol population.

Hull Airway Reflux Questionnaire

At 12 months, the mean HARQ score was 23.0 (SD 15.6) among 153 theophylline-adherent/compliant participants and 24.4 (SD 15.8) among 141 placebo-adherent/compliant participants. A comparison of the profile of the HARQ scores across the three time points (0, 6 and 12 months) showed an adjusted difference of –1.62 (95% CI –4.25 to 1.01), suggesting no significant difference between the per-protocol treatment groups in reflux-associated respiratory symptoms measured by the HARQ (see *Table 26*).

TABLE 23 Lung function (per-protocol analysis)

Outcome	Trial arm		Adjusted or unadjusted	Overall mean difference	95% CI	*p*-value
	Theophylline	Placebo				
FEV_1% predicted						
Baseline						
Total (*n*)	588	583				
Mean	50.7	52.8				
SD	20.5	20.0				
6 months						
Total (*n*)	471	471				
Mean	52.0	53.7				
SD	20.8	20.8				
12 months						
Total (*n*)	455	432				
Mean	51.3	52.6	Unadjusted	–1.41	–3.65 to 0.82	0.215
SD	20.3	21.8	Adjusted[a]	–1.33	–3.47 to 0.80	0.221
FVC% predicted						
Baseline						
Total (*n*)	586	582				
Mean	84.2	86.6				
SD	22.9	23.5				
6 months						
Total (*n*)	467	467				
Mean	84.3	84.6				
SD	23.0	24.3				
12 months						
Total (*n*)	449	431				
Mean	83.3	82.6	Unadjusted	–0.84	–3.25 to 1.56	0.492
SD	23.2	25.3	Adjusted[a]	–0.65	–2.96 to 1.67	0.584

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

TABLE 24 The mMRC dyspnoea scale (per-protocol analysis)

Time point	mMRC category[75]	Trial arm (*N*, *n* %)	
		Theophylline	Placebo
Baseline	Not troubled by breathlessness except on strenuous exercise	586, 26, 4.4	584, 44, 7.5
	Short of breath when hurrying or walking up a slight hill	586, 160, 27.3	584, 176, 30.1
	Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace	586, 198, 33.8	584, 181, 31.0
	Stops for breath after walking about 100 m or after a few minutes on level ground	586, 157, 26.8	584, 149, 25.5
	Too breathless to leave house, or breathless when dressing/undressing	586, 45, 7.7	584, 34, 5.8
6 months	Not troubled by breathlessness except on strenuous exercise	560, 34, 6.1	552, 46, 8.3
	Short of breath when hurrying or walking up a slight hill	560, 182, 32.5	552, 160, 29.0
	Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace	560, 161, 28.8	552, 155, 28.1
	Stops for breath after walking about 100 m or after a few minutes on level ground	560, 142, 25.4	552, 153, 27.7
	Too breathless to leave house, or breathless when dressing/undressing	560, 41, 7.3	552, 38, 6.9
12 months	Not troubled by breathlessness except on strenuous exercise	535, 32, 6.0	527, 47, 8.9
	Short of breath when hurrying or walking up a slight hill	535, 167, 31.2	527, 149, 28.3
	Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace	535, 146, 27.3	527, 153, 29.0
	Stops for breath after walking about 100 m or after a few minutes on level ground	535, 147, 27.5	527, 135, 25.6
	Too breathless to leave house, or breathless when dressing/undressing	535, 43, 8.0	527, 43, 8.2

TABLE 25 The ORs for the mMRC dyspnoea scale (per-protocol analysis)

OR	Estimate	95% CI	*p*-value
Unadjusted	1.54	1.05 to 2.26	0.028
Adjusted[a]	1.39	0.97 to 1.98	0.074

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

TABLE 26 Patient-reported outcomes (per-protocol analysis)

Time point	Trial arm		Adjusted or unadjusted	Overall mean difference	95% CI	*p*-value
	Theophylline	Placebo				
CAT score						
Baseline						
Total (*n*)	584	583				
Mean	22.7	21.8				
SD	7.5	7.9				
6 months						
Total (*n*)	560	555				
Mean	21.0	20.5				
SD	8.2	8.2				
12 months						
Total (*n*)	534	527				
Mean	21.0	20.9	Unadjusted	0.52	–0.29 to 1.33	0.212
SD	8.2	8.7	Adjusted[a]	0.29	–0.45 to 1.04	0.444
HARQ score						
Baseline						
Total (*n*)	153	152				
Mean	25.2	26.8				
SD	15.9	14.7				
6 months						
Total (*n*)	160	151				
Mean	21.2	22.5				
SD	14.8	15.6				
12 months						
Total (*n*)	153	141				
Mean	22.9	24.4	Unadjusted	–1.39	–4.17 to 1.40	0.329
SD	15.6	15.8	Adjusted[a]	–1.62	–4.25 to 1.01	0.227

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

Sensitivity analysis

We undertook a sensitivity analysis for the primary outcome and a number of secondary outcomes that excluded the 33 participants who died during the 12-month follow-up period. This left 1503 participants in the ITT population (753 theophylline and 750 placebo). *Appendix 5*, *Tables 41* and *42*, give the details of these analyses.

Primary outcome

After excluding participants who died, the adjusted IRR for COPD exacerbations was 0.99 (95% CI 0.91 to 1.07) (see *Appendix 5, Table 41*), indicating that restricting the result to those who were alive for the full 12-month follow-up did not change the result of the original ITT analysis (IRR 0.99, 95% CI 0.91 to 1.08).

Secondary outcomes

Hospital admissions

Excluding the 33 deaths from the analysis of COPD exacerbations necessitating hospital admission, the adjusted IRR was 0.73 (95% CI 0.55 to 0.97) in the remaining 1503 members of the ITT population, which is very similar to the treatment estimate observed for all 1536 members of the ITT population (IRR 0.72, 95% CI 0.55 to 0.94). Data on admission to hospital for non-COPD reasons were available for 1485 people, after excluding those who died. The adjusted IRR for admission for theophylline relative to placebo was 1.03 (95% CI 0.73 to 1.43), compared with 0.99 (95% CI 0.71 to 1.38) in the full ITT population.

Other

Excluding the 33 deaths made very little difference to the estimates of treatment effect on lung function (FEV_1 or FVC) or to the patient-reported outcomes of CAT and HARQ scores (see *Appendix 5, Table 42*). For FEV_1, the adjusted difference was –0.58% (95% CI –2.46% to 1.29%) compared with –0.56% (95% CI –2.42% to 1.30%). For FVC, the adjusted difference was –0.37% (95% CI –2.43% to 1.69%) compared with –0.28% (95% CI –2.33% to 1.76%) for the ITT population. For the CAT score, the treatment difference was 0.02 (95% CI –0.65 to 0.69) compared with 0.01 (95% CI –0.65 to 0.69) in the original ITT population. The HARQ analysis gave an adjusted difference of –0.89 (95% CI –3.27 to 1.50) compared with –1.10 (95% CI –3.46 to 1.26) of the original ITT population. In summary, excluding the 33 deaths made little or no difference to the estimates of treatment effect in the ITT population.

Summary

There was no evidence that, overall, low-dose theophylline significantly reduced the number of COPD exacerbations requiring treatment compared with placebo. There was some evidence that low-dose theophylline reduced exacerbations that necessitated hospital admission, with most benefit being evident in a small [1% (13/1556)] subgroup of patients frequently hospitalised with COPD. The total number of emergency hospital admissions (non-COPD related) did not significantly differ between groups, and nor did total episodes of pneumonia or mortality. Lung function was similar across the 12-month follow-up in the two groups. The impact of the disease on patients was measured by the CAT, mMRC dyspnoea scale and HARQ; no significant differences were found. The safety profile of low-dose theophylline was similar to placebo. There was no evidence that the treatment effect differed in any of the prespecified subgroups.

Chapter 5 Cost-effectiveness

This chapter reports the health economics results from the trial. The objective of the health economics study was to determine the cost-effectiveness of adding low-dose theophylline to ICS therapy over a 12-month period. Mean resource use per participant is presented, along with levels of missing data and mean unadjusted and adjusted costs.

Baseline resource use and costs

Baseline resource use and costs are presented in *Table 27*.

There is no significant difference between the arms for any of these baseline resources.

TABLE 27 Baseline resource use and costs (per participant)

Resource use	Trial arm, mean (SD)	
	Theophylline	Placebo
Resource use		
Exacerbations		
Exacerbations requiring treatment in the previous 12 months	3.63 (2.22); *n* = 772	3.52 (2.08); *n* = 764
Exacerbations resulting in hospitalisation in the previous 12 months	0.404 (0.840); *n* = 768	0.358 (0.918); *n* = 758
Non-exacerbation resource use (mean number of uses per participant in the 6 months prior to randomisation)		
COPD maintenance treatment at baseline	*n* = 769	*n* = 758
Inhaled SABA	0.967 (0.177)	0.972 (0.164)
Inhaled combined ICS LABA	0.966 (0.181)	0.960 (0.195)
Inhaled short-acting muscarinic antagonist	0.068 (0.251)	0.065 (0.246)
Inhaled ICS	0.043 (0.203)	0.040 (0.195)
Inhaled non-combination LABA	0.018 (0.134)	0.029 (0.168)
Inhaled LAMA	0.805 (0.397)	0.817 (0.387)
Nebulised ipratropium	0.051 (0.291)	0.041 (0.246)
Nebulised SABA	0.204 (0.536)	0.185 (0.491)
Oral mucolytics	0.247 (0.432)	0.248 (0.432)
Oral leukotriene antagonists	0.042 (0.200)	0.041 (0.198)
Long-term antibiotics	0.066 (0.249)	0.059 (0.236)
Regular medication		
Count[a]	4.65 (3.64); *n* = 772	4.41 (3.54); *n* = 764
Costs[b] (£)		
Baseline COPD maintenance treatment costs[c]	*n* = 769	*n* = 758
Inhaled SABA	17.50 (3.20)	17.60 (3.00)
Inhaled combined ICS and LABA	325.00 (1897)	247.00 (486)
Inhaled short-acting muscarinic antagonist	2.77 (10.30)	2.64 (10.10)

continued

TABLE 27 Baseline resource use and costs (per participant) (*continued*)

Resource use	Trial arm, mean (SD)	
	Theophylline	Placebo
Inhaled ICS	7.28 (50.80)	8.27 (71.20)
Inhaled non-combination LABA	3.89 (28.60)	6.20 (35.90)
Inhaled LAMA	164.00 (80.90)	167.00 (79.00)
Nebulised ipratropium	4.78 (26.30)	4.19 (24.00)
Nebulised SABA	8.55 (21.30)	8.14 (20.40)
Oral mucolytics	34.70 (60.70)	34.90 (60.80)
Oral leukotriene antagonists	0.44 (2.10)	0.43 (2.08)
Long-term antibiotics	21.00 (88.00)	25.70 (275)
Total baseline COPD maintenance treatment costs	590.00 (1904)	522.00 (571)

a Count (medication); mean number of non-COPD medications taken by each participant.
b Baseline resource use was collected for current use of COPD maintenance treatment and regular medication. For calculating baseline resource use and costs, we have assumed this usage to be for the 6 months prior to baseline.
c Baseline costs are calculated for the previous 6 months, based on the medications used at baseline.

Resource use

Table 28 reports the mean resource use per participant for complete cases, during the 12-month follow-up period.

As discussed in *Chapter 4*, the treatment of exacerbations at hospital was significantly different between groups: more exacerbations were treated in hospital in the placebo group than in the theophylline group ($p = 0.02$).

TABLE 28 Twelve-month resource use for complete cases (per participant)

Resource use	Trial arm, mean (SD)	
	Theophylline ($n = 743$)	Placebo ($n = 727$)
Exacerbation resource use[a] (mean number of uses per participant in the 12-month follow-up period)		
Increased use of SABA	1.01 (1.51)	1.04 (1.60)
Increased/started nebulised bronchodilator	0.288 (0.836)	0.318 (0.910)
OCS	1.72 (1.87)	1.68 (1.79)
Antibiotics	2.01 (1.83)	2.01 (1.84)
Oxygen	0.129 (0.511)	0.142 (0.541)
Other	0.075 (0.320)	0.076 (0.354)
Treated at home	2.08 (1.92)	2.10 (1.90)
Care by services to prevent hospitalisation	0.086 (0.379)	0.100 (0.416)
Admitted to hospital	0.179 (0.497)	0.253 (0.676)

TABLE 28 Twelve-month resource use for complete cases (per participant) (*continued*)

Resource use	Trial arm, mean (SD)	
	Theophylline ($n = 743$)	Placebo ($n = 727$)
Non-exacerbation resource use		
COPD maintenance treatment (mean number of uses per participant in the 12-month follow-up period)		
Inhaled SABA	0.926 (0.262)	0.934 (0.248)
Inhaled combined ICS LABA	0.918 (0.275)	0.922 (0.269)
Inhaled short-acting muscarinic antagonists	0.069 (0.253)	0.062 (0.241)
Inhaled ICS	0.039 (0.194)	0.044 (0.205)
Inhaled non-combination LABA	0.032 (0.177)	0.047 (0.211)
Inhaled LAMA	0.817 (0.387)	0.824 (0.381)
Nebulised ipratropium	0.046 (0.209)	0.037 (0.189)
Nebulised SABA	0.157 (0.364)	0.176 (0.381)
Oral mucolytics	0.285 (0.452)	0.294 (0.456)
Oral leukotriene antagonists	0.046 (0.209)	0.044 (0.205)
Long-term antibiotics	0.092 (0.289)	0.085 (0.279)
Non-exacerbation health services use		
Inpatient		
General medical ward stays (number of stays)	0.059 (0.263)	0.084 (0.406)
Long-stay ward stays (number of stays)	0.004 (0.063)	0 (0)
Other inpatient services (number of contacts)	0.027 (0.192)	0.022 (0.173)
Outpatient		
Hospital day-case admissions (number of admissions)	0.187 (0.900)	0.169 (0.530)
Hospital outpatient appointments (number of appointments)	1.68 (2.63)	1.58 (2.66)
Accident and emergency (no overnight admission; number of visits)	0.137 (0.490)	0.128 (0.513)
Other inpatient services (number of admissions)	0.514 (2.87)	0.476 (2.23)
Primary care services		
Emergency GP visit	1.03 (1.97)	1.01 (2.10)
Routine GP visit	3.18 (4.33)	2.84 (3.83)
Community district nurse (number of appointments)	0.801 (9.64)	0.631 (3.50)
Hospital at home team (number of contacts)	0.101 (1.01)	0.158 (2.92)
Other primary care services (number of contacts)	2.16 (5.37)	1.77 (3.68)
Non-COPD emergency hospital admissions		
Emergency hospital admissions	0.150 (0.555)	0.158 (0.468)
Regular medication count		
Regular medication count[b]	4.34 (3.55)	4.32 (3.51)

a Mean number of times each treatment was used for exacerbations per participant.
b Count (medication); mean number of non-COPD medications taken by each participant.

Missing data

The disaggregated level of missing data affecting resource use is reported below; these are broken down into exacerbations, COPD maintenance treatment and non-COPD emergency hospital admissions.

Exacerbations (length of exacerbation, treatment costs and location of treatment)

A total of 3430 exacerbations were recorded:

- In 329 participants, data on length of exacerbation were missing (5.9% missing data points).
- In 210 recorded exacerbations, the location of treatment marker was missing (3.4% missing data points).
- In 46 participants with exacerbations treated in hospital, length of stay data were missing.
- In 171 recorded exacerbations, treatment cost was missing (1% missing data points).

Maintenance chronic obstructive pulmonary disease treatment

A total of 82 participants had missing total COPD maintenance costs (5.6% missing data points); these missing data were replaced with a treatment-specific mean.

Non-chronic obstructive pulmonary disease emergency hospital admissions

A total of 235 non-COPD emergency hospital admissions were recorded:

- Nine participants had missing length of stay data for emergency hospital admissions (2.8% missing data points).

All missing resource data were replaced using pragmatic, naive methods suitable for use when < 10% of data are missing.

Table 29 presents the missing economic data for resource use and EQ-5D-3L completion.

Resource use data were available for 743 participants in the theophylline arm and 727 in the placebo arm; resource use data during the follow-up period were not captured for 29 (3.8%) participants in the theophylline arm and 37 (4.8%) participants in the placebo arm. Overall, 66 (4.3%) participants were missing resource use data for the whole 12-month follow-up period.

The number of participants with missing EQ-5D-3L data was 137 (17.7%) in the theophylline arm and 156 (20.4%) in the placebo arm. Overall, 293 (19.1%) EQ-5D-3L questionnaires were missing.

TABLE 29 Missing resource use and EQ-5D-3L data

Data	Trial arm, *n* (%)		Total, *n* (%)
	Theophylline	Placebo	
Cost			
ITT population	772 (100)	764 (100)	1536 (100)
No resource use captured during follow-up	29 (3.8)	37 (4.8)	66 (4.3)
Complete cases	743 (96.2)	727 (95.2)	1470 (95.7)
EQ-5D-3L			
ITT population	772 (100)	764 (100)	1536 (100)
Missing EQ-5D-3L data at baseline/6 months or 12 months	137 (17.7)	156 (20.4)	293 (19.1)
Complete cases	635 (82.3)	608 (79.6)	1243 (80.9)

Costs

Table 30 reports complete-case costs (unadjusted). Differences between arms are calculated using a GLM with identity link, gamma family and a cluster for centre number. Regular medication was not included in these costs because there was no significant difference between arms in regular medication count.

There is a significant difference of £452 (95% CI £133 to £771) in the mean total costs between arms, with placebo being more costly than theophylline. This difference is driven by the difference in exacerbation mean costs between arms: £447 (95% CI £186 to £709) higher in the placebo arm. The difference in exacerbation costs is driven by the location of the treatment of an exacerbation. The mean 'location of exacerbation treatment' cost is £422 (95% CI £171 to £673) higher in the placebo arm than in the theophylline arm. As presented in *Chapter 4*, this is driven by a higher number of exacerbations treated in hospital in the placebo arm than in the theophylline arm. This is reflected in the health economics analysis for which the location of treatment costs are further broken down into 'treatment at home', 'care by services to prevent hospitalisation' and 'admitted to hospital'. The 'treatment at home' and 'care by services to prevent hospitalisation' resource use costs show no significant differences between arms; however, the 'admitted to hospital' cost is £416 (95% CI £177 to £655) higher in the placebo arm than in the theophylline arm, which is a statistically significant result.

At a per-exacerbation level, this difference can be explored further. The mean cost per exacerbation treated in hospital is £3613 [standard error (SE) £342] in the placebo arm and £2671 (SE £220) in the theophylline arm, a significant difference of £941 (SE £386) (95% CI £140 to £1743). The 10 most costly observations (> £10,000) were all in the placebo arm, and were the result of hospital stays of > 40 days. Because of the lack of treatment effect, we believe this difference to be a chance finding and not a real result of the trial. The distribution for length of hospital stay is similar for both arms apart from a small excess of participants in the placebo arm with longer stays. It is important to note that the proxy for hospital length of stay is length of exacerbation and that this is likely to overestimate length of stay in hospital. In total, 319 exacerbations were treated in hospital: 185 in the placebo arm and 134 in the theophylline arm.

TABLE 30 Complete-case costs (unadjusted)

Costs	Trial arm, mean (SD) (£)		Difference (£)	95% CI (£)
	Theophylline	Placebo		
Intervention costs	22 (0.24)	0 (0)	22	22 to 22
Exacerbation costs				
Total exacerbation costs	585 (1682)	1033 (3383)	–447	–709 to –186
Total location costs	535 (1594)	958 (3185)	–422	–673 to –171
Location				
Home	67 (61)	68 (60)	–1	–6 to 4
Services	33 (145)	38 (159)	–5	–23 to 12
Hospital	436 (1538)	852 (3142)	–416	–655 to –177
Treatment	50 (167)	75 (296)	–25	–41 to –8
Non-exacerbation costs				
COPD maintenance treatment	974 (379)	978 (416)	–4	–45 to 38
Health services resource use (not exacerbation related)	819 (1,224)	862 (1812)	–43	–175 to 89
Non-COPD-related emergency hospital admissions	282 (1529)	262 (1136)	20	–102 to 143
Total costs	2684 (2882)	3136 (4851)	–452	–771 to –133
Non-intervention, non-exacerbation costs	2075 (2079)	2101 (2528)	–26	–234 to 181

The cost of treatment of exacerbations differed significantly between arms, the mean cost per participant being £25 lower in the theophylline arm. At a per-exacerbation level, this is driven by treatment with oxygen. The mean cost of oxygen use per exacerbation treated with oxygen was £141 (SE £52) (95% CI £40 to £243) lower in the theophylline arm than in the placebo arm. The difference in oxygen treatment is driven by the fact that seven participants, six of whom were in the placebo group, were treated with oxygen for > 51 days, at a cost per exacerbation of > £1000.

