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TITLE: % H W NHVU %I OR RU F W K H 3 U H Y HRQI W & R 3Q ' R I

PRINCIPAL INVESTIGATOR: Mark T. Dransfield, MD

CONTRACTING ORGANIZATION: University of Alabama at Birmingham
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REPORT DATE: 2 F W2016 E H U

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Beta Blockers for the Prevention of Acute Exacerbations of COPD

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6. AUTHOR(S)

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5d. PROJECT NUMBER

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
We are conducting a randomized, placebo-controlled trial to definitively assess the impact of metoprolol succinate on the rate of COPD exacerbations. This is a multicenter, placebo-controlled, double-blind, prospective randomized trial that will enroll 1028 patients with at least moderately severe COPD over a 3-year period. Major activities for this reporting period have centered on contracting, regulatory approvals, training, site initiation and enrollment at clinical sites. Upon execution of contracts and IRB approvals enrollment has been steadily increasing. The monthly enrollment goal is 28.5 across all sites, with each site enrolling an average of 2-3 participants per month. Several sites have met and exceeded this goal in August and September and we expect this trend to continue.

15. SUBJECT TERMS
beta blockers , cardiovascular disease, COPD, exacerbation , metoprolol succinate, placebo-controlled, randomized

16. SECURITY CLASSIFICATION OF: a. REPORT	b. ABSTRACT	c. THIS PAGE	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON / 19b. TELEPHONE NUMBER *(include area code)*
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Table of Contents

Page

INTRODUCTION:

A substantial majority of chronic obstructive pulmonary disease (COPD)-related morbidity, mortality and healthcare costs are due to acute exacerbations, but existing medications have only a modest effect on reducing their frequency, even when used in combination. Observational studies suggest β-blockers may reduce the risk of COPD exacerbations; thus, we are conducting a randomized, placebo-controlled trial to definitively assess the impact of metoprolol succinate on the rate of COPD exacerbations. This is a multicenter, placebo-controlled, double-blind, prospective randomized trial that will enroll 1028 patients with at least moderately severe COPD over a 3-year period. Participants with at least moderate COPD will be randomized in a 1:1 fashion to receive metoprolol or placebo; the cohort will be enriched for patients at high risk for exacerbations. Patients will be screened and then randomized over a 2-week period and will then undergo a dose titration period for the following 6 weeks. Thereafter, patients will be followed for 42 additional weeks on their target dose of metoprolol or placebo followed by a 4-week washout period. The primary endpoint is time to first occurrence of an acute exacerbation during the treatment period. Secondary end points include rates and severity of COPD exacerbations; rate of major cardiovascular events (MACE); all-cause mortality; lung function (forced expiratory volume in 1 s (FEV1)); dyspnea; quality of life; exercise capacity; markers of cardiac stretch (pro-NT brain natriuretic peptide) and systemic inflammation (high-sensitivity C reactive protein and fibrinogen). Analyses will be performed on an intent-to-treat basis.

KEYWORDS:
beta blockers
cardiovascular disease
COPD
exacerbation
metoprolol succinate
placebo-controlled
randomized

ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aims to be achieved through the conduct of the proposed clinical trial:
Primary: To determine the effect of once daily metoprolol succinate compared with placebo on the time to first exacerbation in moderate to severe COPD patients who are prone to exacerbations and who do not have absolute indications for beta-blocker therapy.
Secondary: To estimate the effect of metoprolol succinate compared with placebo on the rate and severity of COPD exacerbations over 12 months, major adverse cardiac events (MACE), combined exacerbations and MACE, incidence and severity of metoprolol-related side effects including those that require cessation of drug, lung function, dyspnea, quality of life, exercise tolerance, hospitalization rates, and all-cause mortality.

Activity	Timeline	achieved
Milestone 1: Finalize Study Protocol and Consent	***2 months***	21 SEP 2015
Milestone 2: Drug and matching placebo received and logged in at sites	***6 months***	Initial shipments of Drug and placebo packaging have been shipped to all sites approved for enrollment
Milestone 3: Executed all	***6 months***	100% complete, 15 of

subcontracts		15 subcontracts are fully executed.
Milestone 4: Initiate sites for recruitment	***6 months***	13 of 15 sites have been initiated to for recruitment. One site, the Minneapolis VA is working through data security issues; a second (Brigham and Women's) is awaiting final pharmacy approval
Milestone 5 - Conduct interim analysis	***18 months***	N/A
Milestone 6 – Conduct 2nd interim analysis	***30 months***	N/A
Milestone 7 – Complete Study enrolment	***42 months***	N/A
Milestone 8 – Complete patient visits	***55 months***	N/A
Milestone 9 – Database lock	***56 months***	N/A
Milestone 10 - Submit primary manuscript	***60 months***	N/A

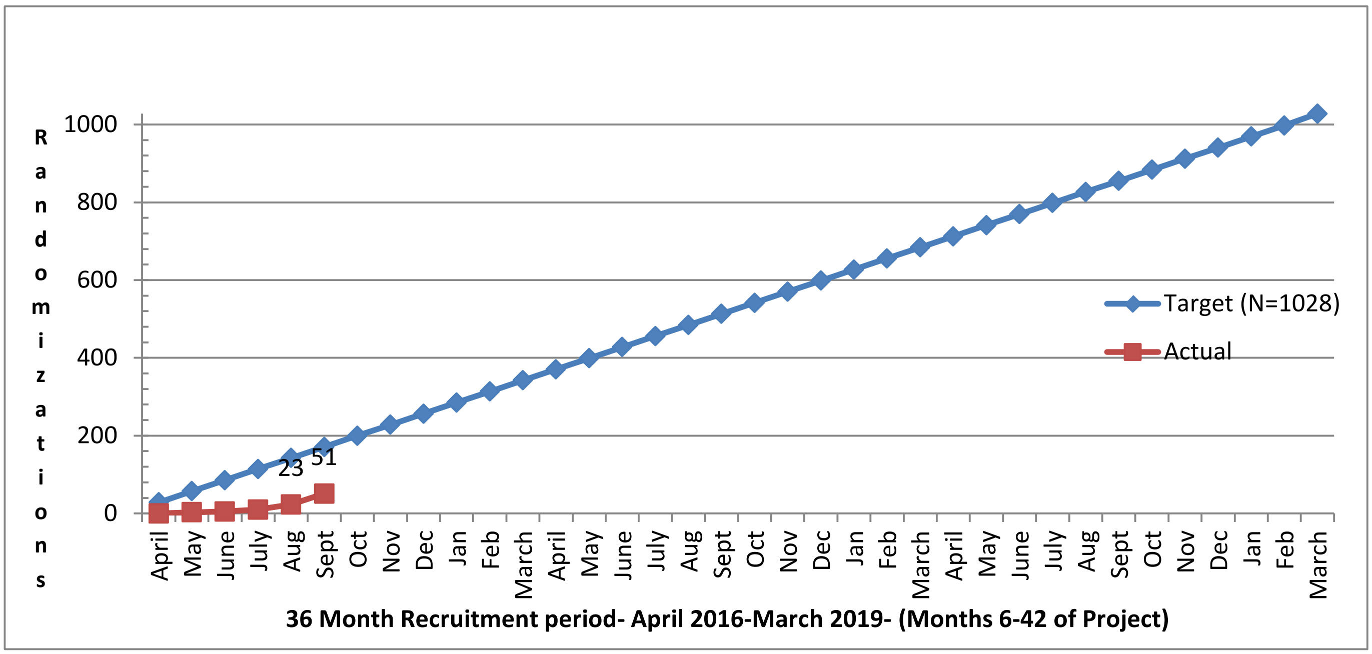
What was accomplished under these goals?

