

# Theophylline With Inhaled Corticosteroid (ICS)

<b>Submission date</b> 18/09/2013	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 19/09/2013	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 26/07/2019	<b>Condition category</b> Respiratory	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

Chronic Obstructive Pulmonary Disease (COPD) is a lung disease that causes obstruction of the airflow. In the UK, it affects around 3 million people. It is the fifth leading cause of death and costs the NHS about £1 billion each year. Recommended treatment for COPD includes inhaled corticosteroids (ICS) to reduce worsening of symptoms and improve lung function. However, this is not very effective and even high doses fail to prevent worsening of the disease. Research shows that low dose theophylline may be effective, and when used with ICS will reduce worsening of the disease. In this study we will find out the clinical and cost effectiveness of adding low dose theophylline to ICS therapy in patients with COPD.

### Who can participate?

We will recruit male and female patients aged 40 and over, who have COPD, who are taking inhaled corticosteroids and who have had two or more instances of worsening of symptoms in the previous year.

### What does the study involve?

After they have agreed to take part, participants will be randomly allocated to receive either theophylline or placebo (dummy) for 12 months. We will follow up participants at six and 12 months to assess the number of occurrences of worsening of symptoms. We will also collect information on side effects, usage of the available health care, quality of life and breathlessness, and lung function.

### What are the possible benefits and risks of participating?

Higher doses of theophylline have been used for more than 70 years to treat asthma and COPD. Side effects (such as anxiety, sleeplessness, dizziness, headache, rapid heart beat, upset stomach, rash, urine retention) can occur. It is estimated that at a low dose (as will be used in our study), less than 5% of participants will experience side effects. Participants who receive the theophylline may benefit as a result of receiving this drug because the risk of worsening may be less than without the drug. Participants who receive placebo may benefit because of evidence that participation in a clinical study improves the condition possibly due to better adherence to the background therapy.

Where is the study run from?

We will recruit participants from GP surgeries and hospitals across seven areas of the UK (Grampian, Glasgow, Newcastle, Hull, Liverpool, Birmingham and East Anglia).

When is the study starting and how long is it expected to run for?

Recruitment started in February 2014 and was completed by August 2016. Follow-up within the study will be completed by September 2017. The study will report its findings in 2018.

Who is funding the study?

The study is funded by the National Institute for Health Research (NIHR), UK.

Who is the main contact?

The TWICS study office

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Email: [twics@abdn.ac.uk](mailto:twics@abdn.ac.uk)

### **Study website**

<https://w3.abdn.ac.uk/hsru/TWICS/>

## **Contact information**

### **Type(s)**

Scientific

### **Contact name**

Dr Seonaidh Cotton

### **Contact details**

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## **Additional identifiers**

### **EudraCT/CTIS number**

2013-001490-25

### **IRAS number**

### **ClinicalTrials.gov number**

### **Secondary identifying numbers**

14832; HTA 11/58/15

# Study information

## Scientific Title

A randomised, double-blind placebo controlled trial of the effectiveness of low dose oral Theophylline as an adjunct to Inhaled Corticosteroids in preventing exacerbations of chronic obstructive pulmonary disease (COPD)

## Acronym

TWICS

## Study objectives

Preclinical and pilot studies demonstrate that low dose theophylline may increase the sensitivity of the airway inflammation to ICS, and thus when used with ICS will reduce the rate of COPD exacerbation. In this study we will determine the clinical effectiveness and cost-effectiveness of adding low dose theophylline to ICS therapy in patients with COPD. Low dose theophylline is cheap (10p/day) and, if shown to make current ICS therapy more effective in a cost effective manner, it will improve the quality of life of COPD patients and reduce the burden of COPD on the NHS.

More details can be found at <http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=14832> and <http://www.nets.nihr.ac.uk/projects/hta/115815>

Protocol can be found at [http://www.nets.nihr.ac.uk/\\_\\_data/assets/pdf\\_file/0004/81166/PRO-11-58-15.pdf](http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0004/81166/PRO-11-58-15.pdf)

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

Medical Research Ethic Committee (MREC), 28/06/2013, ref: 13/SS/0081

## Study design

Randomised; Interventional; Design type: Prevention, Treatment

## Primary study design

Interventional

## Secondary study design

Randomised controlled trial

## Study setting(s)

Hospital

## Study type(s)

Treatment

## Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

## Health condition(s) or problem(s) studied

Topic: Primary Care Research Network for England, Respiratory; Subtopic: Not Assigned, Respiratory (all Subtopics); Disease: Respiratory, All Diseases

### **Interventions**

Participants will be randomised to theophylline (200 mg once or twice daily depending on smoking status and weight) or placebo for 12 months.