The wide SDs for hospitalised exacerbations, treatment of exacerbations, non-COPD emergency hospital admissions and other health services use indicate a wide range of individual participants' costs in these resource groups.

No other resource use costs are significantly different between arms, which is reflected in the fact that there was no difference between arms for the non-intervention, non-exacerbation costs presented in *Table 30*.

Economic outcome

Complete-case EQ-5D-3L data and QALYs are reported in *Table 31*.

Utilities from the EQ-5D-3L data at baseline and the 6- and 12-month follow-ups and QALYs are higher in the placebo arm than in the theophylline arm; however, these differences are not significant.

Multiple imputation

Multiple imputation results are presented in *Table 32* for costs and QALYs.

TABLE 31 Complete-case EQ-5D-3L utilities and QALYs for the 12-month trial period

	Trial arm, mean (SD)		
Time point	Theophylline	Placebo	Difference (95% CI)
Baseline	0.629 (0.280)	0.643 (0.279)	–0.014 (–0.045 to 0.017)
6 months	0.630 (0.296)	0.642 (0.295)	–0.012 (–0.045 to 0.021)
12 months	0.622 (0.292)	0.623 (0.308)	–0.001 (–0.034 to 0.032)
QALYs over 12 months[a]	0.626 (0.259)	0.637 (0.263)	–0.011 (–0.040 to 0.018)

a There were 33 deaths in the ITT population; these participants had QALYs allocated to them for the period they were alive, on a monthly basis.

TABLE 32 Multiple imputation results (unadjusted)

	Trial arm, mean (SE)		
Costs and QALYs	Theophylline	Placebo	Difference (95% CI)
Total costs (£)	2702 (110)	3141 (148)	–439 (–846 to –32)
Total QALYs	0.617 (0.010)	0.621 (0.010)	–0.004 (–0.031 to 0.024)

Multiple imputation results mirror the complete-case results, with costs significantly higher in the placebo arm (a difference of £439). Total QALYs are higher in the placebo arm; however, this is not a statistically significant result (a difference of 0.004).

Bootstrapping

To explore the robustness of these results, 1000 non-parametric bootstrapped samples were taken from the observed data. The results were plotted using a cost-effectiveness plane to illustrate the mean differences between the arms in incremental costs and QALYs.

Non-adjusted bootstrapped results are presented in *Figure 7*. This cost-effectiveness plane clearly illustrates that the majority of total mean costs are lower in the theophylline arm than the placebo arm, with the majority of incremental samples falling in the south-east and south-west quadrants of the cost-effectiveness plane (below the horizontal axis of £0). The majority of total mean QALYs are lower in the theophylline arm than in the placebo arm, represented by the majority of bootstrapping samples falling in the south-west quadrant where the placebo arm has higher mean QALYs than the theophylline arm. The cost-effectiveness plane includes an ellipse to illustrate the 95% confidence level.

This uncertainty is explored further using cost-effectiveness acceptability curves.

The unadjusted bootstrapped results are presented in *Figure 8*. At a willingness-to-pay threshold of £20,000, there is a 75% chance of theophylline being cost-effective. At £30,000, there is a 64% chance of theophylline being cost-effective. However, these results should be viewed with caution as there is no significant difference

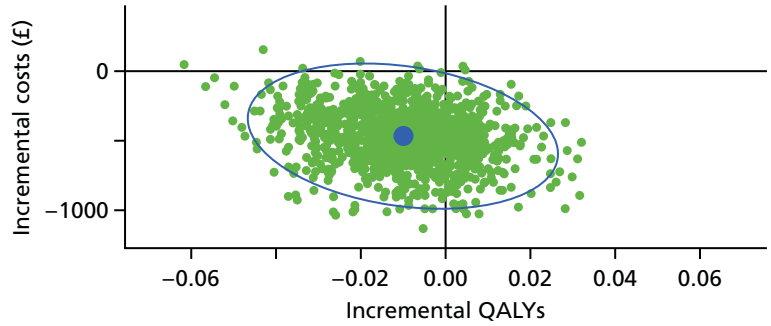

FIGURE 7 Cost-effectiveness plane (unadjusted).

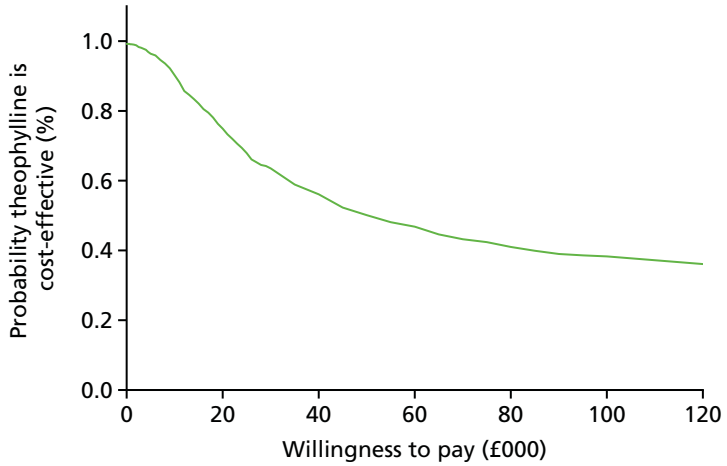

FIGURE 8 Cost-effectiveness acceptability curve (unadjusted).

in QALYs or clinical effect, and the difference in costs is driven by a very small number of participants with prolonged hospital admissions and the likelihood that the finding of a difference between arms for exacerbations treated in hospital is a chance finding. Moreover, as discussed in *Adjusted analysis*, the cost benefits of theophylline are not evident in multivariate models.

Adjusted analysis

Multiple imputation total mean costs were adjusted for baseline variables that were significant predictors of cost. These were medication count at baseline, EQ-5D-3L data at baseline, offset time (time spent in the trial), age, number of hospitalisations for exacerbations in the 12 months prior to randomisation and number of exacerbations in the 12 months prior to randomisation. A cluster command was used for centre number.

Multiple imputation total mean QALYs were adjusted for baseline variables that were significant predictors of QALYs. These were baseline EQ-5D-3L data, medication count at baseline, offset time, age, sex, hospitalisation for exacerbations in the 12 months prior to randomisation and exacerbations in the 12 months prior to randomisation. A cluster command was used for centre number. These results are presented in *Table 33*.

When multiple imputation total costs are adjusted, there is a trend towards higher costs in the placebo arm; however, this difference is not significant.

Adjusting QALYs for baseline characteristics results in theophylline having higher QALYs than placebo; however, this difference is not significant.

Figure 9 illustrates that, when the results are adjusted for baseline characteristics, the results are more uncertain: the majority of total mean costs in the theophylline arm are still lower than in the placebo arm, although this is now not a significant result. In addition, the QALYs are marginally higher in the theophylline arm, again not a significant result. The ellipse represents the 95% confidence levels.

The adjusted bootstrapped results are presented in a cost-effectiveness acceptability curve in *Figure 10*. At a willingness-to-pay threshold of £20,000, there is a 90% chance of theophylline being cost-effective. At £30,000, there is an 85% chance of theophylline being cost-effective. Again, these results should be viewed with caution as there was no significant difference between arms for QALYs or treatment effect.

Exacerbation costs were also adjusted separately to explore the adjustment on the significant difference in exacerbation costs between arms. Strong predictors of exacerbation costs were offset time, hospitalisation for exacerbations in the 12 months prior to randomisation and exacerbations in the 12 months prior to randomisation. A cluster command was used for centre number. These results are presented in *Table 34* and show that, for adjusted exacerbation costs, although there is a trend for higher costs in the placebo arm, this difference is not significant. The mean cost difference has decreased from £447 to £67.

TABLE 33 Multiple imputation results (adjusted)

	Trial arm, mean (SE)			
Costs and QALYs	Theophylline	Placebo	Difference (95% CI)	Cost-effectiveness
Total costs (£)	2784 (125)	3006 (167)	–222 (–472 to 27)	Theophylline dominates: fewer costs and higher QALYs
Total QALYs	0.621 (0.006)	0.616 (0.007)	0.005 (–0.015 to 0.025)	

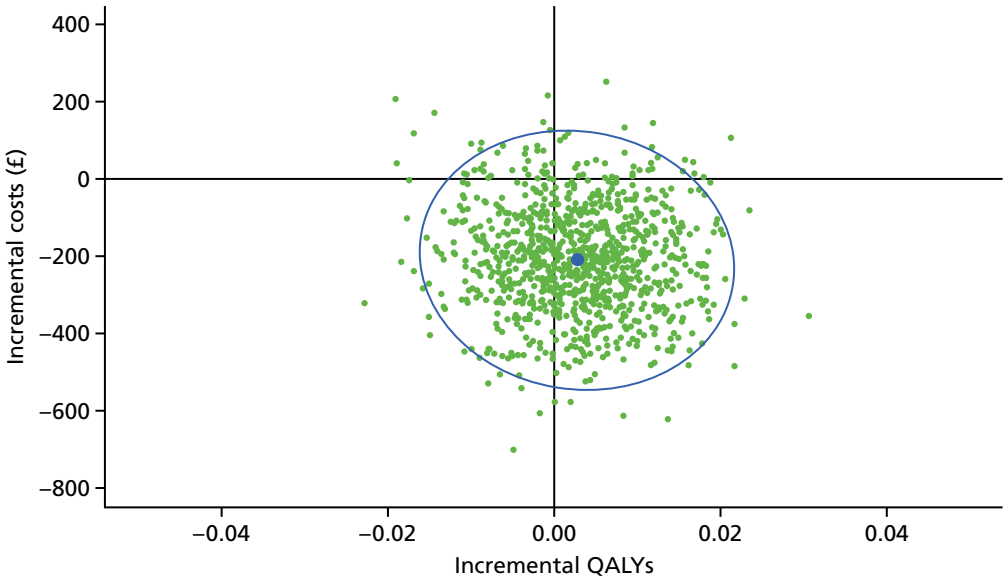

FIGURE 9 Cost-effectiveness plane (adjusted).

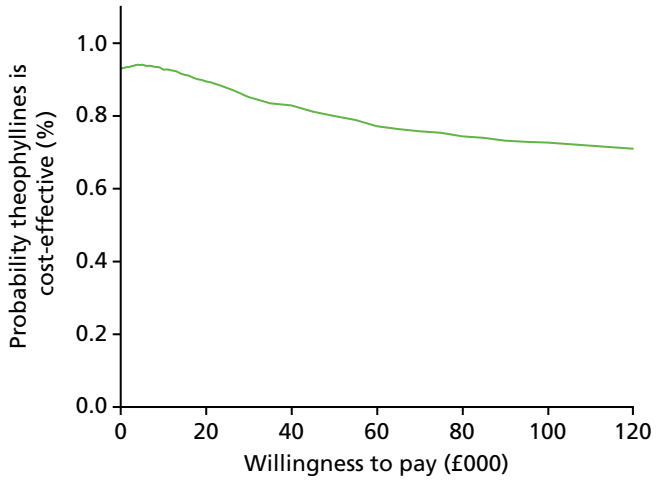

FIGURE 10 Cost-effectiveness acceptability curve (adjusted).

TABLE 34 Complete-case adjusted exacerbation costs

	Trial arm, mean (SE) (£)			
Costs	Theophylline	Placebo	Difference (£)	95% CI (£)
Total exacerbation cost	732 (96)	799 (71)	–67	–196 to 61
Location costs	675 (98)	735 (72)	–60	–190 to 68
Treatment costs	58 (11)	64 (8)	–6	–19 to 7

Cost-effectiveness

For cost per QALY, the unadjusted results suggest that, although theophylline is cheaper than placebo (significant result), the QALY gain is higher in the placebo arm than in the theophylline arm (non-significant result). The adjusted results suggest that theophylline dominates: it is cheaper than placebo and results in a higher QALY gain. However, this result should be interpreted with caution because the difference in QALYs is not significant. This is mirrored by the trial primary outcome: theophylline is not clinically effective in terms of reducing exacerbations.

Chapter 6 Discussion

Main results

The results of this trial show that, for people with COPD at high risk of exacerbation, the addition of low-dose oral theophylline to a drug regimen that includes an ICS confers no overall clinical or health economic benefit. This result was evident from both the ITT and the per-protocol analyses. The primary outcome measure for this trial was the total number of exacerbations of COPD requiring changes in management (minimum management change: use of OCSs and/or antibiotics) during the 1-year treatment period, as reported by the participant. For the 11 prespecified secondary outcome measures, the addition of low-dose theophylline had no clinical or health economic benefit in 10 of these measures. The addition of low-dose theophylline did reduce the number of COPD exacerbations necessitating hospital admission (often classified as 'severe')[68] (adjusted IRR 0.72, 95% CI 0.55 to 0.94); however, further inspection of the data indicated that this difference was the consequence of a small excess of participants allocated to placebo (n = 10) having three or more hospital-treated exacerbations, which accounted for 39 of the extra 51 hospital-treated exacerbations in the placebo arm. This effect on hospital admissions was also evident in the per-protocol analysis. Given that adjustments for multiple comparisons were not performed, it is possible that this finding could be due to type I error. However, in the light of a 2018 report[96] showing that another PDE inhibitor (roflumilast) is most beneficial in people with prior COPD hospitalisation for exacerbation and greater exacerbation frequency, this finding warrants further investigation. The safety data demonstrated that the addition of low-dose theophylline was not associated with an increase in SAEs or ARs.

Relevance to existing literature

Oral theophylline has been used in the treatment of COPD and asthma for > 70 years. Conventionally, oral theophylline has been used as a bronchodilator in COPD, this effect being mediated by inhibition of PDE. However, in order to achieve modest clinical effects, relatively high blood concentrations (of 10–20 mg/l) are required, but, at these concentrations, non-specific inhibition of PDE is also associated with a wide range of well-recognised side effects, for example nausea, palpitations and headaches. A Cochrane review published in 2002 and updated in 2010[83] identified 20 randomised placebo-controlled trials of theophylline in COPD, all of crossover design, using dosing schedules to obtain conventional plasma theophylline levels in the therapeutic range (10–20 mg/l), that is conventional high-dose theophylline. The number of participants in these trials ranged from 8 to 60; the total number of participants in the 20 trials was 488. The duration of the studies was 9–90 days, the mean age of participants ranged from 58 to 69 years and four of the studies were graded as being of high quality. The systematic review demonstrated that use of high-dose conventional theophylline resulted in a small but significant increase in FEV_1 of 100 ml (95% CI 40 to 160 ml). This was derived from 13 studies with 244 participants. Two studies with a total of 45 participants reported on the incidence of exacerbations, concluding that high-dose conventional theophylline had no effect on the incidence of exacerbations. Three studies with a total of 64 participants reported data on nausea, with the risk of experiencing nausea when on theophylline treatment being significantly increased (RR 7.67, 95% CI 1.47 to 39.94). When compared with previous trials of conventional high-dose theophylline in COPD, the current trial of low-dose theophylline that recruited 1578 participants is clearly somewhat larger and the treatment period is longer in duration. Moreover, in contrast to conventional high-dose theophylline trials with their focus on lung function, the primary outcome of the current study was exacerbations of COPD and the study population comprised participants at high risk of exacerbating. When compared with these trials of high-dose conventional theophylline, the current trial, as expected, showed no effect of low-dose theophylline on lung function (FEV_1) and, reassuringly, no increase in side effects. One of the findings from the Cochrane review[83] was that very few participants withdrew from intervention trials of high-dose conventional theophylline for any reason. In the review,[83] nine studies reported no dropouts, and in the

remaining studies the dropout rate was generally very low; the only exception to this low dropout rate was the study of Guyatt *et al.*,[97] who reported eight withdrawals out of 27 recruited participants (30%). The sample size of the current trial included an estimate of 6% of participants ceasing taking their trial medication, based on the four high-quality studies reported in the Cochrane review,[83] in which three out of 51 (6%) participants dropped out. The 26% of participants ceasing trial medication in the current study is greater than anticipated (although balanced across the arms) and more in keeping with the study of Guyatt *et al.*,[97] probably reflecting the pragmatic nature of the current trial, the fact that participants in the current trial were older than those in the Cochrane review and that the trial lasted longer.[83]

The use of high-dose conventional theophylline has declined over the years because of its narrow therapeutic index, modest clinical effect, side effect profile, drug interactions, the need for blood concentration monitoring and the availability of more effective inhaled therapies.[98] High-dose conventional theophylline is now included in current COPD guidelines as a third-line therapy.[1]

The concept of using low-dose theophylline to augment the anti-inflammatory effects of corticosteroids on the airway inflammatory processes in COPD originated from in vitro and animal studies investigating the molecular mechanisms contributing to the reduced corticosteroid sensitivity of COPD.[32,38–40,43,46] The key observation was that the reduced HDAC2 activity of COPD can be reversed by low concentrations (1–5 mg/l) of theophylline; moreover, theophylline reduces corticosteroid insensitivity in COPD, such that there is a marked synergistic interaction between theophylline and corticosteroids in suppressing the release of inflammatory mediators from alveolar macrophages obtained from COPD patients.[43,44] These basic research studies suggest that low-dose (i.e. 1–5 mg/l) theophylline could increase HDAC activity and, hence, reduce corticosteroid resistance in COPD patients, thereby enabling ICSs to switch off inflammation and potentially more effectively reduce exacerbation rates.

Prior to commencing the current study, the concept of using low-dose theophylline in conjunction with corticosteroids in COPD had been explored in two small RCTs. The first RCT was in 35 patients admitted to a Spanish hospital with an acute exacerbation of COPD who were treated with a regime that included systemic corticosteroids.[48] Participants were randomised to receive additional low-dose theophylline or nothing in a single-blind design; participants not on ICSs at admission were commenced on ICSs. After 3 months of treatment, low-dose theophylline increased sputum macrophage HDAC activity and reduced sputum concentrations of the pro-inflammatory mediators IL-8 and tumour necrosis factor alpha (TNF-α). There were no clinically significant effects in this small study,[48] although fewer participants in the theophylline group than in the control group had a subsequent exacerbation (12.5% vs. 26%). This study[48] differed from the current study in the following ways: small sample size, single blinded, no placebo control, 3-month follow-up, participants were recruited only during hospitalisation with exacerbations of COPD, all were male and only 14% had experienced two or more exacerbations in the previous year. Notably, 26% of participants were not followed up at 3 months.

The second small ($n = 30$) RCT of COPD patients was a double-dummy (low-dose theophylline vs. placebo, standardised dose of ICS vs. placebo), randomised, double-blind, parallel study, based in the UK.[49] After 4 weeks of low-dose theophylline, there was no effect on the primary outcome of absolute number of sputum neutrophils. The combination of low-dose theophylline/ICS significantly reduced a number of secondary end points (e.g. sputum percentage neutrophils, sputum total eosinophil count). In an open-label extension of the trial, the combination of low-dose theophylline/ICS increased peripheral blood mononuclear cell HDAC activity ninefold. The study concluded that the combination of ICS and low-dose theophylline may attenuate airway inflammation in patients with COPD. One of the limitations of this study was that the significant findings were for low-dose theophylline/ICS versus theophylline, rather than low-dose theophylline/ICS versus ICS, suggesting perhaps that the observed effects were a consequence of the ICS and not the low-dose theophylline. This study[49] differs from the current study in the following ways: 4-week duration, small numbers, 83% male and younger average age (61 years). Lung function (mean FEV_1 54%) was similar.

