Pragmatic Trial to Enhance Quality, Safety, and Patient experience in COPD (EQuiP COPD)

Funding Agency: Patient-Centered Outcomes Research Institute (PCORI); PCS-2021C2-23668

Principal Investigator: David Au

Co-Principal Investigator: Lucas Donovan

02/24/2026

Version 8.5

Revision History

Revision #	Version Date	Summary of Changes
V8.5	02/24/2026	Section 9.5 Study Evaluations • Addressed typo in Table 2 describing secondary outcome of COPD care quality • For secondary outcome of patient-incurred cost, we clarified that we will estimate patient incurred costs for COPD services that may be provided as a result of the intervention. • Corrected information in Table 3 to state that data informing Veterans drive time will be derived from the corporate data warehouse (CDW). • Updated Table 4 to align with intervention elements described in Table 2. Section 17 Privacy & Confidentiality • Addressed two typos in text
V8.4	12/15/2025	Section 1.0 Key Personnel • Updated VISN 17 Jennifer Gunter qualification description to new job position Section 9.5: Aims 1 and 2 • Clarified that we will use EHR/administrative data from the corporate data warehouse as well as chart review to obtain quality of care outcomes and clinical outcomes. Section 9.5.2 **Aim 4** (*heterogeneity in treatment effect)* • Added details to heterogeneity of treatment effect description re: additional analyses to assess associations between patient, provider and health system characteristics/processes with care delivery and patient outcomes.
V8.3	09/04/2025	Section 1.0 Key Study Personnel • Removing Dr. John T. Huggins from Ralph H. Johnson VA Study Personnel
V8.2	08/18/2025	Section 1.0 Key Study Personnel • Replaced Dr. Givens as site PI at Mann-Grandstaff VA with Dr. Lambert
V8.1	07/01/2025	Section 1.0 Key Study Personnel • Updated Dr. Givens' credentials and qualifications
V8.0	5/07/2025	**Updated entire Protocol to current cIRB template version 1.2. New sections with content not in previous version include**: • 2.0 Participating Local Sites • 4.0 Collaborations • 6.0 Risk/Benefit Ratio • 9.7 Data and/or Specimen Use • 15 Sharing of Results **Changes to Protocol in this submission**: Section 1.0 Key Study Personnel

		• Added biostatistician co-investigator to ECHCS • Change in co_PI at Mann-Grandstaff VA from Dr. Lambert to Dr. Givens Section 9.6.2 EHR Abstraction/CDW • Clarified wording in Description column for some of the cost elements Section 11.2 Recruitment Methods-Patients • Updated survey collection methods to be more general and include either Qualtrics or REDCap Section 17.1 Data Protection • Updated survey collection methods and storage to be more general and include either Qualtrics or REDCap Section 17.2 Online Surveys • Changed section header for “Qualtrics” to “Online Surveys” to include both Qualtrics and Redcap • Generalized language to include both Qualtrics and Redcap as data capture tools Section 18.2 Data Analysis • Consistent with best practices in clinical trials advocated by FDA, we updated analytic model to add stratification variables for randomization as covariates (site and clinician type: physician or advanced practice practitioner). Section 18.4: Sample Size and Power • In alignment with executive orders, we removed the term gender.
v7.1	3/10/2025	Section 5.3.4 Recruitment Methods: Pharmacists and Pulmonologists • Added new information around the recruitment of interventionists for qualitative interviews Section 5.4.4 Informed Consent Procedures: Pharmacists and Pulmonologists • Added new information around the recruitment of interventionists for qualitative interviews Section 5.7.3 Qualitative Interviews: • Added additional interviews of pharmacists and pulmonologists as part of Aim 5.
v7.0	1/23/2025	Section 5.1 Study Design • Updated Figure 3 to reflect the cost outcomes added 1/20/2023 Section 5.7.2 EHR abstraction/CDW: • Added minor correction to imprecise language Section 5.8 Data Analysis • Revised model back to the originally planned general linear mixed model (GLMM). Through ongoing discussions with our biostatisticians, we decided to pursue a generalized linear mixed model as this approach will average treatment effects over the PCP population. Since PCPs comprise the unit of randomization, we felt that GLMM was the most appropriate approach.
v6.7	11/22/2024	Section 5.1 Study Design

		• Updated Figure 4 to reflect prior change to one primary outcome (composite of COPD exacerbation, pneumonia, hospitalization, or death) Section 5.7.2 EHR Abstraction/CDW • Updated Table 2 to clarify eligible patients for each quality-of-care outcome Section 5.7.3 Qualitative Interviews • For PCP and Leadership interviews: Added that we may use email or Teams to arrange the interview times, and may follow up for minor clarifications via encrypted email or Teams
v6.6	10/03/2024	Sections 1.0 Study Personnel • Removed Dr. George Sayre as Key Personnel because he retired from VA • Revised this section to show only Key Personnel Sections 5.8.6 Qualitative Data Analysis • Replaced Dr. George Sayre with Dr. Lucas Donovan who will oversee qualitative data analysis
v6.5	8/14/2024	Section 1.0 Study Personnel • Added: Kristine Beaver and Jennifer Ives • Removed: Dyuti Shreya Nandy Section 5.2 Inclusion/Exclusion Criteria • Caregiver qualitative interviews: exclude caregiving paid for by the VA or other healthcare organization Sections 5.4.3 and 5.4.4: Informed Consent • Corrected typo Section 5.7.3 Qualitative Interviews • Increasing number of caregiver interviews from 10 to 20 to increase ability to detect themes • Clarified language to reflect that we may continue to interview beyond the target enrollment until saturation is reached for all qualitative interview participant groups
v6.4	05/09/2024	Throughout: • Corrected outcomes periods chosen a priori to reflect 90 days (previously stated three months) for Quality of Care and Quality of life, and 180 days (previously stated six months) for Clinical and Cost outcomes Section 6.3 Adverse Event Monitoring • Clarified ambiguous language defining what adverse events are considered expected in the EQuiP population of participants who have COPD to correspond with DSMB approved Charter v2.1
v6.3	04/05/2024	Section 5.7.3 Qualitative Interviews • For qualitative interviews, we clarified that we will *invite* providers with a variety of characteristics, which may not result in *inclusion* depending on willingness to participate Section 5.7.5 Payments • Adding option of paying participants by gift card

v6.2	03/08/2024	Section 1.0 Study Personnel • Removed Scott Coggeshall and Kevin Duan as key personnel Section 6.3 Adverse Event Monitoring • Our trial defines SAEs as events that result in hospitalization or death. The protocol uses ambiguous instructions around identifying SAEs, causing coordinators to flag emergency room visits or outpatient COPD exacerbations as SAEs. Emergency room visits and outpatient COPD exacerbations are not considered serious unless they result in a hospitalization. We have updated the Protocol and DSMB Charter accordingly.
v6.1	01/10/2023	Section 1.0 Study Personnel • Added Fiona Gillen and Alison McGrath at VA Puget Sound • Removed Anna Pannick, Taran Paul, and Katie Tirtanadi at VA Puget Sound • Removed Erik Sorenson from Mann Grandstaff VA • Added Matthew Griffith and Kevin Josey at Eastern Colorado Heath Care System • Added missing emails Section 2.3 Study population and research settings • Removed specifications for subgroups Sections 3.0 Objectives, 5.2 Inclusion/Exclusion criteria, 5.3 Recruitment Methods, 5.4 Informed Consent Procedures, 5.7 Study Evaluations, and 5.8 Data Analysis: • Modified to reflect activities around addition of new Patient Cost Aim Section 5.7.2 EHR abstraction/CDW • Updated Table 2: added “continuation” to “Escalation of smoking cessation medications”; removed “tapering” from “Discontinuation /tapering of COPD treatment”; added “COVID vaccination”. Section 5.4.3, 5.4.4, and 5.7.3 Qualitative interviews • Removed outdated text about requesting patient consent at a future date • Added recruitment and consent details for Caregivers and VA Leadership • Added that we will revise interview guides iteratively based on data collected and to address any participant comprehension or clarity issues that arise Section 5.7.5 Payments • Clarified that only patients and patient caregivers will receive payment for completing the qualitative interviews Section 6.3 Adverse Event Monitoring • We lengthened the SAE reporting period from 90 days to 180 days to match the primary outcome timeframe

v5.0	07/18/2023	Section 1.0 Study Personnel • Added Howard Li at Ralph H. Johnson VA Section 5.3.2. Recruitment Methods: Patients • Added text messaging to options for sending reminders and/or Qualtrics links • Updated the timeframe to contact non-responders to one week to account for faster delivery time for those who received an email Section 5.4.2 Informed Consent Procedures Patient, 5.7.3 Qualitative Interviews, and 7.1 Data Protection • Updated description of qualitative interviews including recording and transcription via VA Microsoft Teams • Removed interview guides from appendix Section 5.8.1 Data Analysis • Clarified who are eligible patients and what we consider the index date
v4.1	06/21/2023	Cover Sheet: added NCT number List of abbreviations: updated Section 1.0 Personnel • Updated staff Abstract, Section 3.0 Objectives and 5.8 Data analysis: • Based on recommendations and feedback from the DSMB around multiple comparisons, we decided to focus on a single primary outcome. The composite outcome of exacerbation, pneumonia, hospitalization, or death within 180 days will remain as the primary. We reclassified CCQ and quality of care received as secondary endpoints • Revised model from Generalized linear mixed model (GLMM) to generalized linear models (GLM) to account for correlation of outcomes among PCPs. We chose GLM since we do not believe that conditioning on PCPs leads to substantial precision gains in estimating adverse events and since it is robust to model misspecification of the within PCP correlation (i.e., random effects) Section 5.2 Inclusion/Exclusion criteria • Added diagnosis of COPD to pathway 5 to ensure we identify all patients who may benefit from the intervention Section 5.3.2.2 Qualtrics and 7.2 Qualtrics online surveys: • Link to Qualtrics will be via generic unencrypted email because of new IT limitations on mail merging to an encrypted email Section 5.6.1 Patient identification: • Removed list of patient priorities because already listed in Section 5.2 • Included EHR notation as a means of notifying pharmacists and pulmonologists about patients they will review Section 6.3 Adverse Event Monitoring:

		• Added the following as an expected event: Known side effects from recommended pharmacologic and non-pharmacologic treatments (e.g., ICS-thrush, pneumonia, pulmonary rehabilitation – musculoskeletal injuries) Appendix 1 and 2: • Removed from protocol because recommendations will occur as part of usual care and will vary accordingly
v3.0	2/14/2023	Section 1.0 Personnel • Added pharmacists and coordinators • Indicated that LSI staff will not obtain consent Section 5.2 Inclusion/Exclusion Criteria and 5.6.1 Patient Identification • Removed Pathway 6 (evidence of COPD); these patients are less likely to benefit from the intervention than the other five categories which identify sufficient numbers of patients Section 5.3.1 Recruitment Methods, Providers and 5.4.1 Informed Consent Procedures, Providers • Providers who want to opt out will email the study team instead of answering a REDCap survey question to minimize barriers to opt out Section 5.5 Randomization • Removed median panel size as a stratification for randomization (determined no empirical justification to include) Section 5.6.2 Intervention Delivery • Clarified text around order entry to recognized differences in order entry between sites. Section 5.7.3 Qualitative interviews • Clarified that PCP and leadership interviews are under waiver of informed consent; informed consent for pt interviews is pending Section 6.3 Adverse Event Monitoring • Updated timing to query the EHR for AEs to 180 days • Clarified that we will report unexpected, serious, related AEs to the IRB Section 8.0 Communication Plan • Added study-specific SharePoint as a method of collaboration
v2.0	10/24/2022	Section 1.0 Study Personnel • Added staff, updated roles Abstract and Section 2.3: Study population and research settings • Changed Massachusetts to South Carolina per pervious change in study site not corrected on prior protocol version Sections 5.1 Study Design, 5.6: Intervention, and 8.0 Communication Plan • Modified language to clarify the pragmatic approach for recommendation delivery that

		includes placing e-consults to pulmonologists and pharmacists to conduct standard-of-care review • Replaced “interventionist” with “specialist” to better reflect standard-of-care activities
v1.2	9/20/2022	Section 5.7.3: Qualitative Interviews • Added information about recording and transcribing interviews Section 5.7.5: Payments • Added information about method of payment and frequency and SIBCR’s access to identifying information
v1.1	8/23/2022	(edits requested by CIRB before review and included in v01.2) Section 1.0: Study Personnel • Added Jennifer Gunter for V17 Section 5.2: Inclusion/Exclusion Criteria • Clarified inclusion criteria for ICS use is for those who do not meet criteria “for ICS use” Section 5.3.2, 5.4.2: Recruitment Methods, Patients and Section 5.7.3: Study Evaluations, Qualitative Interviews • Added details around the interview process and timing • Revised consent method for patient interviews from Waiver of Documentation of Consent to full written consent given that the interview is recorded • Clarified process for sending secure link to Qualtrics Sections 5.4: Randomization and Section 5.5: Informed Consent Procedures • Sections swapped to reflect flow of the protocol Section 5.9: Withdrawal of Subjects • incorrectly stated that patient activity was restricted to the CCQ; corrected to include qualitative interview Section 6.0: Reporting • Corrected outlining levels
v1.0	8/11/2022	• Major revisions to Procedures, Reporting, Privacy and Confidentiality, and Communication plan to conduct full trial including recruitment, enrollment, and outcome assessment for five VA sites. • Outline subheadings changed from alphabetical to numerical; and some reworded to better reflect content • Minor grammatical/formatting changes throughout
v00.3	6/2/2022	List of Abbreviations: • Entries added Section 5.1: Study Design • Indicated no participant contact during Phase 1 Section 5.2: Recruitment Methods • Clarified EHR information accessed Section 7.0: Privacy and Confidentiality • Specified no data sharing for Phase 1

		• Clarified EHR information accessed
v00.2	5/16/2022	Section 1.0: Study Personnel • Removed staff no longer with the project Section 5.4: Inclusion/Exclusion Criteria • Clarified criteria involving COPD

Abstract

Background and Significance: Over 26 million Americans have chronic obstructive pulmonary disease (COPD), and for most of these patients, the quality of COPD care is poor. Few patients receive evidence-based therapies that are known to improve outcomes, and many patients experience avoidable harms after receiving therapies that are known to have safer alternatives. Efforts to address poor quality care through education and outreach have been largely unsuccessful, primarily due to the competing demands of primary care providers (PCPs) who manage COPD for over 90% of patients. To overcome these barriers, our research team developed a population management approach where pulmonary specialists provide evidence-based recommendations as an E-consult with unsigned orders to PCPs. PCPs then review the E-consult and sign or discontinue these orders. We found this intervention led to marked improvements in the quality-of-care delivered and patients' COPD-related quality-of-life. While promising, this population management approach is limited by a paucity of pulmonary providers nationwide. There are regional efforts to involve clinical pharmacists into this type of care as pharmacists are 20 times more prevalent as pulmonary specialists. However, the relative effectiveness of pharmacist-led management is yet to be established, limiting uptake of pharmacist-led population management in usual care.

Specific Aims: assessing the patient-centered outcomes and health system processes impacted by population management:

- Aim 1: Examine whether quality of COPD care is non-inferior among patients with COPD who receive proactive population management performed by clinical pharmacists relative to pulmonary specialists.
- Aim 2: Examine whether patient-centered outcomes are non-inferior among patients with COPD who receive proactive population management performed by clinical pharmacists relative to pulmonary specialists. Patient-centered outcomes will include COPD-related quality of life (Aim 2a) and adverse clinical outcomes (Aim 2b).
- Aim 3: Examine whether patient and caregiver cost burdens are non-inferior among patients with COPD who receive proactive population management performed by clinical pharmacists relative to pulmonary specialists.
- Aim 4. Examine heterogeneity of treatment effect among patients known to be at risk for lower quality services.
- Aim 5. Seek patient, caregiver, primary care, and health system leaders' perspectives on acceptability, engagement, satisfaction and/or costs through qualitative interviews.

Study Description: We propose a cluster randomized clinical trial at 5 medical centers and associated clinics within the Department of Veterans Affairs (VA) in the states of Washington, Oregon, Minnesota, and South Carolina. We will randomize PCPs to population management conducted by either pulmonary specialists or pharmacists. Within PCPs' panels, we will use the electronic medical record to identify patients diagnosed with COPD who have evidence of a recent COPD exacerbation or potentially inappropriate treatment. Pulmonary specialists and pharmacists will review patients identified within panels of their assigned PCPs. After review, pulmonary specialists and pharmacists will deliver evidence-based recommendations through E-consults coupled with unsigned orders for primary care providers to sign, modify or decline.

Outcomes:

- Primary: Incidence of a composite endpoint of COPD exacerbation, pneumonia, hospitalization, or death.
- Secondary: 1) the proportion of guideline recommended therapies received by patients, 2) COPD-related quality-of-life as measured by the Clinical COPD Questionnaire, 3) PCP acceptance of recommendations, and 4) incidence of each individual outcome within the primary composite endpoint above.

Timeframe: We will follow patients for 180 days after intervention for the primary outcome.

List of Abbreviations

CBOC: community-based outpatient clinic

CCQ: Clinical COPD Questionnaire

CDW: corporate data warehouse

Co-I: co-investigator

COPD: chronic obstructive pulmonary disease

CRADA: Cooperative Research and Development Agreement

DISCUSS COPD: De-implementing Inhaled Steroids to Improve Care and Safety in COPD

DUA: Data Use Agreement

EHR: electronic health record

EQuiP COPD: Enhance Quality Safety, and Patient experience in COPD

ER: emergency room

FTE: full-time equivalent

GEE: Generalized estimating equation

GLM: Generalized linear model

ICC: Intra-cluster correlation

ICS: inhaled corticosteroid

InCasE: Integrating Care After Exacerbation of COPD

ISO: information security officer

JLV: Joint Legacy Viewer

MID: minimal important difference

NCT: National Clinical Trial

NIH: National Institutes of Health

OI&T: Office of Information and Technology

PBM: Pharmacy Benefits Management

PCORI: Patient-Centered Outcomes Research Institute

PCP: primary care provider

PHI: protected health information

PI: principal investigator

PO: privacy officer

PRECIS: Pragmatic Explanatory Continuum Indicator Summaries

RCI: referral coordination initiative

RCS: Record control schedule

REDCap: Research Electronic Data Capture

SD: standard deviation

SIBCR: Seattle Institute for Biomedical and Clinical Research

VA: Veterans Affairs

VHA: Veterans Health Administration

VINCI: VA Informatics and Computing Infrastructure

VISN: Veterans Integrated Service Network

VSSC: Veterans Support Service Center

Contents

1.0 Key Study Personnel

Role	Name	Cred	Contact Information (Email and Phone)	Affiliation	Qualifications	Access SPI
VA Puget Sound						
Co-Principal Investigator	**Lucas M. Donovan**	MD, MS	Lucas.Donovan@va.gov 206 – 277 – 6783	8/8th VA	Pulmonary, Critical Care, and Sleep physician, Co-Associate Director of the VA HSR&D Denver-Seattle COIN, Associate Professor of Medicine at the UW SOM	Y
Co-Principal Investigator	**David H. Au**	MD, MS	david.au@va.gov 206 – 277 – 6132	8/8th VA	Professor of Medicine, University of Washington; Director, VA Center for Care and Payment Innovation	Y
Co-Investigator	**Laura Feemster**	MD, MS	Laura.Feemster@va.gov 206 – 764 – 2504	8/8th VA	Pulmonologist and critical care Physician, Co-Associate Director of the Seattle-Denver COIN, Associate Professor of Medicine at the University of Washington School of Medicine.	Y
Mann-Grandstaff VA						
Co-Investigator	**Allison Lambert**	MD, MHS	Allison.Lambert3@va.gov 509 – 434 – 7264	8/8th VA	Pulmonologist, critical care physician, and an NIH-funded investigator and clinical researcher	Y
Portland VA						
Co-Investigator	**Christopher Slatore**	MD, MS	Christopher.Slatore@va.gov 503 – 220 – 8262	8/8th VA	Professor, Pulmonary & Critical Care Medicine; VAPORHCS/OHSU	Y
Minneapolis VA						
Co-Investigator	**Anne Melzer**	MD, MS	Anne.Melzer2@va.gov 612 – 725 - 2000	8/8th VA	Associate Professor of Medicine at the University of Minnesota Medical School and a Core investigator at the Center for Care Delivery and Outcomes Research (CCDOR)	Y
Site Co-Investigator	**Arianne Baldomero**	MD	Arianne.Baldomero@va.gov 612 – 725 - 2000	8/8th VA	Associate Professor of Medicine at the University of Minnesota Medical School and a Core investigator at the Center for Care Delivery and Outcomes Research (CCDOR)	Y
Ralph H. Johnson VA						
Co-Investigator	**Nichole Tanner**	MD	Nichole.Tanner@va.gov 843 – 789 – 7341	8/8th VA	Professor of Medicine, Director of the Lung Precision Oncology Program (LPOP).	Y
Site Co-Investigator	**Tatsiana Beiko**	MD	Tatsiana.Beiko@va.gov 843 – 577 – 5011	8/8th VA	Associate Professor of Medicine, Pulmonologist	Y

					specializing in asthma, COPD, critical care medicine, and pleural disease.	
Site Co-Investigator	**William McManigle**	MD	William.McManigle@va.gov 843 – 789 – 7187	8/8th VA	Assistant Professor of Medicine Division of Pulmonary, Critical Care, Allergy & Sleep Medicine Medical University of South Carolina, Charleston, SC, Staff Pulmonologist Pulmonary Section of the Medical Service Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC Department of Veterans Affairs	Y
Site Co-Investigator	**Howard Li**	MD	Howard.Li@va.gov 843 – 577 - 5011	8/8th VA	Deputy Chief of Pulmonary, Ralph H. Johnson Veterans Affairs Medical Center	Y
VISN 17						
Site Co-Investigator	**Jennifer Gunter**		Jennifer.Gunter@va.gov 817 – 385 – 5978	8/8th VA	Neurology Clinical Pharmacist Practitioner, VISN17 Clinical Resource Hub	Y
Eastern Colorado Health Care System						
Site Co-Investigator	**Matthew Griffith**		Matthew.Griffith@va.gov 720 – 723 – 6091	8/8th VA	Staff Pulmonary and Critical Care Medicine Physician at the Rocky Mountain Regional VA Medical Center (RMR VAMC), Assistant Professor in the Division of Pulmonary Sciences and Critical Care Medicine at the University of Colorado School of Medicine	Y
Site Co-Investigator	**Kevin Josey**		Kevin.Josey@va.gov 303-827-8524	IPA VA	Assistant Professor of Biostatistics, University of Colorado, Denver; University of Colorado Denver Research affiliate	

2.0 Participating Local Sites

5 sites

Site name	Role in Project
Seattle, WA - Puget Sound Health Care System	*Primary site-recruitment, data collection, data storage*
Spokane, WA - Mann-Grandstaff VAMC	*Local site for patient care activities*
SC - Ralph H. Johnson VAMC	*Local site for patient care activities*
Portland, OR - Portland VAHCS	*Local site for patient care activities*
Minneapolis, MN - Minneapolis VAHCS	*Local site for patient care activities*
Aurora, CO - Eastern Colorado VAHCS	*Co-investigator Site*
Temple, TX - Central Texas VAHCS	*Co-investigator Site*

3.0 Coordinating Center

There is no coordinating center for this project.

4.0 Collaborations

Data Safety and Monitoring Board:
See more information around DSMB procedures and role in section 16. All information shared with the DSMB will be deidentified.

5.0 Background and Rationale

5.1 Research Question/Background

Chronic obstructive pulmonary disease (COPD) affects up to 26 million Americans and is not only the fourth leading cause of disability adjusted life years but also the fourth leading cause of death.[1,2] COPD frequently causes symptoms of shortness of breath, cough, and wheeze that impair quality of life. These chronic daily symptoms escalate quickly during periods of exacerbation, which are life-threatening and can lead to permanent reductions in functional capacity.[3] Opportunities to improve the well-being of patients exist,[4,5] yet few patients receive therapies that are known to improve outcomes.[6-10] In addition, many patients experience avoidable harms[6,11] after receiving therapies that are known to have safer alternatives. At a population level, the overall quality of care for COPD is poor, and efforts to improve care have been largely unsuccessful. Due to this lack of progress, the National Institutes of Health (NIH) set forth the first national COPD action plan in 2017 that addresses important goals for COPD and emphasizes innovation, quality, and delivery of services to improve the well-being of patients with COPD. [12]

Ninety percent of patients receive their COPD care within primary care settings, where providers face an increasing number of competing demands. For most Americans, primary care providers (PCPs) serve

as the central point of care for health maintenance and the treatment of acute and chronic conditions. Over the past several decades, primary care also became the center of care coordination.[13] At the same time, medical knowledge and innovation for COPD and other conditions expanded at exponential rates, creating greater degrees of specialization.[14] These forces create tension in healthcare delivery. Innovation drives potential improvements in patient well-being but creates quality gaps when those innovations are adopted heterogeneously. For purposes of productivity and revenue generation, PCPs have less time with patients while needing to address greater documentation and insurance authorization burdens.[15-17] PCPs are also held to a growing set of quality measures that are increasingly difficult to achieve. This accumulation of tasks is untenable and forces PCPs to choose among many different priorities.[15] As many as 90% of patients with COPD have competing conditions that often rise in importance over COPD during PCP visits. These include common comorbidities, such as hypertension and diabetes, as well as the need for screening and health maintenance.[18,19] Though this issue of de-prioritization of COPD has been well established, few innovations have sought to address this problem.