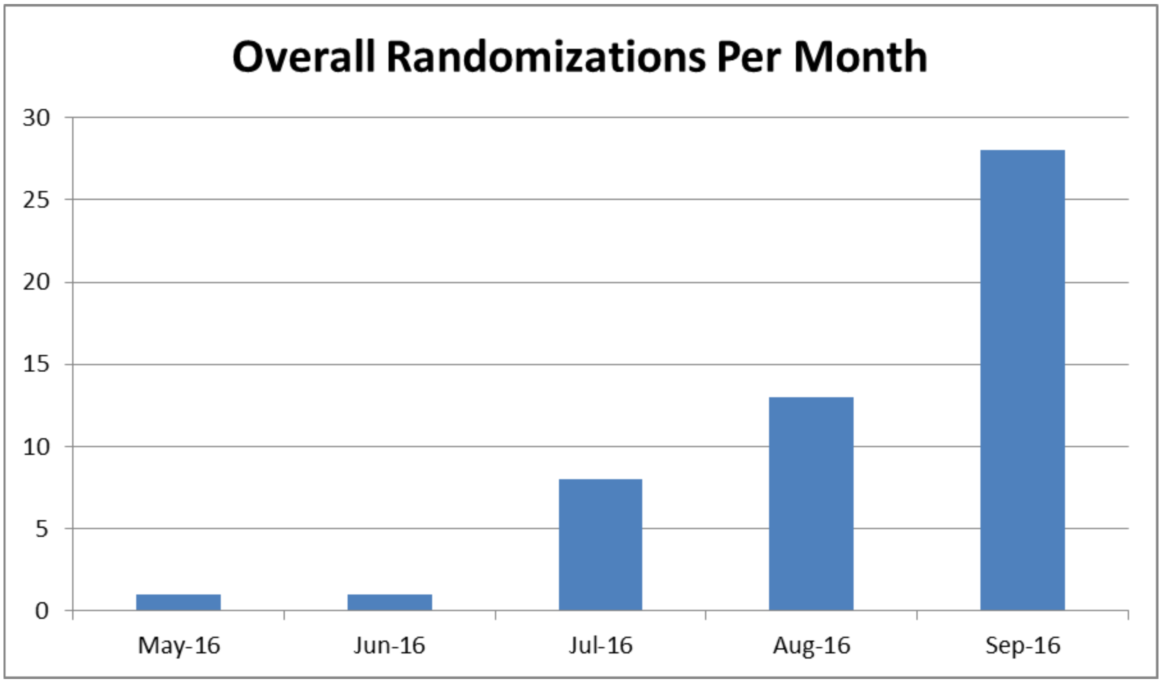
Major activities for this reporting period have centered on study start up and enrollment at clinical sites. Upon execution of contracts and IRB approvals enrollment has been steadily increasing. The monthly enrollment goal is 28.5 across all sites, with each site enrolling an average of 2-3 participants per month. Several sites have met and exceeded this goal in August and September and we expect this trend to continue.

Screen 4-6 subjects/month	6-42 months	Screening has started at all initiated sites
Randomize 2-3 subjects per site /month	6-42 months	The first subject was randomized in May 2016, two months later than anticipated based on delays in regulatory approvals. Since that time enrollment has been steadily increasing over all sites. See enrollment graphs below.
Complete study visits for 1 year + 1 month washout following enrolment	6-55 months	Ongoing
Data entry	6-55 months	No issues
Issue queries	6-56 months	No issues
Resolve queries	6-56 months	No issues
Adverse event assessment and reporting	6-55 months	No issues
Maintain IRB approval	6-60 months	Ongoing
Develop reports for DSMB	6-60 months	First DSMB meeting is scheduled for 8 NOV

		2016. The DCC is developing the necessary reports.
Conduct monthly coordinator calls	6-56 months	Calls have been conduct monthly since August 2016. Weekly to biweekly call have been conducted with PIs and other study staff since April 2016
Provide drug and placebo as needed to sites	6-55 months	Ongoing
Return unused drug and placebo to DPMD	56-58 months	N/A

Overall Randomizations April 2016 – September 2016





What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

The following article has been published: β-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease (βLOCK COPD): a randomised controlled study protocol. PMID: 27267111

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period clinical sites continue ongoing recruitment efforts and begin and continue enrolling subjects.

IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

CHANGES/PROBLEMS:

Changes in approach and reasons for change

Modifications to the protocol have been made to clarify and allow more PI discretion regarding drug titration along with several other minor changes for clarity. Protocol version date 27 JLUY 2015 incorporated feedback from DoD/HRPO reviews and was the original version submitted to clinical sites for IRB review. The protocol was amended on 21 SEPT 2015 to include page numbers per the request of some clinical sites. Since the 21 SEPT 2015 version there have been two revisions, both of which included the correction of typos throughout, and focused on providing clarity regarding eligibility criteria and study visit flow. Both of these revisions have been reviewed and approved by the UAB IRB and have disseminated to all clinical sites for IRB review and approval. The revisions do not meet DOD HRPOs threshold for substantive amendments, and therefore no further action was required from DOD HRPO regarding the revisions.

Actual or anticipated problems or delays and actions or plans to resolve them

There was a slightly slower than expected start-up due to delays in regulatory approvals at the clinical sites. However, all but two sites are actively recruiting and monthly randomizations have met our goal for the months of September and October. As some sites have exceeded enrollment expectations, we anticipate that the enrollment gap between actual and goal will continue to decrease.

Early in the startup process National Jewish Health was added as a site to replace Denver Health and Hospital Authority. The PI at Denver Health and Hospital Authority was unable to participate in this project due to other obligations and work load.

The privacy officers at the Minnesota VA have concluded that they will not be able to use the DCC's website for any data entry or for receiving queries. Because of this, they are currently developing another system that will satisfy that institution's data security policy. Once this system is developed they will be able to begin enrolling participants.

Brigham and Women's Research Pharmacy is requesting additional information before they accept study drug. Once this is resolved this site will begin enrolling.

Changes that had a significant impact on expenditures

There was a delay in site start-up and lower than expected subject recruitment in year one that resulted in a lower than expected expenditures. We plan to amend the subcontracts for each site to allow for the use of remaining year 1 funds.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Modifications to the protocol have been made to clarify and allow more PI discretion regarding drug titration along with other minor protocol modification for clarity. Protocol version date 27 JLUY 2015 incorporated feedback from DoD reviews and was the original version submitted to clinical sites for IRB review. The protocol was amended on 21 SEPT 2015 to include page numbers per the request of some clinical sites. Since the 21 SEPT 2015 version there have been two revisions, both of which included the correction of typos throughout, and focused on providing clarity around eligibility criteria and study visit flow. Both of these revisions have been reviewed and approved by the UAB IRB and have disseminated to all clinical sites for IRB review and approval. The revisions do not meet DOD HRPOs threshold for substantive amendments, and therefore no further action was required from DOD HRPO regarding the revisions.

Detailed summary of protocol changes:
March 20, 2016 revision clarifications included:

1. Page 6- Secondary Aims, 'Combined rate of acute exacerbations and MACE" (major adverse cardiovascular events) has been added.
2. Page 7 – eligibility criteria – inclusion - has been clarified to add a history of receiving antibiotics in addition to steroids and to add clarifying language about use or prescriptions for supplemental oxygen.
3. Page 7- eligibility criteria –exclusion- asthma exclusion has been clarify by adding "…as the primary cause of respiratory symptoms …"
4. Page 8 – exclusion – "Patients currently on beta blockers including beta blocker eye drops are also excluded" has been added.
5. Page 9- "Combined rate of acute exacerbations and MACE" has been added to secondary endpoints
6. Page 10 - secondary end points #13 – for consistency troponin has been deleted from list of lab tests and the word injury has been removed.
7. Page 13 Clarifications about the physical exam, spirometry and EKG have been added to the schedule of study interventions
8. Pages 16-18- Clarifying language has been added regarding scheduling unscheduled visits and un-blinding.