While the current trial was being conducted, two trials investigating the therapeutic consequences of low-dose theophylline were published.[52,99] The first study,[99] from India, was a hospital-based, single-blinded, prospective, randomised, placebo-controlled study that investigated the effects of adding low-dose theophylline to the combination of formoterol plus budesonide. A total of 58 patients with moderate/severe COPD were commenced on a standardised ICS/LABA therapy (budesonide and formoterol) and were randomised to receive in addition either low-dose theophylline or placebo for 60 days. Fifty participants completed the trial and their data were presented.[99] The addition of low-dose theophylline resulted in a greater improvement in total symptom scores, a greater increase in FEV_1 and a greater increase in 6-minute walking distance than did the addition of placebo. Of note, however, is that the method of randomisation was not described, the actual number of participants randomised to each treatment group was not presented, the nature of the 'single blind' was not explained and there was no ITT analysis. The randomisation appeared not to have eliminated potential sources of bias, as the participants allocated to low-dose theophylline were clearly more severely affected by COPD: their respiratory rate was greater (20.7 vs. 18.7 breathes per minute; $p = 0.003$), their FEV_1 values were lower (49% vs. 57% predicted; $p = 0.05$), their symptom scores were greater (10.17 vs. 8.37; $p = 0.003$), their 6-minute walking distance was shorter (373 m vs. 409 m; $p = 0.07$) and more were classified as having severe COPD (54% vs. 27%; $p = 0.09$).[99] Moreover, the placebo tablets were described as similar rather than identical. These differences could reflect a bias for the more severely affected participants to be preferentially allocated to the low-dose theophylline arm of the trial. This study[99] differs from the current study in the following ways: the sample size was much smaller and hospital based, 92% of participants were male, participants were younger (≈55 years), BMI was lower (≈17 kg/m^2), there was a 60-day treatment period and the trial was single blinded. In addition to the issues regarding blinding and randomisation, the results of the trial[99] also raise the possibility that, although the intention was to investigate low-dose theophylline, in reality, conventional high-dose theophylline was being tested: an improvement in FEV_1 was described with theophylline treatment and the dosing regimen for this study was 400 mg of theophylline for a weight of > 50 kg, 300 mg for a weight of 40–50 kg and 200 mg for a weight of < 40 kg. However, a significant proportion of participants appeared to be underweight, with a mean BMI of ≈17 kg/m^2, and theophylline treatment resulted in higher incidences of typical high-dose theophylline toxicity symptoms such as nausea, vomiting, headache, palpitation and insomnia. In the current study, this was avoided by basing theophylline dose on IBW and smoking status.

The second study, the Spanish ASSET trial,[52] was a multicentre, randomised, double-blind, placebo-controlled trial that recruited patients with COPD while they were hospitalised for a COPD exacerbation. Participants were randomised to low-dose theophylline (100 mg twice a day) or matched placebo in addition to ICS/LABA treatment; participants not routinely taking ICS/LABA were established on ICS/LABA. In total, 70 patients were randomised (theophylline, $n = 36$; placebo, $n = 34$) and 46 completed the year of treatment (theophylline, $n = 23$; placebo, $n = 23$). The co-primary outcomes were change in HDAC and exacerbation frequency during the 1-year treatment period. The addition of low-dose theophylline had no effect on plasma/sputum HDAC concentrations and no effect on COPD exacerbation rate [theophylline 0.97 (SD 0.94) vs. placebo 0.88 (SD 0.89)]. This trial[52] has some similarities with the current trial: primary outcome of exacerbation, same definition of exacerbation, 1-year treatment period, similar participant age, CAT score and levels of cardiovascular comorbidity at baseline, and no significant difference in ARs between groups. However, there are some important differences between the ASSET trial[52] and the current trial (TWICS). The current trial is much larger ($n = 1578$) than the ASSET trial ($n = 70$), being designed to detect a 15% reduction in exacerbations with 90% power, whereas the ASSET trial was designed to detect an arguably implausibly large 50% reduction in exacerbations with 80% power. The exacerbation rate in the ASSET trial was about half that observed for the TWICS trial (0.92 vs. 2.23 per year). Perhaps the most plausible explanation for this is that all participants in the ASSET trial were recruited while hospitalised with an exacerbation of COPD, irrespective of exacerbation history, whereas participants in the TWICS trial were clinically stable; 60% were identified from primary care and all had a history of two or more exacerbations in the previous year requiring treatment with antibiotics and/or corticosteroids. The proportion of participants ceasing trial medication was higher in the ASSET trial than in the TWICS trial (34% vs. 26%); however, it should be noted that 14% of participants in the ASSET trial ceased trial medication because their FEV_1 improved to > 50% predicted during the 1-year treatment period. This is most likely to be a consequence of the ASSET trial recruiting in the

peri-exacerbation period and the TWICS trial recruiting when participants were clinically stable. When compared with the TWICS trial, participants in the ASSET trial were more likely to be male, had more severe COPD (lower FEV_1) and were more likely to be hospitalised during the treatment period, but were less likely to be diabetic [probably reflecting the higher mean BMI of the TWICS trial participants (27 vs. 22 kg/m^2)].

The GOLD management strategy guideline[1] highlights that the clinical relevance of low-dose theophylline has not been fully established and that clinical evidence for an effect of low-dose theophylline, particularly on exacerbations, is limited and contradictory. The TWICS trial is the first large, pragmatic, community-based trial to investigate the effect of adding low-dose theophylline to the treatment regimen of people with COPD who are at a high risk of exacerbating despite a treatment regime that includes maintenance ICSs in COPD.

Pre-clinical work convincingly demonstrates that the combination of low-dose theophylline and corticosteroids has a strong biological effect, increasing HDAC and inhibiting the release of pro-inflammatory mediators.[38,39,41–44] The trials conducted to date have been small (n = 30–70), hospital based and have tended to focus on biological outcomes with short treatment periods.[48,49,52,99] The largest trial[52] to date in this field has reported that low-dose theophylline had no effect on HDAC or exacerbations; however, as the authors of the ASSET trial acknowledge, 'we might have overestimated the potential clinical benefit when we calculated the sample size, which may have precluded us from identifying a clear-cut clinical effect'.[52] The TWICS trial avoids many of the limitations of previous studies and clearly demonstrates that, in a NHS setting, the addition of low-dose oral theophylline to a drug regimen that includes an ICS confers no overall clinical benefit for people with COPD. The participants in the TWICS trial were a group of people with COPD who were at high risk of experiencing an exacerbation based on their history of exacerbating in the previous year. This group was deliberately chosen because of their impact on the NHS and it enabled us to design a trial of realistic (but ambitious) sample size. Although the TWICS trial did not investigate whether or not people with COPD who are at low risk of exacerbation would benefit from low-dose theophylline, the combination of the findings of the TWICS trial and the absence of a biological effect (HDAC concentrations) in the ASSET trial, despite a sample size that was 'more than enough to demonstrate a biological effect of the intervention',[52] make it highly unlikely that low-dose theophylline would be beneficial in COPD patients who are at low risk of exacerbation. A possible explanation for the disparity between the biological effects observed in previous studies, with short treatment periods, and the absence of beneficial effects in the TWICS trial, with a year-long treatment period, is that any biologically beneficial effect of low-dose theophylline is not sustained in the long term.

Cost-effectiveness

The health economics results indicate that, after adjustment for baseline characteristics, there was no significant difference between the total health economic costs associated with treatment with low-dose theophylline and the costs associated with placebo treatment: adjusted mean difference £222 (95% CI –£27 to £472). With unadjusted complete-case data, the total costs are higher in the placebo arm than in the theophylline arm: a significant difference of £452 (95% CI £132 to £771). This difference was driven by the fact that more participants in the placebo arm than in the theophylline arm received treatment for exacerbations in hospital. The 10 most costly observations (> £10,000) were all in the placebo arm, and were the result of hospital stays of > 40 days. The multiple imputation results mirror the complete-case results with a significant difference in unadjusted costs of £439 (95% CI £32 to £846) higher in the placebo arm.

The difference between arms in total costs is driven solely by the hospital-treated exacerbations and exacerbations treated with oxygen; no other resource group differs significantly between arms. The difference in the number of exacerbations necessitating hospital treatment is likely to be the result of a small number of participants in the placebo arm having very frequent hospital admissions. Therefore, these results should be interpreted with caution.

Exacerbation costs are 22% and 33% of the total costs (theophylline and placebo, respectively), somewhat less than the 60% reported by Britton *et al.*[27] in 2003, perhaps reflecting differences in management between 2003 and 2015/6, particularly in increased use of preventative drugs, pulmonary rehabilitation and more structured chronic disease management in primary care.

In the unadjusted complete-case analysis, QALY gain was higher in the placebo arm than in the theophylline arm (difference 0.011 QALYs, 95% CI –0.018 to 0.040 QALYs); however, the difference is not significant. Multiple imputation results mirrored the complete-case results; there were no significant differences, with unadjusted results favouring the placebo arm and adjusted results favouring the theophylline arm.

These results reflect the primary outcome of number of exacerbations needing treatment during the 12-month follow-up period; there was no significant difference between arms.

Hettle *et al.*[100] reported 4-year UK costs in their paper on tiotropium versus usual care in the UK and Belgium. Exacerbation costs ranged from £2295 to £2744 (£574–686 per year) and maintenance costs ranged from £2935 to £3937 (£737–984 per year). This compares to the 1-year costs from this research of exacerbations, ranging from £585 to £1033, and maintenance costs ranging from £2074 to £2101. Although the annual exacerbation costs in the current trial are similar to those of Hettle *et al.*,[100] the maintenance costs are somewhat higher, reflecting the older average age of participants in the current study (68.4 years vs. 64 years), and the facts that, in the current study, 80% of the participants were prescribed LAMAs (none for the usual care group in the Hettle *et al.*[100] study), participants with COPD using long-term oxygen were included and participants were more likely to be in the severest GOLD category (14% vs. 8%). Hettle *et al.*[100] also reported that in Belgium the cost of exacerbations resulting in hospitalisation was 33 times higher than the cost of exacerbations not necessitating hospitalisation, substantiating the increased cost of hospital treatment compared with non-hospital treatment of exacerbations that we found in this research.

The strengths of this research include the fact that there were few participants with no outcome or resource use (low proportion of missing cases: 4.3%), that uncertainty was explored using non-parametric bootstrapping and that, when there was a significant difference in exacerbation costs, this was explored further to identify what was driving this difference.

The two main limitations to the cost-effectiveness analysis are the large number of missing EQ-5D-3L questionnaires (19.1%) and the fact that small numbers of missing data were imputed using naive methods at a disaggregated level.

Strengths and limitations

The main strength of the TWICS trial is that it was a large, pragmatic, predominantly community-based, suitably powered, double-blind, randomised, placebo-controlled, UK multicentre clinical trial with a high follow-up rate for the primary clinical outcome. A total of 1578 individuals were recruited in 121 UK sites; 60% of these were identified in primary care, making it highly likely that the TWICS trial participants reflected normal clinical practice across both primary and secondary care in the UK. The 1-year treatment period allowed for capture of the seasonality of exacerbations.[101]

Originally, the TWICS trial aimed to recruit 1424 participants, the sample size being primarily based on the findings of the observational ECLIPSE cohort study of 2138 COPD patients recruited in 46 centres from 12 countries.[21] The ECLIPSE study demonstrated that the best predictor of an exacerbation in a year was a treated exacerbation in the previous year. The ECLIPSE study also identified a frequent exacerbator phenotype, defined as two or more exacerbations in the previous year; moreover, this frequent exacerbator phenotype was relatively stable for 3 years and could be reliably identified by patient report. For the patients experiencing frequent exacerbations recruited into the TWICS trial, data from the ECLIPSE study predicted a mean of 2.22 (SD 1.86) exacerbations in the year of treatment; the sample size for the TWICS trial was based on this. This prediction proved to be remarkably close to what we observed, increasing confidence in the findings, with a mean number of exacerbations in the theophylline arm of 2.24 (SD 1.99) and in the placebo arm of 2.23 (SD 1.97). A notable finding of the TWICS trial was an apparent disparity between the number of exacerbations reported by participants in the year prior to the trial [mean 3.59 (SD 2.15)] and the number of self-reported exacerbations in the treatment year, which was somewhat lower [mean 2.23 (SD 1.99)]. The most likely explanation for this disparity is that we did not ask for dates for the reported exacerbations in the year prior to the trial, whereas, during the trial, we asked for dates and the conventional minimum of 2 weeks between consecutive exacerbation episodes was necessary to consider exacerbations as separate.[68] This resulted in exacerbations that were separated by < 2 weeks being merged. Although further factors contributing to the disparity in exacerbations before and during the trial may include an over-reporting bias by participants and regression to the mean, the exacerbation frequency during the treatment period was remarkably consistent with that predicted by the ECLIPSE study. Although the exacerbation rate observed in the current trial is somewhat higher than in recent explanatory trials,[102,103] it is entirely consistent with the recent pragmatic UK Salford Lung Study.[104] The Salford Lung Study, with an inclusion criterion of one or more exacerbations in the previous year, reported exacerbation rates of 1.74–1.90 per year. The slightly higher exacerbation rate in the current trial most probably reflects the participants' increased propensity to exacerbate (two or more exacerbations in the previous year), as well as the lack of requirement to withhold therapy other than theophylline, meaning that investigators were happier to recruit patients at a higher risk of exacerbation. Although the diagnosis of COPD was confirmed by post-bronchodilator FEV_1/FVC of < 0.7, 18.3% of participants reported a concurrent/previous diagnosis of asthma. This may, in part, reflect a diagnostic bias towards the more socially acceptable diagnosis of asthma in the past, but it is possible that the current trial included up to 18% of participants with asthma–COPD overlap syndrome. Although it is possible that these patients may respond differently to the theophylline, whether or not people with asthma–COPD overlap syndrome responded differently to theophylline was not one of the trial objectives.

By recruiting 1578 individuals, 60% of whom were identified in primary care, the TWICS trial exceeded its original recruitment target of 1424 with at least 50% being recruited in primary care. It was initially envisaged that the TWICS trial would recruit from a limited number (seven) of secondary care sites, with primary care sites acting as PIC sites for these secondary care centres. Recruitment to the TWICS trial was delayed by 5 months because of a worldwide shortage of bottle tops for the drug bottles. Initially, recruitment in 16 primary and six secondary care sites was on target and the TWICS trial achieved its recruitment targets for the feasibility phase by recruiting 100 participants in months 7, 8 and 9, with 55% identified in primary care. Within 4 months, it became apparent that it would not be possible to sustain recruitment, with recruitment falling below the required 59 participants per month to a nadir of 26 in month 15 (October 2014). To address this, a change in recruitment strategy was implemented in month 12 (July 2014), with rapid increases in the number and rate of opening up of primary and secondary care sites. Ultimately, 121 recruiting sites were opened up, comprising 88 primary care sites and 33 secondary care sites. Other primary care practices acted as PICs for primary and secondary care sites. In total, 477 participants were recruited and followed up entirely in primary care, 464 participants were identified in primary care but recruited and followed up in secondary care (this was particularly the case in Scotland) and 637 participants were identified, recruited and followed up in secondary care. This change in recruitment strategy was successful, with monthly recruitment remaining above 50 per month from month 19 and reaching a peak of 81 in month 35.

Primary outcome data (number of COPD exacerbations) were collected on 98% of the 1567 participants who commenced the 1-year treatment period (1578 recruited minus 11 post-randomisation exclusions). Several factors contributed to the high follow-up rate. The TWICS trial was designed to be as inclusive as possible by facilitating participation of people with COPD who would normally find it too difficult to participate in a trial because of their ill health. The trial was designed to be relatively 'light touch', with three study visits to a local study centre. If participants were unable to attend for assessment, they were visited at home, contacted by telephone or sent the questionnaires to complete at home. Participation and remote follow-up were further facilitated by delivering the trial drug to participants' homes using a third-party distributor. All participants who ceased taking the trial drug were invited to remain in the trial for follow-up, by face-to-face assessment, telephone assessment or postal questionnaire. If participants could not be followed up directly, for example if they failed to attend follow-up, various methods of follow-up, independent of participant involvement, were used. In the first instance, the participant's GP was sent a questionnaire enquiring about exacerbations (number, dates, how and where treated); the minimum information requested was the number of exacerbations in the treatment period. Failing this, GP surgeries were contacted by telephone or a request was made for a redacted copy of patient encounter summaries from which the co-chief investigator extracted exacerbation data. The combination of follow-up methods enabled the ITT analysis to include 1489 years of participant follow-up data. Inevitably, there were some participants who did not provide a full 12 months of follow-up data, for example because they died, or for whom 12 months of follow-up data were not available even using a remote follow-up method. A strength of the TWICS trial was that the statistical analytical methods used enabled inclusion of these participants up to the point at which they were lost to follow-up, with their time in study utilised in the offset variable during analysis.

Previous studies investigating the potential anti-inflammatory effects of low-dose theophylline in COPD and asthma (not in conjunction with ICS) have used a 'one size fits all' dosing approach, that is all participants received 100 mg bd or 200 mg bd.[43,44,48,99,105–107] In contrast, one of the strengths of the TWICS trial was that theophylline dosing was somewhat personalised, being determined by IBW and smoking status. As noted in the protocol paper,[55] population studies have demonstrated that theophylline pharmacokinetics are influenced by weight, COPD disease status (reduced clearance) and smoking (increased clearance).[57–66,108] Smoking increases theophylline clearance by ≈60%, but the plasma theophylline level gradually returns to normal following smoking cessation. This was incorporated into the definition of a non-smoker in the TWICS trial and procedures were implemented to modify, when necessary, the dose of the trial drug in a timely manner if participants changed their smoking status during the treatment period. The use of IBW in preference to actual weight avoided the potential for giving an inappropriately high dose of theophylline to obese participants. In the TWICS trial, theophylline dosing was based on pharmacokinetic modelling, incorporating the major determinants of theophylline C_{ss}, namely weight, smoking status and clearance of theophylline (low, normal or high), and was designed to achieve a steady-state plasma theophylline concentration of 1–5 mg/l and certainly < 10 mg/l.[55] Theophylline is metabolised in the liver by the enzyme CYP1A2, which is induced by smoking and inhibited by a number of medications, with a consequent increase in plasma theophylline concentration. For this reason, the exclusion criteria included long-term use of drugs with the potential to increase plasma theophylline concentration;[94] conversely, concomitant use of drugs with the potential to lower plasma theophylline concentration was permitted in the trial. Reassuringly, the dosing regimen used for the TWICS trial appeared to be effective in establishing low-dose plasma theophylline concentrations of 1–5 mg/l because there was no evidence of the typical sequelae of conventional high-dose theophylline, such as an improvement in FEV_1. In addition, when compared with the placebo group, there was no evidence that participants allocated to low-dose theophylline experienced more SAEs or ARs, nor did they report SAEs or ARs typical of theophylline toxicity, namely gastrointestinal, cardiac, psychological or neurological symptoms. Furthermore, when the reasons for ceasing trial medication were analysed, there were no significant differences between the arms, notably for gastrointestinal, cardiac, psychological or neurological symptoms typical of theophylline toxicity. A consequence of the personalised dosing of the trial drug to achieve a low-dose plasma theophylline concentration well below that associated with typical side effects was that there was no need for blood sampling to monitor plasma theophylline, a necessity that would have greatly increased the complexity of the trial and increased the likelihood of

unblinding the participant and/or investigator. The absence of blood testing reduced costs and was extremely popular with primary care sites and contributed to the willingness of many primary care sites to participate in the TWICS trial. The potential limitation of relying on participant-reported smoking status is perhaps less important in this trial, as any smoker claiming to be a non-smoker would have been prescribed the lower dose of theophylline, thereby ensuring that plasma theophylline remained in the low-dose range of 1–5 mg/l.

