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TITLE: Beta Blockers for the Prevention of Acute Exacerbations of COPD

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CONTRACTING ORGANIZATION: University of Alabama at Birmingham
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14. ABSTRACT

We are conducting a multicenter, randomized, placebo-controlled trial to definitively assess the impact of metoprolol succinate on the rate and severity of COPD exacerbations. The trial will enroll 1028 patients with at least moderately severe COPD over a 3-year period. Major activities for this reporting period have centered on recruiting and enrollment at clinical sites, launching recruitment advertising campaigns locally, and the addition of new clinical sites to remediate recruitment lag including regulatory approvals, training, and site initiation. The monthly enrollment goal is 28.5 across all sites, with each site enrolling an average of 2-3 participants per month. Some sites have met and exceeded this goal overall while others are underperforming. At the time of this report 441 subjects have been randomized. We have initiated discussions with the DOD, UAB, and clinical sites regarding extending the recruitment period and redistribution of funds to high performing centers in order to reach the overall enrollment goal.

15. SUBJECT TERMS

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

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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 stu ies suggest -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 time to first, rate, and severity 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 dose weaning 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 as measured by 6 minute walk test; 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 capacity, hospitalization rates, and all-cause mortality.

What was accomplished under these goals?

Major activities for this reporting period have centered on continued recruiting and enrollment efforts at clinical sites, launching advertising campaigns locally, and the addition of clinical sites to remediate recruitment lag including regulatory approvals, training, and site initiation and enrollment at these new clinical sites. The original monthly enrollment goal was 28.5 across all sites, with each site enrolling an average of 2-3 participants per month. Some sites have met and/or exceeded this goal but others are underperforming. After their meeting on December 1, 2017, the DSMB recommended we perform an in-depth recruitment assessment with input from

all clinical sites. A report was compiled and distributed to the DSMB and sites in February 2018. All current sites participated in the assessment and indicated a favorable and renewed commitment to meeting revised recruitment goals based on the addition of sites and a tentative plan to extend the enrollment period through at least April 2020. Since the last annual report we have added 8 additional centers, including 2 to the NYPH consortium (Brooklyn and Queens), and the following stand-alone sites: Cincinnati VA, North Florida/Georgia VA, UCSF- Fresno, University of Vermont, and University of Utah.

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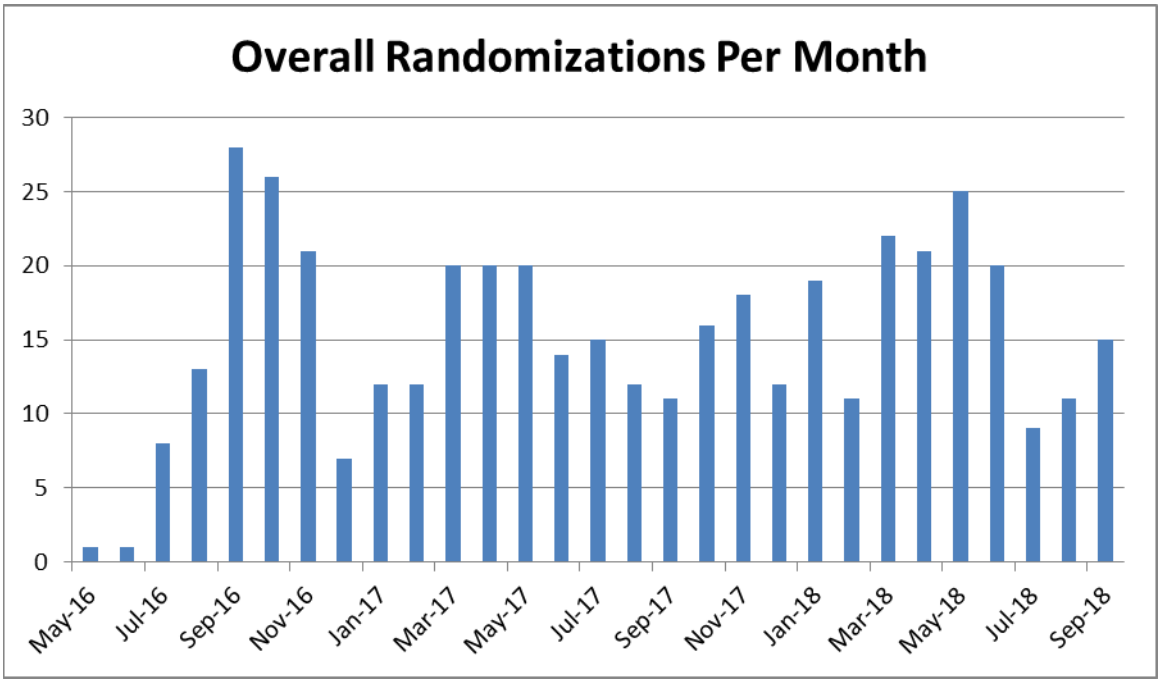
Screen 4-6 subjects/month	**6-42 months**	**Screening has started at all initiated sites**
Randomize 2-3 subjects per site /month	**6-42 months**	**The first subject was randomized in May 2016, two months later than anticipated based on delays in regulatory approvals. Since that time enrollment has been 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**	**DSMB meetings have been held on 2 DEC 2016, 25 MAY 2017, 01 DEC 2017 and 29 MAY 2018 and scheduled for 30 NOV 2018. The DCC has developed reports as necessary.**
Conduct monthly coordinator calls	**6-56 months**	**Calls have been conduct monthly since August 2016. Monthly calls have also 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 Per Month - April 2016 – September 2018



Overall Randomizations and Goals By Site

	Actual Randomizations (28 SEP 2018)	**Original Goal**	**Revised Goal**	**Percent of Revised Goal**
Ann Arbor VA/U Michigan	47	86	86	62%
Brigham Women's	29	86	50	58%
NYPH-Columbia; NYPH-Weill –Cornell; NYPH – Brooklyn; NYPH - Queens	18	86	60	30%
Cleveland Clinic	11	20	20	55%
Health Partners	11	27	27	41%
LA BIOMED	29	86	66	44%
LSU	15	20	30	50%
Maryland	32	86	76	42%
Mayo	17	27	27	63%
Minnesota VA	7	28	20	35%
National Jewish	12	45	35	34%
Northwestern	50	86	75	67%
Pittsburgh	22	86	66	33%
San	6	86	50	12%

Francisco				
Temple	61	86	100	61%
Birmingham VA/UAB	62	86	120	52%
Cincinnati VA	10	N/A	20	50%
Fresno	2	N/A	20	10%
North FL VA	0	N/A	20	0
Spokane	0	N/A	20	0
Utah	0	N/A	20	0
VT	0	N/A	20	0
TOTAL ALL SITES	**441**			

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

Numerous pulmonary fellows and junior faculty have been involved in the study across sites providing experience and education regarding clinical trial execution.

How were the results disseminated to communities of interest?

During the first reporting period the following article was ublishe -Blockers for the prevention of acute exacerbations of chronic obstructive ulmonar isease LOC COPD : a randomised controlled study protocol. PMID: 27267111.

Nothing to report during second and third reporting periods. Efforts have focused on recruitment, enrollment, and additional clinical sites.

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

During the next reporting period clinical sites will continue recruitment and enrollment efforts.

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

Because of the continuing recruitment lag and in order to enroll a sufficient number of participants we have begun discussing extending the recruitment period through month 54 of the project. Initial discussions with the scientific officer and the grants officer have been supportive of this plan. The revised recruitment goals presented above reflect an extended recruitment period, analysis, manuscript preparation, etc.

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

We have experienced ongoing recruitment lags even with the addition of 10 clinical sites. Our next course of action is to extend the enrollment period. We are currently in discussions with the DOD, UAB, and other clinical sites about funding this extension.

Changes that had a significant impact on expenditures

Because of the lower than expected subject recruitment in years 1 and 2 we amended the subcontracts for each site to allow for the use of remaining year 1 and 2 funds during years 2 and 3. We will utilize this strategy again when issuing year 4 subcontracts. However, we are also reducing the amount budgeted for capitated per patient payments for existing subcontracts in year 4 based on actual enrollment performance in years 1-3 to allow for additional sites to be added without impacting the overall budget.

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

During this third reporting period the modifications out lined below have been made. These revisions have been reviewed and approved by the UAB IRB and at clinical sites. The revisions do not meet DOD HRPOs threshold for substantive amendments, and therefore no further action was required from DOD HRPO regarding the revisions.

Protocol version 03 dated 24 FEB 2017.

During the December 1, 2017 DSMC meeting the DSMC approved revising the interim analysis plan from the 12 and 24 month time points to one third and two thirds of the expected primary outcomes events in the placebo group have occurred.

Protocol page 23:

Interim analysis plan has been revised from:
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. That is, analyses of efficacy will be presented to the DSMC beginning 12 months after the first patients are randomized and continuing at 12-month intervals thereafter until all patients have completed follow-up. A final analysis will be conducted at 48 months. Two-sided tests of significance will be assumed.

To:
We propose to carry out interim formal testing for efficacy at two interim time points when approximately one third and two thirds of the expected primary outcome events (first exacerbation) in the placebo group have occurred. However, exacerbations will be included in the safety analyses presented to the DSMC beginning twelve months after the first patient is randomized and continuing at twelve month intervals until all patients have completed follow-up.

A final analysis will be conducted at study completion. Two-sided tests of significance will be assumed.

Note the first interim analysis is planned for November 2018.

The consent form was not changed as a result of the protocol revisions.

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

First reporting period:

Journal publications

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

-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease LOC COPD a ran omise controlle stu rotocol

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

Second Reporting period:

Nothing to report.

Third Reporting period:

Nothing to report

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)

First reporting period:

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 clinical sites.

url: http://blockcopd.org/

Second reporting period:

Nothing to report.

Third reporting period:

Nothing to report

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

First reporting period:

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.

Second Reporting period:

Nothing to report.

Third Reporting period:

Nothing to Report

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: 3

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: .9
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: .24
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.

Name: Mary Kay Hamby
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 9.84
Contribution to Project: Mary Kay will perform adverse event assessment, questionnaire administration, spirometry, 6MW test, office visits, phone call visits, data entry and all activities associated with conducting study visits.

Name: Lisa McCloskey
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Lisa will perform adverse event assessment, questionnaire administration, spirometry, 6MW test, office visits, phone call visits, data entry and all activities associated with conducting study visits.

Weill Cornell Medical College

Name: Robert Kaner
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .36
Contribution to Project: Dr. Martinez is the PI for the Weil Cornell Medical College site. Dr. Martinez oversees day to day research

Name: Ghiasian Choncheh
Project Role: Regulatory Coordinator
Research Identifier: N/A
Nearest Person Month worked: 4.74
Contribution to Project: Ghiasian assists the Study Coordinator with the preparation, submission, and maintenance of clinical trial regulatory data and documentation.

Name: Elizabeth Peters
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 2.76
Contribution to Project:
Elizabeth is the study coordinator for the Weil Cornell Medical College site. She assists the PI with recruitment and study visits as outlined in the protocol. She will also act as a representative between the primary site (Cornell) and the subsites

Name: Keith Brenner
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .375
Contribution to Project: Dr. Brenner is the PI for Columbia University, a subsite of Weil Cornell Medical College site. Dr. Brenner assists in recruiting and evaluating patients for this study at the Columbia subsite

New York Presbyterian Queens (NYPQ)

Name: Anthony Smith
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Smith is the PI at the New York Presbyterian Queens site. This is a subsite of Weill Cornell Medical College. Dr. Smith will oversee recruitment at this site.

New York Methodist (NYM)

Name: Jeremy Weingarten
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Weingarten is the PI at the New York Methodist site. This is a subsite of Weill Cornell Medical College. Dr. Weingarten will oversee recruitment 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.

Name: Allison Rogowski
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 7.13
Contribution to Project: Allison assists Dr. Kalhan with obtaining informed consent, screening and recruiting patients, coordinating patient visits, conducting phone calls and collecting data.

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.

Name: Kelsey Elliott
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 12
Contribution to Project: Kelsey assists the PI with the day-to-day activities associated with this project. She is also responsible for the regulatory documentation at this site.

Temple University

Name: Gerard Criner
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .60
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: 3.8
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 recruits and enrolls patients as well as see patients at each visit as outlined in the protocol. Dee also collects patient data.

Minneapolis VA

Name: Ken Kunisaki
Project Role: PI
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 presentation

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: 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.

Name: Tami Krpata
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.58
Contribution to Project: Tami assists Dr. Scanlon with recruiting, consenting patients, administering all questionnaires, maintaining all regulatory documents, entering data into an electronic data capturing system, and dispensing and collecting the investigational product.

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: Charlene McEvoy
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .48
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.

Name: Natalie Woodruff
Project Role: Project Manager
Research Identifier: N/A
Nearest Person Month worked: 2.16
Contribution to Project: Pam assists the PI with the day-to-day activities associated with this project. She is also responsible for the regulatory documentation 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.

Los Angeles Biomedical Research Institute

Name: William Stringer
Project Role: PI

Research Identifier: N/A
Nearest Person Month worked: .5
Contribution to Project: Dr. Stringer is the PI for the Los Angeles Biomedical Research Institute. Dr. Stringer oversees the day to day research activities at this site.

Name: Richard Casaburi
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .3
Contribution to Project: Dr. Casaburi assists with the day to day research activities at this site and serve as a resource for this project. He will assist with data analysis and manuscript preparation.

Name: Leticia Diaz
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 3
Contribution to Project: Leticia assists Dr. Casaburi with the day to day research activities at this site and serve as a resource for this project.

University of San California, San Francisco

Name: Stephen Lazarus
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .58
Contribution to Project: Dr. Lazarus is the PI for UCSF. Dr. Lazarus is responsible for overall implementation and oversight of this project at the UCSF site.

Name: Prescott Woodruff
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Woodruff is the Co-Investigator at UCSF. Dr. Woodruff assists Dr. Lazarus with the day to day research activities at this site.

Louisiana State University

Name: Matthew Lammi
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .72
Contribution to Project: Dr. Lammi is the PI at the Louisiana State University site. He is responsible for the overall supervision and direction of the project at LSUHSC.

Name: Connie Romaine
Project Role: Clinical Research Nurse
Research Identifier: N/A
Nearest Person Month worked: .72
Contribution to Project: Connie screens potential participants and assists Dr. Lammi with data and sample collection, staff education, meetings and teleconferences.

Cleveland Clinic Foundation

Name: Umur Hatipoglu
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Hatipoglu is the PI at the Cleveland Clinic Foundation site. He is responsible for the overall supervision and direction of the project at Cleveland Clinic Foundation.

Name: Rick Rice
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 3.0
Contribution to Project: Rick is responsible for obtaining informed consent on all subjects enrolled. He is responsible for screening/enrolling participants as well as collect and enter data.

Cincinnati VA Medical Center

Name: Ralph Panos
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Panos is the PI at the Cincinnati VA (CERV) site. He is responsible for the overall supervision and direction of this project at CERV.

UCSF Fresno

Name: Vipul Jain
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6
Contribution to Project: Dr. Jain s is the PI at the UCSF Fresno site. He is responsible for the overall supervision and direction of this project at UCSF Fresno.

Name: Janna Blaauw
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 2.28
Contribution to Project: Janna Blaauw is the research coordinator for the UCSF-Fresno Site. Janna will assist in study recruitment and patient visits.

University of Vermont

Name: David A. Kaminsky
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Kaminsky is the PI at the University of Vermont & State Agricultural college site. He is responsible for the overall supervision and direction of this project at the University of Vermont.

University of Utah

Name: Richard Kanner
Project Role: PI
Research Identifier: N/A

Nearest Person Month worked: .12
Contribution to Project: Dr. Kaminsky is the PI at the University Utah site. He is responsible for the overall supervision and direction of this project at the University of Utah.

North Florida Foundation for Research and Education, Inc.

Name: Peruvemba Sririam
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .60
Contribution to Project: Dr. Sririam is the PI at the North Florida Foundation for Research and Education site. He is responsible for the overall supervision and direction of this project at NFFRE. He will oversee the study and perform physical examinations on study participants.

Name: Nataliya Kirichenko
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 3.6
Contribution to Project: Nataliya is the study coordinator for this site. She will perform all study related tasks per protocol.

Name: Angie Smith
Project Role: Regulatory Specialist
Research Identifier: N/A
Nearest Person Month worked: 1.56
Contribution to Project: Angie is the regulatory specialist at NFFRE site. Angie performs regulatory set-up and IRB continuation tasks related to this study.

Providence Health & Services - Washington

Name: Allison Lambert
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6
Contribution to Project: Dr. Lambert is the PI at the Providence Health & Services – Washington site. She is responsible for the overall supervision and direction of this project at Providence. She will oversee the study and perform physical examinations on study participants.

Name: Lisa Davis
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 2.4
Contribution to Project: Lisa is the clinical research coordinator at the Providence Health & Services – Washington site. She will perform the required patient visit procedures as outlined in the study protocol.

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

Nothing to report

What other organizations were involved as partners?

Nothing to Report

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable

QUAD CHARTS: See attachment 1

APPENDICES:

Third reporting period: Recruitment Plan Summary

PR140170: Beta Blockers for the Prevention of Acute Exacerbations of COPD

PI: Mark Dransfield, University of Alabama at Birmingham

Budget: $11,241,567 **Topic Area:** Respiratory Health **Mechanism:** Clinical Trial Award

Research Area: Chemoprevention, Chemotherapy **Award Status:** Open; 9/30/2015 - 9/29/2020

Study Goals:

Carry out a clinical trial to examine the potential role of beta-blockers in the treatment of chronic obstructive pulmonary disease (COPD).

Specific Aims:

(1) 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 do not have absolute indications for beta-blocker therapy. (2) Estimate the effect of metoprolol succinate, compared with placebo, on the rate and severity of COPD exacerbations over 12 months, incidence and severity of metoprolol-related side effects, lung function, dyspnea, exercise tolerance, quality of life, hospitalization rates, rate of combined cardiovascular events (myocardial infarction, percutaneous coronary intervention, sudden death, stroke), and all-cause mortality.

Key Accomplishments:

- Ended September 2018 (30th month of the original 36 month recruitment period) at 52% of projected target randomized.
- 8 additional clinical sites and subsites added to boost recruitment.
- Local advertising campaigns launched including television and Facebook.
- December 1, 2017 and May 29, 2018 the DSMC recommended the trial proceed according to the protocol.
- 24 subcontracts successfully executed including DCC, pharmacy, original clinical sites, and add on clinical sites.
- 26 clinical and clinical subsites successfully initiated to begin recruiting. 1 remaining new clinical subsite has training to complete prior to initiation.

Key Outcomes:

Publications: BMJ Open, vol. 6(6) pp. e 2292, -Blockers for the prevention of acute exacerbations of chronic obstructive ulmonar isease LOC COPD a ran omise controlle stu 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

Patents: N/A

Funding Obtained: N/A

Block-COPD COPD Recruitment, Randomization, and Retention Plan Summary

All currently active Block-COPD sites completed the Block-COPD Recruitment, Randomization, and Retention Plan. Full text copies of each plan are included as attachments to this document. Beyond the usual and expected barriers to eligibility tied to inclusion/exclusion criteria such as COPD severity, exacerbation risk, and stability, comorbidities, and exclusionary medication use, sites reported the following barriers to successful recruitment; staffing issues including change in PI, understaffing and maternity leave, lack of funds for advertising, lack of travel funds to present the study to other providers , inadequate PI salary support, COPD patients being seen by a large number of providers at a given center, needing provider permission to contact potentially eligible subjects, and high data security standards limiting use of the study website. All currently active sites reported they could meet their revised recruitment goal. Table 1 summarizes recruitment strategies currently in use or planned in order to meet revised recruitment goals.