August 26, 2016 revision clarifications included:

1. Page 12- Study Flow has been revised to include, "Note: screening and randomization visits can be combined as long as all procedures are conducted and eligibility can be confirmed." to clarify that these visits may be conducted on the same day.
2. Page 13 - Table 2 - Schedule of Study Interventions has been revised to include "Screening and randomization visits may occur on the same day as long as all procedures are conducted and eligibility can be confirmed." to clarify that these visits may be conducted on the same day.
3. Page15 – *Visits 5: Clinic Visit for dose adjustment at 14 day,* item number six has been revised with the following clarifying language, " … and the PI believes that it is unsafe to continue study drug then it will be discontinued."
4. Page 16 "Heart rate from vital signs (not EKG) will be used." has been added to Table 3 - Dose adjustment to clarify the source of heart rate.
5. Page17 – *Visits 8: Clinic Visit for dose adjustment at 28 days,* item number six has been revised with the following clarifying language, " … and the PI believes that it is unsafe to continue study drug then it will be discontinued."
6. Page 19- *Recruitment and consent information* has been revised to clarify that while medical records are not necessary to document exacerbation history, they may be requested and reviewed to help determine other eligibility criteria.
7. Page 21 – *Unmasking* information has been revised to clarify information the wallet card will contain and who may be contacted, specifically reference to the DCC has been removed.
8. Pages 24 - Randomization information has been revised to add updated website information and to clarify that randomization cannot occur if data is missing.
9. Page 24-25 - Data Security information has been updated to include updated software and password information.

Significant changes in use or care of vertebrate animals.

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

PRODUCTS:

Publications, conference papers, and presentations

Journal publications

BMJ Open, vol. 6(6) pp. e012292

β-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease (βLOCK COPD): a randomised controlled study protocol.

Bhatt, SP; Connett, JE; Voelker, H; Lindberg, SM; Westfall, E; Wells, JM; Lazarus, SC; Criner, GJ; Dransfield, MT
PMID: 27267111
URL - http://www.ncbi.nlm.nih.gov/pubmed/27267111?dopt=Citation

acknowledgement of federal support - yes

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers, and presentations.

Nothing to report.

Website(s) or other Internet site(s)

The trial has been listed on ClinicalTrials.gov. The NCT number is NCT02587351.

url: https://clinicaltrials.gov/

We have developed an informational website for participants and providers. This site provides a broad overview of the trial including contact information for UAB, the DCC, the research pharmacy and all clinicial sites.

url: http://blockcopd.org/

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

We have developed a separate protocol for the collections and storage of serum, plasma and whole blood samples. The protocol has been approved by the UAB IRB. We ask other interested clinical sites that have the internal resources available to participate in the specimen collection protocol as well.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

University of Alabama at Birmingham

Name: Mark T. Dransfield
Project Role: PI
Research Identifier: 0000-0003-0346-1956
Nearest Person Month worked: 2.4
Contribution to Project: Dr. Dransfield is the PI of the Project. He oversees protocol related activities at all research sites and is the local site PI at UAB.

Name: Elizabeth Westfall
Project Role: Program Director
Research Identifier: N/A
Nearest Person Month worked: 2.4

Contribution to Project: Ms. Westfall assists in the regulatory and financial administration of this grant. This includes initiating subcontracts and overseeing disbursement of payments to subaward sites as well as overseeing human subject approvals.

Minnesota DCC

Name: Dr. John Connett
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 1.8
Contribution to Project: Dr. Connett oversees the project at the DCC site. He supervises the day-to-day operation of the Data Coordinating Center. Dr. Connett oversees the development of data collection procedures and methods for data transmission and management.

Name: Helen Voelker
Project Role: Information Technologies Manager
Research Identifier: N/A
Nearest Person Month worked: 4.2
Contribution to Project: Ms. Voelker develops database schemas, edits, and updates procedures for study data. Ms. Voelker develops the distributed data entry and data transmission system.

Name: Sarah Lindberg
Project Role: Protocol Manager
Research Identifier: N/A
Nearest Person Month worked: 3.6
Contribution to Project: Ms. Lindberg assists with writing sections of the Manual of Procedures, designing study data forms, and analyzing data for Steering Committee and DSMB meeting.

Name: Irene Olson

Project Role:	Data Quality Control
Research Identifier:	N/A
Nearest Person Month worked:	3
Contribution to Project:	Ms. Olson assists Ms. Voelker in creating schemas and databases for forms.

Temple University School of Pharmacy

Name:	David Lebo
Project Role:	PI
Research Identifier:	N/A
Nearest Person Month worked:	2.4
Contribution to Project:	Dr. Lebo is the PI for the Temple Pharmacy site. Dr. Lebo is responsible for producing, labeling, and distributing the study drug for this project. Mr. Lebo oversees the supply chain of the medication and monitors it for labeling and packaging deviations.

University of Michigan

Name:	MeiLan Han
Project Role:	PI
Research Identifier:	N/A
Nearest Person Month worked:	.6
Contribution to Project:	Dr. Han is the PI for the University of Michigan site. Dr. Han oversees day-to-day research activities at this site.

Name:	Jeffrey Curtis
Project Role:	Co-PI
Research Identifier:	N/A
Nearest Person Month worked:	.6
Contribution to Project:	Dr. Curtis is the Co-PI for the University of Michigan site and the PI at the VAAAHS site. Mr. Curtis oversees day to day research activities at this site.

Weil Cornell Medical College

Name:	Fernando Martinez
Project Role:	PI
Research Identifier:	N/A
Nearest Person Month worked:	.23
Contribution to Project:	Dr. Martinez is the PI for the Weil Cornell Medical College site. Dr. Martinez oversees day to day research activities at this site.

University of Maryland

Name:	Robert M. Reed
Project Role:	PI
Research Identifier:	N/A
Nearest Person Month worked:	1.44
Contribution to Project:	Dr. Reed is the PI for the University of Maryland, Baltimore site. Dr. Reed oversees day to day research activities at this site.

Northwestern University

Name: Ravi Kalhan
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .36
Contribution to Project: Dr. Kalhan is the PI for the Northwestern University site. Dr. Kalhan oversees day to day research activities at this site.

Name: Sharon Rosenberg
Project Role: Co-PI
Research Identifier: N/A
Nearest Person Month worked: .18
Contribution to Project: Dr. Rosenberg is the Co-Investigator for the Northwestern University site. Dr. Rosenberg assists Dr. Kalhan with day to day research activities at this site and supervise in data analysis and preparation of manuscripts.

University of Pittsburgh

Name: Frank Sciurba
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6
Contribution to Project: Dr. Sciurba is the PI for the University of Pittsburgh site. Dr. Sciurba oversees day to day research activities at this site.

Temple University

Name: Gerard Criner
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .47
Contribution to Project: Dr. Criner is the PI for the Temple University – Clinical site. Dr. Criner oversees day to day research activities at this site.

Name: Nathaniel Marchetti
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .24
Contribution to Project: Dr. Marchetti is the Co-Investigator for the Temple University – Clinical site. Dr. Marchetti assists Dr. Criner with day to day research activities at this site. In addition Dr. Marchetti assists with recruitment, enrollment, and retention.