As with all studies, there are limitations associated with the TWICS trial. The primary outcome for the trial was the number of participant-reported exacerbations during the 1-year treatment period; to facilitate recall, participants were given a diary card to make notes on exacerbations, treatment and health-care usage. The definition of an exacerbation was the widely used ATS/ERS guideline recommendation of a worsening of a patient's dyspnoea, cough or sputum beyond day-to-day variability sufficient to warrant a change in management.[68] The minimum management change was treatment with antibiotics or OCSs; consequently, the TWICS trial quantified only moderate and severe exacerbations. However, these exacerbations are the ones that are the most burdensome to patients and health-care services. A limitation of the TWICS trial is that the relatively conservative definition of exacerbation probably underestimates the frequency of symptom-defined mild exacerbations that are short-lived and treated by a patient with a temporary increase in bronchodilator therapy.[109] The identification of such mild exacerbations would have required participants to complete daily symptom diary cards, adding to the intrusiveness of the trial and considerably adding to the data-entry burden of research staff. Although the TWICS trial did not quantify mild exacerbations, there were no significant differences between the treatment and placebo arms in QoL/impact on health status as quantified by EQ-5D-3L/CAT, suggesting that either low-dose theophylline had no effect on mild exacerbations or, if there was an effect, it did not impact on health status/health-care usage.

A possible limitation of participant-reported exacerbations is the accuracy of such a report over a 6-month period. Although it would have been possible to obtain such exacerbation data from health-care records, it is well documented that people with COPD do not report all of their exacerbations to health-care professionals.[18,110–112] Patient recall of COPD exacerbations has been shown to be highly reliable over a year: in the London COPD cohort study,[112] there was no significant difference between the number of exacerbations recorded on diary cards and patient estimates of their exacerbation number over the same 1-year period [mean 2.4 (SD 2.2) vs. mean 2.3 (SD 2.1)] and there was 93% agreement between patient-recalled and diary-recorded exacerbations. There was, however, a difference between the number of treated exacerbations recorded on diary cards and the number of treated exacerbations remembered by the patient over the same 1-year period [mean 2.3 (SD 2.1) vs. mean 1.8 (SD 1.8)] and there was 88.6% agreement between patient-recalled and diary-recorded treated exacerbations.[112] The patient representatives helping with the TWICS trial were adamant that it was fairly straightforward to recall the number of exacerbations over a 6-month period. A small validation exercise was conducted at two of the largest sites (Aberdeen and Aintree) during the TWICS trial to confirm that participant recall was indeed valid. The validation was done by requesting a care/encounter summary from the GP and comparing this with the participant report. In Aberdeen, 43 records (a 20% sample) were checked; in 37 there was complete agreement between the participant and GP reports. In Aintree, 24 records were checked and in 16 there was complete agreement between the patient and GP reports. Therefore, in a 4% sample of participants, there was 80% agreement. This rate of agreement was slightly lower than that reported by Quint *et al.*;[112] however, current GP records may not be as reliable a source of exacerbation data as in the past, given that patients have rescue packs at home and can access help for their exacerbations through many non-GP sources, for example pharmacies, emergency and walk-in centres, and accident and emergency departments.

A limitation of the TWICS trial was the proportion of participants who ceased taking their trial drugs (26%) was higher than anticipated (6%), although this was somewhat offset by 10% over-recruitment ($n = 154$). There was no evidence of bias in ceasing trial medication, with the proportion and the reasons given for ceasing trial medication being equally distributed between those allocated to low-dose theophylline and those allocated to placebo. The original sample size for the TWICS trial ($n = 1424$) accounted for 6% of

participants ceasing their trial medication based on the four high-quality studies reported in a Cochrane review[83] of theophylline in COPD, in which 3 out of 51 (6%) participants dropped out. In reality, 413 of the 1578 participants either never started/initiated medication (post-randomisation exclusions, $n = 11$; non-initiation, $n = 8$) or ceased taking the trial medication (non-persistence, $n = 393$). This 26% rate of ceasing trial medication is greater than anticipated, but in keeping with the ASSET trial of low-dose theophylline, which reported a 34% rate of ceasing trial medication.[44] The higher than anticipated rate of ceasing trial medication in the TWICS trial was most likely the consequence of the relatively high rates of comorbidities in participants, giving rise to symptoms that were attributed to the trial medication and a heightened awareness of ARs listed in the PIL and the package insert accompanying the trial medication. This is consistent with 46% of participants reporting ARs typical of high-dose theophylline (but equally distributed between the two trial arms) and why 20% of those ceasing trial medication gave gastrointestinal symptoms as the reason for ceasing trial medication, although there was no significant difference in the incidence of such symptoms in those ceasing low-dose theophylline and those ceasing placebo. Some participants were asked to discontinue trial medication because they had stopped taking an ICS. During the trial, there was an emergent change in prescribing practice away from ICS-containing preparations to LABA/LAMA inhalers; however, this had minimal impact on the trial (certainly < 20 participants), most probably because the participants in this trial were at high risk of exacerbation and were participants in whom there is still a role for ICSs. Although 413 participants ceased trial medication during the TWICS trial, a review of the medication returns indicated that 66 of these participants had > 70% adherence while taking the trial medication when averaged over the 12-month treatment period; for example, they ceased trial medication at 11 months. These individuals were included in the per-protocol analysis. Although per-protocol analyses are biased by their very nature, the per-protocol analysis for this trial included 1142 years of participant data (85% of the 1338 years indicated by the power calculation); therefore, it is not surprising that the results of the per-protocol analysis were almost identical to those of the ITT analysis. Although adherence to the trial medication was quantified through pill counting, it was not practicable to assess adherence to the ICS, as this would have entailed use of non-routine care methodologies such as diaries cards, metered inhalers, etc. The rationale for the use of low-dose theophylline is as an adjunct to ICS therapy; that we were unable to verify adherence to ICS therapy is a limitation of this trial.

Generalisability

This trial has good external validity as it was of a pragmatic design that reflected normal clinical practice across both primary and secondary care in the UK. Participants remained on their existing COPD medications, they were managed in the normal way by their usual health-care teams and the trial recruited from 121 sites (88 primary care and 33 secondary care) that spanned the UK; many of the secondary care sites were district general hospitals. We consider it to be highly probable that the TWICS trial participants are typical of COPD patients in normal clinical practice across both primary and secondary care in the UK and that the findings are generalisable to clinical practice in the UK.

The TWICS trial recruited participants who were highly likely to experience an exacerbation during the 1-year treatment period, as evidenced by the fact that they had experienced two or more treated exacerbations in the previous year. In contrast to many COPD trials, we did not exclude potential participants with mild COPD, as evidenced by FEV_1 of > 80% predicted; 9% of the TWICS trial participants had mild COPD based on spirometry criteria, but fulfilled the frequent exacerbator phenotype,[21] enhancing the generalisability of the trial. Recruitment to the TWICS trial was limited to frequent exacerbators because, in clinical practice, these are the patients who are usually commenced on this 'third-line' therapy;[24] moreover, a trial of participants less likely to experience exacerbation (e.g. those experiencing one exacerbation in the previous year) would have been much larger ($n = \approx 3000$) and somewhat more costly. Although we did not test whether or not the addition of low-dose theophylline to ICSs had an effect on people who experienced less frequent exacerbations, there is no scientific or clinical reason why low-dose theophylline should have a differential effect according to the frequency of exacerbations. Therefore, it would seem reasonable to extend the findings of the current study to people with COPD who are at a low risk of experiencing an exacerbation.

Although the results of this trial are generalisable to the UK and probably to other high-income countries, the findings may not be applicable to low- or medium-income countries, with differing pharmacogenetic profiles, where theophylline remains a frequently used therapy in COPD, most probably because it is inexpensive compared with inhaled therapies.[113–116] The randomised, double-blind, placebo-controlled trial of Zhou *et al.*[117] raises the possibility that, in China at least, there is a therapeutic response to low-dose theophylline in the absence of ICS. In that trial,[117] the addition of low-dose theophylline to usual COPD treatment in 110 people with COPD (theophylline, $n = 57$; placebo, $n = 53$) for a year significantly reduced the frequency of exacerbations when compared with placebo [mean 0.79 (SD 1.16) vs. 1.70 (SD 2.61); $p = 0.047$]. The participants in that trial[117] differed considerably from those taking part in the TWICS trial: only 30% were taking regular medication prior to the trial, and this was restricted to inhaled salbutamol; use of ICS, LABA and LAMA was excluded; and the target plasma theophylline concentration (5–10 mg/l) was also somewhat higher than the target range (1–5 mg/l) identified for optimum synergistic interaction between corticosteroids and low-dose theophylline. The use of low-dose theophylline in conjunction with corticosteroids in China is being addressed by the ongoing Theophylline And Steroids in COPD Study (TASCS), which is recruiting 2400 people with COPD in China.[118] They are being randomly allocated to low-dose prednisolone (5 mg od) or low-dose theophylline (100 mg bd) with low-dose prednisolone (5 mg od) for 48 weeks. The primary outcome is exacerbation rate over the 48-week treatment period. This study has been presented in abstract form[119] and demonstrated that the combination of low-dose theophylline and prednisolone did not reduce the annualised rate of exacerbations. It will be interesting to compare the results of TASCS with the TWICS trial, although it should be noted that the routine use of OCSs as a maintenance treatment for COPD, even though they are cheaper than ICS, would never be contemplated in developed countries for clinical and ethical reasons.

Patient and public involvement

Patient and public involvement in this trial was limited, but effective, and lessons were learnt that have been implemented in a subsequent study funded by the NIHR Health Technology Assessment (HTA) programme (reference 15/130/20),[120] for example a person with COPD is a joint grant holder in that study.

A patient with COPD was a voting member of the TWICS trial TSC; recruitment and retention of a patient representative was hindered by ill health. The first patient approached declined because of ill health. The patient representative nominated by CHSS as part of their Voices Scotland initiative had to resign because of ill health. A third patient representative was identified and he made an active contribution to the TWICS trial. Support of the TSC patient representative was actively undertaken by several members of the local study team. In the subsequent trial funded by the NIHR HTA programme,[120] we have a patient representative who is supported by CHSS's Voices Scotland lead who is not only a voting member of the TSC, but also co-ordinator and representative of a panel of 15 COPD patients (as they like to be called).

A representative of the British Lung Foundation and a person with COPD made important contributions to trial design procedures [what was acceptable (e.g. spirometry) and what was not acceptable (e.g. daily diary cards)]. Perhaps the most important suggestions were to deliver trial medication to home addresses and to facilitate follow-up for ill participants by way of home visits and telephone and postal questionnaires. PPI resulted in many changes to the design and content of the 'short' PIL (a one-page summary PIL) and the 'long' PIL (a more detailed PIL). The importance of these changes is evidenced by the success in recruitment, and there were no changes to the PIL throughout the trial. PPI was particularly insightful during TSC deliberations concerning the validity of patient recall of COPD exacerbations.

The support of the British Lung Foundation and CHSS has been invaluable throughout the trial, identifying volunteers for PPI and publicising the trial.

Conclusions

Main conclusions

To our knowledge, this is the first adequately powered, multicentre, pragmatic, double-blind, randomised, placebo-controlled trial to assess the effectiveness of adding low-dose theophylline to a drug regimen containing ICSs in people with COPD who are at a high risk of exacerbation. The analyses demonstrated that low-dose theophylline has no overall clinical or health economic benefit.

Implications for practice

The trial has shown that low-dose theophylline has no overall clinical impact when added to ICSs in COPD. We anticipate that the results of the trial will be incorporated in an ongoing systematic review of theophylline in COPD.[121] Given that the TWICS trial is one of the largest trials of theophylline to date, we anticipate that it will have a major influence on the meta-analyses and conclusions. National and international COPD guidelines should take the results of the TWICS trial into account when making recommendations on the treatment of COPD and the prevention of exacerbations of COPD. In the meantime, clinical commissioners can now be encouraged to make informed decisions regarding the use theophylline in COPD.

Recommendations for research

The findings from one of the planned secondary analyses was that low-dose theophylline reduces the rate of admission to hospital due to severe COPD exacerbation. Although it is possible that this may be a chance finding, it is consistent with a recent report[96] that roflumilast is most beneficial in people with prior COPD hospitalisation for exacerbation and greater exacerbation frequency. A further study investigating the effect of low-dose theophylline in people with COPD who frequently exacerbate and are admitted to hospital is justifiable, given the disproportionate impact on NHS resources of such exacerbations.

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Site	Staff
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Belfast City Hospital	Peter Gray, Kathryn McDowell, Lorcan McGarvey (PI), Jolene Milligan and Brian Wells
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Lister Hospital (East and North Hertfordshire)	Hannah Beadle, Kelly Chan, Katie Chong, Angela Cook, Carina Cruz, Sura Dabbagh, Pippa de Sousa, Sunita Gohil, Jodie Graham, Alison McMillan, Victoria Oliver, Mahul Patel, Louise Peacock, Anita Rana, Natalie Rahim, Emma Shinn and Thida Win (PI)
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Freeman Hospital, Newcastle	Nicholas Aitken, Angela Bailey, Marion Brooks, Jamie Brown, Gareth Davies, Jade Davison, Margaret Day, Anthony De Soyza (PI), Hazel Douglas, Maureen Foreman, Ben Hood, Rebecca Johnson, Gerry Jones, Karen Martin, Donna McEvoy, Yoko Okada, Jack Oliver, Leeanne Ratcliffe, Sarah Robertson, Therese Small, Graham Soulsby, Julie Stephenson, Hesther Wilson and Sarah Woolcock
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Graham Devereux contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, interpretation of results and writing/editing the report.

Seonaidh Cotton contributed to the design of the trial, was responsible for the day-to-day management of the trial and contributed to the interpretation of results and writing/editing the report.

Shona Fielding contributed to the design of the trial, was responsible for statistical analysis and contributed to the interpretation of results and writing/editing the report.

Nicola McMeekin was responsible for the health economic analysis and contributed to the interpretation of results and writing/editing the report.

Peter J Barnes contributed to the conception and design of the trial, the interpretation of results and writing/editing the report.

Andy Briggs contributed to the conception and design of the trial, oversaw the health economic analysis and contributed to the interpretation of results and writing/editing the report.

Graham Burns contributed to the conception and design of the trial, the interpretation of results and writing/editing the report.

Rekha Chaudhuri contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

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David Price contributed to the conception and design of the trial, the conduct of the trial, the interpretation of the results and writing/editing the report.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Rationale for the low-dose theophylline strategy

Population theophylline pharmacokinetic studies during the 1970s and 1980s demonstrated that disease status, weight and smoking decrease the half-life of theophylline and increase its clearance.[57–62] It has been shown that theophylline clearance is lower in COPD patients who do not smoke than in healthy volunteers.[60] Based on these data and our publications,[63–66] an average population clearance value of theophylline in non-smokers is 40 ml/hour/kg, which is reduced to 32 ml/hour/kg in a patient with COPD, and by a further 20% if they have another related disease (e.g. severe congestive heart failure). This corresponds to the fast, normal and slow categories of plasma theophylline pharmacokinetic modelling for COPD patients provided in *Table 35*. Smoking increases theophylline clearance by ≈60%, and the plasma theophylline level gradually returns to normal levels when a person stops smoking. Another relevant population pharmacokinetic value that is useful for loading doses is a volume of distribution for theophylline of 0.5 l/kg.[57–66]

TABLE 35 The results of pharmacokinetic modelling for theophylline doses of 200 mg bd and od for current smoking/non-smoking participants by weight and theophylline clearance

	Theophylline 200 mg bd			Theophylline 200 mg od		
	Steady-state plasma theophylline concentration (C_{ss}) (mg/l)					
	Participant theophylline clearance					
IBW (kg)	Slow	Normal	Fast	Slow	Normal	Fast
Not current smoker						
40.1–50	17.4	13.0	10.4	8.7	6.5	5.2
50.1–60	13.9	10.4	8.3	6.9	5.2	4.2
60.1–70	11.6	8.7	6.9	5.8	4.3	3.5
70.1–80	9.9	7.4	6.0	5.0	3.7	3.0
80.1–90	8.7	6.5	5.2	4.3	3.3	2.6
90.1–100	7.7	5.8	4.6	3.9	2.9	2.3
100.1–110	6.9	5.2	4.2	3.5	2.6	2.1
110.1–120	6.3	4.7	3.8	3.2	2.4	1.9
> 120	5.8	4.3	3.5	2.9	2.2	1.7
Current smoker						
40.1–50	10.9	8.1	6.5	5.4	4.1	3.3
50.1–60	8.7	6.5	5.2	4.3	3.3	2.6
60.1–70	7.2	5.4	4.3	3.6	2.7	2.2
70.1–80	6.2	4.7	3.7	3.1	2.3	1.9
80.1–90	5.4	4.1	3.3	2.7	2.0	1.6
90.1–100	4.8	3.6	2.9	2.4	1.8	1.4
100.1–110	4.3	3.3	2.6	2.2	1.5	1.2
110.1–120	3.9	3.0	2.4	2.0	1.5	1.2
> 120	3.6	2.7	2.2	1.8	1.4	1.1

Note
The plasma theophylline concentrations using the dosing schedule are shaded mediun green (Professor Henry Chrystyn, Inhalation Consultancy Ltd, 2014, personal communication).

The use of actual weight or IBW has been shown to have an effect on the clearance of theophylline in young adults who smoke.[122] If a patient is obese, they may be given a high dose when their actual weight is used. It is good practice to assume that this occurs in all patients and thus use IBW. IBW can be calculated using the following equations:[67]

$$IBW_{female} = 45 + [0.9(\text{height in cm} - 152)]\ \text{kg}, \quad (3)$$

$$IBW_{male} = 50 + [0.9(\text{height in cm} - 152)]\ \text{kg}. \quad (4)$$

The IBW is used unless the actual weight is lower than the IBW.

For oral theophylline dosing, the pharmacokinetic model is:

$$C_{ss} = \frac{F \times D}{Cl \times \tau}, \quad (5)$$

where C_{ss} is the steady-state theophylline concentration, F is the bioavailability of theophylline (F = 1 for theophylline preparations), D is the dose, Cl is the clearance and τ is the dosage interval (either 12 or 24 hours). Using this model and the population theophylline clearance values for COPD patients described above, in smokers and non-smokers, predicted C_{ss} values are as shown in *Table 35*.

Confidence that plasma theophylline in the low-dose range can be achieved using the above dosing strategy is provided from a detailed analysis of a COPD study that measured theophylline concentrations at three different theophylline dosing regimens.[63] In 33 COPD patients [who had a mean weight of 64.6 (SD 14.3) kg and a mean age of 61.2 (SD 5.8) years], we found that the mean plasma theophylline concentration at steady state when they received a mean of 252 (SD 87) mg bd was 6.3 (SD 2.1) mg/l. This represents a clearance value of 51.6 ml/hour/kg. When the theophylline dose was increased to 430 mg bd and then to 597 (SD 153) mg bd, mean steady-state plasma theophylline concentrations rose to 12.1 (SD 1.9) mg/l and 18.3 (SD 3.0) mg/l, respectively. This represents clearance values of 45.8 ml/hour/kg and 42.1 ml/hour/kg, respectively. This will include smokers and non-smokers (numbers of each not recorded) and the latter clearance value is similar to the 40 ml/hour/kg used in the population pharmacokinetics modelling for the 'fast' category. Our other publications[64,65] (n = 83 patients[64] and n = 15 patients[65]) on plasma theophylline highlight our confidence of using low-dose theophylline in the TWICS trial.

In the clinical situation in which a clinician wished to use intravenous aminophylline to treat a patient participating in the TWICS trial with an acute exacerbation of COPD, the BNF recommends a loading dose of intravenous aminophylline of 5 mg/kg (typically 250 mg); this is usually omitted if the patient is already taking theophylline. This is then followed by an intravenous infusion of aminophylline of 0.5 mg/kg.[86] It is recommended that plasma theophylline be measured after 24 hours to direct the rate of further dosing. The pharmacokinetic model for a loading dose is:

$$Co = \frac{F \times D}{V}, \quad (6)$$

where Co is the concentration immediately after the slow intravenous bolus dose of aminophylline, F is the bioavailability (F = 0.8 for aminophylline) and V is the volume of distribution. A loading dose of 5 mg/kg would provide a Co of:

$$Co = \frac{0.8 \times 5\ \text{mg/kg}}{0.5\ \text{l/kg}} = 8\ \text{mg/l}. \quad (7)$$

Because the predicted C_{ss} shown in *Table 35* ranges from 2.2 to 8.7 mg/l, the maximum theophylline concentration would be 16.7 mg/l. Alternatively, a loading dose of 250 mg of aminophylline could be given, rather than a dose based on weight. A loading dose of 250 mg of aminophylline in COPD patients weighing 40–100 kg would provide a Co ranging from 4 to 10 mg/l. There is a linear relationship between C_{ss} and weight. Similarly, if the loading dose was 500 mg of aminophylline, then the predicted C_{ss} would be double that for the 250-mg dose.