### **Intervention Type**

Drug

### **Phase**

Not Applicable

### **Drug/device/biological/vaccine name(s)**

Theophylline

### **Primary outcome measure**

Exacerbations of COPD necessitating change of management; Timepoint(s): 1 year treatment period

### **Secondary outcome measures**

1. Adverse events; Timepoint(s): During 1 year treatment period
2. Cost per quality-adjusted life year (QALY); Timepoint(s): Cost per QALY during 1 year treatment period
3. Disease specific health status [(COPD Assessment Test (CATest)); Timepoint(s): 6 months, 12 months
4. Emergency hospital admissions; Timepoint(s): During 1 year treatment period
5. EQ-5D (measure of health outcome); Timepoint(s): 6 months, 12 months
6. Exacerbations requiring hospital admission; Timepoint(s): during 1 year treatment period
7. Health care utilisation; Timepoint(s): during 1 year treatment period
8. Inhaled corticosteroid dose/useage; Timepoint(s): during 1 year treatment period
9. Lung function; Timepoint(s): 6 months, 12 months
10. Mortality; Timepoint(s): During 1 year treatment period

### **Overall study start date**

16/09/2013

### **Completion date**

01/09/2017

## **Eligibility**

### **Key inclusion criteria**

1. Aged 40 years
2. A smoking history of at least 10 pack years
3. An established predominant respiratory diagnosis of COPD (post bronchodilator FEV1/FVC<0.7)
4. Current use of ICS therapy (irrespective of long-acting beta agonist (LABA) and/or long-acting anticholinergic agent (LAMA) use)
5. A history of at least two exacerbations requiring treatment with antibiotics and/or oral

corticosteroid in the previous year, based on patient report  
6. Clinically stable with no COPD exacerbation for at least 4 weeks  
7. Able to swallow study medication  
8. Able and willing to give informed consent to participate  
9. Able and willing to participate in the study procedures, undergo spirometric assessment, complete study questionnaire  
Target Gender: Male & Female; Lower Age Limit 40 years

**Participant type(s)**

Patient

**Age group**

Adult

**Sex**

Both

**Target number of participants**

Planned Sample Size: 1424; UK Sample Size: 1424

**Total final enrolment**

1578

**Key exclusion criteria**

1. Severe or unstable ischaemic heart disease
2. A predominant respiratory disease other than COPD
3. Any other significant disease/disorder which, in the investigators opinion, either puts the patient at risk because of study participation or may influence the results of the study or the patient's ability to participate in the study
4. Previous allocation of a randomisation code in the study or current participation in another interventional clinical study
5. Theophylline use currently
6. Known or suspected hypersensitivity to theophylline
7. Current use of drugs known to interact with theophylline and/or increase serum theophylline: antimicrobials: aciclovir, clarithromycin, ciprofloxacin, erythromycin, fluconazole, ketoconazole, levofloxacin, norfloxacin; cardiovascular: diltiazem, mexiletine, pentoxifylline, verapamil; neurological: bupropion, disulfiram, fluvoxamine, lithium; hormonal: medroxyprogesterone, oestrogens; immunological: methotrexate, peginterferon alpha, tacrolimus; miscellaneous: cimetidine, deferasirox, febuxostat, roflumilast, thiabendazole
8. For women, current pregnancy or breast-feeding, or planned pregnancy during the study

**Date of first enrolment**

06/02/2014

**Date of final enrolment**

01/08/2015

**Locations****Countries of recruitment**

Scotland

United Kingdom

**Study participating centre**

**Centre for Healthcare Randomised Trials (CHaRT)**

Aberdeen

United Kingdom

AB25 2ZD

## **Sponsor information**

**Organisation**

University of Aberdeen (UK)

**Sponsor details**

c/o NHS R & D office

Foresterhill House Annexe

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United Kingdom

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**Sponsor type**

University/education

**ROR**

<https://ror.org/016476m91>

## **Funder(s)**

**Funder type**

Government

**Funder Name**

National Institutes for Health Research (NIHR) (UK) - Health Technology Assessment; Grant Codes: 11/58/15

## **Results and Publications**

## Publication and dissemination plan

Not provided at time of registration

## Intention to publish date

31/12/2018

## Individual participant data (IPD) sharing plan

## IPD sharing plan summary

Not provided at time of registration

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Protocol article</a>	protocol	10/06/2015		Yes	No
<a href="#">Results article</a>	results	16/10/2018		Yes	No
<a href="#">Results article</a>	results	01/07/2019	26/07/2019	Yes	No
<a href="#">HRA research summary</a>			28/06/2023	No	No