ISRCTN10497306 https://doi.org/10.1186/ISRCTN10497306

Bisoprolol in COPD study

Submission date	Recruitment status	[X] Prospectively registered
13/08/2018	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
16/08/2018	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
20/05/2025	Respiratory	

Plain English summary of protocol

Background and study aims
Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease characterised by worsening airflow limitation. In the UK, 1.2 million people have COPD, 30,000 people die from COPD annually and COPD costs the NHS £1 billion annually. Sudden deteriorations in symptoms (exacerbations) are an important feature of COPD as they account for 60% of NHS COPD costs and they reduce life expectancy and quality of life. Beta-blockers are drugs widely used to treat blood pressure and heart disease. Non-heart specialists are often unwilling to prescribe beta-blockers to COPD patients because older beta-blockers had lung side effects. However, evidence shows that newer beta-blockers targeting the heart, e.g. bisoprolol, are safe in COPD. In addition, COPD patients who take beta-blockers appear to experience fewer exacerbations. The aim of this study is to determine the clinical effectiveness and cost effectiveness of adding bisoprolol to usual COPD treatment in patients with COPD.

Who can participate?
Patients aged 40 and over with COPD

What does the study involve?
Participants are randomly allocated to take either bisoprolol (maximum dose 5mg a day) or placebo (dummy drug, maximum dose 4 tablets a day) for 12 months. To establish the best dose of bisoprolol (and placebo) for each participant the dose is slowly increased over 4 weeks. Participants are followed up at 6 and 12 months to assess the number of exacerbations to collect data on side effects, healthcare use, quality of life, breathlessness and lung function.

What are the possible benefits and risks of participating?
Bisoprolol is cheap (4p/day) and, if shown to reduce the risk of COPD exacerbations in a cost effective manner, it will improve the quality of life of COPD patients and reduce the burden of COPD on the NHS. Participants will be informed not to expect individual benefit from participation in the study. Some discomfort may be felt at the time of blood taking and biopsy procedures.

Where is the study run from?
1. Aberdeen Royal Infirmary
2. Arrowe Park Hospital
3. University Hospital of North Tees

4. Blackpool Victoria Hospital
5. Royal Lancaster Infirmary
6. Royal Infirmary of Edinburgh
7. Norfolk and Norwich University Hospital
8. Freeman Hospital
9. Musgrove Park Hospital
10. Royal Devon & Exeter Hospital
11. Derriford Hospital
12. South Tyneside District Hospital
13. James Cook Hospital
14. North Tyneside General Hospital
15. Darlington Memorial Hospital
16. Gartnavel General Hospital
17. Ninewells Hospital
18. Castle Hill Hospital
19. Perth Royal Infirmary
20. Wythenshawe Hospital
21. Bedford Hospital
22. Queen Elizabeth Hospital, Gateshead
23. Yeovil District Hospital
24. Worcestershire Acute Hospitals NHS Trust
25. Aintree University Hospital
26. Queens Square Medical Practice
27. Vauxhall Primary Health Care
28. Castlegate and Derwent Surgery
29. Queen Elizabeth Hospital, Birmingham

When is the study starting and how long is it expected to run for?
February 2018 to October 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Prof. Graham Devereux
g.devereux@abdn.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Graham Devereux

ORCID ID
https://orcid.org/0000-0002-0024-4887

Contact details
c/o CHaRT
University of Aberdeen

Health Sciences Building
Foresterhill
Aberdeen
United Kingdom
AB25 2ZD
+44 (0)151 702 9551/(0)1224 438178
g.devereux@abdn.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2017-002779-24

Integrated Research Application System (IRAS)
242190

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 37874, IRAS 242190

Study information

Scientific Title
A randomised, double-blind placebo controlled trial of the effectiveness of the beta-blocker bisoprolol in preventing exacerbations of chronic obstructive pulmonary disease

Acronym
BICS

Study objectives
The aim of this study is to determine the clinical effectiveness and cost effectiveness of adding bisoprolol to usual COPD treatment in patients with COPD.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scotland A REC, 22/05/2018, ref: 18/SS/0033

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic obstructive pulmonary disease (COPD)

Interventions
This is a double-blind placebo-controlled trial to assess the effectiveness and cost effectiveness of adding bisoprolol (maximum dose 5 mg a day) to current therapy for chronic obstructive pulmonary disease (COPD).