For an aminophylline infusion of 0.5 mg/kg/hour[86] and based on a clearance of 40 ml/hour/kg and the following pharmacokinetic model:

$$C_{ss} = \frac{F \times D}{Cl \times \tau}, \tag{8}$$

where C_{ss} is the steady-state theophylline concentration, F is the bioavailability of theophylline (F = 0.8 for aminophylline preparations), D is the dose, Cl is the clearance (using a clearance of 40 ml/hour/kg) and τ is the dosage interval (1 hour for an intravenous infusion). In this case the predicted C_{ss} would be:

$$C_{ss} = \frac{0.8 \times 0.5 \text{ mg/hour/kg}}{0.04 \text{ l/hour/kg} \times 1} = 10 \text{ mg/l}. \tag{9}$$

Note that the predicted C_{ss} is independent of weight (see *Equation 9*). The predicted C_{ss} in non-smokers with COPD with slow, normal or fast theophylline clearance given an infusion of 0.5 mg/hour/kg would be 10.0, 12.5 and 16.7 mg/l, respectively. In smokers, the corresponding predicted C_{ss} values would be 6.3, 7.8 and 10.4 mg/l.

Importantly for the TWICS trial, it was safe for participants to receive a 5-mg/kg loading infusion of aminophylline followed by an infusion of 0.5 mg/kg/hour as the plasma concentration would exceed the target 10–20 mg/l range required for conventional theophylline dosing.

Appendix 2 Validation of patient-reported exacerbations

Initially, we planned to validate the total number of COPD exacerbations for ≈20% of participants by examination of general practice records.

At the TSC meeting of 20 March 2017, the validation exercise comparing the number of exacerbations as recorded in general practice records and reported by the participant was discussed. At that time, the focus of this validation had been in two of the largest sites: Aberdeen and Aintree. The validation was done by requesting a care/encounter summary from the GP and comparing this against the patient report. In Aberdeen, 43 records had been checked; in 37 there was complete agreement between patient report and GP report. In Aintree, 24 records had been checked; in 16 there was complete agreement between patient report and GP report. Therefore, 4% of participants had undergone validation, and there was ≈80% concordance. Concerns were raised that there is no 'gold standard' for the reporting of exacerbations, and that current general practice records may not be as reliable a source of exacerbation data as in the past, given that patients have rescue packs at home and can access help for their exacerbations through many non-GP sources, for example pharmacies, emergency and walk-in centres, and accident and emergency departments. The published evidence is that patients are able to reliably report the number of exacerbations experienced in the previous year.[112] Furthermore, the patient representatives for the TWICS trial are adamant that it is fairly straightforward to remember the number of exacerbations over this time period. It was also noted that the primary outcome of this trial is patient-reported exacerbations and it is this outcome that drives demand for NHS services. The TSC, therefore, recommended that we completed the validation exercise for the participants for whom we had data, but that the validation exercise did not need to be extended beyond these two sites or to include further participants.

Appendix 3 Breaches

Site affected (site number)	Description of breach	Assessment
36	The site consented a patient into the trial on 28 April 2014, before the site agreement had been signed by all parties. The trial processes in place prevented the site from randomising the patient on the live randomisation system and also meant that a drug pack could not be dispensed	Non-serious
18	Participant had rescue medication, including erythromycin (one of the drugs that can increase serum theophylline), and, in response to an exacerbation, the participant started to take the rescue medication without stopping the trial medication. The patient came to no harm, and did not suffer any adverse effects	Non-serious
11	The chief investigator raised concerns about the monitoring process following a routine trial monitoring visit carried out by R&D monitors at the site. For two patients, the monitors recorded amber findings relating to the recording of comorbities and concomitant medication in the case report form, and for one patient indicated that there was contraindicated medication. However, the data recorded in both case report forms were accurate and both patients were eligible. The breach related to the monitors incorrectly noting amber findings and making the research nurses modify the case report form by entering incorrect information	Non-serious
12	Participant was admitted to hospital. Prior to the admission, the participant had been prescribed clarithromycin (one of the drugs that can increase serum theophylline). His trial medication was stopped by the hospital pharmacist. The symptoms experienced by the participant (gastro-oesophageal reflux) may have resulted from clarithromycin per se, and/or an interaction between clarithromycin and theophylline. Gastro-oesophageal reflux is a side effect of both clarithromycin and theophylline	Non-serious
11	The third-party distributor identified that it had despatched a shipment to a participant that contained drug pack numbers 40167 (correctly) and 40166 (in error) on 5 November 2014. The participant was contacted on 29 January 2015 and indicated that he had started using kit number 40167 and that he had not opened kit number 40166. He returned kit number 40166 to the research nurse later that day and it was destroyed. The participant was resupplied with an appropriate box of medication	Non-serious
27	At the point of randomisation (20 April 2014), the participant had been randomised as a smoker (rather than as an ex-smoker) and was allocated and received a dose of twice-daily trial medication (he should have received a once-daily dose). On 5 November 2014, the patient was diagnosed with atrial fibrillation. No palpitations were noted. Atrial tachycardias are a known side effect of theophylline. The patient was unblinded so he could be managed appropriately. The atrial fibrillation experienced by the patient may have been caused by the theophylline. The participant was seen on 6 January 2015 for a routine appointment, and his pulse was noted to be regular, that is spontaneously reverted to sinus rhythm	Serious
12	Noted at the 12-month follow-up, the participant had been on diltiazem hydrochloride (Tildiem LA, Sanofi-Aventis) (300 mg od) since recruitment into the study (26 February 2014). Tildiem LA is a form of diltiazem (diltiazem is one of the drugs listed in the trial protocol as known to interact with theophylline). Although this medication had been recorded on the baseline case report form, the patient was assessed as being eligible for the trial. The patient was well throughout the trial. No AEs were noted	Non-serious
11	During the 12-month follow-up appointment (19 May 2015), the participant mentioned that the community pharmacist had been supplying Uniphyllin 200 mg (theophylline) in his dosette box. After taking the Uniphyllin included in the dosette box for 2 or 3 days, the participant realised that he may be taking theophylline as both the TWICS trial medication and as prescribed medication. He therefore ceased taking the TWICS trial medication. The participant has noted no adverse effects as a result of this	Non-serious

Site affected (site number)	Description of breach	Assessment
78	Participant was randomised to twice-daily trial medication – dosing instruction 'Take ONE tablet every morning and ONE tablet every evening', but took two tablets each morning and two each evening. After 10 days of taking the trial medication, the participant noted that he was experiencing nausea, tremors and disturbed sleep (which, in part, may have been anxiety related because of a forthcoming bypass operation); his dose was reduced by the trial team to one tablet per day and his symptoms settled. At the 6-month follow-up appointment, the participant noted that he was still taking 'one tablet', but as he was feeling well, wished to start taking two tablets again. The trial team agreed that he could increase his dose to two tablets per day (the recommended 'low dose' for a smoker of his height and weight). He did this for 3 days and symptoms of nausea/sickness returned. The participant therefore reduced his dose to 'one tablet' and the symptoms settled. In subsequent discussion with the participant, it became clear that he had misinterpreted the initial instruction on medication use as two tablets twice a day, and had been taking this dose rather than one tablet twice a day. For approximately 10 days between 3 December 2014 and 17 December 2014, he had therefore been taking a dose in the normal therapeutic range (400 mg twice daily) rather than a low dose (200 mg twice daily). For the period between 17 December 2014 and 10 June 2015 he had been taking one tablet twice a day; this was the appropriate 'low dose' used in the trial. For a further 3 days from 10 June 2015, the participant again misinterpreted the instruction on the medication bottle and took two tablets twice a day (i.e. the normal therapeutic range rather than a low dose)	Non-serious
12	Participant was prescribed Elleste Duet (Piramal Healthcare UK Ltd, Morpeth, UK) (which is an oestrogen; oestrogens may raise theophylline levels to within the normal therapeutic range rather than a low dose) by her GP between being recruited into the study and her 6-month follow-up. At the 6-month follow-up (18 June 2015), she was advised to cease taking trial medication. The interaction between Elleste Duet and theophylline is such that the serum levels of theophylline may be raised into the normal therapeutic range, and not to toxic levels. Thus any interaction does not raise safety concerns	Non-serious
Across sites	Following review of emergency hospital admissions captured at follow-up, we identified a number of admissions that should have been captured as SAEs. None was related to trial medication	Non-serious
12	The participant failed to attend for the 12-month follow-up. Follow-up data were sought from his GP, and during this data-collection exercise, it was noted that the participant had been prescribed Uniphyllin on repeat prescription since 8 May 2012. He had not disclosed this at recruitment or the 6-month follow-up, or during any telephone calls. The prescription he brought to the recruitment appointment did not include the Uniphyllin. No AEs were noted during follow-up (last contact with participant was at the 46-week call)	Non-serious
12	Late reporting of a SAE in this participant (strangulated small bowel secondary to hernia, not related to trial medication), who had ceased trial medication prior to the event	Non-serious
125	Participant was randomised on 12 January 2016 (200 mg od); on 26 January it was noted that he was already taking aminophylline (225 mg bd). The participant had taken trial medication as well as routine aminophylline for 8 days. The participant did not experience any ARs. The GP confirmed that the aminophylline (225 mg bd) plus trial medication (if active; 200 mg od) would not have taken the participant over the maximum daily dose	Non-serious
12	The trial office prepared a waybill for the dispatch of trial medication with the house number transposed (so the trial medication was delivered to house number 35 rather than house number 53). The participant was resupplied, and the incorrect delivery was retrieved from house number 35	Non-serious
78	The third-party distributor picked the wrong kit and this was dispatched to the participant. The wrong kit was retrieved from the participant and she was resupplied with the correct kit	Non-serious
14	Participant was recruited into the TWICS trial while participating in another drug study (in breach of the TWICS trial eligibility criteria). There was no documentation in the medical notes in relation to the other study and the participant did not mention it at recruitment. The participant came to no harm	Non-serious

Site affected (site number)	Description of breach	Assessment
145	Participant randomised on 23 June 2016 to once-daily trial medication, and was allocated an appropriate labelled bottle. The participant took the trial medication twice daily for approximately 7 days after commencing medication (this would have brought her into the normal therapeutic range for theophylline rather than a low dose). The participant came to no harm (she noted some initial constipation, which resolved)	Non-serious
122	Participant was randomised to od study medication. The bottle was correctly labelled, but a dispensing label was added at the time the medication was dispensed that indicated a two-a-day dosing regimen. The error was noted and corrected. The participant took twice daily study medication for approximately 10 days (this would have brought him into the normal therapeutic range for theophylline rather than a low dose) and came to no harm	Non-serious
159	In an attempt to prevent medication being prescribed that may interact with theophylline, the practice added theophylline to the repeat prescription as a trial drug. The pharmacist dispensed liquid theophylline as part of the repeat prescription; for a period of 7 days, the participant took a dose of liquid theophylline three times per day and also took their trial medication three times per day. This would have brought the participant into the normal therapeutic range for theophylline rather than a low dose. The participant came to no harm	Non-serious
141	The third-party distributor picked the wrong kit and this was dispatched to the participant. The wrong kit was retrieved from the participant and she was resupplied with the correct kit	Non-serious
115	Participant was recruited to the trial in October 2015. During data checking in January 2017, it was noted that the participant was already taking Phyllocontin (Napp Pharmaceuticals Ltd). The participant took trial medication for a full 12 months, and no AEs were noted. Subsequent data checking identified five other participants who had been recruited while on a medication that may interact with theophylline: • Site 32 – febuxostat; participant took trial medication for 12 months; non-serious gastrointestinal symptoms noted (abdominal pain, two episodes of reflux) • Site 80 – estradiol valerate; participant took trial medication for 2 weeks and experienced non-serious side effects likely to be related to theophylline (nausea, headache, dizziness) • Site 102 – roflumilast; participant took study medication for 12 months; no ARs noted during the 12-month follow-up • Site 131 – elleste duet; participant continues on trial medication (due to complete 12-month follow-up); no ARs noted • Site 131 – estradiol; participant continues on trial medication (due to complete 12-month follow-up); no ARs noted	Non-serious

LA, long acting; R&D, research and development.

Appendix 4 Recruitment by site

Site	Participants recruited (*n*)
***Secondary care sites* (N = *33*)**	***1101***
Aberdeen Royal Infirmary	212
Aintree University Hospital NHS Foundation Trust	127
Belfast City Hospital	6
Queen Elizabeth Hospital Birmingham	54
Blackpool Victoria Hospital	57
Bradford Royal Infirmary	9
Queen's Hospital, Burton Hospitals NHS Foundation Trust	4
Calderdale Royal Hospital, Huddersfield Royal Infirmary, Calderdale & Huddersfield NHS Foundation Trust	4
University Hospital of North Durham	9
Lister Hospital, East and North Hertfordshire NHS Trust	20
Victoria Hospital, Kirkcaldy	29
Freeman Hospital, Newcastle	45
Glasgow Hospitals (Gartnavel, Glasgow Royal, Southern General, Victoria Infirmary, Western Infirmary)	115
Castle Hill Hospital, Hull	114
Raigmore Hospital, Inverness	31
University Hospital Wishaw	12
Royal Lancaster Infirmary	19
Leighton Hospital, Crewe	13
Musgrove Park Hospital	6
Norfolk and Norwich University Hospital	80
University Hospital of North Tees	6
City Hospital, Nottingham	11
Derriford Hospital, Plymouth	4
South Tyneside District Hospital	44
Torbay Hospital	12
New Cross Hospital, Wolverhampton	33
Worcestershire Royal Hospital	11
Yeovil District Hospital	8
York Hospital, York Teaching Hospital NHS Foundation Trust	6
***East of England primary care* (N = *48*)**	***242***
Alconbury and Brampton Surgeries	6
Alexandra and Crestview Surgeries	5
Andaman Surgery	7
Attleborough Surgeries	7

Site	Participants recruited (*n*)
Beccles Medical Centre	7
Bridge Road Surgery	4
Bridge Street Medical Centre, Cambridge	2
Bridge Street Surgery, Downham Market	8
Campingland Surgery	2
Castle Partnership	8
Coltishall Medical Practice	4
Comberton and Eversden Surgeries	3
Cutlers Hill Surgery	2
Davenport House	3
De Parys Medical Centre	5
East Norfolk Medical Practice	1
Elizabeth Courtauld Surgery	1
Gorleston Medical Centre	3
Greyfriars Medical Centre	6
Harvey Group Practice	6
Holt Medical Practice	2
Hoveton and Wroxham Medical Centre	6
Linton Health Centre	5
Long Stratton Medical Partnership	4
Ludham & Stalham Green Surgeries	12
Mount Farm Surgery	3
Mundesley Medical Centre	14
Nuffield Road Medical Centre	4
Orchard Surgery, Dereham	3
Peninsula Practice	6
Portmill Surgery	4
Rosedale Surgery	3
Roundwell Medical Centre	5
Salisbury House Surgery	3
Sheringham Medical Practice	5
Spinney Surgery	4
St Stephens Gate Medical Practice	12
St Johns Surgery, Terrington	5
Staithe Surgery	4
The Over Surgery	1
Trinity and Bowthorpe Medical Practice	2
Vida Healthcare	11
Wells Health Centre	3

Site	Participants recruited (*n*)
Wellside Surgery	3
Woodhall Farm Medical Centre	3
Woolpit Health Centre	19
Wymondham Medical Practice	1
York Street Medical Practice	5
***North of England primary care* (N = *26*)**	***131***
Beacon View Medical Centre	8
Beaumont Park Medical Group	4
Belford Medical Practice	8
Bellingham Practice	1
Benfield Park Medical Centre	6
Burn Brae Medical Group	1
Castlegate & Derwent Surgery	29
Corbridge Medical Group	6
Elvaston Road Surgery	1
Fell Cottage Surgery	2
Grove Medical Group	1
Guidepost Medical Group	7
Haltwhistle Medical Group	2
Haydon and Allendale Medical Practice	1
Hetton Group Practice	4
Humshaugh and Wark Medical Group	3
Marine Avenue Surgery	2
Maryport Health Services	9
Priory Medical Group	2
Prudhoe Medical Group	4
Seaton Park Medical Group	2
Sele Medical Group	6
Temple Sowerby Medical Group	5
The Village Surgery	4
Waterloo Medical Group	11
West Farm Surgery	2
***South West England primary care* (N = *11*)**	***95***
Barton Surgery	6
Bovey Tracey and Chudleigh Practice	9
Brunel Medical Practice	20
Claremont Medical Practice	4
Coleridge Medical Centre	3
Helston Medical Centre	2

Site	Participants recruited (*n*)
Ide Lane Surgery	2
Petroc Group Practice	11
Richmond House Surgery	5
Rolle Medical Partnership	4
Westlake Surgery	29
Wessex primary care (N = 3)	***9***
Friarsgate Practice	1
Park and St Francis Surgery	1
Swanage Medical Centre	7
Total recruitment	***1578***

Appendix 5 Supplementary tables

TABLE 36 Baseline sociodemographic characteristics by location of recruitment

Characteristic	Primary care (*N* = 917)	Secondary care (*N* = 619)	*p*-value
Sex			
Male, *n* (%)	498 (54.3)	330 (53.3)	0.701
Female, *n* (%)	419 (45.7)	289 (46.7)	
Age (years), mean (SD)	68.9 (8.2)	67.7 (8.5)	0.006
Smoking status			
Current smoker, *n* (%)	322 (35.1)	164 (26.5)	< 0.001
Ex-smoker, *n* (%)	595 (64.9)	455 (73.5)	
Pack-years, mean (SD); *n*	46.1 (29.5); 910	48.4 (27.1); 619	0.113
BMI (kg/m^2), mean (SD)	27.4 (6.1)	27.0 (6.1)	0.284
BMI group, *n* (%)			
Underweight	41 (4.5)	29 (4.7)	0.463
Normal	306 (33.4)	214 (34.6)	
Overweight	296 (32.3)	214 (36.6)	
Obese	274 (29.9)	162 (26.2)	
Number of exacerbations in the previous 12 months, mean (SD); *n*	3.35 (1.8); 908	3.92 (2.5); 619	< 0.001
Number of exacerbations requiring hospitalisation in the previous 12 months, mean (SD); *n*	0.22 (0.6); 907	0.61 (1.1); 619	< 0.001
GOLD 2011 category			
N	901	615	0.006
C: two or more exacerbations in the previous year, mMRC dyspnoea score of 0–1 and CAT score of < 10, *n* (%)	60 (6.7)	21 (3.4)	
D: two or more exacerbations in the previous year, mMRC dyspnoea score of ≥ 2 and CAT score of ≥ 10, *n* (%)	841 (93.3)	594 (96.6)	
FEV_1% predicted, mean (SD); *n*	54.5 (19.6); 907	47.7 (19.9); 619	< 0.001
FEV_1% predicted category			
N	907	619	< 0.001
≥ 80% (GOLD mild), *n* (%)	100 (11.0)	40 (6.5)	
50–79.9% (GOLD moderate), *n* (%)	399 (44.0)	207 (33.4)	
30–49.9% (GOLD severe), *n* (%)	320 (35.3)	255 (41.2)	
0–29.9% (GOLD very severe), *n* (%)	88 (9.7)	117 (18.9)	
FVC% predicted, mean (SD); *n*	86.4 (23.3); 904	83.7 (22.1); 619	0.022
FEV_1/FVC ratio, mean (SD); *n*	50.8 (14.2); 904	45.8 (20.4); 619	< 0.001

continued

TABLE 36 Baseline sociodemographic characteristics by location of recruitment (*continued*)

Characteristic	Primary care (*N* = 917)	Secondary care (*N* = 619)	*p*-value
Current treatment for COPD			
ICS, *n* (%)			
ICS only	26 (2.8)	5 (0.8)	0.001
ICS/LABA	176 (19.2)	84 (13.6)	
ICS/LAMA	12 (1.3)	10 (1.6)	
ICS/LABA/LAMA	703 (76.7)	520 (84.0)	
Oral mucolytic use, *n* (%); *N*	162 (17.9); 905	222 (35.9); 619	< 0.001
Long-term antibiotic use, *n* (%); *N*	34 (3.8); 905	62 (10.0); 619	< 0.001
Comorbidities			
Asthma, *n* (%); *N*	186 (20.6); 905	93 (15.1); 618	0.006
Bronchiectasis, *n* (%); *N*	22 (2.4); 905	43 (7.0); 617	< 0.001
Ischaemic heart disease, *n* (%); *N*	107 (11.9); 903	97 (15.7); 618	0.031
Hypertension, *n* (%); *N*	351 (38.8); 905	231 (37.4); 618	0.579
Diabetes mellitus, *n* (%); *N*	102 (11.3); 905	72 (11.7); 618	0.819
Osteoporosis, *n* (%); *N*	99 (10.9); 905	96 (15.5); 318	0.008
Anxiety/depression treated in the previous 5 years, *n* (%); *N*	231 (25.5); 905	195 (31.6); 618	0.010
Cerebrovascular event, *n* (%); *N*	58 (6.4); 905	45 (7.3); 619	0.511

TABLE 37 Baseline patient-reported symptoms and QoL by location of recruitment

Patient-reported outcome	Primary care	Secondary care	*p*-value
Degree of breathlessness (mMRC dyspnoea)			
N	907	617	< 0.001
Not troubled by breathlessness except on strenuous exercise, *n* (%)	65 (7.2)	20 (3.2)	
Short of breath when hurrying or walking up a slight hill, *n* (%)	286 (31.5)	143 (23.2)	
Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace, *n* (%)	267 (29.4)	216 (35.0)	
Stops for breath after walking about 100 m or after a few minutes on level ground, *n* (%)	234 (25.8)	186 (30.2)	
Too breathless to leave the house, or breathless when dressing or undressing, *n* (%)	55 (6.1)	52 (8.4)	
CAT (*N*, mean, SD)	21.6 (7.6); 905	23.9 (7.6); 615	< 0.001
CAT group			
N	905	615	< 0.001
Low (score of 0–9), *n* (%)	60 (6.6)	21 (3.4)	
Medium (score of 10–19), *n* (%)	295 (32.6)	159 (25.9)	
High (score of 20–29), *n* (%)	391 (43.2)	285 (46.3)	
Very high (score of 30–40), *n* (%)	159 (17.6)	150 (24.4)	
EQ-5D-3L utility (*N*, mean, SD)	0.66 (0.28); 908	0.58 (0.29); 619	< 0.001
EQ-5D-3L VAS (*N*, mean, SD)	61.7 (19.3); 907	59.1 (18.9); 617	< 0.001

VAS, visual analogue scale.