Name: Dee Fehrle
Project Role: RN, Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 3.6
Contribution to Project: Dee Fehrle is the Research Nurse Coordinator at the Temple University – Clinical site. Dee manages day to day study activities at this site. Dee recruit and enroll patients as well as see patients at each visit as outlined in the protocol. Dee also collects patient data.

Minneapolis VA

Name: Dennis Niewoehner
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Dr. Niewoehner is the PI for the Minnesota Veterans Research and Education Foundation site. Dr. Niewoehner oversees day to day research activities at this site.

Name: Christine Wendt
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .60
Contribution to Project: Dr. Wendt is the Co-Investigator for the Minnesota Veterans Research and Education Foundation site. Dr. Wendt assists Dr. Niewoehner with protocol related activities at this site.

Name: Ken Kunisaki
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .60
Contribution to Project: Dr. Kunisaki is the Co-Investigator for the Minnesota Veterans Research and Education Foundation site. Dr. Kunisaki assists with protocol related activities at this site. He is also involved with data analysis and will contribute to the manuscript writing and presentations.

Name: Susan Johnson
Project Role: Project Coordinator/ Data Analyst
Research Identifier: N/A
Nearest Person Month worked: 1.44
Contribution to Project: Susan is the Project Coordinator/ Data Analyst for the Minnesota Veterans Research and Education Foundation site. Susan is responsible for patient screening and data analysis throughout the study.

Mayo Clinic

Name: Paul Scanlon
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Scanlon is the PI for the Mayo Clinic site. Dr. Scanlon oversees day to day research activities at this site.

Brigham and Women's Hospital

Name: Carolyn Come
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 3
Contribution to Project: Dr. Come is the PI for the Brigham and Women's Hospital site. Dr. Come oversees the day to day research activities at this site.

Health Partners Institute

Name: Charlen McEvoy
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 3
Contribution to Project: Dr. McEvoy is the PI for the HealthPartners Institute site. Dr. McEvoy Oversees the day to day research activities at this site.

National Jewish Health

Name: Barry Make
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Make is the PI for the National Jewish Health site. Dr. Make Oversees the day to day research activities at this site.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

What other organizations were involved as partners?

Nothing to Report

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable

QUAD CHARTS: Not applicable

APPENDICES:

Appendix 1: Journal publication

BMJ Open

β-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease (βLOCK COPD): a randomised controlled study protocol

Surya P Bhatt,[1] John E Connett,[2] Helen Voelker,[2] Sarah M Lindberg,[2] Elizabeth Westfall,[1] J Michael Wells,[1,3] Stephen C Lazarus,[4] Gerard J Criner,[5] Mark T Dransfield[1,3]

To cite: Bhatt SP, Connett JE, Voelker H, *et al*. β-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease (βLOCK COPD): a randomised controlled study protocol. *BMJ Open* 2016;**6**:e012292. doi:10.1136/bmjopen-2016-012292

▸ Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2016-012292).

Received 13 April 2016
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For numbered affiliations see end of article.

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ABSTRACT

Introduction: A substantial majority of chronic obstructive pulmonary disease (COPD)-related morbidity, mortality and healthcare costs are due to acute exacerbations, but existing medications have only a modest effect on reducing their frequency, even when used in combination. Observational studies suggest β-blockers may reduce the risk of COPD exacerbations; thus, we will conduct a randomised, placebo-controlled trial to definitively assess the impact of metoprolol succinate on the rate of COPD exacerbations.

Methods and analyses: This is a multicentre, placebo-controlled, double-blind, prospective randomised trial that will enrol 1028 patients with at least moderately severe COPD over a 3-year period. Participants with at least moderate COPD will be randomised in a 1:1 fashion to receive metoprolol or placebo; the cohort will be enriched for patients at high risk for exacerbations. Patients will be screened and then randomised over a 2-week period and will then undergo a dose titration period for the following 6 weeks. Thereafter, patients will be followed for 42 additional weeks on their target dose of metoprolol or placebo followed by a 4-week washout period. The primary end point is time to first occurrence of an acute exacerbation during the treatment period. Secondary end points include rates and severity of COPD exacerbations; rate of major cardiovascular events; all-cause mortality; lung function (forced expiratory volume in 1 s (FEV_1)); dyspnoea; quality of life; exercise capacity; markers of cardiac stretch (pro-NT brain natriuretic peptide) and systemic inflammation (high-sensitivity C reactive protein and fibrinogen). Analyses will be performed on an intent-to-treat basis.

Ethics and dissemination: The study protocol has been approved by the Department of Defense Human Protection Research Office and will be approved by the institutional review board of all participating centres. Study findings will be disseminated through presentations at national and international conferences and publications in peer-reviewed journals.

Trial registration number: NCT02587351; Pre-results.

Strengths and limitations of this study

- Although numerous observational studies show a positive association between the use of β-blockers and the reduction in chronic obstructive pulmonary disease (COPD) exacerbations, this study will be the first prospective randomised, double-blind, placebo-controlled trial to examine the issue.
- In addition to collecting data about the occurrence of acute exacerbations, we will also collect major adverse cardiac events allowing examination of the effects of β-blockers on pulmonary and cardiovascular outcomes.
- We will specifically exclude patients with recent cardiovascular events in whom it is likely that β-blockers would be most effective. However, we will perform subgroup analyses based on predicted cardiovascular risk as defined by the Personal HEART Score in an effort to identify those patients most likely to benefit.
- The optimal dose of metoprolol for the prevention of exacerbations in COPD is unknown, and it is possible that the median dose we achieve will be too low to be beneficial.
- The study is not powered to detect an effect on overall mortality which we believe would be the best end point to objectively assess the role of the drug in patients with COPD.

INTRODUCTION

A substantial majority of chronic obstructive pulmonary disease (COPD)-related healthcare costs are due to acute exacerbations.[1 2] The proportional costs associated with exacerbations continue to rise and existing medications have only a modest effect on reducing their frequency, even when used in combination.[1 3] There is therefore an urgent need for more effective therapies targeting exacerbations. Development of such treatment has been hampered by the heterogeneity of these events, which though often triggered by airway inflammation due to bacterial or viral infections or exposure to pollutants can also be caused or made worse by cardiovascular disease, a factor likely not impacted by currently available bronchodilator and anti-inflammatory medications.[4 5]

There is a growing awareness that COPD is a multisystem disease and that it is associated with accelerated atherosclerosis and cardiovascular disease.[4] A significant number of cardiac comorbidities which could potentially result in acute decompensation of respiratory status such as coronary artery disease, diastolic dysfunction and arrhythmias are seen in greater frequency in patients with COPD compared with age-matched and sex-matched controls.[4 5] There is also growing evidence for cardiac injury in the periexacerbation period, and this relationship is likely bidirectional with some of the exacerbations caused by cardiac events.[6]

Multiple observational studies have suggested that existing cardiac medications can improve survival in patients with COPD and also reduce the rate of exacerbations, and these potential benefits are perhaps most pronounced for β-blockers.[6–12] Despite concerns that these drugs may cause bronchoconstriction, the weight of the data suggests that this fear may be misplaced, at least for cardioselective β-blockers. Studies examining the effects of cardioselective β-blockers have found no consistently deleterious effect on lung function. Although forced expiratory volume in 1 s (FEV_1) declines significantly with non-selective β-blockers,[13 14] cardioselective β-blockers do not reduce FEV_1 either acutely or with long-term use.[13 15] Gottlieb *et al* demonstrated that the survival benefits associated with β-blocker use post myocardial infarction are as significant for those with COPD as compared with those without the disease.[7] Rutten *et al*[8] have shown that patients on β-blockers have a significant reduction in exacerbation frequency, and we and others have found comparable results in multiple similar observational cohorts.[8–11] These observations are biologically plausible as in addition to their established cardioprotective effects which could impact the risk of acute exacerbations or their severity, β-blockers may also have beneficial respiratory effects.[12] These results are tempered by the results of Ekström *et al*[16] who showed increased mortality in patients with severe COPD and on home oxygen who were taking β-blockers; in contrast, in the COPDGene study, we found a greater beneficial effect on exacerbation frequency in this subgroup.[9]

Though the observational data suggesting that β-blockers may reduce exacerbations are compelling, these studies are all subject to a number of inherent biases that preclude conclusions about cause and effect. In addition, though the published data do not show a meaningful effect of cardioselective β-blockers on lung function, these drugs are significantly underprescribed in patients with COPD, even when they have absolute indications for their use, suggesting practitioners still have concerns about their safety.