The trialists intend to recruit 1574 patients from a network of 160 primary and secondary care sites across the UK. Participants will be reviewed on 7 occasions during the 1 year study: after recruitment/randomisation participants will be reviewed at 1, 2, 3, 4, 26 and 52 weeks. The assessments at 1, 2, 3, 4 weeks are necessary for guideline compliant beta-blocker dose titration. The assessments at 26 and 52 weeks will capture primary and secondary outcome data.

The interventions will be the cardio-selective beta-blocker bisoprolol (1.25mg tablets) and identical placebo. To ensure patient safety bisoprolol will be started at the lowest possible dose of 1.25mg once a day and up-titrated at weekly intervals up to the maximum tolerated dose or 5mg a day, whichever is the lower. The dose titration schedule is a conservative interpretation of the advice provided in Heart Failure guidelines, the SmPC for bisoprolol and NHS Grampian heart failure guidelines designed for use by appropriately trained nurses in primary care settings. The starting dose for bisoprolol is one 1.25mg tablet taken orally daily and participants will undergo a weekly dose titration regime (i.e. weekly increments of 1.25mg2.5mg3.75mg5mg) which will result in final doses of 1.25mg once daily (od) (1 tab), 2.50 mg od (2 tabs), 3.75mg od (3 tabs), or 5mg od (4 tabs) depending on tolerance to bisoprolol up dosing. Participants allocated to placebo will undergo an identical dose-titration regime, with a final dose of 1, 2, 3 or 4 tablets a day. Following completion of the 12 month dosing period, participants will be weaned off study drug over the following 3 weeks (3-2-1 tab od) in order to avoid possible rebound myocardial ischaemia.

Patients with COPD will be invited to take part in the study. They will be identified from the primary or secondary care setting. Participants who meet the inclusion criteria and who agree to take part in the study will be asked to give written informed consent. Baseline clinical data (including lung function [FEV1, FVC], pulse, blood pressure) will be collected, an ECG (ideally 12 lead) will be recorded (if not possible an ECG within 6 months will suffice) and the participant will be asked to complete baseline questionnaires (COPD assessment test [CAT], health related quality of life [EQ-5D-5L], Baseline Dyspnoea Index [BDI], health service utilisation). The Hull Airways Reflux Questionnaire (HARQ) will be used at some sites to collect data on respiratory and gastro-intestinal symptoms.

Participants will be randomised to receive bisoprolol or identical placebo once daily for 52 weeks. Participants will receive their first eight week supply (ie one bottle containing 168 tablets) of study medication (bisoprolol 1.25mg or placebo) in the week following randomisation delivered to their home by a ‘signed for’ courier service.

At the 1, 2, 3, and 4 week reviews the presence of side effects of bisoprolol (e.g. dizziness, fatigue, headache) will be determined, lung function, pulse and blood pressure will be measured. Depending on the presence of side effects, and the measurements of lung function, pulse and blood pressure the dose of study tablet will either be increased by one tablet a day (to a maximum of 4 tablets a day), fixed or reduced by one tablet a day. Participants will remain on final titrated dose for remaining 48 weeks. [Recruitment to the study was paused during the COVID-19 pandemic; when recruitment was re-opened to the study, the measurement of lung

function was replaced by participant reported changes in breathlessness since their last study visit (added 09/05/2023)].