TABLE 38 Baseline sociodemographic characteristics comparing those with and those without HARQ data

Characteristic	HARQ not completed (*N* = 1134)	HARQ completed (*N* = 402)	*p*-value
Sex (male), *n* (%)	629 (55.5)	199 (49.5)	0.039[a]
Age, mean (SD)	68.9 (8.3)	66.8 (8.2)	< 0.001[a]
Smoking status, *n* (%)			
Current smoker	352 (31.0)	134 (33.3)	0.396[a]
Ex-smoker	782 (69.0)	268 (66.7)	
Pack-years, mean (SD); *N*	46.3 (26.8); 1128	49.2 (33.2); 401	0.076[b]
BMI, mean (SD)	27.2 (6.01)	27.4 (6.4)	0.689[b]

a Chi-squared test.
b Independent samples *t*-test.

TABLE 39 Additional outcomes for the ITT population for treatment of exacerbation

	Trial arm					
Exacerbations	Theophylline	Placebo	Model	Estimate	95% CI	*p*-value
Exacerbations treated with antibiotics only						
Total number included in analysis	772	764				
Number with at least one exacerbation	230	227				
Total number of exacerbations	338	368				
Mean number of exacerbations	0.44	0.48	Unadjusted IRR	0.94	0.78 to 1.13	0.484
SD (number of exacerbations)	0.82	0.97	Adjusted IRR[a]	0.94	0.78 to 1.14	0.541
Exacerbations treated with steroids only						
Total number included in analysis	772	764				
Number with at least one exacerbation	77	88				
Total number of exacerbations	117	124				
Mean number of exacerbations	0.15	0.16	Unadjusted IRR	0.93	0.66 to 1.32	0.697
SD (number of exacerbations)	0.60	0.58	Adjusted IRR[a]	0.88	0.62 to 1.25	0.476
Exacerbations treated with antibiotics and steroids						
Total number included in analysis	772	764				
Number with at least one exacerbation	487	479				
Total number of exacerbations	1171	1106				
Mean number of exacerbations	1.52	1.45	Unadjusted IRR	1.05	0.93 to 1.17	0.446
SD (number of exacerbations)	1.72	1.65	Adjusted IRR[a]	1.02	0.92 to 1.14	0.725

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

TABLE 40 Subgroup analysis for primary outcome (ITT analysis)

Category	Trial arm		IRR[a]	95% CI	Interaction *p*-value
	Theophylline	Placebo			
All participants					
n	772	764			
Mean	2.24	2.23			
SD	1.99	1.97	0.99	0.91 to 1.08	
Sex					
Male					
n	418	410			
Mean	2.23	2.18	1.01	0.87 to 1.17	
SD	2.04	1.92			
Female					
n	354	354			
Mean	2.25	2.28	0.97	0.83 to 1.14	0.609
SD	1.93	2.03			
Age group (years)					
< 60					
n	115	131			
Mean	2.33	2.46	0.91	0.70 to 1.19	
SD	2.01	1.81			
60–69					
n	313	284			
Mean	2.27	2.13	1.07	0.89 to 1.28	0.198
SD	2.06	1.81			
≥ 70					
n	344	349			
Mean	2.18	2.23	0.96	0.82 to 1.13	0.637
SD	1.92	2.01			
Smoking status					
Current					
n	241	245			
Mean	2.40	2.47	0.96	0.80 to 1.16	
SD	2.01	2.07			
Ex-smoker					
n	531	519			
Mean	2.16	2.11	1.01	0.89 to 1.16	0.561
SD	1.97	1.92			

TABLE 40 Subgroup analysis for primary outcome (ITT analysis) (*continued*)

Category	Trial arm		IRR[a]	95% CI	Interaction *p*-value
	Theophylline	Placebo			
BMI category					
Underweight					
n	37	33			
Mean	2.51	2.45	0.93	0.57 to 1.52	0.894
SD	2.34	1.72			
Normal					
n	277	243			
Mean	2.29	2.41	0.95	0.79 to 1.15	
SD	1.91	1.72			
Overweight/obese					
n	458	488			
Mean	2.18	2.13	1.02	0.88 to 1.17	0.478
SD	2.01	1.96			
COPD treatment at baseline					
ICS/LAMA/LABA					
n	610	613			
Mean	2.33	2.36	0.98	0.87 to 1.10	
SD	2.05	1.87			
ICS/LABA or ICS/LAMA					
n	148	134			
Mean	1.89	1.78	1.00	0.76 to 1.32	0.832
SD	1.70	1.87			
ICS only					
n	14	17			
Mean	1.86	1.06	1.63	0.65 to 4.09	0.155
SD	1.92	1.43			
Number of exacerbations in the 12 months prior to baseline					
2					
n	286	308			
Mean	1.61	1.53	1.05	0.86 to 1.28	
SD	1.66	1.85			
3 or 4					
n	317	298			
Mean	2.31	2.25	1.02	0.86 to 1.21	0.785
SD	1.93	1.85			

continued

TABLE 40 Subgroup analysis for primary outcome (ITT analysis) (*continued*)

Category	Trial arm		IRR[a]	95% CI	Interaction *p*-value
	Theophylline	Placebo			
≥ 5					
n	169	158			
Mean	3.16	3.55	0.89	0.73 to 1.09	0.139
SD	2.21	2.38			
GOLD stage					
I–II					
n	370	376			
Mean	1.93	2.03	0.97	0.82 to 1.14	
SD	1.89	1.99			
III					
n	286	289			
Mean	2.38	2.40	1.02	0.85 to 1.21	0.605
SD	2.03	1.99			
IV					
n	113	92			
Mean	2.90	2.58	0.99	0.75 to 1.32	0.849
SD	2.03	2.04			
OCSs at baseline					
No					
n	418	410			
Mean	2.23	2.18	0.99	0.88 to 1.10	
SD	2.04	1.92			
Yes					
n	354	354			
Mean	2.25	2.28	1.20	0.65 to 2.20	0.420
SD	1.93	2.03			
ICS dose at baseline					
≥ 1600 µg per day					
n	549	547			
Mean	2.38	2.31	0.98	0.87 to 1.12	0.642
SD	1.98	2.03			
< 1600 µg per day					
n	221	215			
Mean	1.91	2.01	1.03	0.83 to 1.27	
SD	1.98	1.80			

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

TABLE 41 Sensitivity analysis for the ITT population excluding the 33 participants who died during the 12-month follow-up: exacerbations and hospital admissions

Exacerbations and hospital admissions	Trial arm		Model	Estimate	95% CI	*p*-value
	Theophylline	Placebo				
Total exacerbations						
Total number included in analysis	753	750				
Person-years of follow-up	738.6	735.1				
Number with at least one exacerbation	619	596				
Total number of exacerbations	1690	1678				
Mean number of exacerbations	2.24	2.24	Unadjusted IRR	1.00	0.91 to 1.09	0.934
SD (number of exacerbations)	1.99	1.98	Adjusted IRR[a]	0.99	0.91 to 1.07	0.729
Exacerbations requiring hospital treatment						
Total number included in analysis	753	750				
Person-years follow-up	738.6	735.1				
Number with at least one exacerbation	99	118				
Total number of exacerbations	126	172				
Mean number of exacerbations	0.17	0.23	Unadjusted IRR	0.73	0.55 to 0.97	0.032
SD (number of exacerbations)	0.49	0.66	Adjusted IRR[a]	0.73	0.55 to 0.97	0.031
Non-COPD hospital admissions						
Total number included in analysis	744	741				
Number with at least one admission	77	87				
Total number of admissions	111	111				
Mean admission rate	0.15	0.15	Unadjusted IRR	0.99	0.71 to 1.38	0.949
SD (admission rate)	0.54	0.45	Adjusted IRR[a]	1.03	0.74 to 1.43	0.875

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

TABLE 42 Sensitivity analysis for the ITT population excluding the 33 participants who died during the 12-month follow-up: lung function and patient-reported outcomes

Outcome	Trial arm		Model	Overall mean difference	95% CI	*p*-value
	Theophylline	Placebo				
% predicted FEV_1						
Baseline						
Total *n*	750	743				
Mean	51.4	52.4				
SD	20.0	19.8				
6 months						
Total *n*	548	535				
Mean	52.4	53.2				
SD	20.4	20.9				
12 months						
Total *n*	533	488				
Mean	51.5	52.2	Unadjusted	–0.59	–2.54 to 1.36	0.551
SD	20.4	21.6	Adjusted[a]	–0.58	–2.46 to 1.29	0.543
% predicted FVC						
Baseline						
Total *n*	748	742				
Mean	84.5	86.5				
SD	22.2	23.5				
6 months						
Total *n*	543	531				
Mean	84.0	84.6				
SD	22.74	24.8				
12 months						
Total *n*	525	485				
Mean	83.1	82.5	Unadjusted	–0.45	–2.59 to 1.69	0.678
SD	23.8	25.1	Adjusted[a]	–0.37	–2.43 to 1.69	0.723
CAT score						
Baseline						
Total *n*	745	742				
Mean	22.7	22.3				
SD	7.6	7.9				
6 months						
Total *n*	668	653				
Mean	21.2	21.1				
SD	8.1	8.3				

TABLE 42 Sensitivity analysis for the ITT population excluding the 33 participants who died during the 12-month follow-up: lung function and patient-reported outcomes (*continued*)

Outcome	Trial arm		Model	Overall mean difference	95% CI	*p*-value
	Theophylline	Placebo				
12 months						
Total *n*	633	615				
Mean	21.4	21.4	Unadjusted	0.16	–0.56 to 0.89	0.661
SD	8.2	8.6	Adjusted[a]	0.02	–0.65 to 0.69	0.950
HARQ score						
Baseline						
Total *n*	193	197				
Mean	25.2	25.8				
SD	16.1	14.9				
6 months						
Total *n*	189	187				
Mean	21.9	22.8				
SD	15.13	15.7				
12 months						
Total *n*	184	172				
Mean	24.1	24.2	Unadjusted	–0.62	–3.15 to 1.91	0.631
SD	15.70	15.94	Adjusted[a]	–0.89	–3.27 to 1.50	0.468

a Adjusted for centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, sex (male/female), smoking in pack-years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment and treatment with long-term antibiotics.

Appendix 6 Line listings of serious adverse events

TABLE 43 Events recorded as suspected unexpected serious adverse reactions

Case ID	Country, sex, age (years)	Event	Outcome	Date of onset	Assessment of relatedness to trial drug	Daily dose route formulation	Dates of treatment	Comments
System Organ Class: cardiac disorders								
ID 070	UK, female, 72	2 : 1 AV block	Recovered with sequelae	April 2015	Possible	200 mg of theophylline od	4 March–12 April 2015	*PI disputed diagnosis of AV block made by cardiology team. Chief investigator noted normal ECG after discontinuing study drug prior to development of AV block, also noted that theophylline increased heart rate rather than to slow it and therefore unlikely to be related to study drug*
ID 143	UK, female, 59	STEMI, PCI to LCx and OM arteries, cor pulmonale, mild to moderate LVSD on ventriculogram	Recovered	30 March 2016	Possible	200 mg of theophylline od	21–27 March 2016	*PI suggested that there was possible association with study drug. Chief investigator noted that the participant had ceased study medication 3 days prior to the cardiac event and therefore highly unlikely to be related to study drug*

AV, atrioventricular; ECG, electrocardiogram; ID, identification; LCx, left circumflex; LVSD, left ventricular systolic dysfunction; OM, obtuse marginal; PCI, percutaneous coronary intervention; PI, principal investigator; STEMI, ST elevation myocardial infarction.

TABLE 44 Events recorded as possible serious adverse reactions

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Assessment of relatedness to trial drug	Daily dose route formulation	Dates of treatment	Comments
System Organ Class: cardiac disorders								
007	UK, male, 66	Atypical atrial flutter/atrial tachycardia	Recovered	25 August 2014	Possible	200 mg theophylline bd	6–12 August 2014 and 19–25 August 2014	
018	UK, male, 79	Syncopal episode resulting in fracture to right fourth metacarpal	Recovered	8 November 2014	Possible	200 mg theophylline od	30 March 2014–31 March 2015	
029	UK, male, 81	Atrial fibrillation	Not recovered	31 October 2014	Possible	200 mg theophylline bd	30 April 2014–26 January 2015	
072	UK, male, 82	Non-sustained ventricular tachycardia	Recovered with sequelae	14 August 2015	Possible	200 mg theophylline od	25 August 2014–14 August 2015	
186	UK, male, 76	Palpitations	Not recovered	11 August 2016	Possible	200 mg placebo od	4–11 August 2016	
189	UK, female, 73	Palpitations and tachycardia	Not recovered	16 August 2016	Possible	200 mg theophylline od	16 February–5 September 2016	
213	UK, female, 54	Palpitations	Unknown	12 October 2016	Probable	200 mg placebo od	27 May–17 October 2016	
233	UK, male, 73	Sinus tachycardia	Recovered	18 November 2016	Possible	200 mg placebo od	25 November 2015–ongoing at time of event	
System Organ Class: gastrointestinal disorders								
103	UK, female, 71	Dyspeptic pain	Recovered	22 October 2015	Possible	200 mg placebo od	12–27 October 2015	
System Organ Class: investigations								
268	UK, male, 76	Weight loss, lethargy	Unknown	19 April 2017	Possible	200 mg placebo od	9 June 2016–ongoing at time of event	

ID, identification.

TABLE 45 Events recorded as SAEs[a]

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
System Organ Class: infections and infestations							
012	UK, male, 74	Infected elbow	Recovering	30 September 2014	200 mg of placebo od	12 September 2014–ongoing	
055	UK, female, 54	Right leg cellulitis	Recovered	10 June 2015	200 mg of theophylline od	9–11 December 2014	
060[b]	UK, female, 82	UTI	Unknown	9 July 2015	200 mg of placebo od	Never commenced trial medication (trial medication not dispensed)	*Did not start/initiate study medication*
071	UK, female, 76	Sepsis	Recovered with sequelae	19 August 2015	200 mg of placebo od	1 July 2015–ongoing at time of event	
081	UK, male, 70	Left arm cellulitis	Recovered	16 September 2015	200 mg of placebo od	3 April–16 September 2015	
110	UK, female, 75	Cellulitis lower leg secondary to cat bite	Unknown	13 December 2015	200 mg of theophylline od	2 December 2015–ongoing at time of event	
120	UK, female, 77	Cellulitis, delirium	Recovered	13 December 2015	200 mg of theophylline od	13 February 2015–ongoing at time of event	
127	UK, female, 82	UTI	Recovered	29 December 2015	200 mg of theophylline od	27 February–29 December 2015	
128	UK, female, 71	Sepsis	Unknown	8 February 2016	200 mg of placebo od	26 January 2016–ongoing at time of event	
134	UK, male, 79	UTI and reduced mobility	Recovered	26 November 2015	200 mg of theophylline bd	16 September 2015–25 January 2016	
174	UK, female, 64	Infection, unknown source	Recovered	28 May 2016	200 mg of theophylline od	23 June 2015–ongoing at time of event	

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
181	UK, female, 76	Atrial flutter secondary to sepsis from lower-limb cellulitis	Recovering	4 August 2016	200 mg of theophylline od	19 May 2016–ongoing at time of event	*Recorded as infection as this was the primary driver of atrial flutter*
201	UK, male, 57	Exacerbation of COPD, leading to type 2 respiratory failure, bilateral leg swelling and also became infected *Clostridium difficile* while in hospital	Unknown	13 June 2016	200 mg of placebo od	19 April 2016–13 July 2017	*Recorded as infection because of clostridium difficile infection. The exacerbation of COPD captured as primary outcome*
203	UK, female, 78	Gram-negative bacteraemia	Recovered	20 August 2016	200 mg of placebo od	15 July–5 September 2016	
217	UK, male, 69	Cellulitis	Recovered	12 February 2015	200 mg of theophylline od	7 July–24 November 2014	
220	UK, female, 77	Infective gastroenteritis	Recovered	4 May 2016	200 mg of theophylline od	Never commenced trial medication	*Did not start/initiate study medication*
221	UK, female, 77	Cellulitis	Recovered	10 July 2016	200 mg of theophylline od	Never commenced trial medication	*Did not start/initiate study medication*
222	UK, female, 77	Confusion, possible secondary to cellulitis	Recovered	2 October 2016	200 mg of theophylline od	Never commenced trial medication	• *Did not start/initiate study medication* • *Recorded as infection as this was the primary driver of confusion*
225	UK, male, 78	Sepsis	Recovered	13 November 2016	200 mg of placebo od	14 June 2016–ongoing at time of event	
239	UK, male, 74	Fall/possible sepsis	Unknown	28 December 2016	200 mg of theophylline od	2 August 2016 ongoing at time of event	*Recorded as infection as this was the primary driver of falls*
244	UK, male, 66	Ankle joint infection	Recovering	7 January 2017	200 mg of placebo od	22 January 2016–ongoing at time of event	
247	UK, female, 65	UTI	Recovered	10 October 2016	200 mg of placebo od	3 August 2016–ongoing at time of event	

continued

TABLE 45 Events recorded as SAEs[a] (*continued*)

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
249	UK, male, 77	UTI	Recovered	19 January 2017	200 mg of theophylline od	9 February 2016–ongoing at time of event	
251	UK, female, 71	Periumbilical abscess	Recovered	6 October 2016	200 mg of theophylline od	27 November 2015–ongoing at time of event	
253	UK, female, 60	UTI and possible viral gastroenteritis	Recovered	10 December 2016	200 mg of theophylline od	21–29 March 2016	
281	UK, male, 71	Gastroenteritis	Recovered	6 February 2017	200 mg of theophylline od	9 June–20 July 2016	
System Organ Class: neoplasm (benign, malignant and unspecified)							
010	UK, female, 74	Moderately differentiated squamous cell carcinoma of supraglottic submucosal T3 N2c M0	Recovered	Unknown: reported 29 September 2014	200 mg of theophylline od	14 April 2014–28 February 2015	
011	UK, male, 68	Lung cancer	Not recovered	Unknown: reported 30 September 2014	200 mg of placebo od	19 May–30 September 2014	
017	UK, female, 71	Left lower lobe lesion with pleural effusion	Unknown	29 October 2014	200 mg of theophylline od	19 May–13 November 2014	
019	UK, male, 68	Metastatic lung cancer stage T2a N3 M1b	Fatal	18 November 2014	200 mg of theophylline od	7 July–27 August 2014	
021	UK, female, 85	Metastatic bladder cancer	Fatal	7 October 2014	200 mg of placebo od	2 April–2 June 2014	
022	UK, male, 70	Perforated caecal tumour	Fatal	24 November 2014	200 mg of theophylline od	24 July–November 2014	
039	UK, female, 70	Intermediate-grade neuroendocrine tumour/atypical carcinoid	Recovering	16 January 2015	200 mg of placebo od	7 March–3 June 2015	
040	UK, female, 77	Large pelvic mass/sigmoid carcinoma	Not recovered	12 April 2014	200 mg of theophylline od	21 May 2014–25 April 2015	

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
059	UK, female, 79	Lung malignancy	Unknown	6 June 2015	200 mg of theophylline od	17 July 2014–July 2015	
068	UK, male, 83	Lung cancer	Fatal	12 August 2015	200 mg of theophylline od	18 August 2014–27 May 2015	
078	UK, female, 66	Metastatic colonic malignancy	Fatal	16 July 2015	200 mg of placebo od	16 December 2014–19 January 2015	
109	UK, male, 63	Left breast cancer	Recovering	4 November 2015	200 mg of theophylline twice daily	24 June 2015–ongoing at time of event	
112	UK, male, 61	Laryngeal cancer	Fatal	11 September 2015	200 mg of placebo od	Never commenced trial medication	*Did not start/initiate study medication*
117	UK, female, 64	Right hilar mass	Not recovered	15 December 2015	200 mg of theophylline od	5–25 August 2015	
123	UK, male, 80	Metastatic disease in the liver with no obvious primary	Unknown	11 December 2015	200 mg of placebo od	21 July–31 August 2015	
132	UK, female, 67	Central tumour, mediastinal lymphadenopathy, cerebral metastases	Not recovered	12 February 2016	200 mg of theophylline od	4–19 February 2016	
141	UK, male, 67	Metastatic cancer	Unknown	17 March 2016	200 mg of placebo od	14 April 2015–13 April 2016	
147	UK, female, 72	Lung cancer	Not recovered	1 April 2016	200 mg of theophylline od	15 October 2015–ongoing at time of event	
148	UK, female, 72	Haemoptysis secondary to lung cancer	Recovering	1 April 2016	200 mg of theophylline od	15 October 2015–ongoing at time of event	
160	UK, female, 76	Pancreatic malignancy with biliary obstruction	Fatal	3 May 2016	200 mg of theophylline od	17 March–17 May 2016	

continued

TABLE 45 Events recorded as SAEs[a] (*continued*)

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
202	UK, male, 61	T2 N2b squamous cell carcinoma of his right pyriform fossa	Unknown	8 March 2016	200 mg of placebo od	28 August 2015–ongoing at time of event	
219	UK, female, 68	Lung neoplasm	Not recovered	Unknown	200 mg of theophylline od	19 July 2016–3 January 2017	
228	UK, female, 59	Investigation following CT scan showing nodule – primary lung tumour	Unknown	15 November 2016	200 mg of placebo od	1 June 2016–ongoing at time of event	
231	UK, male, 70	Lung cancer	Not recovered	4 November 2016	200 mg of placebo twice daily	3 December 2015–ongoing at time of event	
238	UK, male, 70	Grade 2 prostate cancer	Unknown	22 December 2016	200 mg of placebo od	28 July 2016–ongoing at time of event	
241	UK, female, 58	Mastectomy for breast cancer	Recovering	19 December 2016	200 mg of theophylline od	18 February 2016–ongoing at time of event	
254	UK, female, 67	Right breast cancer	Unknown	2 March 2017	200 mg of theophylline od	27 May 2016–ongoing at time of event	
260	UK, female, 81	Uterine cancer	Recovering	27 February 2017	200 mg of theophylline od	3 March 2016–ongoing at time of event	
263	UK, female, 64	Chronic lymphocytic leukaemia	Not recovered	5 April 2017	200 mg of placebo od	25 August 2016–ongoing at time of event	
286	UK, male, 70	Hepatic flexure cancer (Dukes' B)	Recovering	20 July 2017	200 mg of theophylline od	4 August 2016–ongoing at time of event	
289	UK, female, 82	Classification of death: Ia metastatic cholangiocarcinoma, II COPD	Fatal	8 November 2017	200 mg of placebo od	Never commenced trial medication	*Did not start/initiate study medication*

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
System Organ Class: blood and lymphatic system disorders							
173	UK, male, 71	Iron deficiency anaemia	Recovered	18 February 2016	200 mg of placebo od	29 June 2015–ongoing at time of event	
184	UK, female, 72	Abdominal haematoma	Recovering	3 May 2016	200 mg of placebo od	7 August 2015–ongoing at time of event	
System Organ Class: immune system disorders							
None							
System Organ Class: endocrine disorders							
None							
System Organ Class: metabolism and nutrition disorders							
245	UK, male, 79	Dysphagia	Unknown	27 January 2017	200 mg of theophylline od	14 July 2016–31 January 2017	
246	UK, male, 79	Refeeding syndrome	Unknown	28 January 2017	200 mg of theophylline od	14 July 2016–31 January 2017	
System Organ Class: psychiatric disorders							
073	UK, male, 57	Overdose of amitriptyline and alcohol	Recovering	1 September 2015	200 mg of placebo od	4 August–2 September 2015	
098	UK, male, 58	Overdose of amitriptyline and alcohol	Not recovered	8 November 2015	200 mg of placebo od	4 August–2 September 2015	
146	UK, male, 59	Admission to psychiatric ward with a depressive episode	Recovered	24 July 2015	200 mg of placebo bd	8 April–30 June 2015	
183	UK, male, 73	Death (suicide) as a result of asphyxiation	Fatal	13 July 2016	200 mg of theophylline od	9 September 2015–13 July 2016	
System Organ Class: nervous system disorders							
014	UK, male, 76	TIA, atrial fibrillation	Recovered with sequelae	1 September 2014	200 mg of theophylline bd	3 June 2014–9 January 2015	

continued

TABLE 45 Events recorded as SAEs[a] (*continued*)

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
025	UK, male, 76	Stroke	Recovering	11 November 2014	200 mg of theophylline bd	3 June 2014–November 2014, restarted briefly at start of January 2015	
027	UK, male, 66	Seizure secondary to intracerebral haemorrhage	Recovered	13 January 2015	200 mg of theophylline od	31 March 2014–26 March 2015	
033	UK, female, 44	Headache	Recovered	19 February 2015	200 mg of theophylline od	7 January 2015–ongoing at time of event	
043	UK, male, 65	Subdural bleed/haematoma as result of fall prior to trial inclusion	Unknown	1 April 2015	200 mg of theophylline od	23 April 2015–ongoing at time of event	
050	UK, female, 78	Suspected cerebral infarct	Recovering	23 May 2015	200 mg of placebo od	30 April–21 May 2015	
064	UK, male, 78	Subdural haemorrhage	Fatal	20 June 2015	200 mg of theophylline od	23 April–23 July 2015	
077	UK, male, 73	Spinal canal stenosis	Recovered	10 September 2015	200 mg of theophylline od	21 April–9 September 2015	
080	UK, female, 82	Partial anterior circulation infarct	Recovered	7 September 2015	200 mg of theophylline od	27 February–7 September 2015	
085	UK, male, 73	Chest pain/spinal stenosis	Recovered	20 July 2015	200 mg of theophylline od	13 October 2014–12 October 2015	
099	UK, male, 78	Lewy body dementia	Recovered	6 November 2015	200 mg of placebo od	1 December 2014–ongoing at time of event	
107	UK, female, 82	Right total anterior circulation stroke syndrome or Todd's palsy	Recovered	21 October 2015	200 mg of theophylline od	27 February 2015–ongoing at time of event	
114	UK, male, 76	Bilateral thalamic infarct	Not recovered	31 December 2015	200 mg of theophylline od	15 September 2015–ongoing at time of event	

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
118	UK, male, 81	CVA	Recovering	31 December 2015	200 mg of placebo od	30 January 2015, then stopped trial drugs as soon as admitted	
131	UK, female, 58	Possible TIA	Recovering	18 January 2016	200 mg of placebo od	24 March–18 August 2015	
140	UK, female, 72	Dizziness and vomiting	Recovered with sequelae	22 March 2016	200 mg of theophylline od	1 April 2015–ongoing at time of event	
151	UK, male, 62	Confusion with worsening headache	Recovered	16 December 2015	200 mg of placebo od	10 April 2015–15 April 2016	
172	UK, male, 72	Ischaemic stroke, community-acquired pneumonia	Recovering	1 July 2016	200 mg of theophylline od	2 February 2016–ongoing at time of event	
176	UK, female, 79	Subarachnoid haemorrhage	Unknown	6 June 2016	200 mg of placebo od	15 September 2015–6 June 2016	
269	UK, male, 68	Frontal lobe dementia	Fatal	Unknown	200 mg of placebo od	12 April–18 October 2016	
System Organ Class: eye disorders							
None							
System Organ Class: ear and labyrinth disorders							
None							
System Organ Class: cardiac disorders							
004	UK, female, 84	Pulmonary oedema	Recovered	24 June 2014	200 mg of placebo od	9 April–20 June 2014	
013	UK, male, 72	Death: cause of death – myocardial infarction, infective exacerbation of COPD, atrial fibrillation	Fatal	1 October 2014	200 mg of placebo od	30 May–13 August 2014	
026	UK, male, 90	Orthostatic hypotension	Recovered with sequelae	28 December 2014	200 mg of theophylline od	7 May–6 June 2014	

continued

TABLE 45 Events recorded as SAEs[a] (*continued*)

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
031	UK, male, 75	Out-of-hospital cardiac arrest; end-stage COPD; mitral valve prolapse	Fatal	8 January 2015	200 mg of theophylline od	21 June–4 September 2014	
032	UK, male, 57	Chest pain	Recovered	1 December 2014	200 mg of placebo od	31 March 2014–2 April 2015	
036	UK, male, 71	Anterolateral NSTEMI (myocardial infarction)	Recovered	26 February 2015	200 mg of placebo od	13 March 2014–26 February 2015	
042	UK, male, 75	Cardiac arrest at home; carcinoma of the right upper lobe and COPD	Fatal	28 April 2015	200 mg of placebo od	18 August 2014–April 2015	
052	UK, female, 76	Angina	Recovered with sequelae	11 July 2014	200 mg of theophylline od	3 April 2014–2 April 2015	
053	UK, female, 76	Angina	Recovered with sequelae	31 July 2014	200 mg of theophylline od	3 April 2014–2 April 2015	
056	UK, male, 65	Atrial fibrillation/flutter	Recovered with sequelae	16 June 2014	200 mg of placebo od	1–16 June 2015	*Initially reported as possibly related to the study medication; at SAE follow-up, reported as having no relationship to study medication*
062	UK, female, 78	Carotid vascular disease	Recovered with sequelae	4 June 2015	200 mg of placebo od	29 April–12 May 2015	
063	UK, female, 78	Angina	Recovered with sequelae	5 June 2015	200 mg of placebo od	29 April–12 May 2015	
079	UK, female, 82	Missed STEMI versus broken heart syndrome	Recovered	16 August 2015	200 mg of theophylline od	27 February–16 August 2015	
082	UK, female, 70	Fast atrial fibrillation	Recovering	2 October 2015	200 mg of placebo od	25 November 2014–28 July 2015	
086	UK, male, 59	Unstable angina	Recovered	9 September 2015	200 mg of placebo od	8 April–30 June 2015	
097	UK, female, 74	Left ventricular failure	Recovered	1 November 2015	200 mg of placebo od	6 January 2015–ongoing at time of event	

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
102	UK, male, 82	Collapse not otherwise specified	Unknown	25 November 2015	200 mg of placebo od	21 May 2015–ongoing at time of event	
119	UK, female, 77	Exacerbation of COPD; pulmonary congestion	Recovered	4 December 2015	200 mg of theophylline od	13 February 2015–ongoing at time of event	
122	UK, female, 77	Left ventricular failure, secondary to acute MI, secondary sepsis, secondary to pneumonia	Fatal	17 January 2016	200 mg of theophylline od	14 February 2015–18 January 2016	*Recorded as cardiac because of pulmonary congestion, the exacerbation of COPD was captured as primary outcome*
126	UK, female, 82	Congestive cardiac failure	Recovered	16 December 2015	200 mg of theophylline od	27 February–16 December 2015	
133	UK, male, 69	Cardiac arrest	Fatal	26 January 2016	200 mg of placebo od	21 October 2015–26 January 2016	
149	UK, female, 62	Heart failure	Recovered	1 February 2016	200 mg of placebo od	14 April 2015–ongoing at time of event	
164	UK, male, 79	Cardiac arrest	Fatal	12 May 2016	200 mg of theophylline od	31 October–19 December 2015	
178	UK, male, 78	Heart failure, acute kidney injury	Fatal	21 July 2016	200 mg of theophylline od	1 June–21 July 2016	
179	UK, male, 68	Cardiac arrest	Fatal	9 July 2016	200 mg of theophylline od	27 November 2015–8 July 2016	
185	UK, male, 76	Possible heart attack	Not recovered	12 August 2016	200 mg of placebo od	3 June–23 September 2016	
192	UK, female, 64	Narrow complex tachycardia, exacerbation of COPD	Recovering	29 June 2016	200 mg of theophylline od	26 August 2015–ongoing at time of event	
195	UK, male, 86	Chest pain – probably angina	Recovered	11 February 2015	200 mg of placebo od	5–11 September 2014	
196	UK, male, 86	Unstable angina	Recovered	9 June 2015	200 mg of placebo od	5–11 September 2014	

continued

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TABLE 45 Events recorded as SAEs[a] (*continued*)

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
205	UK, male, 55	Acute coronary syndrome	Unknown	14 September 2016	200 mg of placebo twice daily	5 February 2016–ongoing at time of event	
223	UK, male, 73	Acute myocardial infarction	Unknown	24 October 2016	200 mg of placebo od	7 June 2016–ongoing at time of event	
240	UK, female, 78	Heart failure, moderate to severe aortic stenosis	Unknown	29 November 2016	200 mg of placebo od	15 July–5 September 2016	
242	UK, male, 73	NSTEMI	Recovered with sequelae	15 October 2016	200 mg of theophylline od	1 February 2016–9 January 2017	
243	UK, male, 63	Congestive heart failure	Recovering	21 December 2016	200 mg of placebo twice daily	26 July 2016–ongoing at time of event	
250	UK, female, 69	STEMI	Recovered	23 February 2016	200 mg of placebo od	27 February–30 July 2015	
258	UK, male, 88	NSTEMI	Recovered	9 October 2016	200 mg of placebo od	13 November 2015–ongoing at time of event	
265	UK, male, 64	End-stage congestive cardiac failure	Fatal	12 April 2017	200 mg of placebo twice daily	26 July 2016–30 April 2017	
276	UK, male, 68	Acute pulmonary oedema	Fatal	1 June 2017	200 mg of theophylline od	14 July 2016–1 June 2017	
282	UK, female, 65	Atrial fibrillation and heart failure	Recovered	10 June 2016	200 mg of placebo od	11 May 2016–ongoing at time of event	
284	UK, female, 69	Postural hypotension	Recovered	31 May 2017	200 mg of placebo od	11 August 2016–ongoing at time of event	

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
System Organ Class: vascular disorder							
001	UK, male, 57	Old cerebellar gliosis/ stroke	Recovered	25 April 2014	200 mg of placebo od	31 March 2014–ongoing at time of event	
066	UK, male, 62	COPD with lower respiratory tract infection and DVT	Recovered	20 June 2015	200 mg of placebo od	18 September–October 2014 (18 doses in total)	*Recorded as vascular because exacerbation of COPD captured as primary outcome*
105	UK, male, 75	Ruptured abdominal aortic aneurysm	Fatal	29 November 2015	200 mg of theophylline twice daily	14 October–29 November 2015	
168	UK, female, 76	Right leg DVT	Recovering	14 June 2016	200 mg of theophylline od	2 December 2015–ongoing at time of event	
182	UK, female, 72	Collapse	Unknown	5 August 2016	200 mg of placebo od	26 January 2016–ongoing at time of event	
224	UK, male, 78	Intracerebral haemorrhage	Recovered	6 November 2016	200 mg of placebo od	14 June 2016–ongoing at time of event	
252	UK, male, 69	Right ICA occlusion	Recovering	26 December 2016	200 mg of placebo od	1 March 2016–17 February 2017	
255	UK, male, 74	Bilateral subdural haematomas	Recovered with sequelae	28 December 2015	200 mg of theophylline od	21 April–17 September 2015	
256	UK, male, 74	DVT/pulmonary embolism	Recovered with sequelae	28 December 2015	200 mg of theophylline od	21 April–17 September 2015	
267	UK, female, 73	Uncontrolled hypertension	Recovered	13 April 2017	200 mg of theophylline od	13 April 2016–ongoing at time of event	
270	UK, male, 68	Collapse, cause unknown	Recovered	17 June 2016	200 mg of placebo od	12 April–18 October 2016	
285	UK, male, 77	Ruptured abdominal aortic aneurysm	Fatal	7 August 2017	200 mg of theophylline od	17 August–9 October 2016	

continued

TABLE 45 Events recorded as SAEs[a] (*continued*)

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
System Organ Class: respiratory, thoracic and mediastinal disorders							
002	UK, male, 70	Death: pneumonia, diabetic hypoglycaemia	Fatal	12 May 2014	200 mg of theophylline od	24 April–11 May 2014	
003	UK, female, 74	Pulmonary embolism	Recovered	24 June 2014	200 mg of placebo od	16 June 2014–ongoing at time of event	
015	UK, female, 65	Death: exacerbation of COPD	Fatal	30 October 2014	200 mg of placebo od	24 June–30 October 2014	
023	UK, female, 69	Chest infection/chest pain/left upper rib fracture	Recovered	17 October 2014	200 mg of placebo od	25–29 July 2014	
024	UK, female, 68	Death: type 2 respiratory failure, COPD, multiple sclerosis	Fatal	20 December 2014	200 mg of theophylline od	22 May–27 August 2014	
034	UK, male, 74	Death: severe COPD	Fatal	16 February 2015	200 mg of placebo od	16 June 2014–February 2015	
035	UK, male, 46	Hyperventilation	Recovered	11 November 2014	200 mg of placebo bd	10 September 2014–ongoing at time of event	
044	UK, male, 73	Death: exacerbation of COPD	Fatal	11 April 2015	200 mg of theophylline od	18 February–7 April 2015	
046	UK, male, 90	Symptomatic pleural effusions, hospital-acquired pneumonia	Recovered with sequelae	11 May 2015	200 mg of theophylline od	7 May 2014–18 May 2015	
047	UK, male, 47	Shortness of breath; most likely exacerbation of COPD	Recovered	6 December 2015	200 mg of placebo bd	10 September 2014–ongoing at time of event	
057	UK, female, 73	Death: end-stage COPD	Fatal	15 June 2015	200 mg of placebo od	3–31 March 2015	
058	UK, female, 74	Pleuritic chest pain	Recovered	15 March 2015	200 mg of theophylline od	10 July–11 August 2014	

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
061	UK, male, 72	Pleuritic chest pain	Recovered	20 July 2015	200 mg of theophylline od	10 July 2015–ongoing at time of event	
067	UK, male, 62	Community-acquired pneumonia, vomited, aspirated and cardiac arrest	Fatal	17 July 2015	200 mg of placebo od	18 September–October 2014 (18 doses in total)	
069	UK, female, 67	Pleuritic chest pain	Recovered	24 February 2015	200 mg of theophylline od	27 August–9 November 2014	
083	UK, male, 71	Increased breathlessness	Recovered	1 April 2015	200 mg of theophylline od	23 September 2014–12 October 2015	
088	UK, male, 79	Cor pulmonale secondary to COPD	Fatal	4 October 2015	200 mg of placebo od	21 April–7 September 2015	
089	UK, male, 83	Infective exacerbation of COPD, pleural effusion	Unknown	11 July 2015	200 mg of theophylline od	18 August 2014–27 May 2015	
093	UK, male, 78	Shortness of breath	Recovering	9 October 2015	200 mg of placebo od	1 December 2014–ongoing at time of event	
116	UK, female, 71	Pulmonary embolism	Recovering	19 December 2015	200 mg of placebo od	7 August 2015–ongoing at time of event	
124	UK, male, 73	(1a) Acute kidney injury, (1b) septicaemia, (1c) lower respiratory tract infection; (2) COPD, atrial fibrillation, acromegaly	Fatal	9 April 2015	200 mg of placebo od	1 May 2014–8 April 2015	*Recorded as respiratory because the prime driver was lower respiratory tract infection and acute kidney injury, with septicaemia a secondary driver*
125	UK, male, 80	Pneumonia	Fatal	31 December 2015	200 mg of placebo od	24 November–30 December 2015	
154	UK, female, 72	Pleuritic chest pain	Recovered	12 January 2016	200 mg of theophylline od	14 November–20 December 2015	
155	UK, male, 55	Renal failure, secondary to chest infection	Fatal	12 April 2016	200 mg of placebo bd	20 October 2015–April 2016	*Recorded as respiratory because prime driver was lower respiratory tract infection, renal failure secondary*

continued

TABLE 45 Events recorded as SAEs[a] (*continued*)

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
165	UK, male, 71	Haemoptysis	Recovered	11 May 2016	200 mg of placebo od	29 June 2015–ongoing at time of event	
166	UK, male, 76	Bronchiectasis	Recovered	7 March 2016	200 mg of placebo od	10 December 2015–ongoing at time of event	
170	UK, male, 72	Pneumothorax	Recovered	1 May 2016	200 mg of placebo od	8 July 2015–ongoing at time of event	
175	UK, female, 64	Respiratory failure and CO_2 narcosis following exacerbation of COPD and chest infection	Recovering	12 May 2016	200 mg of theophylline od	14 March–12 May 2016	
177	UK, female, 71	Pulmonary embolism	Recovering	18 July 2016	200 mg of theophylline od	28 November 2015–ongoing at time of event	
197	UK, male, 70	Pneumonia, pulmonary embolism, cavitating lesion on CT scan of chest	Recovered with sequelea	22 August 2016	200 mg of placebo od	4 May–23 August 2016	
208	UK, male, 63	Right pneumothorax	Recovered	27 June 2014	200 mg of theophylline od	24 April–23 June 2014	
209	UK, male, 63	Right pneumothorax	Recovered	31 August 2014	200 mg of theophylline od	24 April–23 June 2014	
212	UK, female, 64	Pleurisy or musculoskeletal pain	Recovered	10 February 2016	200 mg of theophylline od	9 April 2015–ongoing at time of event	
226	UK, female, 59	Bronchiectasis	Unknown	15 November 2016	200 mg of placebo od	1 June 2016–ongoing at time of event	
230	UK, female, 55	Hypoxia	Recovering	28 November 2016	200 mg of placebo od	20 January 2016–ongoing at time of event	
234	UK, male, 62	COPD	Fatal	Unknown	200 mg of theophylline od	19 January 2016–ongoing at time of event	

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
248	UK, male, 79	Aspiration pneumonia	Fatal	2 February 2017	200 mg of theophylline od	14 July 2016–31 January 2017	
257	UK, male, 88	Chest infection	Fatal	20 February 2017	200 mg of theophylline od	6 March 2016–25 February 2017	
264	UK, male, 68	• Bilateral bronchopneumonia • Pulmonary oedema secondary to heart failure and acute kidney injury • Progressive frontal lobe dementia and COPD	Fatal	22 November 2016	200 mg of placebo od	12 April–18 October 2016	
266	UK, female, 71	Pleuritic chest pain	Recovered	12 July 2015	200 mg of placebo od	15 September 2014–2 February 2015	
288	UK, female, 78	Death, pneumonia, severe COPD, frailty	Fatal	9 December 2015	200 mg of theophylline od	20 April–17 November 2015	
System Organ Class: gastrointestinal disorders							
009	UK, male, 55	Adhesional bowel obstruction	Recovered	11 September 2014	200 mg of theophylline od	24 May–1 September 2014	
016	UK, male, 76	Blockage in oesophagus	Recovered	1 November 2014	200 mg of theophylline od	2 October 2014–ongoing at time of event	
020	UK, male, 72	Inflammation of oesophagus	Recovered	16 September 2014	200 mg of placebo od	8 July 2014–24 June 2015	
030	UK, female, 82	Viral gastroenteritis	Recovered	15 January 2015	200 mg of placebo od	1 April 2014–15 January 2015	
037	UK, female, 43	Abdominal pain and liver steatosis	Unknown	11 March 2015	200 mg of theophylline od	13 January 2015–ongoing at time of event	
038	UK, female, 79	Vomiting, fever, severe abdominal pain	Recovering	21 March 2015	200 mg of placebo od	4 February–8 August 2015	

continued

TABLE 45 Events recorded as SAEs[a] (*continued*)

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
048	UK, male, 78	Diverticulitis	Recovered	8 September 2014	200 mg of placebo od	6 March–15 October 2014	
049	UK, male, 78	Diverticulitis	Recovered	8 December 2014	200 mg of placebo od	6 March–15 October 2014	
051	UK, female, 72	Severe constipation	Recovered	7 June 2015	200 mg of theophylline od	2–5 May 2014	
054	UK, female, 54	Gastritis	Recovered	25 April 2015	200 mg of theophylline od	9–11 December 2014	
065	UK, female, 58	Diverticulitis	Recovered	26 July 2015	200 mg of placebo od	3 July 2015–ongoing at time of event	
074	UK, male, 66	Appendicitis	Recovered	28 August 2015	200 mg of theophylline od	29 July–27 August 2015	
087	UK, male, 71	Laparoscopic appendectomy	Recovered	9 November 2014	200 mg of theophylline od	5 September 2014–ongoing at time of event	
090	UK, female, 82	Abdominal pain	Recovered	5 October 2014	200 mg of theophylline od	14–17 May 2014	
100	UK, female, 59	Strangulated small bowel secondary to hernia	Recovered	1 November 2014	200 mg of placebo od	4 August–1 September 2014	
101	UK, female, 60	Oesophagitis and oesophageal stricture	Recovered	6 July 2015	200 mg of placebo od	4 August–1 September 2014	
111	UK, male, 71	Haematemesis	Recovered	22 November 2014	200 mg of placebo od	20 March 2014–ongoing at time of event	
121	UK, male, 58	Perforated duodenal ulcer	Recovered	25 September 2015	200 mg of theophylline od	3 February 2015–15 January 2016	
129	UK, male, 49	Laparotomy and adhesiolysis following severe abdominal pain	Recovering	15 February 2016	200 mg of theophylline bd	23 April 2015–ongoing at time of event	

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
136	UK, male, 70	Rectal bleed; possible Infective/ischaemic colitis	Recovering	6 March 2016	200 mg of theophylline od	12 August–31 December 2015	
150	UK, male, 71	Diverticular disease	Recovered	6 April 2016	200 mg of theophylline od	22 March 2016–ongoing at time of event	
158	UK, female, 72	Nausea and vomiting, acute abdominal pain	Recovering	3 May 2016	200 mg of theophylline od	26 November 2015–ongoing at time of event	
163	UK, male, 56	Anal abscess/fistula	Not recovered	10 January 2016	200 mg of theophylline twice daily	4 July 2015–ongoing at time of event	
171	UK, male, 71	Diverticulitis	Unknown	27 June 2016	200 mg of theophylline od	21 March–29 June 2016	
193	UK, male, 59	Bowel obstruction	Recovered	5 August 2016	200 mg of theophylline od	29 July 2016–ongoing at time of event	
198	UK, female, 59	Gastroenteritis	Recovered	1 May 2016	200 mg of theophylline od	21–29 March 2016	
210	UK, female, 71	Acute pancreatitis	Recovering	6 October 2016	200 mg of theophylline od	27 November 2015–ongoing at time of event	
235	UK, male, 68	(COPD) and acute upper gastrointestinal haemorrhage due to duodenal ulcer	Fatal	Unknown	200 mg of theophylline bd	28 June–19 December 2016	*Recorded as gastrointestinal because exacerbation of COPD captured as primary outcome*
262	UK, male, 80	Constipation	Recovered with sequelae	5 March 2017	200 mg of placebo od	11 May 2016–ongoing at time of event	
275	UK, female, 88	Constipation	Recovered	6 December 2016	200 mg of placebo od	1 June 2016–ongoing at time of event	
277	UK, male, 76	Constipation	Recovered	28 December 2016	200 mg of theophylline od	3–22 June 2016	

continued

TABLE 45 Events recorded as SAEs[a] (*continued*)

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
279	UK, female, 73	Diverticulitis 'flare-up'	Recovered	2 March 2017	200 mg of theophylline od	18 July–2 August 2016	
287	UK, male, 77	Constipation	Unknown	8 May 2017	200 mg of theophylline od	17 August–9 October 2016	
System Organ Class: hepatobiliary disorders							
008	UK, male, 66	Acute hepatitis	Recovered	25 August 2014	200 mg of placebo bd	23–25 August 2014	
130	UK, female, 67	Obstructive jaundiced and evidence of intraductal calculi	Recovered	11 January 2016	200 mg of placebo od	24 February 2015–ongoing at time of event	
138	UK, female, 68	Vomiting	Recovered	22 November 2015	200 mg of theophylline od	20–11 March 2016	
152	UK, female, 72	Cholangitis and laparoscopic cholecystectomy	Recovered	21 December 2015	200 mg of theophylline od	14 November–20 December 2015	
236	UK, male, 76	Groin pain (possible biliary sepsis)	Recovered	12 August 2016	200 mg of placebo od	7 June 2016–ongoing at time of event	
273	UK, male, 87	Gallstones	Recovered with sequelae	1 November 2016	200 mg of placebo od	24 August 2016–ongoing at time of event	
System Organ Class: skin and subcutaneous tissue disorders							
135	UK, male, 80	Skin rash	Recovered	29 December 2015	200 mg of theophylline od	3 February 2015–14 February 2015	
System Organ Class: musculoskeletal and connective tissue disorders							
006	UK, male, 61	Suspected fractured ribs	Recovering	31 May 2014	200 mg of placebo od	4 March–10 May 2014	
084	UK, female, 55	Chest pain	Recovered	3 July 2015	200 mg of placebo od	24 April 2015–ongoing at time of event	

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
092	UK, female, 58	Atypical chest pain	Recovered	27 August 2015	200 mg of placebo od	11 May 2015–ongoing at time of event	
139	UK, female, 69	Chest tightness	Recovered	11 January 2016	200 mg of theophylline od	23 September 2015–ongoing at time of event	
144	UK, male, 82	Acute stiff neck	Recovering	25 February 2016	200 mg of placebo bd	21 May 2015–25 February 2016	
145	UK, male, 82	GP referral owing to swallowing problems and neck pain ongoing at time of event for 2 or 3 weeks	Recovered with sequelae	21 March 2016	200 mg of placebo bd	21 May 2015–25 February 2016	
156	UK, female, 72	Left rib fracture (osteoporotic, not traumatic)	Recovering	25 April 2016	200 mg of placebo od	7 August 2015–ongoing at time of event	
159	UK, male, 71	Musculoskeletal chest pain	Recovering	10 May 2016	200 mg of theophylline od	17 November 2015–17 May 2016	
161	UK, male, 56	Hyperaesthesia of insulin injection site	Recovered	11 December 2015	200 mg of placebo od	25 June 2015–ongoing at time of event	
162	UK, male, 56	Right ankle pain possibly due to cellulitis	Recovering	3 May 2016	200 mg of placebo od	25 June 2015–ongoing at time of event	
187	UK, male, 61	Musculoskeletal chest pain	Recovered	3 May 2014	200 mg of theophylline od	24 April–23 June 2014	
188	UK, male, 71	Chest pain	Recovered	16 August 2016	200 mg of placebo od	17 November 2015–ongoing at time of event	
199	UK, female, 59	Musculoskeletal pain	Recovered	3 July 2016	200 mg of theophylline od	21–29 March 2016	
211	UK, female, 76	Back pain following fall	Recovered	14 May 2015	200 mg of placebo od	5–9 June 2014	

continued

TABLE 45 Events recorded as SAEs[a] (*continued*)

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
259	UK, female, 72	Primary diagnosis of gout of her left big toe, with a secondary diagnosis of infection	Unknown	1 March 2017	200 mg of theophylline od	18 April 2016–ongoing at time of event	
261	UK, female, 76	Abdominal pain	Recovered	1 February 2017	200 mg of placebo od	26 August 2016–ongoing at time of event	*Considered to be of musculoskeletal origin*
System Organ Class: renal and urinary disorders							
076	UK, male, 60	Kidney stones	Recovering	2 September 2015	200 mg of placebo od	6 January 2015–ongoing at time of event	
104	UK, male, 83	Urinary retention	Recovering	18 November 2015	200 mg of placebo od	28 May 2015–ongoing at time of event	
106	UK, female, 82	Acute kidney injury	Recovered	30 November 2015	200 mg of theophylline od	27 February 2015–ongoing at time of event	
157	UK, male, 63	Right renal colic	Recovered	29 Feb 2016	200 mg of placebo bd	4 November 2015–5 January 2016	
200	UK, female, 59	UTI with stage 1 acute kidney injury	Recovered	16 August 2016	200 mg of theophylline od	21–29 March 2016	
207	UK, female, 75	Multiresistant *Escherichia coli* UTI	Recovered	25 November 2014	200 mg of theophylline od	28 August–1 September 2014	
229	UK, female, 73	Deranged renal function, lower respiratory tract infection	Recovered	20 November 2016	200 mg of theophylline od	11–20 April 2016	
237	UK, male, 76	Haematuria	Recovering	2 December 2016	200 mg of placebo od	7 June–12 August 2016	
280	UK, male, 83	Shortness of breath due to fluid overload, secondary to renal disease	Recovered	30 March 2016	200 mg of theophylline od	2 March–12 April 2016	

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
283	UK, female, 78	Proximal ureteric stone causing obstruction of left kidney	Recovered	5 December 2016	200 mg of theophylline od	26 July 2016–ongoing at time of event	
System Organ Class: pregnancy, puerperium and perinatal conditions							
None							
System Organ Class: reproductive system and breast disorders							
None							
System Organ Class: congenital, familial and genetic disorders							
None							
System Organ Class: general disorders and administration site conditions							
None							
System Organ Class: investigations							
113	UK, female, 55	Asymptomatic raised calcium levels	Recovered	4 December 2015	200 mg of placebo od	23 June 2015–ongoing at time of event	
System Organ Class: injury, poisoning and procedural complications							
005	UK, female, 68	Left tibial plateau fracture	Recovering	1 July 2014	200 mg of theophylline od	8 May 2014–ongoing at time of event	
028	UK, female, 67	Fractured pubic ramus and right acetabulum	Recovered	12 November 2014	200 mg of theophylline od	22 August–9 November 2014	
041	UK, male, 55	Death: head injury	Fatal	19 April 2015	200 mg of theophylline od	13 March–19 April 2015	
075	UK, male, 90	Fall (mechanical)	Recovered	12 March 2015	200 mg of placebo od	4 September 2014–3 September 2015	
091	UK, female, 58	Rectus sheath haematoma	Recovered	23 September 2015	200 mg of placebo od	11 May 2015–ongoing at time of event	*Secondary to trauma*
094	UK, male, 85	Fractured neck of femur	Recovered	14 August 2015	200 mg of placebo od	23 March 2015–ongoing at time of event	

continued

TABLE 45 Events recorded as SAEs[a] (*continued*)

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
095	UK, female, 82	Fracture left wrist	Recovered	28 April 2015	200 mg of placebo od	30 October–5 November 2014	
096	UK, female, 65	Fractured distal radius and ulna	Recovered	4 September 2015	200 mg of placebo od	15 June 2015–ongoing at time of event	
108	UK, male, 49	Laceration to left hand	Unknown	29 September 2015	200 mg of theophylline bd	23 April 2015–ongoing at time of event	
115	UK, female, 76	Fall	Recovered	26 December 2015	200 mg of placebo od	12–31 December 2015	
137	UK, male, 60	Lower back pain lasting 2 hours since fall on floor during the night	Recovered	7 March 2016	200 mg of theophylline od	7 April 2015–ongoing at time of event	
153	UK, female, 72	Post-operative wound infection	Recovered	9 January 2016	200 mg of theophylline od	13 November–20 December 2015	
169	UK, male, 80	Raised INR of 4.2 and HB 97; possibly due to GI bleed	Recovering	1 July 2016	200 mg of theophylline od	21 October 2015–ongoing at time of event	*Inappropriately high dose of warfarin*
180	UK, male, 83	Head injury	Recovered	6 July 2016	200 mg of placebo od	10 February 2016–ongoing at time of event	
190	UK, male, 69	Fractured rib	Not recovered	19 August 2016	200 mg of placebo od	21 March 2016–ongoing at time of event	
204	UK, female, 81	Right distal fibula and medial malleolus	Unknown	3 September 2016	200 mg of theophylline od	19 July–19 December 2016	
206	UK, male, 74	Fell down stairs and fractured clavicle and shoulder, and broke ribs	Recovering	1 August 2016	200 mg of placebo od	24 August 2015–11 February 2016	
214	UK, male, 63	Fall	Recovered	15 January 2015	200 mg of placebo od	4 March 2014–ongoing at time of event	

Case ID	Country, sex, age (years)	SAE	Outcome	Date of onset	Daily dose route formulation	Dates of treatment	Comments
216	UK, male, 69	Persistent vomiting	Recovered	17 January 2015	200 mg of theophylline od	7 July–24 November 2014	*Thought to be related to chemotherapy*
218	UK, male, 69	Confusion (steroid-induced psychosis)	Recovered	4 April 2015	200 mg of theophylline od	7 July–24 November 2014	
271	UK, female, 76	Closed fracture neck of femur	Unknown	14 May 2017	200 mg of placebo od	27 May 2016–ongoing at time of event	
272	UK, male, 58	Fall-like syncopal attack	Recovered	26 March 2015	200 mg of theophylline od	12 March–18 April 2015	
274	UK, male, 84	Fall	Fatal	14 October 2016	200 mg of placebo od	23 May–6 October 2016	
278	UK, female, 61	Fractured neck of femur	Recovered	8 May 2017	200 mg of placebo od	17 May 2016–ongoing at time of event	
System Organ Class: surgical and medical procedures							
045	UK, male, 69	Optical urethrotomy	Recovered	27 March 2015	200 mg of theophylline bd	30 July 2014 to 29 July 2015	
System Organ Class: social circumstances							
None							

CT, computerised tomography; CVA, cerebrovascular accident; DVT, deep-vein thrombosis; HB, haemoglobin; ICA, internal carotid artery; ID, identification; INR, international normalised ratio; M, metastasis; N, node; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; T, tumour; TIA, transient ischaemic attack; UTI, urinary tract infection.

a Seven other events were recorded by sites as SAEs. These are not reported in *Table 43*–45 (or in *Table 17*) for the following reasons: two were retracted because they were not considered to be serious (IDs 167 and 191); one was retracted and resubmitted as a follow-up (ID 194); and four captured primary (COPD exacerbation) or secondary (pneumonia) outcome data and are reported as such in *Chapter 4* (IDs 142, 215, 227 and 232).

b Event not included in *Table 17* as this person did not start the trial medication.

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