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Theophylline With Inhaled CorticoSteroid (ICS)

Submission date
18/09/2013

Recruitment status
No longer recruiting

Registration date
19/09/2013

Overall study status
Completed

Last Edited
26/07/2019

Condition category
Respiratory

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] 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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Study website
https://w3.abdn.ac.uk/hsru/TWICS/

Contact information

Type(s)
Scientific

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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

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, clarithromiycin, 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
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Sponsor information

Organisation
University of Aberdeen (UK)

Sponsor details
c/o NHS R & D office
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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?
Protocol article	protocol	10/06/2015		Yes	No
Results article	results	16/10/2018		Yes	No
Results article	results	01/07/2019	26/07/2019	Yes	No
HRA research summary			28/06/2023	No	No