Each participant will receive further supplies of medication, this will depend on the medication dose determined during the dose titration. Participants who remain on 1.25mg per day will receive two further supplies, each of one bottle of 168 tablets. Participants who titrate up to 2.5 mg per day will receive two further supplies, each of two bottles of 168 tablets. Participants who titrate up to 3.75mg per day will receive two further supplies, each of three bottles of 168 tablets. Participants who titrate up to 5mg per day will receive two further supplies, each of four bottles of 168 tablets. These supplies will be delivered to participants via a courier service (or other signed for delivery service) operated by a third party. These shipments will be made around week 8 and month 5 to enable continuity of supply. Receipt of trial medication will be confirmed by signature on receipt. If the signature does not match that on record participants will be telephoned shortly after receipt of the medication to check that it has arrived. Written informed consent to pass on participant's name and address to the third party distributer will be obtained. The medication label will inform participants of dosing. Each supply pack will contain information on interacting drugs and side effects.

Participants will be reviewed at 26 and 52 weeks for the collection of the following outcome data: history of exacerbations, health care utilisation, disease-related quality of life status (CAT), Transition Dyspnoea Index [TDI), EQ-5D-5L, lung function (FEV1, FVC), adverse reactions and serious adverse events. The HARQ will be used at some sites to collect data on respiratory and GI symptoms. Compliance (pill counting) pulse and blood pressure will also be measured. If the participant is not able to attend for a review appointment, we will attempt to collect outcome data either by arranging to visit the patient at their home, collecting information over the telephone, or sending them a postal questionnaire. At the 52 week review participants asked to wean their study drug off over following 3 weeks (3-2-1 tab od). This will be confirmed by a telephone call at the end of the 3 weeks. [During and after the COVID-19 pandemic lung function was not measured as part of the study. In addition, visits were not face-to-face so pill counting was not possible; participants were asked to return unused medication to their local pharmacy for destruction (added 09/05/2023)]

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Bisoprolol

Primary outcome(s)
The primary outcome measure will be the total number of exacerbations of COPD necessitating changes in management (minimum management change - use of oral corticosteroids and/or antibiotics) during the one year treatment period, as reported by the participant at 6 and 12 months. If participants do not attend for follow-up, the trialists will attempt to get this information from medical records.

The primary economic outcome measure will be cost-per-QALY gained during the one year treatment period.

Key secondary outcome(s))
1. Total number of COPD exacerbations requiring hospital admission during the one year treatment period, as reported by the participant at 6 and 12 months. If participants do not attend for follow-up, the trialists will attempt to get this information from medical records.
2. Time to first exacerbation of COPD, as reported by the participant at 6 and 12 months. If participants do not attend for follow-up, the trialists will attempt to get this information from medical records.
3. Total number of emergency hospital admissions (all causes), as reported by the participant at 6 and 12 months. If participants do not attend for follow-up, we will attempt to get this information from medical records.
4. Total number of major adverse cardiovascular events (MACE) (defined by cardiovascular death, hospitalisation for myocardial infarction, heart failure, or stroke, percutaneous coronary intervention or coronary artery bypass grafting), as reported by the participant at 6 and 12 months. If participants do not attend for follow-up, the trialists will attempt to get this information from medical records.
5. Lung function (FEV1, FVC) post bronchodilator measured using spirometry performed to ATS /ERS standards at the follow-up visits at 6 and 12 months [(during the COVID-19 pandemic, lung function cannot be assessed easily and safely and so this outcome will not be available on all participants (added 09/05/2023)]
6. Breathlessness measured using Baseline and Transition Dyspnoea Indices (BDI & TDI) [standardised schedules] as reported by participants at baseline, 6 and 12 months
7. All-cause, respiratory and cardiac mortality obtained from medical records, supplemented with death certificates if required
8. Serious adverse events, adverse reactions, as reported by the participant during the titration period and at 6 and 12 months. If participants do not attend for follow-up, the trialists will attempt to get information on any serious adverse events from medical records.
9. Health-related quality of life measured using EuroQoL 5D (EQ-5D-5L) Index at baseline, 6 and 12 months
10. Disease-specific health status measured using the COPD Assessment Test (CAT) at baseline, 6 and 12 months
11. Utilisation of primary or secondary healthcare for respiratory events, as reported by the participant at 6 and 12 months. If participants do not attend for follow-up, the trialists will attempt to get some information from medical records
12. Change in disease associated symptoms measured using the Hull Airways Reflux Questionnaire (HARQ) [this will only be done at some recruitment sites] at baseline, 6 and 12 months
13. Modelled lifetime incremental cost per Quality Adjusted Life Year, based on quality of life and cost data described above