Table 1: Recruitment Strategy in order of usage:

Code	Strategy	Number of sites reporting usage (N=18)
1	Medical records prescreening	12
2	In clinic recruiting	10
3	Advertising - Offsite flyers, newspaper, mailings to potential participants	8
4	Records review based on billable codes, ED visits records, pharmacy records for steroid/antibiotic use, daily census review (admissions records for exacerbations), specialty clinics and services such as Oxygen clinic, Pulmonary rehab, PFT lab, screening CT program enrollees	8
5	Regular team meetings/teleconferences to discuss recruiting	7
6	Advertising -Onsite flyers and/or study board	5
7	Patient registries/ review of prior study participant data bases	6
8	Engage Faculty and fellows and staff through Blast emails, EMR	6

	messaging, Study inclusion/exclusion cards to hand out, faculty meeting presentations	
9	Hire/utilize additional personnel/volunteers	5
10	Outside referrals. Engaged through referral letters or host regional lectures	4
11	Advertising - TV	3
12	Advertising- Internet, Social media, Institution-based online referral system	3
13	Add sub/multiple sites	3
14	Advertising- Transit authority ads	1
15	Expand recruitment to Family practice and Internal Medicine clinics including purchasing spirometry to non-pulmonary clinics to use.	1
16	CTSC support	1
17	Develop non-English forms and consents	1
18	In clinic chart flags for potentially eligible subjects	1
19	Annual educational seminar for COPD patients/family	1

Table 2 summarizes each site's usage of these strategies and randomizations (actual and goals).

TABLE 2:

	Actual Randomizations (01 FEB 2018)	Original goal	Current Rate per Month	Revised goal	Revised Rate goal per month*	Meet new goal	Strategies Utilized code
Ann Arbor VA	4	20	.3	16	.4	Y	2,3,6,9
Brigham Women's	13	86	1.3	50	1.3	Y	4,7
New York Consortium: NYPH-Columbia; NYPH-Weill –Cornell; NYPH – Brooklyn; NYPH - Queens	9	86	.3	60	1.85	Y	1,2,3,4,5,8,9, 10,12,13,15,16,17
Cleveland Clinic	5	20	.8	20	.5	Y	2, 4,6,13
Health Partners	8	27	.5	27	.7	Y	1, 3, 4, 5,6,7,8
LA BIOMED	18	86	1.0	66	1.75	Y	2, 4, 5, 7, 8,10
LSU	11	20	1.5	30	.7	Y	1,2,3,4,5,7,8
Maryland	28	86	1.5	76	1.8	Y	1,2,9
Mayo	15	27	1.0	27	.5	Y	None listed
Michigan	29	66	1.6	70	1.6	Y	1, 3, 4, 10,11
Minnesota VA	1	28	0	20	.7	Y	1,4
National Jewish	10	45	.6	35	.9	Y	1, 2, 3, 5, 8, 18
Northwestern	33	86	2	75	1.5	Y	1,9, 11, 14
Pittsburgh	21	86	1.1	66	1.7	Y	1,7, 9, 11, 12,

	Actual Randomizations (01 FEB 2018)	Original goal	Current Rate per Month	Revised goal	Revised Rate goal per month*	Meet new goal	Strategies Utilized code
San Francisco	6	86	.35	50	1.6	Y	1, 6, 7, 8, 12, 13,
Temple	47	86	2.4	100	2.04	Y	2,3, 5, 6,8,19
UAB	46	66	2.3	100	1.96	Y	1, 2, 3, 6, 11
Birmingham AL VA	4	20	.3	20	.4	Y	1, 2, 5, 10
TOTAL	**308**	**1027 (28.5/month)**	**18.9**	**908**	**22**		
Proposed New Sites							
Cincinnati VA				20	.8	NA	NA
Fresno				20	.8	NA	NA
North FL VA				20	.8	NA	NA
Spokane				20	.8	NA	NA
Utah				20	.8	NA	NA
VT				20	.8	NA	NA
TOTAL ALL SITES				**1028**	**26.8**	**NA**	**NA**

*Assumes 28 more months of recruiting (Jan 2018- April 2020) for existing sites. For news sites it assumes 24 months of recruiting (April 2018-April 2020)