Outdated structures of specialty care involvement further limit the health system's capacity to promote high-quality care in COPD. The traditional approach to receiving specialized care for COPD and other conditions relies on referrals.[20] Unfortunately, specialty care referrals are dependent on a number of factors that drive disparities within and between patients.[21,22] Referrals require numerous actions on the part of the PCP, including the need to accurately recognize, diagnose, prioritize, and refer[20,21] patients. Furthermore, patients referred to specialty care are typically more severe than those who are not, and specialists miss the opportunity to intervene earlier when COPD is less severe and potentially more amenable to preventive care.[23,24] Finally, the timing of PCP visits may not align with a patient's need for specialty services, missing an important opportunity to provide "the right care at the right time".[21] Improving equity and quality in referral is necessary, but not sufficient to encompass all the limitations of the current approach. For example, specialists are typically concentrated at large urban medical centers that are distant from patients and primary care settings. This concentration creates specific challenges for patients who live in rural areas or where access to public transportation is limited.[25,26] Rurality and social determinants of health also affect care delivery and coordination between specialty and primary care settings. Moreover, for COPD, the number of available patients vastly overwhelms the number of available pulmonary specialists. For instance, in the Department of Veterans Affairs (VA) there are 4,000 patients with COPD for every pulmonary specialist.[27] How to address gaps in care delivery, improve quality of care, and patients' well-being is at the heart of this application.

Our research group is uniquely suited to face this challenge. As we describe below, our research team, operational leaders, and organization have focused on how to improve delivery of specialty care within existing health systems. We have strong evidence to support a population management approach to COPD care that realigns existing care structures and processes around patients' needs while incorporating modern behavioral economics. Our evidence demonstrates improvements in access, care quality and well-being for patients with a population management approach.

While promising, key uncertainties remain including: 1) the type of provider who is capable of delivering population management (pulmonary specialist or clinical pharmacist), 2) treatment heterogeneity among those at risk for low-quality services, and 3) patient and staff perspectives around acceptability, engagement, and satisfaction.

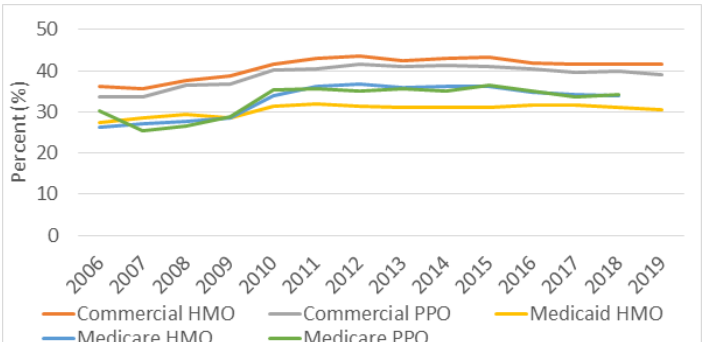
5.2 Preliminary Data

The current application arises out of decades of work from our group in identifying gaps in quality of care for COPD and uncovering strategies to address them.

Persistent evidence of poor quality of care for COPD: Efforts over previous decades have failed to improve basic delivery of care for patients with COPD. The National Lung Health Education Program was established in 1997 and sought to increase the use of spirometry to confirm the diagnosis of COPD.[28] A decade later, National Committee on Quality Assurance implemented quality measures focused on that target. Consistent across many healthcare systems, there was little improvement in the use of spirometry (Figure 1). We found similar poor-quality care across the NIH funded CONCERT consortium that engaged academic

centers, health maintenance organizations, and VA Medical Centers.[29] Similarly, CMS instituted the Hospital Readmission and Reduction Protection in 2014 that penalized hospitals for excessive COPD readmission rates.[30] The underlying premise was that poor-quality hospital care was leading to excessive readmissions. We showed that over time, there was little objective evidence of change in quality over time with only 18% of patients receiving all recommended services.[31] In separate analyses, we found important deviations from evidence-based recommendations known to decrease exacerbation risk and, in some cases, mortality. Patients frequently did not receive smoking cessation counseling and pharmacotherapy, long-acting bronchodilators, or follow-up to correct treatment after misdiagnosis.[8,32,33] We also found notable gaps around prescribing of inhaled corticosteroids (ICS). ICS increase risk of pneumonia and are indicated only for the small subset of patients with frequent or severe exacerbations.[4,5] Nevertheless, we found that nearly 80% of patients being treated for COPD were exposed to unnecessary ICS.

Figure 1. Percent of patients with COPD diagnosis and confirmatory spirometry



Limited capacity and priority for COPD management in primary care. To better understand the context for our findings, we performed qualitative interviews of VA PCPs to assess perspectives around COPD care. We found several themes that helped us understand the findings. For example, PCPs did not prioritize COPD among other common conditions such as heart failure, diabetes, or hypertension. PCPs also discounted the use and value of spirometry to exclude COPD as a source of symptoms.[34] More recently, we asked PCPs about overuse of ICS. They reported challenges in keeping up to date on disease specific guidelines and were generally unaware of evidence regarding the risk of pneumonia associated with ICS.[35] These results highlighted the challenges driving change in primary care settings.

Lack of organizational structures and processes to support COPD care. Given the low priority expressed by clinicians,[36] we hypothesized that poor quality of COPD care also reflected a low degree of organizational engagement with structures and processes to support evidence-based care. We surveyed all VA medical centers about their organizational structures and processes to support COPD relative to chronic heart failure, an equally prevalent condition. Consistent with our hypothesis, we found significant differences in organizational structures and processes including fewer COPD clinics (COPD 13 vs. Chronic Heart Failure 51%), performance indicators (17 vs. 70%), and home monitoring programs (51 vs. 87%).[37]

Based on our quantitative and qualitative findings, we inferred that an approach that relied on primary care to adapt or change would fail. We determined that it was necessary to utilize and reorganize existing structures and develop processes to engage those with expertise to support the delivery of care for COPD in primary care settings. We tested and demonstrated that a population approach, using pulmonary specialists with proactive, unsolicited virtual electronic consultation was effective at improving quality of life and care for patients with COPD. At the same time, VA's national pharmacy benefits management (PBM) followed an analogous approach by developing programs and incorporating clinical pharmacists in the population management of patients with COPD.

Redesigning the specialty care approach: population management to improve quality of care in COPD: We have completed two multi-site clinical trials demonstrating the effectiveness of a population-based, specialist driven proactive intervention to improve care quality and clinical outcomes among patients with COPD. Common elements of the interventions included: 1) Engaging all PCPs at VA medical centers and community based outpatient clinics (CBOCs) 2) Interrogation of VA electronic health information system to identify patient populations; 3) Pulmonary specialists' engagement to develop evidence-based COPD care recommendations (e.g., diagnostic testing, medications therapies/referrals, and follow-up care); 4) Provision of a single proactive E-consult note in the chart summarizing the clinical review and providing recommendations

timed to coincide with an upcoming PCP visit; and 5) Facilitating uptake of recommendations by entering unsigned orders for PCPs to sign, modify or discontinue.

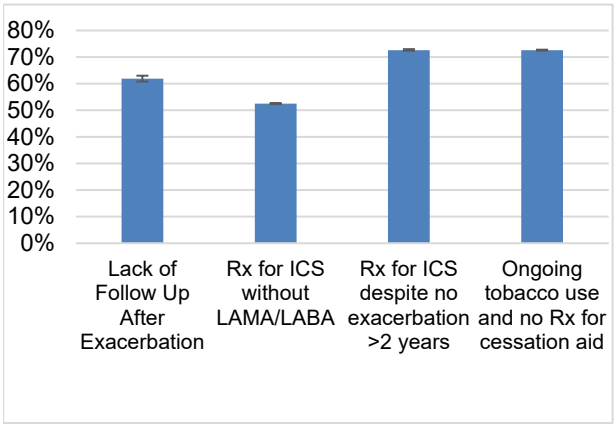
- Integrating Care After Exacerbation of COPD (InCasE) (Principal Investigator (PI):[32] We used VA's Electronic Health Record (EHR) to identify recent discharge from hospital after a COPD exacerbation. The trial included VA Puget Sound Health Care System, the Boise VAMC and their 10 CBOCs. Using a stepped-wedge design we enrolled 98% of the 372 eligible PCPs. Between 5/2015-11/2017, 352 of patients were discharged. Of the 161 patients in the intervention arm, we made a total of 892 recommendations. Of the 519 recommendations entered as unsigned orders, 401 (77.3%) were endorsed by PCPs. Recommendations focused on additional therapies (n=281), changes to medications (n=91), and additional diagnostic testing (n=147). Patients in the intervention arm experienced better quality of life (Clinical COPD Questionnaire (CCQ): adjusted difference -0.47 (95% CI, -0.88 to -0.06) , minimal important difference (MID) =0.4), and a non-statistically significant [adjusted OR 0.78 (95% CI, 0.47 to 1.31)] risk of readmission. 100% patients in the intervention arm had a pulmonary E-consult with recommendations in average 7 days (standard deviation (sd) 4.32) days after discharge. In contrast to less than 50% nationally for primary care, let alone pulmonary services (Figure 2).
- De-implementing Inhaled Steroids to Improve Care and Safety in COPD (DISCUSS COPD) (PIs: Au/Helfrich, Co-Investigators (Co-I): Feemster, Sayre, Wiener-NCT 02896257): We identified 550 patients with COPD prescribed an ICS without an identifiable indication using EHR data. Patients were seen at the VA Puget Sound Health Care System, Bedford VA Medical Center, and their 11 CBOCs. We randomized 181 PCPs to either the intervention (academic detailing to promote unlearning combined with proactive E-consult) or control groups (academic detailing alone). Of the 269 patients in the intervention arm, we made recommendations to discontinue ICS in 180 (67%) of patients. 171 had accompanying unsigned orders, of which 161 (94%) were accepted by PCPs. At six months, patients cared for by intervention providers were more than 3 times less likely to be on an ICS [adjusted OR 3.66 (95%CI, 2.50 to 5.38)]. We found no increased risk of exacerbation [adjusted OR 0.80 (95% CI, 0.44 to 1.47)] and a non-significant reduction in pneumonia [adjusted OR 0.63 (95% CI, 0.20 to 1.96)– not designed to detect effect].

Collectively, these interventions demonstrate the potential of proactive specialty care consultation. The intervention systematically overcame geospatial, referral and other access barriers while utilizing existing clinical and data infrastructure to improve care delivery and outcomes. We improved specialty care with minimal burden to PCPs, patients, or the health system (no new clinic structures or visits required).

While effective, pulmonary specialists remain a scarce resource nationwide, which has spurred interest in other staff capable of engaging in population management. Pharmacists are one such option, given their skillset in pharmacotherapy and their prevalence. There are over 20 pharmacists for each pulmonary specialist nationwide.[38,39]

In the past several years, the VA PBM has engaged pharmacists to improve management of numerous chronic conditions including COPD.[40] PBM created a national tracking dashboard to monitor progress and identify patients who may benefit from intervention, either directly with primary care based clinical pharmacy specialists or academic detailing pharmacists. Their dashboard highlights that among the 7,723 patients with COPD hospitalized each year, 60% do not have follow-up within 14 days of discharge. Among the 203,964 patients with COPD who are prescribed an ICS, 75% do not have an indication for ICS in the EHR. Finally, among the 266,319 patients nationwide with COPD and evidence of tobacco use, 70% do not receive pharmacotherapy for smoking cessation (Figure 2).

Figure 2. Widespread gaps in care delivery.



Pharmacist-led population management of COPD is feasible and extends evidence-based practices. Modeled on the population health approach for pulmonary specialists, Jennifer Gunter, PharmD led a similar approach to COPD in seven medical VA centers in Texas (Veterans Integrated Service Network (VISN)-17). Starting in February 2021, academic detailing pharmacists have conducted proactive patient reviews and made recommendations on more than 120 patients. These recommendations included comprehensive guideline-based recommendations around ICS discontinuation (88%), inhaler education (15%), spirometry (46%), tobacco cessation (28%), and vaccination (56%). Dr. Gunter's local activities mirror those of the national pharmacist-led COPD Care initiative. This initiative is active in 17 facilities nationwide and engages in the transition period after discharge from hospital after COPD exacerbations.

Although pharmacist-led management of COPD is promising, current deployment of these services is on a small scale relative to the magnitude of the problem. As confirmed by VA policy leaders, the main barrier to wider adoption is a lack of evidence around the effectiveness of pharmacist-led care relative to the default specialist physician-led option. The EQuiP trial directly addresses this question. Our non-inferiority design mirrors the approach taken previously in assessing the role of pharmacists in other conditions (e.g., antimicrobial stewardship) where pharmacist-led care is now widespread.[41]

Experience translating programs of non-physician led specialty care services to widespread national roll-out: Decision-making in specialty care has traditionally been restricted to physicians and advanced practice providers.[42] Such gatekeeping is intended to promote quality, but can limit capacity.[42,43] To challenge the specialist-only approach, we tested a system known as the referral coordination initiative (RCI) to include registered nurses in the decision-making for new specialty care referrals. Nurses and specialists collaboratively developed protocols for nurses to make initial management decisions among patients referred to sleep medicine. We found nurses in our program were able to make guideline-based decisions in a manner that exceeded that of board-certified specialists (Risks of guideline-discordant care 0.5, 95%CI 0.3-0.9).[44] Expanding the pool of decisionmakers led to marked improvement in specialists' capacity (800 additional patient visits/1000 referrals sent to RCI nurses) and timely access to care[42]. On the basis of our robust quantitative and qualitative evaluation, policy leaders in the Office to Veterans Access to Care have supported nationwide expansion. Currently, RCI is utilized at over 80% of VA facilities nationwide across multiple specialties.

5.3 Study population and research setting(s)

The VA healthcare system is the largest integrated healthcare system in the country. VA serves as an important safety net system caring for more than nine million Veterans per year. VA includes over 170 VA Medical Centers and their associated CBOCs nationwide.[45] Nearly 1.3 million Veterans have COPD, and COPD is the second leading cause of medical hospitalization within VA nationwide.[27,46] Our trial will recruit all non-trainee PCPs practicing at five VA Medical Centers and their 38 associated outpatient clinics in Washington, Oregon, Minnesota, and South Carolina. These academic and non-academic centers are geographically and clinically diverse with full and part time PCPs (294 full-time equivalent (FTE) across 495 individual providers) who together care for nearly 30,000 Veterans diagnosed with COPD. Within each PCPs' panel, we will identify patients with COPD using previously validated algorithms.[47] We propose to enroll and intervene on at least 200 PCPs and make recommendations on approximately 4,000 patients (100 PCPs, and 2,000 patients per arm). We will include specific subgroups that have been previously shown to receive lower quality services, including patients receiving care at rural facilities.

6.0 Risk/Benefit Ratio

This is a minimal risk project, which tests two ways of promoting existing evidence-based and guideline concordant usual care. The probabilities and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Anticipated risks to participants include potential invasion of privacy and/or confidentiality. To minimize this risk, we will remove identifying information from data and store data using a coded number.

Participants do not receive any direct medical benefit from their participation, as stated in our Information Statements. Potential benefits to science and society include the potential to provide a model for integrating pharmacists into population-based COPD care that, if adopted, may improve access, care quality, and well-being for Veterans living with COPD.

7.0 Objectives

7.1 Specific Aims

We are conducting a large pragmatic clustered randomized trial to Enhance Quality Safety, and Patient experience in COPD (EQuiP). Directed at PCPs (minimum n=200), we will assess if proactive, population management recommendations by clinical pharmacists and pulmonary specialists lead to non-inferior outcomes for patients with COPD.

- **Aim 1:** Examine whether quality of COPD care is non-inferior among patients with COPD who receive proactive population management performed by clinical pharmacists relative to pulmonary specialists.
    - *Hypothesis 1a:* Patients whose PCP was randomized to clinical pharmacist will have non-inferior quality of care when compared to pulmonary specialists.
    - *Hypothesis 1b:* PCPs will accept a non-inferior proportion of recommendations from clinical pharmacists compared to pulmonary specialists.
- **Aim 2**: Examine whether patient-centered outcomes are non-inferior among patients with COPD who receive proactive population management performed by clinical pharmacists relative to pulmonary specialists.
    - **Aim 2a:** Assess whether COPD-related quality of life is non-inferior among patients with COPD who receive proactive population management performed by clinical pharmacists relative to pulmonary specialists
        - *Hypothesis 2a*: Patients whose PCP was randomized to a clinical pharmacist will have non-inferior COPD-related quality of life compared to pulmonary specialists
    - **Aim 2b**: Assess whether clinical outcomes are non-inferior among patients with COPD who receive proactive population management performed by clinical pharmacists relative to pulmonary specialists
        - *Hypothesis 2b* **(PRIMARY HYPOTHESIS FOR TRIAL):** Patients whose PCP was randomized to a clinical pharmacist will have non-inferior clinical outcomes compared to pulmonary specialists.
- **Aim 3:** Examine whether patient and caregiver cost burdens are non-inferior among patients with COPD who receive proactive population management performed by clinical pharmacists relative to pulmonary specialists.
    - *Hypothesis 3:* Patients and caregivers with population health management conducted by pharmacists will incur non-inferior personal costs of care when compared to those with care conducted by pulmonary specialists.
- **Aim 4**. Examine heterogeneity of treatment effect among patients known to be at risk for lower quality services.
    - **Aim 4a:** Examine heterogeneity for the primary and secondary outcomes described in aims 1 and 2.
        - *Hypothesis 4a*: The intervention will have non-inferior effects for patients with higher degrees of complex multimorbidity, those living in rural areas, and those of different race and sex.
    - **Aim 4b:** Across both arms, assess heterogeneity in patient and caregiver incurred costs among groups known to be at high risk for access barriers and lower quality care.
        - *Hypothesis 4b:* Patient/caregiver-incurred costs will be higher for patients with greater degrees of complex multimorbidity, those living in rural areas, underrepresented minority groups, and women

- **Aim 5.** Assess qualitative perspectives across a range of stakeholders.
    - **Aim 5a**: Elicit patient, primary care, and health system leaders' perspectives on acceptability, engagement, and satisfaction through qualitative interviews.
    - **Aim 5b**: Assess patient and caregiver perspectives about their costs of care incurred through qualitative interviews.

7.2 Relevance to Veterans and the VA

The intervention is currently standard practice at sites in VISN 12 and 17. Our successful intervention will provide a model for integrating pharmacists into population-based COPD care nationwide that, if adopted, may improve access, care quality, and well-being for Veterans living with COPD.

8.0 Study and Safety Outcomes

We carefully chose outcomes based on importance to patients, caregivers, and key stakeholders. Table 1 shows a summary of measures, power, and non-inferiority thresholds. More detail is included in section 9.

Table 1. Primary and Secondary Outcomes

Aim	Name of outcome	Specific measure to be used	Source	Timing (days)	Power	Non-Inf Thresh
Aim 1a (Secondary)	Quality of COPD care	Proportion of evidence-based practices received (Table 2)	EHR/CDW	90	>0.95	5%
Aim 1b (Secondary)	Acceptance of Recommendations	Proportion of recommendations that are accepted by PCPs	EHR/CDW	90		
Aim 2a (Secondary)	COPD-related quality- of-life	Clinical COPD Questionnaire (CCQ)	Self-report	90	>0.95	0.25 pts
Aim 2b (**Primary trial outcome**)	Clinical Outcomes (composite outcome)	Proportion of COPD exacerbation, pneumonia, hospitalization, or Death	EHR/CDW	180	0.90	6%
Aim 2b (Secondary)	Clinical Outcomes (individual outcomes)	Individual outcomes COPD exacerbation, pneumonia, hospitalization, and death.	EHR/CDW	180		
Aim 3 (Secondary)	Patient costs	Patient-perspective cost burdens	EHR/CDW	180	NA	NA
Aim 4 (Secondary)	Heterogeneity of treatment effect	Compare heterogeneity for primary and secondary outcomes	EHR/CDW	180	NA	NA
Aim 5 (Secondary)	Qualitative perspective	Acceptability, engagement, satisfaction, and experience: patient, caregivers, primary care, and health system leaders	Interview	90	NA	NA

9.0 Research Design and Methods

9.1 Study Intervention

Theoretical basis of the intervention: The goal of our intervention is to improve quality of care in a way that overcomes barriers arising from clinician biases (i.e., beliefs about COPD) and clinical inertia (prioritization). The basis of the intervention is grounded on Nobel Prize winning behavioral economic principles referred to as "nudging".[57] Nudges seek to improve the quality of decision-making by changing the way that choices are presented. Nudges do not limit choices, reduce agency, or change economic incentives.[57,58] Instead, nudges use our knowledge of human decision making to make selecting the recommended choice easy. In our trial, we will alert pulmonary specialists and pharmacists to create nudges for PCPs in the form of recommendations with evidence-based explanations of next steps coupled with

unsigned orders that providers can quickly review and sign. This approach aligns with usual care processes and permits autonomy by allowing PCPs the ability to decline any recommendations they do not believe are appropriate.

9.1.1 Patient identification:

Weekly, we will run previously validated algorithms to query the CDW to identify patients with COPD within the panels of randomized providers at each site. We will prioritize patients who may benefit most from intervention as described in Section 10.2. We will identify qualifying patients each week within each arm and disseminate, via secure network folder or EHR notation, to pulmonologists and pharmacists at the participating sites.

9.1.2 Intervention delivery:

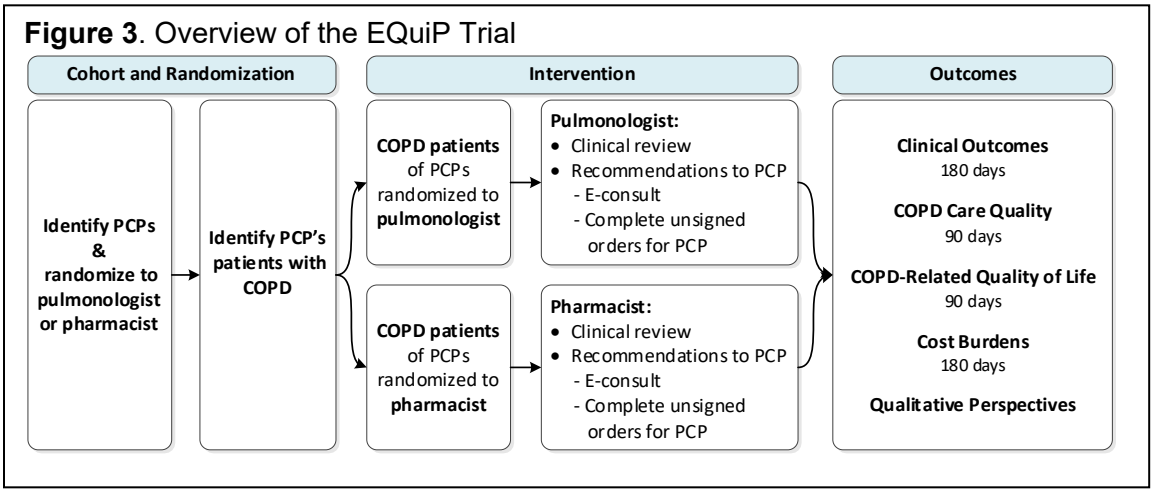
The core population health management approach will be the same between trial arms. The only difference will be whether patients are forwarded to pulmonary or pharmacy staff at each center for usual care review. Proactive recommendations around COPD quality from pulmonologists or pharmacists are part of usual care in VA (e.g., COPD cares program, DISCUSS program). As part of this process, pulmonologists and pharmacists review Veterans' relevant history and generate an E-consult detailing their rationale and recommendations. Pulmonologists and pharmacists also create orders as needed in the electronic medical record for PCPs to either endorse (sign), modify, or delete. As part of the trial, we will distribute draft guides to pulmonologists and pharmacists at each institution outlining guideline-recommended best practices, which the pulmonologists can use if they wish. All final decisions regarding care will be made by the PCP and their patients as part of usual care. We will monitor orders placed by the pharmacists and pulmonologists and follow-up with them for greater education around order placement as appropriate.

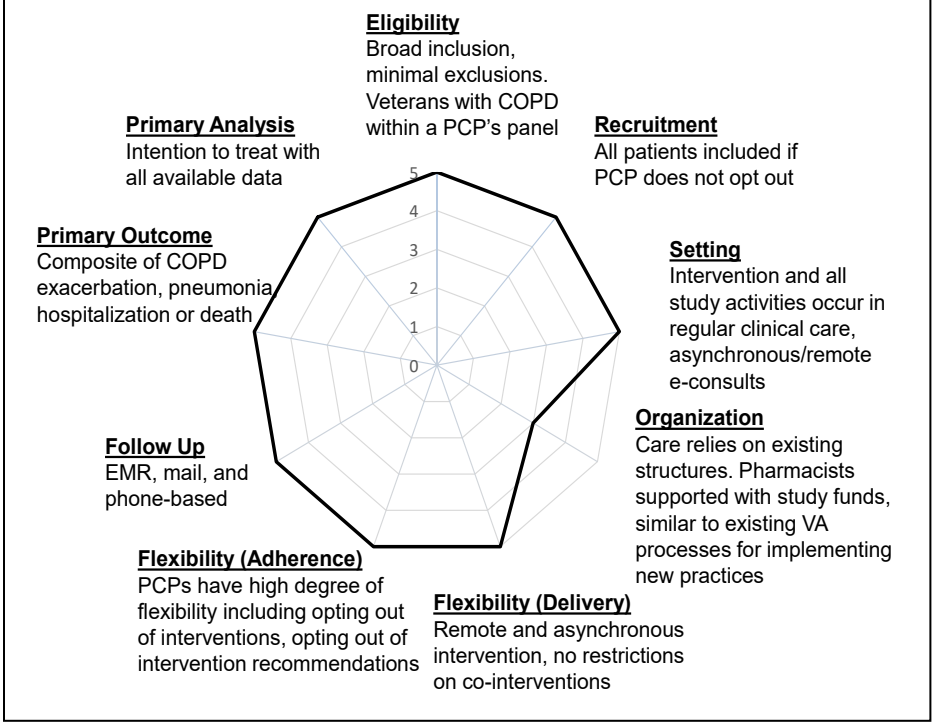
9.1.3 Intervention fidelity:

Fidelity refers to the degree to which an intervention is delivered as intended. Consistent with Thorpe's recommendations for maximizing external validity of pragmatic trials,[59] we will monitor fidelity but will not artificially control it. We will use a fidelity rubric based on intervention templates and procedures finalized during the kickoff meetings, with revisions as necessary based on regular meetings as described above. Every six months, study staff will review at least 5% of intervention E-consults in each arm and compare documented care against the fidelity rubric.

9.2 Study Design

Our goal is to test the non-inferiority of pharmacist-led relative to pulmonary specialist-led population management to improve meaningful and patient-centered outcomes in COPD. We will conduct a two-arm clustered randomized trial with PCPs being the unit of randomization and patients clustered within providers. We chose cluster randomization as the intervention is focused on providers. We considered individual-level randomization, but we chose against this approach out of concerns for contamination.[48] We will use the VA EHR to systematically identify patients who may benefit from the intervention. The trial will alert pharmacists or pulmonary specialists to provide usual care clinical reviews and any resulting recommendations to PCPs through E-consult. Consistent with usual care, they will facilitate adoption by preparing unsigned orders for PCPs, in consultation with their patients, to accept, modify, or discontinue as appropriate. Figure 3 shows the trial flow.

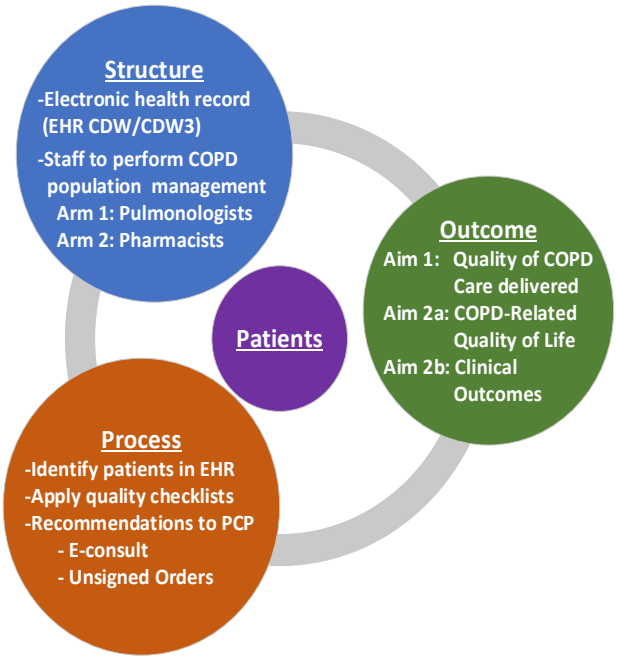




Rationale for proposed design and methods: To align with the major knowledge gaps around population health management in COPD, we will compare pulmonary and pharmacist-led management in real-world settings. We designed this trial to align with principles of pragmatic trials, applying the Pragmatic Explanatory Continuum Indicator Summaries (PRECIS-2) Wheel to assess its pragmatic nature.[49] While emphasizing data quality, EQuiP scores 43 out of 45, indicating a highly pragmatic trial (Figure 4). **Research addresses major public health issue of clinical importance:** Over 1.3 million Veterans have COPD.[27] While evidence-based practices exist for COPD that can substantially improve patient-centered outcomes, Veterans frequently receive care that is not evidence-based.[6-10,27,50-54] **Design should be scientifically rigorous and practically feasible:** EQuiP preserves internal validity through PCP randomization and maximizes external validity by testing an intervention capable of dissemination in a remote and asynchronous manner. **Participants are representative of everyday patients:** Broad eligibility criteria with minimum exclusions will facilitate inclusion of representative PCPs and patients. **Intervention should be suitable for real-world implementation:** The population health interventions tested in this trial leverage clinical information systems and trained personnel (e.g., pulmonary specialists and clinical pharmacists) who are available across the VA. Similar systems led by pulmonologists and clinical pharmacists are already ongoing in facilities across the enterprise. Results from this trial will inform choices around wider expansion. **Outcomes should be clinically meaningful:** Our outcomes are highly relevant to patients (CCQ, clinical outcomes, quality of care) and payor/health system (clinical outcomes, quality of care, health system efficiency and value).

Conceptual framework: Broadly, we conceptualized a Donabedian framework when considering how to have patients experience high quality outcomes[36] (Figure 5). Structure refers to the physical facilities, human resources, and organization of a healthcare system and its personnel. Our interventions are structural in nature, as they adapt the roles and activities of pulmonologists and pharmacists. Importantly for adoption, we are reorganizing existing, rather than creating new data infrastructure and staff. Process refers to the care delivered by a healthcare system. We have changed the processes of care using a population-based model along with proactive e-consults and facilitation/nudging to promote adoption. We will track the delivery of evidence-based care for COPD, and the avoidance of care that is not evidence based. Outcomes refer to quality of care and patient-centered outcomes (e.g., symptoms, quality of life, mortality) achieved as a result of care delivery.

Figure 5. Donabedian model of quality (SCI-2, SCI-5)



9.3 Study Procedures

9.3.1 Providers:

As described in Section 11.1, we will consider a provider consented after one week from sending the invitation if they have not opted out. For providers who opt-out, we will not make further contact.

9.3.2 Patients:

Surveys: As described in Section 11.2.1, we will consider patients consented if they choose to complete the outcome and demographic survey (section 9.5.1).

Qualitative Interviews: Patients who complete the surveys and indicate on the interview opt in/opt out sheet that they are interested in participating in the interview are considered consented for interviews.

9.3.3 Caregivers:

Qualitative Interviews: We will interview Caregivers who agree to participate under a Waiver of Documentation of Informed Consent. We consider Caregiver consented upon agreeing to participate in the interview.

9.3.4 VA Leadership, pulmonary and pharmacist interventionists:

Qualitative Interviews: We will interview VA leaders as well as pulmonologists and pharmacists who provided treatment recommendations to PCPs at study sites. These interviewees will agree to participate under a Waiver of Documentation of Informed Consent. We consider these leaders consented upon agreeing to participate in the interview.

9.4 Randomization

Among PCPs who do not opt out, we will randomize them 1:1 to pulmonologist-led or pharmacist-led population health management within strata using block sizes of 4. We will stratify randomization by site and clinician type (physician or APP) for 4 total strata. Stratification is intended to avoid potential maldistribution of confounding factors potentially associated with readiness to accept intervention recommendations and quality of care[56] (e.g., severity of patient illness).

Given the nature of primary care staffing, we expect there to be turnover in PCPs. We will repeat recruitment and randomization efforts every month at each site among new providers.

Patient participants are not randomized; their PCPs are the unit of randomization.

9.5 Study Evaluation

We carefully chose outcomes based on importance to patients, caregivers, and key stakeholders. Table 1 in Section 8 shows a summary of measures, power, and non-inferiority thresholds.

We will collect study outcomes as follows:

9.5.1 Self-reported patient questionnaires:

CCQ: We will measure patient symptoms using the well-validated CCQ. The CCQ assesses symptoms, functional status, and COPD control and has been used widely in the setting of clinical trials to discriminate across a range of COPD severity. The CCQ possesses strong internal consistency (Cronbach's alpha 0.91), stability (test-retest, r = 0.94), convergent and divergent validity.[60-62] The CCQ also is highly responsive to change, with improvements detected in healthy smokers just two months after smoking cessation.[62] The CCQ includes 10 items encompassing three domains (symptoms, functional state, and mental state). Response options range from "never" to "almost all the time" and are scored from 0-to-6. The total score is calculated by the addition of each item divided by the total number of items, producing a range of scores between 0-6 with a minimally important difference (MID) of 0.39 and a standard error of 0.21. The instrument has been administered by telephone in previous studies.[63] We estimate the time to complete will be approximately 5 minutes. We will ask patients to complete the survey by the methods described in Section 9.3.2.

Costs: We will measure caregiver involvement using a locally developed survey.

9.5.2 EHR abstraction/CDW:

Aim 1 (*quality of COPD care; proportion of evidence-based practices):*

Study staff will abstract pertinent information from the EHR using an appropriate application such as Joint Legacy Viewer (JLV). We will integrate data queried from the CDW with this abstracted data. We will measure quality of COPD care based on the presence or absence of key evidence-based practices listed in Table 2.[4,5,64,65] These evidence-based practices are supported by current guidelines,[4,5,64-66] and we will adapt this list as guidelines are updated. For each patient, we will calculate the proportion of evidence-based practices that are performed. The denominator will be the number of evidence-based practices that apply to a particular patient. The numerator will be the number of those practices received. We will also assess the proportion of recommendations made by pulmonary specialists and pharmacists that are signed by primary care. As additional secondary outcomes, we will assess the proportion of evidence-based practices delivered that are general vs. COPD-specific and pharmacologic vs. non-pharmacologic in nature.

Table 2: Key evidence-based practices used to define quality of COPD care

Evidence-based practice	Eligible COPD patients
1. Completion of spirometry-C,NP	All
2. Assessment of smoking status-G , NP	All
3. Influenza vaccination during appropriate season-G, P	All
4. Pneumococcal vaccination-G, P (PSV23, PCV-13)	All
5. COVID-19 vaccination – G, P	All
6. Assessment of resting O_2 saturation or PaO_2, C,NP	All
7. Assessment of respiratory symptoms burden-C, NP	All
8. At least one long-acting bronchodilator (LABA, LAMA) as first-line therapy- C, P	Symptomatic
9. Referral/counseling for smoking cessation G,NP	Active smoker at index
10. Prescription of smoking cessation aide –G, P	Active smoker at index
11. Continuation or escalation of smoking cessation medications- G, P	Active smoker at index – received cessation medication in past 12 months
12.Addition of at least one controller agent (e.g., ICS) to first-line therapy –C, P	Prior severe or frequent exacerbations in past 12 months
13. Discontinuation of ICS-C, P	No frequent or severe exacerbations past 12 months and no asthma diagnosis
14. Discontinuation/tapering of COPD treatment –C, P	Patients without evidence of COPD
15. Provision of O_2 for long-term continuous therapy-C, NP	Resting $SpO_2 \leq 88\%$ or $PaO_2 \leq 55$mhg
16. Offer/referral to pulmonary rehabilitation program-C, NP	Dyspnea or severe exacerbation in past 12 months
Legend: C-Metric applies to COPD-specific care quality. G-Metric of General Care Quality; P-Pharmacologic Management; NP-Non-Pharmacologic Management	

Aim 2b (*composite endpoint of COPD exacerbation, hospitalization, pneumonia, or death)*: We will manually abstract from the electronic health record and query the CDW using validated algorithms to identify these outcomes in the 180 days following intervention consultation.[33,67] These clinical outcomes are important because high quality care has been demonstrated to modify these events.[4,5,64-66] While each component outcome is important on its own, we will use a composite outcome to address issues of competing risks and minimize misclassification.[68] For instance, pneumonia and COPD exacerbation are often clinically difficult to distinguish and may lead to misclassification.

Aim 3 (*patient costs*)
We will capture patient-perspective cost burdens for care that may be provided as a result of the intervention (Table 2). We will prioritize EHR data where possible to maximize generalizability in this pragmatic trial. Given the role of the intervention in preventing downstream events of hospitalizations, COPD exacerbations, and pneumonia, we also will capture costs related to those events (Table 3,4). Cost-related burdens of care include transportation (e.g., gas/vehicle depreciation), copays for visits and medications, and opportunity costs for time spent on care.[69-71] We will inform these cost estimates by integrating data from chart reviews, and electronic medical record data from VA's corporate data warehouse (CDW, Table 3).

Table 3. Components of Patient-incurred Cost Calculation		
Cost Element	**Source**	**Description**
Transportation costs	CDW	• Drive distance derived from Veterans' home address and site of care for in-person encounters multiplied by standard mileage rates.[72]
Co-pays	CDW	• Veteran's assigned co-payment tier multiplied by number of visits and prescriptions[73]
Opportunity Costs		
1)Drive time	CDW	• Drive time for patients' travel to each in-person encounter.
2)Outpatient visit time (virtual or in-person)	CDW/ NAMCS /ATUS	• Encounter Duration: Average NAMCS/NHAMCS visit duration for billing code, location (primary care vs. ER)[74] • Waiting room: (In-person only) using ATUS estimates[75]
3)Hospitalizations	CDW	• Total duration based on admit and discharge time
4)Caregiver involvement	Survey	• Patient-reported caregiver presence for: in-person encounters, virtual encounter, hospitalizations
Opportunity Costs	All	• Cumulative patient/caregiver time multiplied by average hourly wage for age/sex[69,71]
CDW-Corporate Data Warehouse; NAMCS-National Ambulatory Medical Care Survey; NHAMCS- National Hospital Ambulatory Medical Care Survey; ATUS-American Time Use Survey; ER-Emergency room		

Aim 4 (*heterogeneity in treatment effect)*: we will compare heterogeneity in treatment effect for the primary and secondary outcomes. We will assess effect modification between treatment arm and patient characteristics thought to potentially impair access to treatment and delivery of high-quality care. Specifically, we will assess effect modification with 1) complex multimorbidity, 2) those living in urban and rural areas, and those of different 3) race and 4) sex.[33,76,77] We will conduct additional analyses to assess associations between patient, provider, and health system characteristics and processes with care delivery and patient outcomes. For patient-incurred costs, we will pool data from both arms and assess differences in costs according to these four characteristics of interest.

Table 4. Evidence Based Practice for review	**Anticipated direct patient costs**
1. Confirmation of COPD by spirometry	Time, transportation costs, co-pay
2. Influenza vaccination during appropriate season	Time, transportation costs,
3. Pneumococcal and COVID-19 vaccination	Time, transportation costs,
4. Assessment of resting oxygen saturation	Time, transportation costs, co-pay
5. Assessment of smoking status and respiratory symptom burden	Time, transportation costs, co-pay
6. Use of at least one long-acting bronchodilator as first-line therapy if symptomatic	Medication co-pay
7. Appropriate smoking cessation therapy	Medication co-pay
8. Appropriate prescribing of medications to prevent exacerbations	Medication co-pay
9. Discontinuation of inhaled corticosteroid when not appropriate	Absence of co-pay
10. Appropriate supplemental oxygen prescribing	Time, transportation costs, co-pay
11. Appropriate pulmonary rehabilitation referrals	Time, transportation costs, co-pay

9.5.3 Qualitative interviews (Aim 5: qualitative perspectives):

We will assess experiences with the intervention among patients, PCPs, and health system leaders, and perspectives on acceptability, engagement, and satisfaction. Consistent with a Donabedian model of quality[36], our interviews will also address perspectives related to structures, processes, and outcomes of care. We will assess perspectives around incurred costs among patients and their caregivers. We will audio record and transcribe the interviews using VA Microsoft teams under a waiver of documentation of informed consent. Study staff will verify the transcriptions. Interviews will focus on interviewee's perceptions of COPD population management in the EQuiP trial. We will specifically address the intervention's perceived acceptability, feasibility, and sustainability, as well as perceptions around engagement and communication with the program (e.g., PCPs engagement with pulmonary specialists /pharmacists, patients' engagement with PCPs). Consistent with the Donabedian model of quality,[36] we will address perceived positive and negative impacts on care processes/workflows and patient outcomes. We will revise interview guides iteratively based on data collected and to address any participant comprehension or clarity issues that arise.

Veteran Patients: We will conduct an interview for a subset of patients soon after they complete the CCQ. We will invite patients with diverse demographic and regional characteristics, and baseline levels of quality of care. The interview may be about their experiences with the EQuiP intervention or about their incurred costs. For the former, we will interview about 40 participants (aiming for 20 in each arm), or until saturation is reached. For the cost perspective, we will interview about 30 patients (15 in each arm), or until saturation is reached.

Caregivers: Among patients who participate in an interview and indicate they received support from a family member, friend, or other caregiver for their COPD care, we will invite the caregiver to participate in an interview. The interview will help evaluate costs of COPD care at the VA and how those costs may shape care decisions. We will interview about 20 caregivers, or until saturation is reached.

PCPs: We will invite about 40 PCPs (aiming for 20 in each arm), or until saturation is reached, to participate in interviews. We will invite providers from urban and rural facilities, physicians and APPs, and those practicing in CBOCs as well as medical centers. We may use email or Teams to arrange the

interview time. After the interview, we may follow up for minor clarifications via encrypted email or Teams.

Local Leadership, Pulmonologists, and Pharmacists: We will aim to interview about 10-15 site leaders, or until saturation is reached, in the fields of primary care, pharmacy, and pulmonary medicine. We will also include additional pharmacists and pulmonologists (n=5-15) who also deliver intervention recommendations to PCPs. We may use email or Teams to arrange the interview time. After the interview, we may follow up for minor clarifications via encrypted email or Teams.

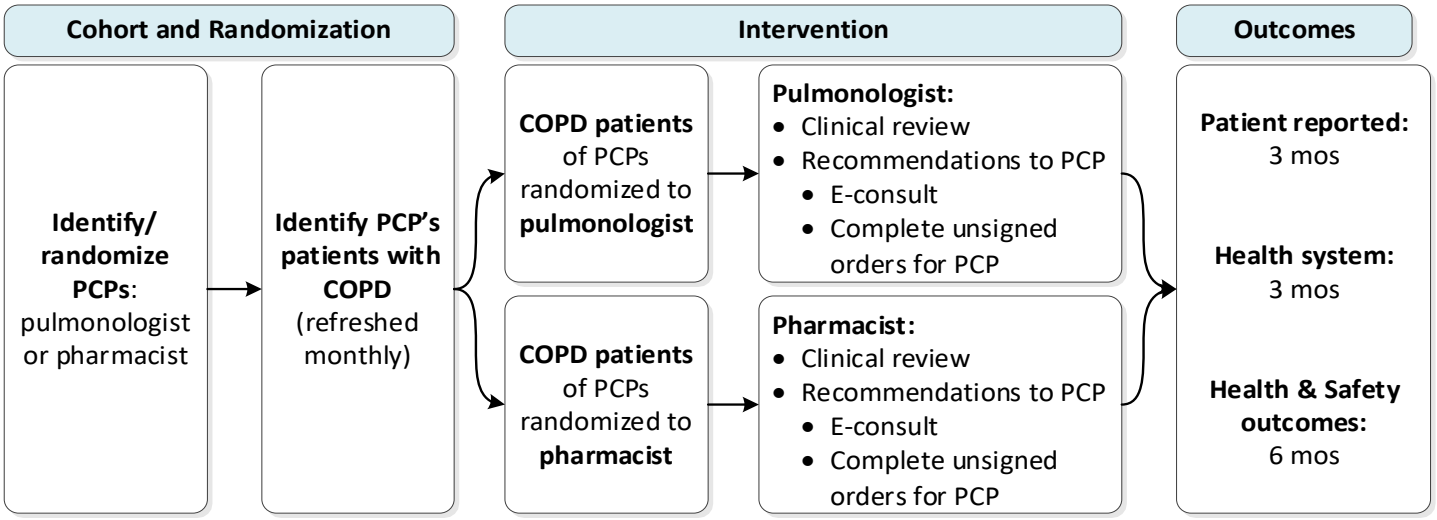
9.5.4 COVID-19 considerations:

Given the remote nature of the intervention and outcome collection, we do not anticipate difficulty in conducting our trial despite evolving health system responses to the COVID-19 pandemic.

9.5.5 Payments:

The Seattle Institute for Biomedical and Clinical Research (SIBCR) will compensate patient participants $25 after completing the one-time survey, and another $25 to patients and patient caregivers who participate in the one-time qualitative interview. SIBCR will have access to participant names and addresses for the purpose of mailing payment in the form of a check or gift card. Envelopes containing payment will not have study identifiers on the exterior. We will not compensate providers or healthcare leadership for their participation.

9.6 Study Duration



9.7 Data and/or Specimen Use

As outlined in section 8.0, data is collected from EHR/CDW, self-report, chart abstraction and interview.

Data sources:

- VA Internal Data (eg. CAPRI, CDW, VINCI, JLV, MVP, CPRS, etc...)
- Research Subject (Questionnaires, Surveys, Interview, Audio/Recordings, Wearable Technologies, Biospecimens, Radiological Imaging, etc...)
- VHA Support Services Center (VSSC)

Data collection methods are listed below. See section 9.5 for specific procedures used to collect data.

Data collection methods:

- Audio recordings
- Chart Reviews
- Interviews
- Questionnaires (paper/electronic)
- MS Teams
- Download data from CDW and VSSC

Information sharing:
IRB approved staff at participating VA sites will have access to study data as needed to complete study. IRB approved staff at each participating VA sites (VA Puget Sound HCS; Mann-Grandstaff VAMC; Ralph H. Johnson HCS; Portland HCS; Minneapolis HCS; Central Texas VHCS, Eastern Colorado VHCS) will be able to access data stored on VA Puget Sound servers (described previously); data will stay on VA Puget Sound servers, and not moved to the other VA sites.

Storage:
Facility Name: Seattle, WA - Puget Sound Health Care System
Building: Seattle VAMC,
Building 101, 4th floor
Room Number: locked file room 4W75
Secured Information:
4th floor is a locked floor accessible to authorized personnel via PIV, fileroom 4W75 is a locked fileroom accessible by authorized personnel only and within the fileroom, hard copies are stored in a locked file cabinet.
Electronic VA File Location(s):
VA Network
VA REDCap
HSR&D SQL server OITPUGSQLRES019.va.gov\HSRDSQLSERVER;
VINCI servers: vhacdwrb02.vha.med.va.gov; local study drive \r01pughsm03.r01.med.va.gov\research\Projects\Donovan_EQuiP_IRBN1682961
Electronic File Storage Details:
Electronic questionnaire responses will be stored initially on TLS 1.1, TLS 1.3 encrypted Qualtrics servers: https://vhaordfedramp.gov1.qualtrics.com or VAREDCap server (https://varedcap.rcp.vaec.va.gov/redcap/); data is then ingested and stored on HSR&D SQLserver OITPUGSQLRES019.va.gov\HSRDSQLSERVER; VINCI servers vhacdwrb02.vha.med.va.gov; local study drive \r01pughsm03.r01.med.va.gov\research\Projects\Donovan_EQuiP_IRBN1682961

Website/Cloud-Based Software:
Name: VA REDCap **URL:** https://varedcap.rcp.vaec.va.gov/redcap/index.php
Website Owner Type: VA Non-VA
Purpose:
Provider recruitment: We will attempt to invite all eligible providers via email. Under a Waiver of Documentation of Informed Consent, we will use REDCap or Qualtrics to send an introductory email including a study description, Information Statement, study contact information for those who have questions, instructions on how to opt out, and a survey with demographics questions.

Patient recruitment: For patients that have an email address in CDW, we will send an email with link to a secure online platform (ie Qualtrics or REDcap). The link will show a study flyer, invitation letter, Information Statement, and surveys.
Name: VA Qualtrics **URL:** https://
vhaordfedramp.gov1.qualtrics.com/
Website Owner Type: VA Non-VA
Purpose:
Provider recruitment: We will attempt to invite all eligible providers via email. Under a Waiver of Documentation of Informed Consent, we will use REDCap or Qualtrics to send an introductory email including a study description, Information Statement, study contact information for those who have questions, instructions on how to opt out, and a survey with demographics questions.
Patient recruitment: For patients that have an email address in CDW, we will send an email with link to a secure online platform (ie Qualtrics or REDcap). The link will show a study flyer, invitation letter, Information Statement, and surveys.
Name: VINCI **URL:** https://sps.vinci.med.va.gov:28001/
projects/CorrespondenceSite/
- 4 - Generated on IRBNet
Donovan_202207055D/SitePages/
Home.aspx
Website Owner Type: VA Non-VA
Purpose:
VINCI services: Communicate with the VINCI team to coordinate data pulls to the study VINCI database.

Study data will be coded with a unique study ID. See section 17.1.

9.8 Data and/or Specimen Banking

Not applicable.

10.0 Study Population

10.1 General Characteristics

As described in section 5.3, our trial will recruit all non-trainee PCPs practicing at five VA Medical Centers and their 38 associated outpatient clinics in Washington, Oregon, Minnesota, and South Carolina. These academic and non-academic centers are geographically and clinically diverse with full and part time PCPs (294 full-time equivalent (FTE) across 495 individual providers) who together care for nearly 30,000 Veterans diagnosed with COPD. Within each PCPs' panel, we will identify patients with COPD using previously validated algorithms.[47] We propose to enroll and intervene on at least 200 PCPs and make recommendations on approximately 4,000 patients (100 PCPs and 2,000 patients per arm). We will include specific subgroups that have been previously shown to receive lower quality services, including patients receiving care at rural facilities.

10.2 Inclusion and Exclusion Criteria

Participants may be PCP physicians and advance practice providers (APP) practicing at participating sites, and their patients who are diagnosed with or treated for COPD based on the following criteria:

1) Recent discharge from hospital for COPD exacerbation

2) Recent outpatient exacerbation (emergency room (ER), primary care)

3) Received prescription for an ICS but does not meet criteria for ICS use

4) Diagnosis of COPD and/or treatment and active smoker not receiving smoking cessation aide

5) Treatment for or diagnosis of COPD without evidence of spirometry within 10 years, or no airflow obstruction on existing spirometry

We may identify up to 2500 PCPs to approach for enrollment. For patients, we will access up to 450,000 patient records and enroll up to 25,000 individuals.

For patients who indicate they receive support for their COPD care by a family member, friend, or other caregiver, we may invite their support person to participate in an interview. We are examining personal costs of care; therefore, will exclude caregiving paid for by the VA or other healthcare organization.

10.3 Populations Requiring Additional Considerations

Not applicable.

11.0 Recruitment Methods

Before we begin recruitment, we will refine the algorithms that we will apply to the Corporate Data Warehouse (CDW)/ Veterans Support Service Center (VSSC) data to identify potentially eligible participants and verify with chart review using approved platforms such as Joint Legacy Viewer.

11.1 Providers:

Information Sharing Before the Intervention: A few months prior to trial launch, we will work with primary care leadership to provide information to PCPs at each site. We will hold tele/videoconference-based information sessions with the opportunity for question and answer for PCPs at each site. We will provide a brief overview of the study's rationale, previous trials, and overall approach. We will review the overall COPD quality of care and how the trial is intended to improve and measure changes in our outcomes.

Approaching providers: Using validated algorithms, we will obtain names and contact information for PCP physicians and APPs at participating sites via the CDW/ VSSC [55]. We will not approach trainee providers (e.g., residents) given frequent turnover. Using VA Research Electronic Data Capture (REDCap) or Qualtrics, we will attempt to invite all eligible providers via email. Under a Waiver of Documentation of Informed Consent, we will use REDCap or Qualtrics to send an introductory email including a study description, Information Statement, study contact information for those who have questions, instructions on how to opt out, and a survey with demographics questions. We will consider them enrolled in the study if they do not respond within one week (default opt-in), and that they may withdraw at any time without penalty.

Providers hired after trial launch: Every month, we will identify any new PCPs operating at any of the study sites. Similar to our initial recruitment strategy, we will use REDCap to email these new PCPs an information sheet and provide them with instructions about how to opt out if desired.

11.2 Patients:

11.2.1 Surveys: Providers are the target of the intervention. We will engage patients only at the time of CCQ administration, described in section 9.5.1. Potential patient participants are Veterans diagnosed with or treated for COPD whose PCP is a randomized provider in this trial. Using a Waiver of Documentation of Informed Consent, we will approach patients for survey completion as follows:

11.2.2 *Mail*: Around 90 days after the intervention, we will mail the CCQ, a brief patient cost survey, a brief sociodemographic survey, and an interview opt in/out sheet. The mailing will include a flyer, letter informing them that their provider is taking part in the study, and an Information Statement providing more detail. The letter will invite them to indicate interest by completing one of the following:

- return a postcard requesting to receive a telephone call with a research coordinator to learn more about the study
- return an opt-out card to avoid further contact
- participate (i.e., consent) by completing and returning the outcomes and sociodemographic surveys using a self-addressed stamped envelope.

11.2.3 *Electronic/Online (see Section 17.2)*: For patients that have an email address in CDW, we will send an email with link to a secure online platform (ie Qualtrics or REDcap). The link will show a study flyer, invitation letter, Information Statement, and surveys. To emulate paper surveys, the online version will prompt participates to respond to questions if they accidently left them blank and will direct participants to the next action. Other slight modifications (e.g., bolded fonts, transition pages, and sub-headers) will facilitate the online interface. The electronic survey link can be re-sent via email or text at the request of the participant.

11.2.4 Telephone: For those who do not respond to the above or indicate that they want to speak with study staff, we will administer the surveys over the telephone if the participant prefers. We also will ask if we may contact them soon about participating in a telephone interview to learn their opinions about the study.

For those who do not respond after one week, we will follow up by mail, email, text, and/or telephone call.

11.3 Caregivers:

For patients who participate in an interview (see section 9.5.3) and indicate a family member, friend, or other caregiver provides support for their COPD care, we will ask the patient at the conclusion of the interview if their caregiver might be interested in participating in a similar interview. If yes, we will ask for the caregiver's contact information so that we may mail an invitation containing a letter informing them that the patient is taking part in the study, an Information Statement providing more detail, and an opt-in/out card. The letter will invite them to indicate interest by completing one of the following:

- return the postcard requesting to receive a telephone call with research staff to learn more about the interview
- return an opt-out card to avoid further contact.

For those who do not respond after one week, we may follow up by mail and/or telephone call to review the Information Statement and assess interest.

11.4 VA Leadership including Pharmacists and Pulmonologists:

We will identify local leaders including service line leaders, clinic leaders, and section chiefs for primary care, pharmacy, and pulmonary medicine at EQuiP sites as well as interventionists-pulmonologists and pharmacists who provided treatment recommendations to PCPs at EQuiP sites. We will send an email asking them to share their perspective on the EQuiP intervention. The email will include a study description, Information Statement, study contact information for those who have questions, and instructions on how to opt out.

For those who do not respond after a few days, we may follow up by email, Teams and/or telephone call to review the Information Statement and assess interest.

12 Enrollment Procedures

Enrollment for all participants will be done through the Seattle VA site.

12.2 Screening

Not applicable.

12.3 Informed Consent Process and Documentation

12.3.1 Providers:
As described in Section 11.1, we will consider a provider consented after one week from sending the invitation if they have not opted out. For providers who opt-out, we will not make further contact.

12.3.2 Patients:
Surveys: As described in Section 11.2.1, we will consider patients consented if they choose to complete the outcome and demographic survey (section 9.5.1).

Qualitative Interviews: Patients who complete the surveys and indicate on the interview opt in/opt out sheet that they are interested in participating in the interview are considered consented for interviews.

12.3.3 Caregivers:
Qualitative Interviews: We will interview Caregivers who agree to participate under a Waiver of Documentation of Informed Consent. We consider Caregiver consented upon agreeing to participate in the interview.

12.3.4 VA Leadership, pulmonary and pharmacist interventionists:
Qualitative Interviews: We will interview VA leaders as well as pulmonologists and pharmacists who provided treatment recommendations to PCPs at study sites. These interviewees will agree to participate under a Waiver of Documentation of Informed Consent. We consider these leaders consented upon agreeing to participate in the interview.

13 Participant Payment

The Seattle Institute for Biomedical and Clinical Research (SIBCR) will compensate patient participants $25 after completing the one-time survey, and another $25 to patients and patient caregivers who participate in the one-time qualitative interview. SIBCR will have access to participant names and addresses for the purpose of mailing payment in the form of a check or gift

card. Envelopes containing payment will not have study identifiers on the exterior. We will not compensate providers or healthcare leadership for their participation.

14 Withdrawal of Participants

We do not anticipate a need to withdraw providers from the research. For most patients, participation is a one-time event based on their completion of the CCQ. We will invite a small subset of patient participants who complete the survey to take part in a qualitative interview, which they may refuse. If an enrolled provider informs the research team they no longer wish to participate, we will not include them in future intervention activities, nor invite them to participate in a qualitative interview.

15 Sharing of Results

At the end of the project after analysis is complete, we may send a summary of results to participants via email or mail.

16 Data Safety, Monitoring and Reporting

16.1 Quality Monitoring

The PIs will be primarily responsible for data safety and monitoring and will work closely with the project manager to audit data collection for completeness and accuracy.

16.2 Data Safety and Monitoring Board (DSMB):

We will assemble an external DSMB consisting of a Chair, Executive Secretary, and a member with expertise in biostatistics, epidemiology, and clinical trials. DSMB will meet every six months or as needed. At the first meeting the DSMB will approve the charter and research protocol. At subsequent meetings the DSMB will review adverse event data, other safety data, quality and completeness of study data, and enrollment data to ensure proper trial conduct.

The DSMB will provide objective recommendations, as appropriate, with respect to:

- Determination of any actions to be taken in response to adverse events
- Reports related to study operations and the quality of the data
- Consideration of early termination of the study because of treatment safety concerns or inadequate performance
- Modifications in the study protocol concerning recruitment, participant retention, data quality, outcome assessment, statistical analysis, or general trial operations

16.3 Adverse Event Monitoring:

To ensure unbiased determination across treatment arms, VA Puget Sound staff will query the EHR at least 180 days after treatment recommendations were provided to systematically identify SAEs and UPs that occurred within 180 days as part of a hospitalization. Designated study investigators will review potential AEs for expectedness, seriousness, and relatedness. We will report events to the IRB and DSMB as required by IRB/DSMB policy.

The following are expected adverse events in the EQuiP population of participants who have COPD:

- COPD exacerbation lower respiratory event
- Worsening of COPD (worsening of lung function, development of severe resting hypoxemia, death from COPD)
- Side effects of spirometry/albuterol: Fainting, dizziness; throat irritation, palpitations, nervousness, shakiness, stomach upset, headache, dizziness, weakness, sweating, chest pain

- Development of other conditions associated with unhealthy health behaviors, such as from tobacco and alcohol disorders, (e.g., cancer, CVD); Cancers related to smoking or alcohol are expected, e.g. lung, oral pharyngeal, breast, colon
- Age related illnesses, such as pneumonia, urinary tract, and skin infections
- Known side effects from recommended pharmacologic and non-pharmacologic treatments (e.g. ICS- thrush, pneumonia, pulmonary rehabilitation – musculoskeletal injuries)
- Death from any of the expected causes listed above
- Exacerbation of any pre-existing condition

Upon discovering an unexpected, serious, and possibly related SAE, we will provide the IRB and DSMB a report describing the duration (start and stop dates and times), severity, outcome, treatment, and relation to study activity, according to the required timelines. The DSMB may request additional information if it deems additional deliberation is warranted.

For all other events, staff will summarize and report to the DSMB on a semi-annual basis the numbers and types of all AEs by unidentified treatment arms. At their discretion, the DSMB may request unblinded results to determine the nature and extent of effect of the intervention. Should the DSMB make this request, we will maintain blinding of the investigators and the staff involved in follow-up data collection and analysis. If, at any time, the investigators believe they are seeing an unexpected increase in SAEs that is a cause of concern, they will bring this to the attention of the DSMB. This systematic, non-biased monitoring process will ensure that any group disparities will be effectively addressed.

We will provide DSMB report to the IRB at annual review.

17 Privacy and Confidentiality

We will collect the following protected health information (PHI) from patient participants: name; dates of birth, death, and health care utilization; social security number; street address, and medical record number. We will collect providers names, email addresses, dates of VA employments, and provider class.

17.1 Data protection

We will employ the following procedure to ensure privacy, confidentiality, and data protection:

- Obtain identifiable information only as approved by the IRB
- Process and store data only in the designated VA Informatics and Computing Infrastructure (VINCI) workspace, and on secure password protected and permission-specific VA network server(s) located at the VA Puget Sound Health Care System - Seattle VAMC. Using this network, we will employ the following:
  - Data entry systems will employ automatic, real-time range, logic, and missing value checks
  - Employ double data entry and logic controls to minimize data entry error
  - Maintain one official copy of all the study data and a master data dictionary
- For online surveys,
  - Initial electronic questionnaire responses will be stored on TLS 1.1, TLS 1.3 encrypted Qualtrics servers: https://vhaordfedramp.gov1.qualtrics.com or on the VA REDCap server (https://varedcap.rcp.vaec.va.gov/), hosted on the VA Enterprise Cloud (VAEC)
  - Response data will be downloaded from online servers and stored on \r01pughsm03.r01.med.va.gov\Research\Projects\
  - Response data is then ingested and stored on HSR&D SQL server: OITPUGSQLRES019.va.gov\HSRDSQLSERVER
- For qualitative interviews:
  - Record via VA Microsoft Teams
  - Transcribe recording via VA Microsoft Teams and verify/update manually

    - Save recordings and transcriptions only on HSR&D secure servers
- Identify participants and obtain data for research purposes only
- Use a unique study ID for study data
- Store the file linking the study ID and participant identifiers separately from the study data
- Restrict access to IRB approved staff on a need-to-know basis.
- Store paper copies in a secure office suite in locked files accessible by approved study staff only, or archived and retrievable through R&D service at the National Archives
- Ensure all staff receive and remain current on the following training: Human Subjects and Good Clinical practice; Privacy and HIPAA; VA Privacy, Information Security, and Rule of Behavior
- Notify the Information Security Officer (ISO) and Privacy Officer (PO) about improper use within required timeline
- Follow all local and national VA data security policies

17.2 Online surveys

We will recruit patients and offer the option of responding to questionnaires online via a web-based survey platform licensed by VHA ORD (such as REDCap). The loss of privacy with online surveys is no greater than the risk of responding to questionnaires on paper and by mail. As part of the informed consent decision-making process, we will describe the process of responding to online questionnaires. A limited amount of contact information is stored on the Qualtrics or REDCap platform to allow distribution of unique anonymized survey links. Information is transmitted to Qualtrics or REDCap via secure, encrypted, web-based portal.

We will send survey links to participants via unencrypted email or text message. The message will not specifically mention the EQuiP study or contain PHI. Incoming emails or text messages may either be bounced back to the sender as nondelivered, or an automatic response may contain an out-of-office and unmonitored message. We will confirm telephone number and supported carriers (e.g., T-Mobile, Verizon, AT&T, etc.) prior to delivering text messages. Responses stored on the online servers will be associated with a unique study code, password protected, and encrypted. We will store online questionnaire responses collected through the online platforms on password protected and encrypted servers. We will use online platforms such as REDCap that are is FedRamp authorized, and all data will remain property of ORD.

17.3 Data sharing

We will share limited analytic datasets between authorized study personnel via secure transmission and/or via a secure virtual private network employing industry-standard password protection and data encryption.

The funding entity, PCORI, in their *Policy for Data Management and Data Sharing*, requires that we share a de-identified data set (in accordance with the HIPAA Privacy Rule) to the PCORI-designated repository: *University of Michigan's Inter-University Consortium for Political and Social Research (ICPSR)*. We will seek appropriate approvals (IRB/DUA CRADA, etc.) for data sharing once data collection is complete.

17.4 Data destruction

After the study is completed, the data will be destroyed in accordance with all VA and VHA records disposition requirements. The data will be retained for the minimum period required for records retention in accordance with the National Archives and Records Administration (NARA) VHA Record Control Schedule (RCS). The VA Puget Sound Health Care System Research and Development Office will be responsible for overseeing the storage of the data during the RCS required records retention period and for the eventual destruction of the data as authorized by the RCS. When the minimum data retention period has ended, all data records in the possession of VA Puget Sound will be destroyed. At this same time, VINCI staff will be responsible for destroying project records from any applicable VINCI server(s). For electronic data, the Office of Information and Technology (OI&T) is responsible for maintaining the security of the electronic records during the records retention period. The data will be

destroyed in a manner that is compliant with VA Handbook 6500 and National Institute of Standards and Technology NIST SP 800-88.

18 Data Analysis Plan

18.1 Aims 1, 2 & 3:

We designed this cluster randomized trial to assess the non-inferiority of pharmacist-led versus pulmonary specialist-led population health management among patients with COPD. To do so, we will use generalized linear mixed models (GLMM) to estimate the effect of provider randomization on primary and secondary patient outcomes. Of relevance to our current trial, GLMMs can accommodate continuous outcomes (Hypothesis 1, Hypothesis 2a, Hypothesis 3) and binary outcomes (Hypothesis 2b).[78]

For each analysis we will use the following GLMM model:

$$E\left(Y_{ij} \mid X_i, \boldsymbol{S}\ , Q_i, \boldsymbol{D}_{ij}\right) = g^{-1}\left(\gamma_i + \beta_0 + \beta_1 X_i + \boldsymbol{\beta}_2^T \boldsymbol{S}_i + \beta_3 Q_i + \boldsymbol{\beta}_4^T \boldsymbol{D}_{ij}\right)$$

Where Y_{ij} refers to the aim-specific outcome for patient $j = 1,2,\ldots,m_i$ within primary care provider $i = 1,2,\ldots n$, X_i is an indicator variable for randomization assignment (1=clinical pharmacist, 0=pulmonary specialist), and γ_i is a random intercept with expectation zero included to account for clustering between patients seeing the same provider. Consistent with guidance around analytic model design for randomized trials,[49] we include $\boldsymbol{S}_i$ and Q_i, which refer to the stratification variables for provider randomization site ($\boldsymbol{S}_i$) and provider type (Q_i, physician or advanced practice practitioner). We also adjust the means by $\boldsymbol{D}_{ij}$, which is a vector indicating the qualifying priority group for patient inclusion. $E(Y_{ij}|X_i, \boldsymbol{S}_i, Q_i, \boldsymbol{D}_{ij})$ refers to the expectation of the outcome given provider randomization, randomization strata, and patient pathway. The function $g(\cdot)$ refers to the link function. For continuous outcomes, we will use the identity link function assuming $Y_{ij} \sim N\left[E(Y_{ij}|X_i, \boldsymbol{S}_i, Q_i, \boldsymbol{D}_{ij}), \sigma^2\right]$, whereas for binary outcomes we will set the link function to be the logistic cumulative density function and assume $Y_{ij} \sim Bernoulli\left[E\left(Y_{ij}\middle|X_i, \boldsymbol{S}_i, Q_i, \boldsymbol{D}_{ij}\right)\right]$. We will perform an "intention-to-treat" analysis, including all eligible patients of participating primary care providers regardless of patients' or providers' adherence to treatment or intervention recommendations. Standard errors and confidence intervals of the intervention effect will be estimated using a nonparametric cluster bootstrap, which involves iteratively resampling primary care providers, including all of their patients, with replacement to generate an empirical distribution of estimator of interest.

Missing Data: Our pragmatic trial prioritizes outcome collection from the EHR to reduce participant burden and enhance generalizability. While necessary for our approach, we will likely encounter missing and misclassified data, which we anticipate will be non-differential across arms. We will use established methods to minimize measurement error around COPD and COPD-related events within administrative data.[47] For data entered by study staff, we will employ automatic logic and missing value checks to ensure accuracy. We will document the extent, pattern, and reasons for missing data. Our primary analysis will proceed using multiple imputation using chained equations to impute missing data points and we will conduct sensitivity analyses using a complete case analysis to explore the impact of missing data on the stability of our results.

*18.2 **Aim 4a**:*

In addition to the main effects for primary and secondary outcomes described above, we will evaluate for effect modification to assess treatment heterogeneity. For each outcome, we will specify a regression equation that evaluates for interaction between treatment arm and potential modifiers of interest identified from VA Administrative Data including complex multimorbidity (Charlson comorbidities), rural residence, self-described racial group, and sex. We will also assess interaction based on each of the priority classes for intervention (e.g., recent hospitalization, recent exacerbation). We will display subgroup specific treatment effects to characterize the degree of heterogeneity.

18.3 Aim 4b:

To assess heterogeneity of patient and caregiver costs, we will pool data from both arms. We will assess whether three important social determinants of health (rurality, underrepresented minority group, women) and multi- morbidity (quartile of Charlson Comorbidity index) are associated with patient costs. We will use the same analytical model described above to test the effect of each characteristic on patient/caregiver incurred costs.[79] In the event of one arm having higher costs, we will also account for treatment effect by stratification and entering an interaction to the model. In this model, we will specify a regression equation that evaluates for interaction between randomization arm and each characteristic. We will also assess interaction based on each of the priority classes for intervention (e.g., recent hospitalization, recent exacerbation), and we will display subgroup-specific pooled analyses and treatment effects to characterize the degree of heterogeneity.

18.4 Sample Size and Power:

We designed this trial to have 90% power to detect non-inferiority of pharmacist-led population management for our primary outcome, which is the presence of COPD exacerbation, hospitalization, pneumonia, or death within 180 days. We assume a one-sided type I alpha of 0.05. Based on VA administrative data, there are over 500 PCPs with patients who qualify for our trial across the five study sites. We anticipate enrolling at least 200 PCPs with an average of 20 patients each for whom they receive an e-consult. Based on administrative data at our centers, approximately 25% of patients with COPD will experience our primary outcome. With 200 clusters, assuming an intra-cluster correlation (ICC) of 0.06 and cluster size of 20 patients, we will have 90% power to reject a non-inferiority margin of 6% between groups.

We also explored power for the important secondary outcomes of CCQ and quality measures. For CCQ, we designed our analyses to have greater than 95% power to detect a non-inferiority threshold of 0.25 points for this secondary outcome. The most conservative estimates of minimum important difference for the CCQ is 0.3 points,[80] although most range between 0.4 to 0.5.[81] Based on prior work, we expect patients' responses to CCQ surveys across our population to be ~40% (8 patients per cluster). We will also account for clustering by provider, and in prior trials we found patient-reported outcomes to have an intra-cluster correlation of 0.10. For perspective, our prior trials demonstrate that pulmonary specialist led population health management improved CCQ by 0.5 points. Using these same assumptions, we will also have at least 95% power to rule out non-inferiority margins of 5% for the secondary outcome of proportion of quality-of-care items received (Table 2).

Based on the average cluster size of 20, we will include at least 2,000 Veterans per arm across the course of the trial. Each week, each arm will need to intervene on at least ~13 patients (2-3 on average per site) for us to achieve adequate power. The conservative nature of our intervention will also allow us to maintain adequate power should there be unexpected declines in patients per cluster or greater difficulty than expected in recruiting and retaining PCPs.

Power/Sample Size for Patient/caregiver incurred costs (Aim 3, 4b): The sample size for our trial is fixed based on the overall scope and design of the EQuiP-COPD trial. EQuiP plans for 200 clusters (100/arm) with average cluster size of 20. This leads to 4,000 patients with population health management overall (N=2,000/arm). Our preliminary estimates suggest that Veteran patients enrolled in VA primary care and their caregivers incur $205 (SD $363) in the 180 days following PCP visits, with intracluster correlation by PCP of 0.04. Based on these estimates, we project 85% power to detect a non-inferiority margin of 15% ($31) and 97% power to detect a non-inferiority margin of 20% ($41). With regard to heterogeneity of treatment effect for our four subgroups, the expected minimum detectable differences in incurred costs ranges from $34-$97. The estimates are summarized in Table 7 below.

Table 7. Minimum detectable differences in incurred costs				
Patient Subgroup	**Expected Prevalence (number of patients, % of total)**	**Alpha**	**Power**	**Cost Difference we expect to detect between each subgroup over follow-up period (total cost difference by group)**
Living in rural areas	1,800 (45.0%)	0.05	0.85	$34
Multimorbidity (Charlson Score >1)	2,700 (67.5%)	0.05	0.85	$36
Female	131 (3.3%)	0.05	0.85	$97
Underrepresented minority	579 (14.5%)	0.05	0.85	$49

18.5 Alternate approaches, threats to validity, and limitations:

The primary threat to most trials is failure to recruit. We have more than double the providers needed at our 5 medical centers and associated CBOC's. We have strong relationships with each of the site PI's. If performance issues arise, we may recruit/replace sites from within numerous other VA sites with whom we have worked. *Threats to validity:* We discussed the need to blind. Knowing whether pharmacy and pulmonary recommendations led to similar care quality is a high priority of this study. We therefore could not blind providers to treatment assignment. Practically, we also cannot blind providers as clinicians are required to sign their E-consults. We also considered blinding on outcome assessment. Data collected from patients and the CDW are not subject to bias. Research staff will collect outcome data on quality at 90 days after intervention. Like providers, we will not be able to practically blind staff. We believe that the overall threat to bias is also low in that we have ongoing training and data quality checks. In addition, research staff would have to differentially abstract data based on being a pulmonologist or pharmacist, which we believe is unlikely. If data is not available to us in Cerner, we will manually abstract event data using the joint legacy viewer (JLV). This system is used to syndicate health information between VA EHR and Cerner. A potential limitation is that despite targeting the overall population, women are less represented among veteran populations. Female veterans are also typically younger decreasing their prevalence of COPD overall.

18.6 Aim 5. qualitative data analysis:

Aim 5a, Analysis (General Intervention Experience): We will analyze transcripts using simultaneous inductive and deductive content analysis.[82] Inductive content analysis consists of open (unstructured) coding, allowing for the emergence of previously unidentified themes. In contrast, deductive content analysis is structured and consists of identifying themes that fit within *a priori* categories. *A priori* categories will be based on domains within the Donabedian model of quality, and we will use quotes that do not accurately fit within existing a priori codes to iteratively develop novel codes.[36]

18.7 Aim 5b, Analysis (Patient/Caregiver Incurred Costs): We will analyze interviews around patient and caregiver incurred costs using simultaneous inductive and deductive content analysis.[82] Deductive content will rely on themes and corresponding codes identified a priori based on costs/burdens for caregivers centered around the five domains of access outlined in the Fortney model.[83]

We will use ATLAS.ti analysis software for recording and managing codes. The project team will review the results of the analytic process to assess completeness. Dr. Lucas Donovan will oversee qualitative data collection and analysis.

19 Multi-Site Communication Plan

The staff at VA Puget Sound will manage the Equip trial and conduct data collection and analysis. Pulmonary specialists are located at each of the five sites. Pharmacy specialists for

Puget Sound and Portland are hired through the Puget Sound Research and Development. All other pharmacy specialists will be employed at the remaining three sites. Each local site will hire a part-time coordinator to facilitate administrative/regulatory tasks at their site.

To ensure all sites:

- are IRB approved in a timely manner;
- are informed of changes to the protocol and informed consent;
- are informed of SAEs or UPs that may impact the conduct of the study;
- conduct the study according to the IRB-approved protocol;
- are notified when the trial reaches the point that it no longer requires engagement of the local facility;

We will:

- conduct regular meetings led by the co-PIs and/or project manager with project staff to review study procedures, site status, barriers encountered, and develop remedies to any identified issues
- post templates, working drafts, and approved study documents in a shared network folder accessible by approved study staff
- communicate pertinent ad hoc and/or urgent information to sites via email, study-specific Sharepoint, and/or VA Microsoft Teams

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