Completion date
31/10/2023

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 21/10/2021:
1. Aged ≥40 years
2. A smoking history of ≥10 pack years ([average number of cigarettes per day x years smoked] /20)
3. An established predominant diagnosis of COPD (NICE Guideline definition: post-bronchodilator FEV1<80% predicted, FEV1/FVC<0.7) receiving treatment as per local guidelines.

Patients with asthma COPD overlap syndrome (ACOS) will also be eligible.
4. A history of ≥2 exacerbations requiring treatment with antibiotics and/or oral corticosteroid use in the previous year, based on patient report or a history of ≥2 exacerbations within 12 months of each other requiring treatment with antibiotics and/or oral corticosteroid since March 2019.
5. Clinically stable with no COPD exacerbation for at least 4 weeks
6. Able to swallow study medication
7. Able and willing to give informed consent to participate
8. Able and willing to participate in the study procedures and complete the study questionnaire
9. Able and willing to undergo spirometric assessment, able to perform an FEV1 manoeuvre as a minimum. During the COVID-19 pandemic, measurement of FEV1 is not required as part of the protocol, and therefore this inclusion criteria does not need to be met.

Previous participant inclusion criteria:
1. Aged ≥ 40 years
2. A smoking history of at least 10 pack years
3. An established predominant diagnosis of COPD (NICE Guideline definition: post bronchodilator FEV1<80% predicted, FEV1/FVC<0.7) receiving treatment as per local guidelines'
4. A history of at least two exacerbations requiring treatment with antibiotics and/or oral corticosteroid use in the previous year, based on patient report
5. Clinically stable with no COPD exacerbation for at least 4 weeks
6. Able to swallow study medication
7. Able and willing to give informed consent to participate
8. Able and willing to participate in the study procedures, complete study questionnaire
9. Able and willing to undergo spirometric assessment, able to perform an FEV1 manoeuvre as a minimum

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
519

Key exclusion criteria
1. A current sole respiratory diagnosis of asthma
2. Any diagnosis of asthma before the age of 40 years
3. A predominant respiratory disease other than COPD
4. Any significant disease/disorder which, in the investigator's 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
5. Previous allocation of a randomisation code in the study or current participation in another interventional study (CTIMP or non-CTIMP)

6. Already taking beta-blocker
7. Known or suspected hypersensitivity to beta-blocker
8. For women, current pregnancy or breastfeeding, or planned pregnancy during the study
9. Unable to perform spirometry (FEV1 manoeuvre)
10. Current resting (5 minutes sitting) heart rate < 60 bpm
11. Current resting (5 minutes sitting) systolic blood pressure < 100 mmHg
12. 2nd, 3rd degree heart block (unless pacemaker in situ)
13. Conditions for which beta-blocker use is a guideline recommendation, i.e. heart failure, or within the last year: myocardial infarction, acute coronary syndrome
14. Current tachyarrythmia or bradyarrhythmia (including sick sinus syndrome, sinoatrial block) requiring treatment
15. Current treatment with interacting drugs:
15.1. Heart rate limiting drug such as calcium channel blockers (diltiazem, verapamil), ivabradine)
15.2. Class-I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone)
15.3. Centrally-acting antihypertensive drugs (e.g. clonidine methyldopa, moxonidine, rilmenidine)
16. Severe peripheral arterial occlusive disease, severe forms of Raynaud's syndrome
17. Conditions that are known to be triggered by beta-blockers or beta-blocker withdrawal including myasthenia gravis, periodic hypokalaemic paralysis, pheochromocytoma, thyrotoxicosis and psoriasis/history of psoriasis