To address these issues, we have designed a randomised, placebo-controlled trial, the βLOCK COPD study, to examine the effect of extended-release metoprolol on the rate of exacerbations in patients with COPD at high risk for those events (NCT02587351). We will test the hypothesis that treatment with a cardioselective β-blocker will reduce the time to first exacerbation and exacerbation frequency and that the drug will be well tolerated and not adversely affect lung function, exercise tolerance and quality of life. In this article, we describe the study design, discuss the rationale for the specific approaches employed and outline the prespecified subgroup analyses.

METHODS

βLOCK COPD study design overview

This is a multicentre, placebo-controlled, double-blind, prospective randomised trial that will enrol 1028 patients with at least moderately severe COPD over a 3-year period. Patients will be screened and then randomised over a 2-week period and will then undergo a dose titration of metoprolol for the following 6 weeks. Thereafter, patients will be followed for 42 additional weeks on their target dose of metoprolol or placebo followed by a 4-week washout period. The schedule of study encounters is shown in table 1.

Hypothesis

The primary hypothesis is that metoprolol succinate will reduce the risk of COPD exacerbations as compared with placebo in patients with moderate-to-severe COPD who are prone to exacerbations and who do not have absolute indications for β-blocker therapy. The secondary hypothesis is that metoprolol succinate will not adversely impact lung function, exercise tolerance, dyspnoea or quality of life as compared with placebo.

Inclusion and exclusion criteria

We will enrol patients aged 40–85 years with a clinical diagnosis of at least moderate COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease criteria of postbronchodilator FEV_1/forced vital capacity (FVC)<0.70 and postbronchodilator FEV_1<80% predicted, with or without chronic symptoms such as cough and sputum production. Participants should have a cigarette smoking history of at least 10 pack-years. The study will be enriched for patients at high risk for exacerbations as suggested by at least one of the following: a history of having received a course of systemic corticosteroids and/or antibiotics for respiratory events in the past year, having visited an emergency department for a COPD exacerbation within the past year, hospitalisation for COPD exacerbation within the past year or using or have been prescribed supplemental home oxygen for at least 12 hours a day.[17 18] Participants should have a resting heart rate of at least 70 and not >120 bpm, and resting systolic blood pressure of >100 mm Hg to be eligible. Major exclusion criteria are listed in box 1 and include the presence of an absolute

Table 1 Schedule of study interventions

Assessment	Screening (day 14 to −1)	Randomisation (day 0)	Dose titration (days 14 and 28)	Dose finalisation (day 42)	Clinic visit (day 112)	Clinic visit (day 224)	Wean clinic visit (day 336)	Stop clinic visit (day 350)	Close-out clinic visit (day 364)
Informed consent	X								
Medical history	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X
Safety laboratory assessments*	X								
Questionnaires†	X				X		X		
Troponin	X								
Pro-NT BNP/CRP/fibrinogen		X					X		
Urine pregnancy	X								
Spirometry‡	X		X	X	X		X		
ECG	X		X	X	X		X	X	X
6 min walk		X			X		X		
Randomisation		X							
Drug dispensing		X	X	X	X	X	X		
Adverse event assessment		X	X	X	X	X	X	X	X
Drug return and accountability			X	X	X	X	X	X	

Phone call days 2, 3, 15, 16, 56, 168, 280, 343, 357, 378 for adverse event assessment.
Visit windows ±3 days until dose finalisation visit then ±14 days until Wean visit then ±3 days until close-out visit.
Unscheduled visits will include medical history, adverse event assessment, and ECG and spirometry if during titration period until day 42; after day 42, the ECG and spirometry are at PI discretion.
*Complete blood count, comprehensive metabolic profile including magnesium and liver function tests.
†Modified Medical Research Council Dyspnea Scale, COPD Assessment Test, St George Respiratory Questionnaire, Short Form-36, San Diego Shortness of Breath Questionnaire; Personal HEART Score at screening only.
‡Prebronchodilator and postbronchodilator spirometry at screening, otherwise postbronchodilator only; not done at days 112 and 336 if patient has had an acute exacerbation in the 2 weeks prior.
BNP, brain natriuretic peptide; CRP, C reactive protein.

indication for a β-blocker though patients with stable coronary disease or mild systolic dysfunction with left ventricular ejection fraction >40% can be included.

Randomisation and intervention

After obtaining written informed consent, randomisation will be performed according to a computer-generated blinded algorithm carried out by linking to the Data Coordinating Center (DCC) through a website (beta.umn.edu/betablocker.umn.edu) using a required user ID and password. The clinical trial will use metoprolol succinate extended-release tablets (50 mg) and matching placebo. Drug and matching placebo will be labelled using blinded coding and distributed to the study sites as needed to support enrolment and retention. The planned starting dose for metoprolol succinate extended release or placebo equivalent is one 50 mg tablet taken orally daily, and patients will undergo a dose titration procedure as outlined in table 2, which will result in a final dose of 25 mg (1/2 of one tablet daily), 50 mg or 100 mg (two tablets daily). Matching placebo will be administered similarly. Following completion of the 42-week dosing period, patients will be weaned off study drug over the following 4 weeks in order to avoid possible rebound myocardial ischaemia.

Clinical efficacy: primary and secondary outcomes

The primary end point is time to first occurrence of an acute exacerbation during the 48-week treatment period. Acute exacerbations will be defined as a 'complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness requiring treatment with antibiotics and/or systemic steroids for at least three days'.[23] Severe exacerbations will be defined as those exacerbations that require hospitalisation. A relapse of a previous exacerbation will be defined as the complex of respiratory symptoms of more than one of the following: cough, sputum, wheezing, dyspnoea or chest tightness with a duration of at least 3 days, which recurs and requires retreatment with antibiotics and/or systemic steroids without a return to baseline and within 2 weeks of the start date of a prior treated event.[24] Secondary end points include rates and severity of COPD exacerbations; rate of major cardiovascular events ((major adverse cardiac event (MACE) defined by

Box 1 Exclusion criteria

- A diagnosis of asthma established by each study investigator on the basis of the recent American Thoracic Society/European Respiratory Society and National Institute for Health and Care Excellence guidelines.[19 20] If, after applying the above criteria, investigators are still unsure about the distinction in a specific patient, bronchodilator testing with inhaled albuterol will be performed and patients with changes in forced expiratory volume in 1 s (FEV1) >400 mL will be excluded.
- The presence of a diagnosis other than chronic obstructive pulmonary disease (COPD) that results in the patient being either medically unstable or having a predicted life expectancy <2 years.
- Women who are at risk of becoming pregnant during the study (premenopausal) and who refuse to use acceptable birth control (hormone-based oral or barrier contraceptive) for the duration of the study.
- Current tachyarrhythmias or bradycardia requiring treatment.
- Presence of a pacemaker and/or internal cardioverter/defibrillator.
- Patients with a history of second-degree or third-degree (complete) heart block, or sick sinus syndrome.
- Baseline ECG revealing left bundle branch block, bifascicular block, ventricular tachyarrhythmia, atrial fibrillation, atrial flutter, supraventricular tachycardia (other than sinus tachycardia and multifocal atrial tachycardia) or heart block (second degree or complete).
- Resting heart rate <70 bpm, or sustained resting tachycardia defined as heart rate >120 bpm.
- Resting systolic blood pressure of <100 mm Hg.
- Participants with absolute (class 1) indications for β-blocker treatment as defined by the combined American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons Guidelines which include myocardial infarction, acute coronary syndrome, percutaneous coronary intervention or coronary artery bypass surgery within the prior 3 years and patients with known congestive heart failure defined as left ventricular ejection fraction <40%.[21 22]
- Current therapy with ocular β-blocker medications.
- Critical ischaemia related to peripheral arterial disease.
- Other diseases that are known to be triggered by β-blockers or β-blocker withdrawal including myasthenia gravis, periodic hypokalemic paralysis, pheochromocytoma and thyrotoxicosis.
- Patients on other cardiac medications known to cause atrioventricular (AV) node conduction delays such as amiodarone, digoxin and calcium channel blockers including verapamil and diltiazem as well as patients taking clonidine.
- Hospitalisation for uncontrolled diabetes mellitus or hypoglycaemia within the last 12 months.
- Patients with cirrhosis.
- A clinical diagnosis of bronchiectasis defined as production of greater than one-half cup of purulent sputum per day.
- Patients otherwise meeting the inclusion criteria will not be enrolled until they are a minimum of 4 weeks from their most recent acute exacerbation (ie, they will not have received a course of systemic corticosteroids, an increased dose of chronically administered systemic corticosteroids and/or antibiotics for an acute exacerbation for a minimum of 4 weeks).

Table 2 Dose adjustment protocol

Visit	HR (bpm)	SBP (mm Hg)	Instruction
Enrolment/randomisation	≥70	≥100	Randomise
Dose adjustment visit at 14 days	≥70	≥100	↑ dose to 100 mg
		90–99	↔ maintain same dose
		<90	↓ dose to 25 mg or stop
	50–69	≥90	↔ maintain same dose
		<90	↓ dose to 25 mg or stop
	<50	Any	Stop study drug
Dose adjustment visit at 28 days	≥70	≥90	↔ maintain same dose
		<90	↓ dose by 1/2 or stop
	50–69	≥90	↔ maintain same dose
		<90	↓ dose by 1/2 or stop
	<50	Any	Stop study drug
Dose finalisation visit at 42 days	≥70	≥90	↔ maintain same dose
		<90	Stop study drug
	50–69	≥90	↔ maintain same dose
		<90	Stop study drug
	<50	Any	Stop study drug

bpm, beats per minute; SBP, systolic blood pressure.

cardiovascular death, hospitalisation for myocardial infarction, heart failure or stroke), percutaneous coronary intervention or coronary artery bypass grafting); the combined rate of exacerbations and MACE; all-cause mortality; lung function (FEV_1); dyspnoea as measured by the modified Medical Research Council and San Diego Shortness of Breath Questionnaire Score; quality of life as measured by the Short Form-36 (SF-36), St George Respiratory Questionnaire and the COPD Assessment Test scores; exercise capacity measured by the 6 min walk distance; markers of cardiac stretch (pro-NT Brain Natriuretic Peptide) and systemic inflammation (high-sensitivity C reactive protein and fibrinogen). These parameters will be assessed at screening/randomisation and at conclusion of the study to determine if β blockade impacts volume status and cardiac performance as well as levels of systemic inflammation that portend overall cardiac risk.

Adverse effects and safety monitoring: prior studies of β-blockers and effects on lung function and exercise

Several studies have examined the safety of β-blockers in patients with COPD, though there have been no dose-ranging studies to specifically determine the optimal dose for the prevention of exacerbations. Multiple studies have demonstrated that the effect of cardioselective β-blockers on lung function is minimal, whether administered as a single dose or with continued treatment. A Cochrane analysis revealed that cardioselective β-blockers produced no significant change in FEV_1 or respiratory symptoms compared with placebo, given as a single dose (−2.05% (95% CI −6.05% to 1.96%)) or for longer duration (−2.55% (CI −5.94% to 0.84%)), and did not significantly affect the FEV_1 treatment response to β2 agonists.[15 25] Subgroup analyses revealed no significant change in the results for those participants with severe airflow limitation or for those with a reversible obstructive component. Typical doses of metoprolol in trials of patients with coronary artery disease, congestive heart failure and hypertension range from 12.5 to 200 mg, and doses in this range are well tolerated by patients with COPD including those with moderate-to-severe disease.[25] The dose titration procedure is modelled after the approach used in a pivotal trial of metoprolol succinate in patients with heart failure.[26] In that study, in which daily doses of up to 200 mg (mean dose 159 mg once daily) were used, 10.3% of 1990 patients assigned to metoprolol succinate extended-release tablets discontinued for adverse reactions versus 12.2% of placebo patients. Adverse events that occurred at an incidence of ≥1% in the metoprolol succinate extended-release tablets group and greater than placebo by >0.5% (and regardless of causality) included dizziness/vertigo (1.8% vs 1.0%), bradycardia (1.5% vs 0.4%) and accident and/or injury (1.4% vs 0.8%). The planned median daily dose of metoprolol in the proposed trial will fall between 50 and 100 mg, and these as well as a number of other possible drug-related side effects will be specifically sought and recorded. We will monitor FEV_1 during the dose titration period, and patients whose FEV_1 falls by >200 mL or 15% from baseline will be taken off study drug.

Discontinuation of study drug

There are four instances in which the study drug might be discontinued: (1) development of symptoms that might represent medication-related side effects that are severe enough or persist even with dose reduction; (2) development of an absolute indication for β-blocker such as myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass surgery or new congestive heart failure with ejection fraction <40%. In these instances, study medication will be stopped and the patient referred for appropriate medical treatment; (3) intercurrent illness including medical and/or surgical problems that are unrelated to COPD or to a possible metoprolol-related side effect but warrant treatment. In these instances, the patient's treating physician (or study physician) will decide whether the specific problem encountered warrants discontinuation of the study medication. Each patient will carry a wallet card for the duration of the study that provides information regarding the study and how unmasking of treatment can be accomplished should the indication merit and (4) new prescription of a contraindicated medication (box 1).

Statistical analyses

Sample size and power considerations for this clinical trial are based on the primary outcome of time to first exacerbation. The risk of exacerbation and estimated time to first exacerbation in the placebo group is based on the observations in the control groups of the prior COPD Clinical Research Network trials of azithromycin and simvastatin of similar design.[17 18] The percentage of patients suffering an exacerbation at 1 year in the placebo arm of the azithromycin trial was 69% compared with 57% in those receiving azithromycin. In the simvastatin trial, the probability of patients in the placebo arm suffering an exacerbation was 65%, while the probability in those taking simvastatin was not statistically different (68%). With similar inclusion and exclusion criteria as these prior trials, we anticipate a comparable exacerbation rate. Prior observational studies suggest that β-blockers may reduce the risk of exacerbation by as much as 30%, though it is probable that this overestimates the potential benefit due to residual confounding. We believe a 15% relative reduction (65% vs 55%) in the 48-week-period probability of exacerbation is clinically significant and plausible and have thus selected that as our hypothesised effect size. To find this effect, with a two-sided α of 0.05 and power of 90%, and equal probability of assignment to either arm, we will need a sample size of 912 participants, assuming 12% dropout yields a final sample size of 1028 patients.

All randomised patients will be followed until the end of the study, and the final analysis will be performed on an 'intention-to-treat' basis. The analyses of the time to first COPD exacerbation (and all-cause mortality) will be performed using survival analysis. Kaplan–Meier survival curves will be used to describe the probability of remaining outcome-free in the two treatment arms as a function of time from randomisation into the study. The curves will be compared using the log-rank test statistic. Secondary outcome measures will be assessed at baseline, week 16/day 112 and week 48/day 336. COPD exacerbation rates will be calculated as events/person-year and compared using a rate ratio. Exacerbation rates for each group, and the resultant rate ratio, will be analysed using negative binomial regression modelling. The model will employ time-weighted intention-to-treat analyses with adjustments of the CIs for between-subject variation and overdispersion.[27 28] Continuous outcome measures, including absolute and per cent changes in FEV_1, 6 min walk distance, dyspnoea and quality-of-life scores, will be analysed using multivariate repeated-measures analysis of variance using the SAS Proc Mixed program.

We propose to carry out interim formal testing at the following time points: 12 months and 24 months, and 36 months after initiating the study. We will use the Lan-DeMets approach that requires only specification of the rate at which type I error (which here will be chosen to be α=0.05) will be 'spent'. Two-sided tests of significance will be assumed.

Planned subgroup analyses

Using the approach outlined for primary and secondary analyses, we will perform two subgroup analyses for (1) cardiovascular risk based on the Personal HEART Score[29] and (2) age greater versus <65. These analyses will primarily be hypothesis generating in nature.

DISCUSSION

There is an urgent need for new therapies to reduce exacerbations as existing drugs offer only modest effects even when used in combination and only target bronchoconstriction and airway inflammation when other pathways likely contribute. Stable COPD is strongly associated with cardiovascular disease independent of shared risk factors such as cigarette smoking and age,[4] and there is growing evidence that acute exacerbations of COPD are associated with cardiac injury.[6] It is biologically plausible that the relationship between respiratory decompensation and cardiac affectation is not unidirectional and that a subset of the exacerbations might be cardiac in aetiology. Patel *et al* showed that arterial stiffness, a surrogate for cardiovascular risk, increases in the periexacerbation period and takes up to 5 weeks to return to baseline.[6] They also showed that subclinical increases in troponin I, a marker of cardiac injury, occur in the peri-exacerbation period even in patients without known cardiovascular disease.

There are a number of mechanisms by which subclinical cardiac dysfunction can result in COPD exacerbations which are clinically very difficult to distinguish from usual, primary respiratory-related events. In addition to a higher frequency of ischaemic heart disease, COPD is associated with diastolic dysfunction in a substantial proportion of patients and decompensated diastolic dysfunction can result in subclinical pulmonary congestion.[30–32] Supraventricular and ventricular arrhythmias are common in COPD, and arrhythmias might also cause acute exacerbations.[33] The heightened resting sympathetic activity in COPD has been associated with mortality and β-blockers might alleviate some of this risk by reducing resting tachycardia and arrhythmias.[34–36] β-Blockers may also improve outcomes by decreasing arrhythmogenesis and myocardial ischaemia associated with excessive use of β agonists during periods leading up to and during exacerbation.[37] In addition to their known cardioprotective effects, β-blockers might also have beneficial effects on the lungs. Murine models suggest that long-term administration of β-blockers results in upregulation of pulmonary β adrenoreceptors,[12] as well as decreased bronchoconstriction and an improved response to β agonists.[38] Chronic administration also has been shown in animal studies to reduce airway inflammation and decrease mucus production.[39] Some cardioselective β-blockers can also cause pulmonary vasodilation and thus improve pulmonary haemodynamics.[40]

The selection of metoprolol, a cardioselective agent, as the β-blocker of choice for the trial merits some discussion as does the proposed dosing. Though less cardioselective agents such as carvedilol may offer greater cardioprotective effects, concerns regarding adverse effects on FEV_1 and the risk of respiratory decompensation are greater with these drugs.[13 14 41 42] It is also possible that the cardiac benefit of β-blockers in COPD is due to heart rate control and metoprolol has very low intrinsic sympathomimetic activity.[36] Cardioselectivity for all β-blockers is dose dependent and at higher doses, even selective drugs can result in clinically significant antagonism of β2 receptors.[36] The initial dose of metoprolol and subsequent titration procedures are adapted from the landmark Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure trial, which definitively demonstrated the safety and efficacy of β blockade in patients with symptomatic heart failure, a disease that similar to COPD had been previously considered a contraindication to β-blocker treatment.[26] This study suggested that individualised dosing based on patient tolerability was appropriate, but titration to a dose above 100 mg/day may not be necessary to derive clinical benefits as there was no difference in mortality between those who received higher versus lower doses.[26] Our initial starting dose of metoprolol is based on these data as well as prior studies in patients with COPD, suggesting tolerance with single and continued dosing at comparable doses of the drug and other cardioselective β-blockers.[15 25 42–44] It is anticipated that many patients will tolerate titration to the maximal dose of 100 mg/day, while some will require a dose reduction to remain on study medication.

The trial design has some important limitations. First, it is likely that β-blockers would be most effective in patients with recent cardiovascular events whom we will specifically exclude; however, we will perform subgroup analyses based on predicted cardiovascular risk as defined by the Personal HEART Score in an effort to identify those patients most likely to benefit.[29] Second, as we have discussed, the optimal dose of metoprolol for the prevention of exacerbations in COPD is unknown, and it is possible that the median dose we achieve will be too low to be beneficial. It is also possible the drug will be poorly tolerated and frequently stopped due to side effects in which case a possible beneficial effect on exacerbations will not be found. Last, the study is not powered to detect an effect on overall mortality which we believe would be the best end point to objectively assess the role of the drug in patients with COPD.

In summary, the βLOCK COPD study will be the first randomised controlled study to investigate the effect of β-blockers on COPD exacerbations. By assessing clinical efficacy as well as side effects, the data obtained may guide β-blocker use in COPD.

ETHICS AND DISSEMINATION

The study protocol has been approved by the Department of Defense Human Protection Research Office and will be approved by the institutional review board (IRB) of all participating centres. The trial is registered at ClinicalTrials.Gov (http://www.clinicalstrials.gov identifier NCT02587351). After explaining the risks and benefits of participating in the study, written informed consent will be obtained from each study participant.

Clinical trial monitoring to ensure the trial is conducted in compliance with Good Clinical Practices and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E6) will be multifaceted, including real-time oversight by the local principal investigators, regular and real-time monitoring of entered clinical data by staff at the DCC, as well as by an independent Data and Safety Monitoring Committee (DSMC) which will meet at 6-month intervals by teleconference or in person.[45] The DSMC will be made up of a lead Research Monitor (a pulmonologist), a cardiologist and a statistician. The Research Monitor will oversee the safety of the research and report observations and findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to participants or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human participants from a research protocol and take whatever steps are necessary to protect the safety and well-being of human participants until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the Human Research Protection Office. The DCC will conduct monthly teleconferences throughout the study to review study enrolment and retention, procedures, adherence to protocol, timeliness of data entry and adverse events including those that may warrant protocol changes.

Study findings will be disseminated through presentations at national and international conferences and publications in peer-reviewed journals.

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Contributors MTD and SPB conceived and designed the study. MTD drafted the grant proposal. SPB and MTD drafted the protocol presented. JEC, HV, SML and EW provided methodological and statistical support. MTD, JEC, EW, HV and SML are responsible for study management, staff training and supervision. SCL and GJC are directors of two of the recruitment sites and provided clinical expertise and on-site management of the study. JMW reviewed the manuscript for critical intellectual input. All authors critically reviewed and approved the final version of the manuscript.

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Data sharing statement Pending approval from the Department of Defense; we will make data available for other investigators after publication of the results of the primary analyses as well as the preplanned post hoc secondary analyses.

REFERENCES

1. Blanchette CM, Dalal AA, Mapel D. Changes in COPD demographics and costs over 20 years. *J Med Econ* 2012;15:1176–82.
2. Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2007;4:502–6.
3. Puhan MA, Bachmann LM, Kleijnen J, *et al*. Inhaled drugs to reduce exacerbations in patients with chronic obstructive pulmonary disease: a network meta-analysis. *BMC Med* 2009;7:2.
4. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. *Transl Res* 2013;162:237–51.
5. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005;2:8–11.
6. Patel AR, Kowlessar BS, Donaldson GC, *et al*. Cardiovascular risk, myocardial injury, and exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;188:1091–9.
7. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998;339:489–97.
8. Rutten FH, Zuithoff NP, Hak E, *et al*. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. *Arch Intern Med* 2010;170:880–7.
9. Bhatt SP, Wells JM, Kinney GL, *et al*. beta-Blockers are associated with a reduction in COPD exacerbations. *Thorax* 2016;71:8–14.
10. Farland MZ, Peters CJ, Williams JD, *et al*. beta-Blocker use and incidence of chronic obstructive pulmonary disease exacerbations. *Ann Pharmacother* 2013;47:651–6.
11. Short PM, Lipworth SI, Elder DH, *et al*. Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. *BMJ* 2011;342:d2549.
12. Lin R, Peng H, Nguyen LP, *et al*. Changes in beta 2-adrenoceptor and other signaling proteins produced by chronic administration of 'beta-blockers' in a murine asthma model. *Pulm Pharmacol Ther* 2008;21:115–24.
13. Tivenius L. Effects of muliple doses of metoprolol and propranolol on ventilatory function in patients with chronic obstructive lung disease. *Scand J Respir Dis* 1976;57:190–6.
14. Fogari R, Zoppi A, Tettamanti F, *et al*. Comparative effects of celiprolol, propranolol, oxprenolol, and atenolol on respiratory function in hypertensive patients with chronic obstructive lung disease. *Cardiovasc Drugs Ther* 1990;4:1145–9.
15. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005(4):CD003566.
16. Ekström MP, Hermansson AB, Ström KE. Effects of cardiovascular drugs on mortality in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;187:715–20.
17. Albert RK, Connett J, Bailey WC, *et al*. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011;365:689–98.
18. Criner GJ, Connett JE, Aaron SD, *et al*. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med* 2014;370:2201–10.
19. Qaseem A, Wilt TJ, Weinberger SE, *et al*. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med* 2011;155:179–91.
20. O'Reilly J, Jones MM, Parnham J, *et al*. Management of stable chronic obstructive pulmonary disease in primary and secondary care: summary of updated NICE guidance. *BMJ* 2010;340:c3134.
21. Yancy CW, Jessup M, Bozkurt B, *et al*., Writing Committee Members. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;128:e240–327.
22. Fihn SD, Gardin JM, Abrams J, *et al*. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;60:e44–e164.
23. Niewoehner DE, Rice K, Cote C, *et al*. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005;143:317–26.
24. Anthonisen NR, Manfreda J, Warren CP, *et al*. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196–204.
25. Salpeter SR, Ormiston TM, Salpeter EE, *et al*. Cardioselective beta-blockers for chronic obstructive pulmonary disease: a meta-analysis. *Respir Med* 2003;97:1094–101.
26. Hjalmarson A, Goldstein S, Fagerberg B, *et al*. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;283:1295–302.
27. Aaron SD, Fergusson D, Marks GB, *et al*. Counting, analysing and reporting exacerbations of COPD in randomised controlled trials. *Thorax* 2008;63:122–8.
28. Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:842–6.

29. Mainous AG III, Koopman RJ, Diaz VA, *et al*. A coronary heart disease risk score based on patient-reported information. *Am J Cardiol* 2007;99:1236–41.
30. Malerba M, Ragnoli B, Salameh M, *et al*. Sub-clinical left ventricular diastolic dysfunction in early stage of chronic obstructive pulmonary disease. *J Biol Regul Homeost Agents* 2011;25:443–51.
31. Barr RG, Bluemke DA, Ahmed FS, *et al*. Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med* 2010;362:217–27.
32. Yawn BM, Kalhan Y, Rennard S, *et al*. COPD9USA June 2015. *Chron Obstruct Pulmon Dis (Miami, Florida)* 2015;2:343–66.
33. Bhatt SP, Nanda S, Kintzer JS. Arrhythmias as trigger for acute exacerbations of chronic obstructive pulmonary disease. *Respir Med* 2012;106:1134–8.
34. Warnier MJ, Rutten FH, de Boer A, *et al*. Resting heart rate is a risk factor for mortality in chronic obstructive pulmonary disease, but not for exacerbations or pneumonia. *PLoS ONE* 2014;9:e105152.
35. Chhabra SK, Gupta M, Ramaswamy S, *et al*. Cardiac sympathetic dominance and systemic inflammation in COPD. *Copd* 2015;12:552–9.
36. Egan BM, Basile J, Chilton RJ, *et al*. Cardioprotection: the role of beta-blocker therapy. *J Clin Hypertens (Greenwich)* 2005;7:409–16.
37. Au DH, Curtis JR, Every NR, *et al*. Association between inhaled beta-agonists and the risk of unstable angina and myocardial infarction. *Chest* 2002;121:846–51.
38. Chiarella SE, Soberanes S, Urich D, *et al*. beta(2)-Adrenergic agonists augment air pollution-induced IL-6 release and thrombosis. *J Clin Invest* 2014;124:2935–46.
39. Nguyen LP, Omoluabi O, Parra S, *et al*. Chronic exposure to beta-blockers attenuates inflammation and mucin content in a murine asthma model. *Am J Respir Cell Mol Biol* 2008;38:256–62.
40. Dal Negro R. Pulmonary effects of nebivolol. *Ther Adv Cardiovasc Dis* 2009;3:329–34.
41. Agostoni P, Contini M, Cattadori G, *et al*. Lung function with carvedilol and bisoprolol in chronic heart failure: is beta selectivity relevant? *Eur J Heart Fail* 2007;9:827–33.
42. Jabbour A, Macdonald PS, Keogh AM, *et al*. Differences between beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized crossover trial. *J Am Coll Cardiol* 2010;55:1780–7.
43. Camsari A, Arikan S, Avan C, *et al*. Metoprolol, a beta-1 selective blocker, can be used safely in coronary artery disease patients with chronic obstructive pulmonary disease. *Heart Vessels* 2003;18:188–92.
44. Schimmer JJ, Billups SJ, Delate T. Beta-blocker therapy in patients with left ventricular systolic dysfunction and chronic obstructive lung disease in an ambulatory care setting. *Pharm Pract (Granada)* 2009;7:205–12.
45. Baber N. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). *Br J Clin Pharmacol* 1994;37:401–4.

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