Date of first enrolment
01/09/2018

Date of final enrolment
31/05/2022

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Aberdeen Royal Infirmary (lead site)
Foresterhill
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Arrowe Park Hospital
Arrowe Park Road

Birkenhead
Wirral
United Kingdom
CH49 5PE

Study participating centre
University Hospital of North Tees
Hardwick
Stockton on Tees
United Kingdom
TS19 8PE

Study participating centre
Blackpool Victoria Hospital
Whinney Heys Road
Blackpool
United Kingdom
FY3 8NR

Study participating centre
Royal Lancaster Infirmary
Ashton Road
Lancaster
United Kingdom
LA1 4RP

Study participating centre
Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road
Edinburgh
United Kingdom
EH16 4SA

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Norwich
United Kingdom
NR4 7UY

Study participating centre
Freeman Hospital
Freeman Road
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Musgrove Park Hospital
Taunton
United Kingdom
TA1 5DA

Study participating centre
Royal Devon & Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
Derriford Hospital
Plymouth
United Kingdom
PL6 8DH

Study participating centre
South Tyneside District Hospital
Harton Lane
South Shields
United Kingdom
NE34 0PL

Study participating centre
James Cook Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
North Tyneside General Hospital
Rake Lane
North Shields
United Kingdom
NE29 8NH

Study participating centre
Darlington Memorial Hospital
Hollyhurst Road
Darlington
United Kingdom
DL3 6HX

Study participating centre
Gartnavel General Hospital
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
Ninewells Hospital
James Arrott Drive
Dundee
United Kingdom
DD1 9SY

Study participating centre
Castle Hill Hospital
Castle Road
Cottingham
United Kingdom
HU16 5JQ

Study participating centre
Perth Royal Infirmary
Taymount Terrace

Perth
United Kingdom
PH1 1NX

Study participating centre
Wythenshawe Hospital
Southmoor Road
Manchester
United Kingdom
M23 9LT

Study participating centre
Bedford Hospital
South Wing
Kempston Road
Bedford
United Kingdom
MK42 9DJ

Study participating centre
Queen Elizabeth Hospital
Queen Elizabeth Avenue
Gateshead
United Kingdom
NE9 6SX

Study participating centre
Yeovil District Hospital
Higher Kingston
Yeovil
United Kingdom
BA21 4AT

Study participating centre
Worcestershire Acute Hospitals NHS Trust
Charles Hastings Way
Worcester
United Kingdom
WR5 1DD

Study participating centre
Aintree University Hospital
Lower Lane
Liverpool
United Kingdom
L9 7AL

Study participating centre
Queens Square Medical Practice
Queen Square Surgery
2 Queen Square
Lancaster
United Kingdom
LA1 1RP

Study participating centre
Vauxhall Primary Health Care
111-117 Limekiln Lane
Liverpool
United Kingdom
L5 8XR

Study participating centre
Castlegate and Derwent Surgery
Cockermouth Health Centre
Isel Road
Cockermouth
United Kingdom
CA13 9HT

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Birmingham
United Kingdom
B15 2WB

Sponsor information

Organisation
University of Aberdeen

ROR
https://ror.org/016476m91

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 15/130/20

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the Chief Investigator Graham Devereux (Graham.Devereux@lstmed.ac.uk). The datasets will be made available at the time the main results of the trial are published. The Chief Investigator, will, in collaboration with the sponsor, assess whether requests for data should be fulfilled. Consent is obtained from participants that information collected about them can be shared anonymously with other researchers to support future research.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		19/05/2024	20/05/2024	Yes	No
Results article		19/05/2025	20/05/2025	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version V3	30/05/2018	16/08/2018	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version V4	30/05/2018	16/08/2018	No	No
Protocol file	version 7	14/05/2021	21/10/2021	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes