Official Study Title: High-quality COPD Care for People With Immune Dysfunction Through Proactive E-consults

NCT Number: NCT03856879

Date of Most Recent IRB Approval: 7/17/2025

Documents included:

- Study Protocol
- Statistical Analysis Plan
- Information Statement (Veterans)

Human Subjects Protocol

VA Puget Sound IRB

Advan**C**ing **H**igh-quality COPD care for people with immune dysfunction by **I**mplementing **EV**idence-based management through proactive **E**-consults (ACHIEVE)

MIRB 01683

Funding Source: National Heart Lung & Blood Institute 1 U01 HL142103-01

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V4.3, July 15, 2025

Abstract

As HIV-infected (HIV+) patients age, chronic obstructive pulmonary disease (COPD) is one of the most prevalent comorbid diseases. Of concern among patients with HIV infection, COPD confers substantial morbidity and is associated with increased mortality. Yet, COPD is underdiagnosed and often inappropriately managed in HIV+ patients, likely worsening the morbidity associated with COPD. Optimizing the management of COPD includes improving uptake of recommended and discontinuation of ineffective and harmful practices.

Accurate diagnosis of COPD can identify individuals who will benefit – and those who will not benefit – from COPD therapies. Appropriate use of long-acting inhalers to control COPD improves symptoms, health-related quality of life, functional status, and decrease risk for exacerbations. Discontinuation of inappropriate inhalers – particularly inhaled corticosteroids – can minimize harms from side effects that may be particularly problematic in HIV+ persons, given their concomitant immuno-compromise, multimorbidity, and polypharmacy.

This study tests an intervention to optimize COPD care that promotes effective, evidence-based care and de-implements inappropriate therapies for COPD in HIV+ patients. We are a multidisciplinary team of key stakeholders and investigators with expertise in COPD, HIV and implementation science, with prior experience studying similar interventions. The intervention, grounded in the chronic care model, facilitates specialist support of primary care, which includes infectious disease (ID) physicians who serve as the primary care providers for their HIV+ patients in the ID clinic. Rather than relying on referral-driven specialty care, which may be a barrier to access, we will have pulmonologists proactively support HIV providers to manage a population of HIV+ patients with COPD, delivering real-time evidence-based recommendations tailored to the individual HIV+ patient.

We will leverage the Department of Veterans Affairs (VA) clinical and informatics infrastructures to communicate between team members developing the recommendations and patients' clinical providers through the electronic health record as a proactive (i.e., pulmonary-initiated) E-consult. To offset potential increases in ID providers' workload, we will draft recommendations as preliminary orders for providers to review and endorse (sign), modify or cancel at their discretion, preserving autonomy.

We will use a two-arm, parallel cluster randomized trial design, with outcomes evaluated using the RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) framework. We will evaluate barriers and facilitators of optimal COPD care for HIV+ patients, and of effective adoption, implementation and maintenance of a proactive E-consult program, guided by the Consolidated Framework for Implementation Research. This intervention can enhance the sustainable uptake of proven-effective interventions into routine clinical practice for HIV+ patients, who are at risk of disparities in COPD care and poor health outcomes from COPD.

List of Abbreviations

- Adverse event (AE)
- Antiretroviral Therapy (ART)
- American Thoracic Society (ATS)
- Chronic obstructive Pulmonary Disease (COPD)
- Center of Innovation (COIN)
- Clinical COPD Questionnaire (CCQ)
- Community based outpatient clinic (CBOC)
- Compensation & Pension Record Interchange (CAPRI)
- Computerized Patient Record System (CPRS)
- Confidence interval (CI)
- Corporate Data Warehouse (CDW)
- Consolidated Framework for Implementation Research (CFIR)
- Data Monitoring Safety Board (DSMB)
- Department of Defense (DoD)
- Electronic Health Record (EHR)
- European Respiratory Society (ERS)
- Examinations of HIV Associated Lung Emphysema (EXHALE)
- Forced Expiratory Volume in one second (FEV1)
- Health Services Research & Development (HSR&D)
- Human Immunodeficiency Virus (HIV)
- Infectious Disease (ID)
- Inhaled Corticosteroids (ICS)
- Information Technology (IT)
- Institutional Review Board (IRB)
- Information Security Officer (ISO)
- Long-Acting Beta-Agonists (LABA)
- Long-Acting Muscarinic Antagonists (LAMA)
- Letter of Support (LOS)
- Medical Outcomes 12-item short form (SF-12)
- National Archives and Records Administration (NARA)
- National Institute of Health (NIH)
- National Committee for Quality Assurance (NCQA)
- National Quality Forum (NQF)
- Nurse Practitioner (NP)
- Office of Specialty Care (OSC) Service
- Physician Assistant (PA)
- Physical Component Score (PCS)
- Primary care provider (PCP)
- Protected health information (PHI)
- Principal Investigator (PI)
- Pulmonary Function Test (PFT)
- Randomized controlled trial (RCT)
- Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM)
- Refill Compliance (ReComp)
- Research Electronic Data Capture (REDCap)
- Serious adverse event (SAE)

- Six Minute Walk Test (6MWT)
- Specific Aims (SA)
- Seattle Outpatient Satisfaction Questionnaire (SOSQ)
- Steering Committee (SC)
- Usual care (UC)
- Veterans Aging Cohort Study (VACS)
- VA Extension for Community Health Outcomes (ECHO)
- VA Puget Sound Health Care System (HCS)
- Veterans Affairs (VA)
- Veterans Affairs Medical Centers (VAMC)
- VA Informatics and Computing Infrastructure (VINCI)
- VA Information Resource Center (VIReC)
- VHA Record Control Schedule (RCS)

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2.0 Introduction

1 Background

As HIV-infected (HIV+) patients are aging, chronic obstructive pulmonary disease (COPD) is one of the most prevalent comorbid diseases, affecting ~20% of patients.[1-3] Of concern among patients with HIV infection, COPD confers substantial morbidity and is associated with increased mortality.[4] We have shown that symptoms of COPD are more severe in HIV+ than HIV uninfected (HIV-) patients for similar impairment in lung function;[5] COPD increases risk for hospitalization and pneumonia in those with HIV;[6, 7] and acute exacerbations of COPD occur more frequently in HIV+ patients.[8, 9] COPD and HIV interact to worsen physical function[10] and decrease distance walked in 6-minutes.[11, 12] Yet, COPD is underdiagnosed[13] and we find COPD is often inappropriately managed in HIV+ patients, likely worsening the morbidity associated with COPD.

Optimizing the management of COPD can reduce morbidity and mortality and includes improving uptake of recommended and discontinuation of ineffective and harmful practices. Accurate diagnosis of COPD can identify individuals who will benefit – and those who will not benefit – from COPD therapies. Appropriate use of long-acting inhalers to control COPD improves symptoms, health-related quality of life, functional status, and decrease risk for exacerbations.[14] Discontinuation of inappropriate inhalers – particularly inhaled corticosteroids (ICS) – can minimize harms from side effects that may be particularly problematic in HIV+ persons, given their concomitant immuno-compromise, multimorbidity, and polypharmacy. Unfortunately, the current care of COPD in HIV+ patients falls short of evidence-based recommendations in concerning ways. In prior studies and our preliminary data, HIV care providers are less aware of current smoking in their patients than General Medicine providers, and only 40% of HIV+ patients with clinical diagnoses of COPD had spirometry for confirmation of the diagnosis.[15] Further, we found that the most frequently used controller medication in HIV+ COPD patients was ICS, which are associated with greater risk of pneumonia, fractures and poor diabetes control,[16-23] whereas the first line recommended therapy, long-acting bronchodilators (either long-acting beta-agonists or long-acting muscarinic antagonists), were prescribed less often.

2 Gaps in current knowledge, relevant data, and how the study will add to existing knowledge

With aging of the HIV-infected (HIV+) population with effective antiretroviral therapy (ART), chronic conditions such as chronic obstructive pulmonary disease (COPD) are increasing. These chronic conditions now account for the majority of deaths.[30-35] COPD, inclusive of emphysema and chronic bronchitis, is now one of the most common comorbidities and cause of chronic lung disease in HIV+ adults.[1, 2, 36-41] HIV+ patients are at a greater risk of COPD compared to demographically similar HIV-uninfected (HIV-) patients, even after controlling for smoking.[2, 11, 37, 42-45] We and others have shown that HIV is independently associated with COPD, which is more likely to be the emphysema subtype, and often presents at younger ages and with fewer pack-years of smoking in HIV+ compared to HIV- adults.[2, 3, 43, 45, 46]

COPD is associated with substantial morbidity and mortality in HIV+ patients. COPD has grown as a cause of respiratory admissions,[38] is a risk factor for pneumonia,[7] and is a leading cause of respiratory failure in critically ill HIV+ patients.[39] COPD is associated with more severe respiratory symptoms,[5] and greater risk of exacerbations in HIV+ compared to HIV- patients.[8, 9] COPD is also a risk factor for frailty[29] and mortality in those with HIV.[4] Further, we have shown that COPD interacts with HIV to worsen self-reported functional status,[10] and that markers of COPD – decreased airflow measured by the forced expiratory volume in one second (FEV1), chronic cough, and radiographic emphysema are associated with clinically meaningful decreases in distance walked on 6 minute walk test (6-MWT).[11, 12] Taken together, these data support that HIV+ patients face disparities in poor health outcomes related to COPD: suboptimal management of COPD in HIV+ patients could contribute to these poor outcomes. Studies focused on improving the care of HIV+ COPD patients are acutely needed.

Barriers at the provider, system, and patient levels are known to impede the delivery of evidence-based COPD care in HIV- populations. Quality of care for COPD in general is low with the minority of patients receiving all aspects of ideal care, including when hospitalized for COPD exacerbation.[47-51] COPD is often misdiagnosed and inhalers inappropriately prescribed in the outpatient setting, especially inhaled corticosteroids (ICS).[47-49, 52] We have shown that within VA, COPD care is organizationally unsupported and may account for disparities in outcomes.[53] Hence, the gaps in care that we have identified are not surprising: primary care providers (PCPs) do not regularly order spirometry to confirm the diagnosis of COPD,[54] and acknowledge their general lack of awareness of COPD guidelines and the risks of ICS.[55] PCPs advocate for using symptoms to treat COPD and discount the results of spirometry,[54] however symptoms of COPD – dyspnea, cough and wheeze – are not specific to the condition. Consistent across health systems, we have shown that ~50% of patients who are diagnosed, treated and believe they have COPD do not have spirometry consistent with COPD.[56, 57] Our group has shown that misclassification of diagnosis often follows comorbidities that have symptoms that mimic COPD, including heart failure, and obesity/ deconditioning.[58, 59] Even after obtaining spirometry that does not confirm COPD, providers do not appropriately de-escalate therapies even though there is no potential of benefit.[59] Likewise, in settings where escalation of therapies is appropriate, such as after COPD exacerbation, providers do not escalate therapies known to reduce future exacerbations.[60]

Approaches to educate clinicians alone are not likely to improve care for patients with COPD. PCPs are faced with multiple issues to address during any given clinic visit and prioritize other conditions such as diabetes management over COPD.[54, 55] As the burden of multimorbidity has grown with aging HIV+ patients, it may be even more challenging for HIV providers to stay abreast of the most current guidelines for optimal care of these conditions including COPD. In addition, in our current referral-based specialty-care model, pulmonologists only become engaged when the PCP seeks a referral. Overall, these data support that in current models of care, COPD management is poor and unlikely to improve without substantial intervention.

Emerging data support that similar barriers to high quality COPD care are likely accentuated in HIV+ persons. We have shown that provider awareness of smoking is decreased amongst providers of HIV+ patients compared to HIV- patients.[15] Additionally, COPD is substantially underdiagnosed in HIV+ patients who appear less likely to be referred for pulmonary function testing,[13, 43] despite a higher prevalence of smoking and respiratory symptoms compared to HIV- patients.[5, 61] Even within the context of a research study investigating the implementation of a patient-completed, physician-reviewed COPD screening tool administered in an outpatient HIV clinic at the time of a routine clinic visit, physicians only ordered spirometry in 31% of the HIV+ individuals who qualified (25% of those screened).[62]

Notably, in this study, referrals or orders of any necessary testing were at the discretion of the provider, a major barrier that we address with our proactive E-consult design. Taken together, decreased recognition of smoking, lack of referral for pulmonary evaluation, worse symptoms and greater exacerbation rates point towards low quality of care for COPD in HIV+ patients.

Our preliminary data supports that COPD is inadequately managed in HIV+ patients. We analyzed data from our prior Examinations of HIV Associated Lung Emphysema (EXHALE, PI Crothers) cohort study, a pulmonary substudy to the Veterans Aging Cohort Study (VACS);[63] EXHALE enrolled 189 HIV+ and 161 HIV- participants from 2009-2012 at the Atlanta, Bronx, Houston and Los Angeles Veterans Affairs Medical Centers (VAMC).[5, 12, 64, 65] In preliminary analyses to assess the management of COPD, we found that self-reported respiratory symptoms were significantly more frequent in those with HIV: the prevalence of chronic cough was 25% of HIV+ and 16% of HIV- patients (p = 0.04), and chronic phlegm in 30% of HIV+ and 16% of HIV- patients (p=0.004).[12] Of concern and after excluding asthma, we found that ICS was the most frequently prescribed COPD controller medication, and notably, use increased after the completing pulmonary function tests (PFTs, Table 1) despite a lack of indication. Further, despite being first-line recommended therapy as a controller medication, prescriptions of long-acting beta-agonists (LABA) and long-acting muscarinic antagonists (LAMA) were less commonly prescribed than ICS. Use of LAMA was particularly lower in HIV+ patients. These data demonstrate that current management of COPD in HIV+ patients do not adhere to guidelines, that ICS are over-prescribed, and support the need to improve evidence-based COPD care in HIV+ patients.

Table 1. % of patients with COPD diagnosis who have medication prescription by HIV

Prescription by inhaler type	HIV+ with COPD diagnosis		HIV- with COPD diagnosis	
	1 yr prior PFT	1 yr post PFT	1 yr prior PFT	1 yr post PFT
ICS	20%	29%	23%	27%
LABA	4%	16%	23%	18%
LAMA	8%	4%	5%	14%

Appropriate use of COPD therapies is particularly important for HIV+ patients, as side effects and toxicities could be more harmful in HIV+ patients, given their concomitant multimorbidity and polypharmacy.[66-69] The risk-benefit profile of ICS for HIV+ patients is especially concerning. ICS increase risk of bacterial pneumonia and tuberculosis; interfere with bone health; and worsen glucose control in diabetes; and interact with ritonavir.[16-23, 70, 71] Inappropriate ICS use increases these risks without the potential of benefit. Further, inappropriate prescribing likely increases missed opportunities to identify and address other etiologies of dyspnea common in HIV, such as cardiovascular disease that cannot benefit from ICS.

In summary, an intervention to improve the evidence-based delivery of COPD care can improve outcomes for HIV+ patients. Benefits may extend beyond COPD-related measures. Appropriate use of COPD controller medications can decrease symptoms and exacerbations, and improve HRQL.[14, 72, 73] Our intervention to improve evidence-based COPD care for HIV+ patients addresses underuse, overuse and misuse, potentially reducing polypharmcy.[74, 75] Polypharmacy increases potential drug-drug interactions, decreases the likelihood of receiving indicated therapies, and could influence ART adherence and efficacy.[76, 77] Given the prevalence of COPD; our preliminary data demonstrating inadequate management of COPD in those with HIV; our success and expertise with implementing a multimodal telehealth based intervention; and our partnership with key stakeholders, our proposed study to has a high potential to

substantially improve the quality of care for COPD and patient-centered outcomes for a large number of HIV+ Veterans.

3 Innovation

Our successful intervention will provide a model for integrating specialty care into primary care for the HIV+ patients that, if adopted, may improve health status for patients, increase the use of evidence-based therapies, reduce the use of inappropriate therapies, improve access to specialists, and enhance care-coordination between other specialty and ID clinic providers in managing these complex HIV+ patients. The findings will inform the broader scientific literature on implementation of health information technologies and the systems-level, provider-level and patient-level factors that influence implementation. The potential risks to the study participants are minimal and quite reasonable given the expected study results.

We propose a study that challenges the current approach to specialty care for HIV+ patients with COPD in a number of innovative and important ways and that has generalizability to all learning health systems.

- First, we are using a population management approach to identify all patients within the health system for improvement, and suggest that the role of the specialist within integrated health systems is to be responsible for the overall care for patients who fall within their specialty. This population management approach is paired with actionable recommendations that retain PCP prerogatives, and patient tailored recommendations.
- Second, we are using a proactive vs reactive approach to engage in the care of individuals, and the intervention addresses a number of important access barriers. We do not rely on referrals from providers, but proactively engage patients – eliminating the need to recognize an issue within primary care settings, and eliminating potential disparities in referral due to patient factors. Additionally, we are providing specialty level care within the patient's primary care setting (ID clinic). The intervention thus addresses geo-spatial barriers of the VA's hub and spoke model for provision of specialty care without need to travel, which can be particularly challenging for patients in rural areas, those of lower socioeconomic status and of less mobility where transportation may be problematic. We also do not require additional "new visits" to primary care or in person specialty services that are constrained by capacity of clinical space and personnel.
- Third, we are using a novel multi-modal, electronic, health technology-based approach to not only provide the recommendations but also facilitate adoption of those recommendations by pre-completing orders on behalf of the PCP through the EHR. We also plan to use the VA Extension for Community Health Outcomes (ECHO) model, a provider to provider telehealth approach to train providers at our participating site about the delivery of the intervention, to provide opportunity for learning across medical facilities and harmonize recommendations. This will enable us to have a team of providers working together to develop recommendations, which will include pulmonologists at the participating sites.
- Fourth, we designed the intervention using nationally adopted care processes. E-consults, VA ECHO, and population management approaches to health care delivery are important processes that are fully endorsed by the VA and our operational partners. This significantly increases the likelihood of adoption within the health system by using existing infrastructure without need for additional building of programs.
- Fifth, we included early engagement in the key stakeholders early and throughout the intervention development and testing throughout the multiple levels of healthcare – including patients, providers, health information technology (IT) and health systems.

- Sixth, we have included the end-users in the development process – both patients and PCPs in general medicine clinics have informed the design of the intervention.
- Finally, we are leveraging investments by using an existing health information technology (IT) platform to identify patients through our corporate data warehouse and data from VACS. Our approach can serve as a blueprint and be expanded to other learning health systems that can leverage their EHR to design and implement a proactive E-consult program to improve health outcomes.

4 Target population and setting

Table 2. HIV+ patients and ID providers by training and site

VAMC	HIV+ patients	VACS site	MD	NP/PA	Totals
Atlanta	~1800	Yes	11	3	**14**
DC	~1100	Yes	18	3	**21**
Denver	~320	No	7	1	**8**
Los Angeles	~750	Yes	21	2	**23**
West Haven	~250	No	5	1	**6**
Nashville	~300	Yes	12	2	**14**
Philadelphia	~400	No	8	0	**8**
Totals	**6,720**	**--**	**82**	**12**	**96**

Based on our power estimates, we plan to reach ~6 HIV+ patients with COPD per ID provider at the 7 sites. Collectively, these 7 facilities are geographically diverse, with 82 ID providers (Table 2). Five clinics participate in the Veterans Aging Cohort Study (VACS), which we will leverage for enrollment. VACS is an ongoing longitudinal study of a consented cohort of >3700 HIV+ and 3700 HIV- patients.[63] All HIV+ patients seen in the ID clinics at the participating VAMC are eligible. Each participating ID clinic serves a population ranging from 250 to over 1,100 patients. The HIV+ patients served within this setting are diverse: approximately 50-60% are Black, 10% Hispanic, and over 50% have an annual income less than $25,000.[63] As the VA is the largest single provider of medical care to HIV+ persons in the US, with over 27,000 Veterans with HIV in care, our intervention can be scaled up to be adopted at sites nationwide and reach a significant number of HIV+ patients across the US, including in rural areas (see LOS from Dr. Ohl and from Dr. Ross).[92]

5 Rationale for including or excluding certain populations – in particular vulnerable populations.

Potential provider participants are approximately 150 working-age adults employed by the VA and include physicians, independent physician assistants, and nurse practitioners who provide care to HIV+ patients within the ID clinic at their VA site. Potential patient participants are patients of participating providers who have COPD and are living with HIV+ (approximately 600 patients total, or an average of 4 patients per provider). The typical range in age for these patients is from the late 40s to individuals into their 70s, with an average age near 55 years. Most are male with other co-morbid chronic health conditions including cardiovascular disease, diabetes, hypertension, hyperlipidemia, mental health disorders, and renal disease. Within this cohort, we have no exclusion criteria and will not target populations who are vulnerable other than for HIV infection.

Providers and Veterans who are women and minorities are expected to participate in this study to the extent that they are represented within the VA and within the ID clinics at the participating

sites. Overall, the HIV+ patients receiving care within the VA have a large proportion of minority patients based on data from VACS, with 50-60% Black, 20-30% White, 10% Hispanic, and 5% other. We anticipate that the HIV+ COPD patients in this study will be similar to these estimates in terms of race and ethnicity. The proportion of HIV+ women is 3%, consistent with an overall VA population. No participants will be excluded based on the race, ethnicity or sex/gender. We will conduct unbiased evaluation of the outcomes of study participants, and use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects by sex, race, and/or ethnicity. Prior studies neither support nor negate significant differences in intervention effect among subgroups. In our analyses, we will evaluate whether the effect of our E-consult intervention varies by sex, racial, and/or ethnic subgroups.

We will not include any children in this study because all participants are adult Veterans or health care providers. In addition, COPD is a slowly progressing disease with typical onset in midlife; therefore, we are unlikely to find eligible participants who are less than 40 years of age.

3.0 Objectives

This study tests an intervention to optimize COPD care that promotes effective, evidence-based care and de-implements inappropriate therapies for COPD in HIV+ patients. The intervention facilitates specialist support of primary care, which includes infectious disease (ID) physicians who serve as the primary care providers (PCP) for their HIV+ patients in the ID clinic. Rather than relying on referral-driven specialty care which may be a barrier to access, we will have pulmonologists proactively support ID providers to manage a population of HIV+ patients with COPD, delivering real-time evidence-based recommendations tailored to the individual HIV+ patient. We will leverage the Department of Veterans Affairs (VA) clinical and informatics infrastructures to communicate between team members developing the recommendations (using VA Extension for Community Health Outcomes [ECHO]) and to patients' clinical providers through the electronic health record (EHR) as an E-consult. To offset potential increases in workload, we will draft recommendations as preliminary orders for providers to review and endorse (sign), modify or cancel at their discretion, preserving autonomy. We will use a two-arm, parallel cluster randomized trial design grounded in the chronic care model with outcomes evaluated using the RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) framework.[24] We will evaluate barriers and facilitators of optimal COPD care for HIV+ patients, and of effective adoption, implementation and maintenance of a proactive E-consult program, guided by the Consolidated Framework for Implementation Research (CFIR).[25, 26] We are a multidisciplinary team of key stakeholders and investigators with expertise in COPD, HIV, and implementation science, with prior experience studying similar interventions. We will test the following specific (SA) aims and hypotheses in a multicenter study:

SA 1. Test whether a multi-faceted proactive intervention improves quality of care and health-related quality of life (HRQL) in HIV+ patients with COPD. We hypothesize that the intervention will increase the uptake of appropriate, evidence-based care while decreasing exposure to inappropriate medications for HIV+ patients with COPD. Our primary outcome measure to assess effectiveness of the intervention will be the quality of COPD care. A highly important secondary measure will be change in patient HRQL. We will perform a formative evaluation to understand if barriers to optimal COPD care remain in order to refine the E-consult intervention iteratively.

SA2. Identify key factors influencing the process of adoption, implementation and maintenance of proactive E-consults. We will conduct a mixed-methods assessment guided

by CFIR with a particular focus on the outer setting, inner setting and the individual health professionals and how they influence the process of implementation. If the proactive E-consults are successful, these findings will help inform subsequent efforts to adapt them to other settings and understand what factors may be critical for maintenance of the program.

This project can enhance the sustainable uptake of proven-effective interventions into routine clinical practice for HIV+ patients, who are at risk of disparities in COPD care and poor health outcomes from COPD.

4.0 Sources of Materials

We will derive data from three sources. First, we will extract clinical data from the VA corporate data warehouse (CDW) via the *VA Informatics and Computing Infrastructure (VINCI)* and from CPRS/VistAWeb review (both emulations of VistA). The data warehouse contains near real-time clinical data (refreshed nightly) that permits researchers direct access to patient information. Second, we will also access data from the Veterans Aging Cohort Study (VACS), as Dr. Crothers is the Director of the Pulmonary Disease Core within VACS and will facilitate access to data within the VACS databases to identify potentially eligible patients and to determine outcomes. The VACS study has agreed to share names of eligible patients from the VACS cohort. Names of patients drawn from the VACS cohort will be shared via encrypted email or via a shared folder on the VA Puget Sound HSR&D secure folder. (See section 4.1 below for further detail on data that will be extracted from CDW and VACS.) Third, we will measure patient and provider self-reported outcomes via interviews and surveys. Surveys will be completed online (providers) or by written surveys sent via mail (patients), with an option to complete via telephone. Providers will be e-mailed a secure link to a survey via REDCap, a widely-used, secure web application for building and administering online surveys and databases. The REDCap application is managed and supported by the VA Information Resource Center (VIReC) and is installed and accessible through the VINCI to VA researchers only behind the VA firewall, which provides an exceptional level of data security. Patients may complete surveys via postage-paid mail (preferred) or will have the option to complete a telephone-based interview administered by study staff; the cover letter to patients will include information about arranging to complete the survey via telephone. Both patient and provider surveys will include information about opting out. Finally, we will conduct provider and patient interviews via telephone and/or VOIP conference line that we will audio record directly from the phone to access-controlled data servers at VA Puget Sound Health Services Research & Development.

Only IRB approved study staff will have access to individually identifiable private information about participants.

6 Corporate Data Warehouse and VACS

Refine quality of care outcome measure metric: Before we begin recruitment, we will use the CDW to identify a cohort of up to 50 patients at the VA Puget Sound who have COPD and HIV to refine the algorithms that we will apply to CDW data to measure quality of COPD care.

Comorbidity, COPD severity assessment: We will review the medical record for clinician-assessed diagnoses in the medical notes for 24 common comorbidities that comprised the health inventory checklist used in previous intervention studies.[94, 107] We also calculate the VACS

Risk Index, which is highly predictive of mortality in HIV+ patients.[111, 112] We will assess previous COPD hospitalizations and exacerbations.[8]

Medications: We will collect medication dispensing from the CDW including treatment for HIV and COPD. We will estimate medication adherence using RECOMP – a valid and reliable measure of medication adherence, based on work of Steiner et al. and validated within VA.[113, 114]

Other measures and data from VA databases (Table 7): The VACS database and CDW will provide data on COPD diagnoses of HIV+ veterans in care, and can also be used to gather information about relevant secondary clinical outcomes including hospitalization, pneumonia, and COPD exacerbation.[7, 8, 28]

National cohort: In addition to using VACS and CDW to identify eligible patients of enrolled providers, we will identify a nationwide cohort of HIV+ patients with COPD for the purposes of assessing quality of COPD care across geographical regions.

5.0 Conceptual Model of the Intervention

Our work is informed by three conceptual models. First, the overall multimodal telehealth intervention is adapted from the Chronic Care Model, which proposes that clinical information systems, decision support and delivery system design are fundamental to allow the primary care team to be proactive and prepared for patient encounters. We have designed an intervention that leverages the EHR to allow specialists to take on a proactive role, adopt a population-health perspective, and prepare the primary care, HIV team with patient-specific, concrete recommendations just in advance of a patient visit. Second, the RE-AIM framework will guide our measurement of impacts to ensure we assess the findings most important for clinical leaders and policy makers. We will demonstrate not only how effective proactive E-Consults are in terms of improving patient care, but also how broadly they reach patients, and how well the program can be adopted, implemented and maintained. Finally, CFIR helped inform the proactive telehealth approach, and will guide and organize our analysis of factors influencing implementation. CFIR is a classical implementation model that catalogues and defines the most salient factors influencing the implementation process. CFIR facilitated our using past findings[82, 86, 87] to inform intervention design and implementation strategies, and it will facilitate reporting of our findings in a way that others can identify and apply them to their research and improvement efforts.[89] We used RE-AIM and CFIR in a similar way in the national evaluations of the VA E-Consult and VA ECHO initiatives, which provided actionable findings to operational stakeholders.

Facilitation (CFIR: Access to knowledge; available resources, training; stakeholder engagement; self-efficacy): As providers enter the intervention, we will monitor when patients are scheduled to be seen by their ID providers so that we can deliver recommendations at the time of their usual clinic visit. We will not arrange for new clinic visits. In the E-consult, we will state that the provider's patient was reviewed by the intervention team, provide rationale for and note that these recommendations were tailored to the patient. **Suggested changes to care will be in an easily readable format, and can be accepted, amended or rejected—with or without explanation, within seconds.** In patients who are on inappropriate second line controller agents, which we anticipate mainly will be ICS, we will provide the process for de-implementation of ICS. In our experience thus far, we have often substituted an additional long-acting inhaled bronchodilator if the patient is not already on the medication; among those with no evidence of air flow obstruction on spirometry, we have been targeting recommendations such as de-escalation of inhaled therapies and evaluation of alternative etiologies of the patient's dyspnea,

including pulmonary, cardiology or obesity treatment referrals when appropriate. For this project, we will tailor recommendations to additional etiologies relevant to the HIV+ patient, e.g. infection, heart failure, liver disease, pulmonary hypertension, lung cancer among others.

As part of facilitation, we will enter any recommendations for care (including medication orders, testing and consultation requests) as orders in the EHR on behalf of the provider. This is a key facilitation step lowering the threshold to implement our recommendations by allowing the patient's provider to act on them simply by reviewing the orders and approving them (sign). Because the patient's ID provider is ultimately the best judge of appropriate care, as they are aware of the patient's medical issues (some of which may not be derived from chart abstraction), they can also modify or discontinue the orders. This approach enhances safety through targeted, actionable input from specialists while preserving provider autonomy. Lastly, we will give the provider a correspondence letter detailing treatment plan changes for those patients who miss their appointments. Throughout the intervention period, we will have multiple communication channels for ID providers to engage pulmonary. As part of the intervention, if the patient's provider believes that the patient should be seen in the pulmonary clinic, even if not initially recommended, the intervention team will ensure a timely in-person visit.

Provider engagement and local champions (CFIR: Stakeholder engagement; identifying/designating champions; networks and communication): The investigators are respected leaders in the ID and pulmonary clinics at their facilities and provide essential "face validity" to our attempts to change care practices. We have used similar methods in our prior interventions and our results are consistent with existing literature about the effectiveness of respected thought leaders in aiding with provider behavior change.[98] The intervention has features that facilitate engagement including: direct access to intervention team members and pulmonary specialists, evidence-based recommendations placed as orders in the EHR for review with clear documentation of the rationale for any changes in therapies or additional studies, facilitating in-person pulmonary consultation if desired, and ID providers' maintaining final decision-making for patient care. Also, we plan to interview a purposive sample of ID providers who have had at least 2 patients in the intervention (n~30) to characterize providers' perspectives on the intervention's acceptability (e.g. ease of use, professional autonomy) and effectiveness (e.g. improves care delivery, treatment choice) with a particular focus on barriers and facilitators to successful implementation. These data will allow us to tailor the intervention to ID providers' needs and enhance buy-in and sustainability.

We will use **RE-AIM framework** (Reach, Effectiveness, Adoption, Implementation, Maintenance) to evaluate this program (please see Table 3 for how we will assess each element).[24]

Table 3. Overview of RE-AIM Elements

Element	Definition	How assessed
Reach	Absolute number, proportion and representativeness of individuals who participate in the intervention	Percent of patients for whom the intervention was delivered out of the total number we intended to target, as well as the percent of providers who participate among all those eligible.
Effectiveness/ Efficacy	Impact of the intervention on outcomes	Proportion of evidence-based COPD care recommendations that a patient receives after delivery of the intervention, and patient HRQL (SF-12). Additional outcomes include degree of provider satisfaction and acceptability of the intervention.
Adoption	The absolute number,	We will determine if there are differences in acceptance of E-consults among ID

	proportion, and representativeness of settings and intervention agents who are willing to initiate a program	providers by looking at factors such as panel size (provider level) or vacancies in the clinic (clinic level) that might influence E-consult acceptance. During interviews, we will assess provider and clinic characteristics that are important for adoption to inform roll out of the E-consult program.
Implementation	How closely and consistently the intervention is followed at the setting level	Fidelity of implementation will be assessed as the proportion of COPD recommendations that are fulfilled by each participating provider; qualitative and survey analyses in Aim 2 will also assess patient and operational barriers and the fidelity of the intervention.
Maintenance	Extent to which a program becomes part of routine organizational practices at the setting level	Qualitative and survey analyses will identify factors that may influence whether the intervention can be sustained long-term. Future work to impact maintenance can include budget impact analyses and toolkits for training and disseminating the intervention, if effective.

6.0 Site roles and responsibilities

The division of tasks between the coordinating and local sites is summarized in the table (Table 4) below. More detailed study procedures are outlined in the following sections.

Table 4. Summary of Functions	**Coordinating Center**	**Local Sites**
Overall Management		
Monitor participant retention, adherence	x	
Monitor outcomes/unanticipated problems related to safety	x	
Monitor and report protocol deviations	x	
Process and report Adverse Events per IRB/NHLBI policies	x	x
Generate reports to NHLBI/DSMB	x	
Monitor participant demographics, ensure representative cohort	x	
Protocol/Data Management		
Develop trial protocol	x	
Manage and analyses of study data	x	
Develop/maintain REDCap survey for providers	x	
Randomize participants	x	
ClinicaTrials.gov updates	x	
Disseminate results	x	
Prepare datasets for NHLBI data repository	x	
Recruitment		
Initial email invitation to providers	x	
ID provider meeting at site with ID co-investigator		x
Initial invitation mailing and calls to patients	x	
Track opt-outs and passive enrollment	x	
Intervention		
Query CDW and VACS data to identify eligible patients of enrolled providers with upcoming appointments	x	
Complete chart abstractions prior to pulmonologist review meeting	x	
Participate in pulmonologist review meeting to develop recommendations	x	x

Draft E-consult note, compile list of orders	x	
Input notes and orders into CPRS prior to visit		x
Sign E-consult note in CPRS		x
Outcome measures		
Contact providers and patients to complete surveys and interviews	x	
Query CDW and patient charts to track COPD quality of care metrics following intervention	x	

7.0 Study Procedures

7 Study Design

We will use a two-arm parallel cluster randomized trial design. This design will randomly divide the study participant group (providers) into approximately even-sized intervention and control groups (clusters), stratified by site, provider type and panel size. The intervention is described below in section 7.5. Providers in the control group will provide usual care. Providers will be randomized to either the control arm or the intervention arm using a 1:1 allocation ratio and stratification by site, provider type, and provider panel size. Cluster randomization was chosen to minimize the potential for contamination, which may be present when a given provider alternates between the treatment of control arm patients and the treatment of intervention arm patients.

8 Eligibility Criteria

ID Provider eligibility

- Inclusion: ID providers (MD/PA/NP) at participating sites who treat HIV+ patients
- Exclusion: Resident trainees (residents are excluded; fellows not excluded)

Potential provider participants are approximately 150 working-age adults employed by the VA and include physicians, independent physician assistants, and nurse practitioners who provide care to HIV+ patients within the ID clinic at their VA site.

Patient eligibility

- Inclusion: HIV+ patient of an enrolled provider with diagnosis of COPD; enrolled providers may be assigned to the intervention or control arm
- Exclusion: Significant cognitive dysfunction, language barriers, or severe psychiatric disorder, impairing ability to participate in surveys and interviews.

Potential patient participants are patients of participating providers who have COPD and are living with HIV+ (approximately 600 patients total, or an average of 4 patients per provider). The typical range in age for these patients is from the late 40s to individuals into their 70s, with an average age near 55 years. Most are male with other co-morbid chronic health conditions including cardiovascular disease, diabetes, hypertension, hyperlipidemia, mental health disorders, and renal disease. Within this cohort, we will not target populations who are vulnerable other than for HIV infection.

9 Recruitment and Informed Consent

We will recruit two categories of participants: patients and providers. We will initially recruit ID providers at each of the participating local sites, as ID providers are the target of the intervention. Following an appointment with an enrolled provider, patients will be recruited to complete interview and surveys for the purposes of outcomes measurement.

Provider recruitment and consent:

Local site ID Co-Investigators will use standard clinic processes (to be specified at each site) to schedule an initial kick-off meeting with all ID providers at that site. For providers that join the clinics after the initial kick-off meeting, the local site ID co-Investigators will communicate with them individually or as a small group. Local site ID co-Investigators will communicate the date of these meetings to coordinating center study staff. One week prior to the scheduled meeting, coordinating site study staff will send an invitation email to ID providers describing the study and inviting them to participate. This email will include a description of the study, an information statement, and information about how to contact coordinating site study staff to opt out of the study or get more information. Coordinating center study staff will identify providers at each site either via CDW or from ID co-investigators at that site.

At the meeting, presentations to providers about the study, including the opportunity to opt-out, will be made by local site co-investigators or coordinating site staff. Study staff will describe the study, explain the potential risks/benefits to providers and patients, and provide an opportunity to answer questions. Providers will have the opportunity to speak with a study team member at the Coordinating Center at SIBCR on the phone upon request.

Providers will be given a passive consent. If they do not respond within 2 weeks of the initial invitation email, they will be considered enrolled for the duration of the study, and will receive links to web-based questionnaires; a sample will also be invited to participate in interviews.

Patient recruitment and consent:

Only patients of enrolled providers (including both intervention and control providers) will be recruited to participate in the study. Patients will be recruited centrally from the coordinating center. Through medical record review, we will exclude patients if they have significant cognitive dysfunction, language barriers or severe psychiatric disorder, impairing ability to participate in surveys and interviews.

The components of the study that patient participants opt-in/out for are the survey and interviews. As we have done in previous similar interventions, we will seek a waiver of informed consent and HIPAA Authorization for activities not directly engaging Veterans, e.g., chart review and treatment recommendation activities. For health status and satisfaction self-report surveys, we will request a Waiver of Documentation of Informed Consent, allowable under 45 CFR 46.117 because the research activity presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Coordinating center staff will recruit a sample of patients to participate in interviews. Patients recruited to participate in interviews will be mailed a packet within one week of

an appointment with their ID provider. This packet will include a written statement about the study (information sheet), and a postage-paid opt-in/opt-out response card. The statement will explain the study, give them a telephone number that they can call with questions, and explain that a study staff member will telephone them in one week to answer any questions they may have and see if they are interested in participating in the study. For patients who would like to participate but do not want to wait for study staff to contact them, they can return the response card opting into the study and we will contact them following receipt of the card. For patients who do not wish a call, the statement will instruct them to return the postage-paid opt-out card. Patients who return the opt-out card will not be contacted. For interested patients or those who do not return a response card, study staff will call them to conduct the informed consent process and schedule an interview as appropriate. Patients whom study staff are able to contact will be asked whether they would be willing to complete surveys at 6 weeks post-appointment, regardless of whether they choose to complete an interview.

For all eligible patients, with the exception of those who were recruited to complete interviews and opted out of the study or opted out of completing surveys, coordinating center study staff will send a packet 6 weeks after an appointment with their ID provider that includes a written statement about the study (information sheet), copies of the surveys, and a postage-paid opt-in/opt-out response card. The statement will explain the study, give them a telephone number that they can call with questions, and explain that a study staff member will telephone them in one week to answer any questions and to ask them the survey questions. For patients who would like to participate but do not want to wait for study staff to contact them, they can return the response card opting into the study and we will contact them following receipt of the card. For patients who do not wish a call, the statement will instruct them to return the postage-paid opt-out card. Patients who return the opt-out card will not be contacted. For interested patients or those who do not return a response card, study staff will call them to conduct the informed consent process (for those who have not already consented to participate in the study) and administer the surveys over the phone as appropriate. No more than 3 phone contacts would be attempted to enroll potential patient-subjects that did not return an opt-out postcard. Participants who mail back completed surveys will be considered consented into the study as indicated by their completion of study instruments.

Participants will be paid $20 as compensation for their time for completing the set of surveys, and $50 for interviews. Total compensation if patients complete the set of surveys and the interview would be $70.

10 Pre-screen, chart abstraction, initial review

Coordinating center study staff will interrogate VACS data and the VA corporate data warehouse (CDW) weekly to identify eligible patients (i.e. HIV+ patients with COPD who are seen by enrolled ID providers) and their upcoming clinic visits. VACS data from 2001-present include EHR, VA national administrative databases, Medicare/Medicaid, and yearly surveys. We will identify patients being treated for COPD using methods we have previously published. We will consider a patient as having COPD if they have: 1) ≥2 outpatient diagnoses of COPD, 2) Have an inpatient discharge diagnosis of COPD, 3) ≥1 outpatient diagnosis of COPD and receive 2 or more dispensing treatments for COPD maintenance medication (LABA, ICS or LAMA), oxygen therapy, or nebulized medications, or 4) ≥3 dispensings (typically a 9 month supply in one year) of an inhaled anticholinergic medication.[1, 57]

Prior to the clinical review meeting, coordinating center study staff will review patient charts to confirm diagnoses of HIV and COPD. Study staff will then abstract pertinent information to an abstraction template for review by the intervention team. CAPRI/ Joint Legacy Viewer as national data sources will be used for medical record access and/or medical chart abstraction.

11 Intervention

The intervention consists of a clinical intervention study team reviewing the medical chart of eligible HIV+ patients with COPD diagnoses whose infectious disease (ID) provider is participating in the study. The intervention team (Table 5) will include at least one pulmonologist from the coordinating center (two if no site pulmonologist is able), a pharmacist, and may include one of the site pulmonologists.

Table 5. E-consult Intervention Team Members
Coordinating Center (one or more will attend meeting)
Pulmonologists (Au, Crothers, Feemster, Donovan, Spece)
Pharmacist (Woo)
Clinical Site (may attend meeting to review patients of providers enrolled at their local site)
Pulmonologists (Akgun, Maximos, Soo Hoo, Wongtrakool, Griffith)

The study team identifies any gaps in evidence-based care for COPD. For providers randomly selected to the intervention arm of the study, the study team offers the ID provider tailored evidence-based treatment recommendations, via electronic health record (EHR) E-consult and pre-filled order sets, aimed at filling those gaps. The ID provider may accept, modify, or decline any or all the recommendations based on their personal knowledge of the patient's history. The ACHIEVE intervention team follows-up with interpretation of diagnostic testing or to answer questions and provide guidance as desired by the ID team. At any point, providers can communicate with the intervention team via any of the usual modalities (VA ECHO, secure email, telephone, EHR) or request an in-person consult with a pulmonary provider at their facility. Due to the nature of the intervention, it is impossible to conceal treatment assignment from providers.

We have tested all the procedures in this protocol and have direct experience with using this type of approach for multiple QI initiatives and research studies including clinical trials.[93-95] The design of the intervention is also informed by our prior work on specialty care initiatives[82, 85-88], others' research on HIV-remote access models in VA[83, 84, 96] and work outside VA;[89] and by CFIR constructs.

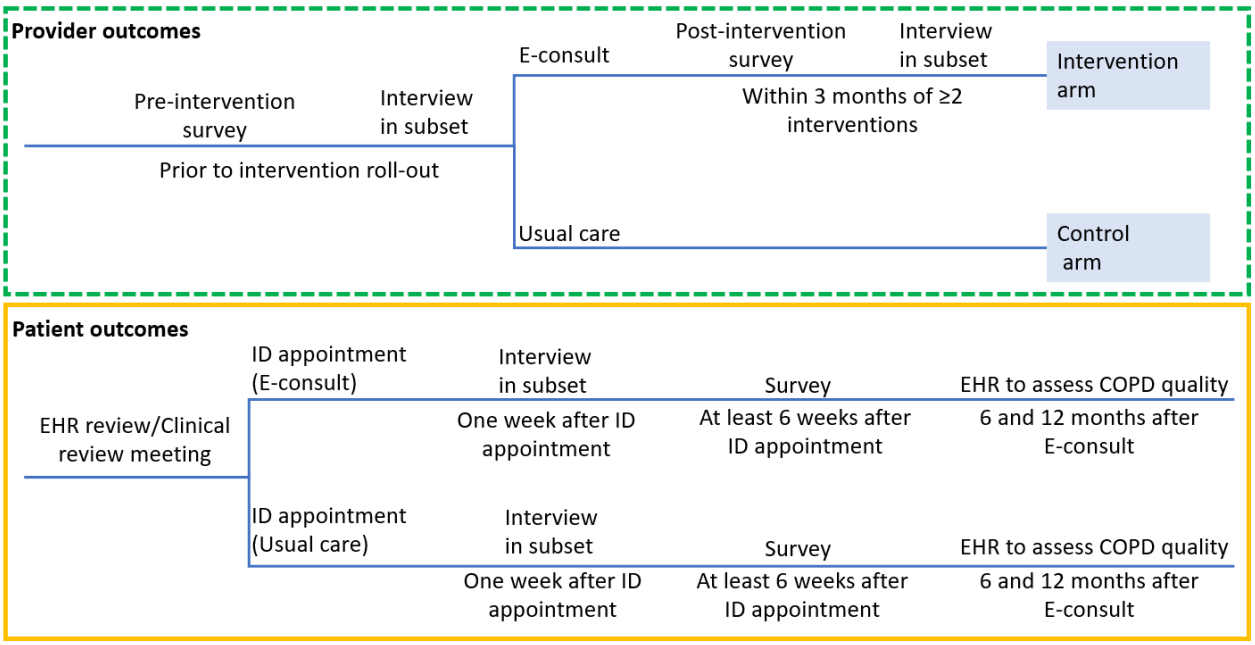
Table 6. Key recommendations in the E-consult intervention to implement evidence-based, high quality COPD care for people living with HIV	
Evidence-based recommendations	**Eligible COPD patients**
Diagnostics	
1. Confirmation of COPD by lung function assessment (e.g. spirometry)	All
Preventative Therapy	

2. Assessment of smoking status	All
3. Referral/counseling for smoking cessation, provision of pharmacological therapy	All who currently use tobacco products
4. Influenza vaccination during appropriate season	All
5. Pneumococcal vaccination as recommended for PWH	All
6. SARS-CoV2 vaccination as recommended for PWH	All
Assessment of Severity and Disease Control	
7. Assessment of resting O_2 saturation or PaO_2	All
8. Assessment of respiratory symptoms and symptom burden	All
Assessment of appropriateness of pharmacological and other therapeutics	
9. Addition of at least one long-acting bronchodilator (LABA, LAMA) in symptomatic patients who are no long-acting bronchodilators as first-line therapy or addition of second, other long-acting bronchodilator (LABA, LAMA) in symptomatic patients who are only on one long-acting class of bronchodilator	Those with respiratory symptoms
10. Addition of ICS to patients with prior exacerbation (one inpatient or two outpatient) in the past year who are on first line therapy, or with features of asthma-COPD overlap	Prior exacerbation in past year or asthma-COPD overlap features
11. Addition of another controller agent (roflumilast or azithromycin) to triple inhaler therapy (LABA, LAMA, ICS)	Prior exacerbation, more severe COPD
12. Discontinuation of roflumilast, and/or azithromycin	Mild COPD, no exacerbations in past year
13. Discontinuation of ICS	Mild COPD, no exacerbations in past year
14. Provision of O_2 for long-term continuous therapy	If resting SpO_2<88% or PaO_2<55mhg
15. Referral to pulmonary rehabilitation program	Symptomatic, functionally limited patients

We have developed a standardized approach to providing evidence-based recommendations for high-quality COPD care (Table 6).[14, 73, 97] New evidence that is published can be included in recommendations, if appropriate. Because the intervention team is spread throughout the country, we will formalize our review process using the VA ECHO infrastructure. Prior to launch we will meet one to two times per week to review sample charts of patients and develop an inventory of common situations as we have done for other projects. In our study of de-implementing ICS, we found that 2-3 months of review was sufficient to identify the majority of situations we would experience. We will abstract pertinent health information from the EHR to review (including pulmonary function test results, medication lists, allergies, exacerbation history, relevant comorbidities, prior hospitalizations and clinical notes describing symptoms). After launch, in the week prior to a patient's scheduled appointment with their ID provider, the intervention team will review the abstracted information and EHR notations. We will tailor recommendations for COPD care in context of HIV+ patients, paying particular attention to drug-drug interactions with antiretroviral therapies. Templates developed will be refined and ultimately used as part of implementation tool kits to the field.

12 Outcomes Assessment

Figure 1 (below) summarizes outcomes assessment timeframes.



Timeline depicting data collection for ID PCPs and patients for intervention vs. control arms of the study.

Our primary outcome measure to assess effectiveness of the intervention will be the quality of COPD care. We will assess the overall quality of COPD care at 6 months after the indexed appointment date (that is, the date of the appointment of an HIV+ patient with COPD of an enrolled provider whose care was reviewed by the intervention team) as the primary outcome, and again at 12 months as a secondary outcome. This period allows adequate time for patients to receive the recommended care and to help assess maintenance. The quality of COPD care after the development of the E-consult is defined by the proportion of recommendations fulfilled by the provider out of all the recommendations that were made. We will abstract this information from the EHR or CAPRI/Joint Legacy Viewer, including notations (all clinical notations, discharge summaries), orders, referrals, medication lists, and durable medical equipment supplies. We will use a composite measure of quality metrics endorsed by the NQF, NCQA and ATS/ERS.[73, 97] The measure can be expressed as the proportion of recommendations that a patient is or has received out of the total number of recommendations that they are eligible for.[51] We can also dichotomize this measure to include those patients who achieved all of the recommended care processes for which they were eligible (score =1) versus those who did not (score =0). Measures may be assessed individually or grouped based on whether they apply to all HIV+ COPD patients (tobacco use, vaccinations, spirometry) or specific to symptoms and severity of COPD (medications, pulmonary rehabilitation). These recommended processes are listed in Table 6. We will also review the number of orders that were accepted, declined and modified.[81]

Highly important secondary outcome. As a patient centered outcome, we will assess health status using the SF-12 PCS score; a difference of four is considered clinically meaningful.[103] A generic measure is preferable in this intervention as a number of the patients that we intervene upon will likely not have COPD once spirometry is obtained.

Interviews

We will use provider and patient interviews to identify key factors influencing adoption, implementation and maintenance of the intervention.

Provider interviews. A sample of providers will be interviewed in the 3-month period prior to starting the intervention, as well as after receiving at least 2 E-consults. Providers and service line leader interviews are structured to elicit descriptions of: 1) facilitators or barriers to adoption, implementation and maintenance; 2) strategies that may be useful in the refinement of subsequent roll-out phases; and 3) further feedback on improving the rationale for recommendations in the E-consult. The providers will be selected purposively to represent a range of demographic (e.g., sex, age, race/ethnicity) and intervention-utilization characteristics (e.g., acceptance/rejection and number of recommendations).[99] The goal for this sample will be to capture the depth and breadth of providers' experiences, including acceptability, feasibility and satisfaction with the intervention and its effectiveness. We will interview specialty service line leaders (ID, pulmonary) about organizational and programmatic characteristics that may influence acceptability and future implementation.

Patient interviews. A sample of patients will be interviewed as soon as possible after an indexed appointment with their ID provider. (See section 7.3 for a description of patient recruitment for interviews.) Patient interviews are structured to elicit descriptions of patients' experiences of HIV and COPD care; care continuity; satisfaction and access to specialty care. This will be important for understanding patient-level factors that may affect optimal COPD care, e.g. negative reaction to having medications taken away, and patient-level factors that may affect implementation of E-consults, e.g. preferences to receive care directly from specialists vs. from their own PCP. Guides will be adapted iteratively to incorporate emerging themes. We will purposively sample patients based on site, seeking to recruit roughly equal numbers of patients from each of the 5 sites. We will also purposively sample patients to capture the demographic characteristics of the HIV+ population. We will interview patients until we reach thematic saturation, which is anticipated to be a minimum of 30 interviews or possibly more. After thematic saturation is reached, we will stop the interviews and thus do not anticipate offering the interview to all patients.

Structured surveys

Surveys will be administered to participating providers and to HIV+ COPD patients after the intervention (Figure 2). Survey data will be used to assess potential patient and provider-level implementation determinants and to assess changes in perceptions of ID provider awareness of optimal COPD care before and after the E-consult intervention.

Provider surveys will be web-based and fielded using REDCap in the 3-month period prior to beginning the study, and after the provider has received at least 2 interventions. Links to ID providers will be sent and tracked within the VA firewall. Individualized reminders can be sent to those who have not completed the survey. Consequently, we anticipate achieving a considerably higher response rate than conventional surveys. We will adapt a previously-developed provider survey for an E-Consult intervention that measures some of the constructs in our conceptual model, such as self-efficacy, leadership support and patient needs. We will use baseline interview findings to adapt the survey to include measures of other constructs in the model and any key emergent findings from interviews, similar to our mixed-methods approach that successfully used interview findings to inform survey data collection in our national evaluation of E-Consult and ECHO implementation.[87]

Patient surveys

Patient survey items will include the SF-12, a widely used generic health status instrument[100-102] including among patients with HIV and COPD;[63, 101, 103, 104] the SF-12 can be administered in 3-4 minutes via a number of routes, including telephone and self-completed mailed survey.[105] Other items include the Seattle Outpatient Satisfaction Questionnaire (SOSQ),[106, 107] a valid, reliable instrument will assess patient satisfaction, and the Clinical COPD Questionnaire (CCQ) to assess symptoms, functional status, and COPD control[108-110] across a range of COPD severity. The CCQ also is responsive to change, with improvements detected in healthy smokers two months after smoking cessation.

Table 7. Summary of data elements and outcome measures		
Source		
Outcome measures	*Quality of COPD care (primary): Defined as % of COPD care recommendations accepted by the provider, examined collectively for each patient and individually by type of recommendation (e.g. use of spirometry, long acting bronchodilator, smoking cessation, vaccination, etc.)*	*Record review, VA data abstraction*
	SF-12 (Highly important secondary outcome measure)	*Patient self-report via survey*
	Clinical COPD Questionnaire (Secondary)	*Patient self-report via survey*
	Provider satisfaction (Secondary)	*Provider self-report via survey*
	Patient satisfaction (Secondary)	*Patient self-report via survey*
	Resource utilisation (clinic visits, hospitalizations, etc.)	*VA data warehouse*
Covariates (patient and provider)	*Demographics including: Age, income, education, marital status, race, gender; and utilization characteristics: care at VAMC, outside VA care, travel distance to VA*	*Patient self-report; VACS data*
	Habits (tobacco, alcohol); Comorbidity; VACS Risk Index scores; labs (CD4, HIV viral load)	*VACS data, VA EHR data and record review*
	Medication use (antiretrovirals, other)	*VA EHR data*
	COPD severity (COPD hospitalizations, exacerbations, oxygen use)	*Record review, VA EHR data*
	Training type (e.g. PA vs. MD) and status of the provider	*Provider self-report via survey*
	Turnover and vacancies in the PCP's clinic	*Provider self-report via survey*
	Panel size of the provider	*Record review*
	Length of VA service of the provider	*Provider self-report*

13 Withdrawal of Subjects

PCP subjects will be instructed to email the coordinating center study team email address to indicate if they wish to withdraw from the study. If we are contacted by phone by a participating PCP indicating they wish to withdraw, we will confirm their withdrawal via email. This is explained in the information statement. We will use a tracking database for participating providers and will include a data field for study withdrawal. We will use the tracking database to produce current participant lists for any study activities, including for identifying patient charts for review, fielding surveys and conducting interviews. If a provider chooses to withdraw from the study, we will contact patients of that provider with whom we have already made contact and give them the option to withdraw from or remain active in the study (i.e. to complete surveys or interviews still outstanding).

For patients, their engagement in research activities is limited to surveys and interviews, which are not repeated. If a patient indicates they do not wish to participate in a survey or interview, their decision to not participate will be tracked in the tracking database and they will not be contacted again. If a patient has begun a survey or interview and indicates they do not wish to

complete the survey or interview, we will record their decision to not participate in the tracking database and they will not be contacted further. We will confirm with the individual that we may continue to follow his/her EHR. If the individual declines, we will respect his/her choice and not collect additional data; however, we will use any data collected up to their withdrawal from the study.

8.0 Data Analysis

SA1 Data analysis: Our two-arm parallel cluster randomized controlled trial design, through its randomized intervention allocation, offers several advantages to validity compared to observational approaches. The clustered design also requires additional analytic evaluation compared to a simple two-arm randomized trial. We will perform an intention-to-treat analysis as we have done in previous studies;[48] and will include all patients for providers assigned to the intervention arm, even if the patient does not show for their scheduled visit or adhere with the recommendations (e.g., completing spirometry).

For our primary outcome, we will assess quality of COPD care at 6 months using a mixed-effects logistic regression model that explains variation in log odds of accepting a given COPD care recommendation. The primary analysis model will include a fixed effect indicator of treatment arm to allow testing for a non-zero treatment effect and random effects to account for clustering of outcomes within provider. The secondary analysis model will additionally adjust for observed variables that (1) are known to have an association with the outcome, and (2) are imbalanced across treatment arm with respect to mean (continuous variable) or proportions (dichotomous and categorical variables).

Our SF12 PCS score secondary outcome will be modeled using mixed-effects linear regression. Covariate adjustment in SF12 PCS primary and secondary analysis models will be handled similarly to the approach used in modeling the primary outcome.

For the proportion of recommendations for COPD care that providers accept (sign), we will determine outcomes through the EHR or CAPRI/Joint Legacy Viewer and anticipate a high degree of outcome completion. For the analyses of SF12 scores, we estimate our response rate on the surveys from our prior work to be about 50% (conservatively 250 responders out of 600 patients surveyed). We will perform sensitivity analysis to assess for the effect of missing data. We will compare information from the EHR on those that complete and do not complete the survey. “Imputation using chained equations” will be used for patients who were lost to follow up or those who had any missing covariate information.[94, 117, 118] The sensitivity of findings to missing data approach will be assessed through comparisons of complete-case analyses to analyses of data completed through multiple imputation.

SA1 Sample size: To estimate sample size, we rigorously considered a range of scenarios . Using an informed estimate for number of providers at our 5 sites, an average number of patients per provider, an average number of recommendations per patient, and an mmax (maximum number of recommendations per provider), we present one such reasonable estimate to illustrate the magnitude of effect we could detect with a power of 80%: We assume that, among enrolled sites, we will have (X1=55) providers seeing an average of (X3=5) patients each. Patients are assumed to have an average of (X2=4) recommendations each, implying (X6=1,100) total recommendations among (X4=276) patients. Based on a significance level of 0.05, 80% power, provider cluster sizes not exceeding 50 recommendations, and intracluster correlation (ICC) of 0.134 (estimated from our preliminary data from Dr. Au’s InCasE study), we conservatively

estimate having the ability to detect Cohen's h effect sizes greater than 0.47 as statistically significant. If we assume that the control arm percentage of patients receiving recommended, high-quality COPD care at 6 months is 25%, then intervention arm percentages of either ≤8.2% or ≥47.1% will lead to rejecting the null hypothesis of zero effect size. With all else unchanging, if we instead assume that ICC is equal to twice our data-driven estimate of 0.134, our minimum detectable effect size increases from 0.47 to 0.64, with intervention arm percentages ≤4.2% and ≥55.6% leading to null hypothesis rejection given a 25.0% control arm percentage. If ICC is equal to half our data-driven estimate, our minimum detectable effect size decreases from 0.47 to 0.35, with intervention arm percentages ≤11.7% and ≥41.3% leading to null hypothesis rejection given a 25.0% control arm percentage.

SA2 Data analysis: Qualitative data analysis. We will use a rapid qualitative analytic process[120] to analyze interview data at the site level in order to provide formative feedback to the intervention team. Immediately after interviews, the qualitative team will review and revise interview notes. Within two weeks of the interview, the team will compile all interview notes, and create tables summarizing and categorizing key barriers, facilitators and recommendations by provider type and site. This will allow us to immediately produce structured summary findings to the E-Consult intervention team about potential changes to consider for the formative evaluation, while retaining more detailed notes for subsequent analyses related to our more theoretically oriented analysis of CFIR constructs to contribute to implementation science. Interview guides will be adapted iteratively during data collection to better understand themes as they emerge. Following rapid analysis the audio and notes will be analyzed using simultaneous deductive content analysis guided by CFIR and inductive content analysis.[121] Data management and analysis will be performed using Atlas.ti ® software.

Mixed methods process. We will also conduct mixed-methods analyses with interview and survey data to triangulate, and compare the survey (quantitative) analyses and interview (qualitative) datasets.[122, 123] This will provide more robust findings by combining qualitative findings (rich but from a small number of interviews) with quantitative findings from surveys (from a larger sample but limited numbers of question with constrained responses). We will specifically code interviews for constructs assessed in the survey, such as awareness of COPD guidelines and potential harms from suboptimal care such as inappropriate ICS prescriptions.

Sampling and non-response bias and missing data: We will purposively sample PCPs from each site, and will attempt to interview the same PCPs in each wave. If there is turnover or unanticipated difficulty obtaining provider participation we may have to interview different providers after the intervention than at baseline. This could introduce bias comparing baseline and follow-up interview themes, with differences potentially emerging due to the individuals differing and not an effect of the intervention. We will compare findings for just interview participants that we have at baseline and follow-up to see if themes differ.

SA2 Sample size: In accordance with usual qualitative procedures, we will conduct interviews until we reach theoretical saturation, that is, when no new or novel insights (no new themes) are provided.[124, 125] We will conduct an additional 3 interviews after no new themes emerge to ensure that saturation has been reached. We anticipate conducting a minimum of 30 interviews each with patients and with providers. For post-intervention interviews, we will interview providers after a least two of their patients have received intervention recommendations. We will survey all providers participating in the study; the study is not powered on provider survey findings and we anticipate using survey findings primarily in the mixed methods analysis.

9.0 Potential Limitations

Threats to validity: Contamination: The threat to validity because of contamination is small. Contamination, in the current design, may occur if providers in the intervention group influence those in the control group. This is an unlikely scenario as the intervention feedback is highly individualized to the patient-provider unit, and the intervention will occur relatively infrequently for any particular provider. Secular trends: Changes in quality of care for patients with COPD is possible over time. However, we doubt that this would represent a significant threat given the current body of literature. In addition, our analytic models will include fixed terms for modeling time.

Nature of the intervention: We have proposed a multifaceted intervention based on an abundant literature that suggests that one-dimensional interventions are rarely effective at changing provider behavior, and that multifaceted interventions are preferential and more likely to be effective at changing provider behavior. To assess the effects of individual components would require a factorial design, which is not feasible due to the increased complexity and the loss of statistical power. In addition, active interventions are more likely than passive interventions (such as mailing to targeted providers, requiring providers to enter orders) to affect change. We have incorporated interventions that are known to be effective at changing physician behavior including audit and feedback with patient level recommendations for care, direct input and availability of pulmonologists, and local opinion leaders.

Inertia of prior practice: There are many potential reasons for resistance to changes in clinical practices. The principle concern is that we are introducing an intervention that may increase provider workload. We are aware of this potential problem and are committed to working within the contextual features of each clinic and our prior experience makes us confident that we will be able to avoid this pitfall. To minimize workload and facilitate the intervention, orders are pre-entered for providers.

Generalizability: The intervention resides solely within the VA and may therefore limit generalizability to other VA settings and non-VA settings. We believe that our intervention can be adapted by other VA medical centers using currently existing data resources such as the CDW. In addition, with increasing degree of consolidation within healthcare and development of accountable care organizations with EHR infrastructures, approaches like ours will be increasingly feasible throughout the US and internationally. Thus, the blueprint that we are developing for this intervention is promising for wider dissemination to other health systems. Finally, although the patients are Veterans, the HIV+ target population within the VA is racially and ethnically diverse and overall similar to the general demographic of the HIV+ population in the US.

10.0 Reporting

14 Role of collaborating institutions in the oversight of human subjects research.

This proposal is a collaboration between Dr. David Au, Seattle Institute of Biomedical and Clinical Research (SIBCR) PI, Dr. Christian Helfrich, VA Puget Sound, and Dr. Kristina Crothers, based at the VA Puget Sound in Seattle. Participating sites where providers and patients are located are the Atlanta VA Medical Center (VAMC), Denver VAMC, Greater Los Angeles VAMC, Washington DC VAMC, Nashville VAMC, Philadelphia VAMC, and the West Haven VAMC Dr.

Au will serve as the contact PI. SIBCR is a non-profit institute that administers VA grants. By virtue of his SIBCR affiliation, Dr. Au is a Veterans Affairs (VA) salaried health services investigator, and part of his research team is employed through the VA. Drs. Au, Crothers and Helfrich will work closely together to assure that all investigators and staff named on the study will abide by applicable laws and regulations regarding the protection of patient privacy and confidentiality in human subjects research.

15 Data and Safety Monitoring Plan

Data and Safety Monitoring Board (DSMB). An independent DSMB will be established in accordance with VHA Handbooks 1200.05 and 1204.01, NHLBI policy, and in consultation with the VA Puget Sound IRB. The DSMB will examine interim study results on a periodic, scheduled basis to recommend early termination if outcomes are statistically poorer for patients whose provider received the intervention.

16 Safety monitoring.

Project staff will be trained to identify and report all potential adverse events (AE). Coordinating center study staff may query for AEs over the phone when patients are contacted to complete surveys (approximately six weeks after an appointment with an enrolled provider) and systematically by querying patients' electronic health records (EHR) six months after their outpatient clinic visit. The collection of AEs at approximately six weeks and the systematic collection via the EHR at six months will be conducted for patients of providers in both the control and intervention arms of the study. AEs and unanticipated problems (UP) may also be discovered incidentally by coordinating or local site study staff. In the event that an AE/UP be identified by local site study staff, it will be reported to the coordinating site as well as to the local site IRB per that site's IRB requirements. AEs discovered will be reviewed by the MPIs, and reported to the IRB, DSMB, and Sponsor according to their requirements. In addition, a statistical summary of the numbers and types of all adverse events will be prepared and provided to the DSMB on a quarterly basis. This systematic, non-biased monitoring process will ensure that any group disparities will be found and addressed. If, at any time, the investigators believe they are seeing an unexpected increase in SAEs or in AEs that is a cause of concern, this will be specifically brought to the attention of the DSMB and their advice will be sought.

Dr. Au or Dr. Crothers will assess (using chart abstraction) each AE for duration (start and stop dates and times), expectedness in the study population, severity, outcome, treatment and relation to study activity. The following are expected adverse events in the ACHIEVE population of HIV+ patients with COPD:

As this is a population with COPD and HIV, we anticipate that the following events or new diagnoses are likely to occur because these patients are at increased risk for these conditions; we do not anticipate that participating in this study will increase the risk for these events beyond what is normally expected as a result of having these diseases and using standard therapies to treat these diseases:

- COPD exacerbation
- Worsening of COPD (decrease in lung function, development of hypoxemia, death)
- Pneumonia
- Thromboembolic disease
- Sleep-disordered breathing
- Lung or other cancers
- Tobacco use disorder

- Ischemic heart disease
- Cardiac arrhythmias
- Development of other conditions associated with COPD and also with unhealthy health behaviors, such as from tobacco and alcohol disorders (e.g. cancer)
- Other age-related illnesses, such as urinary tract and skin infections
- Mental health disorders prevalent in HIV-infected patients and Veterans including depression
  Cognitive dysfunction, common in HIV-infected patients

Patients who are started on inhaled therapies as a result of the E-consult intervention may experience known side effects from these medications. These anticipated side effects include:

- Side effects of bronchodilators (short and long-acting): throat irritation, palpitations, tachycardia or other arrhythmias, nervousness, shakiness, stomach upset, headache, dizziness, weakness, sweating, chest pain.
- Side effects of inhaled corticosteroids: throat irritation, hoarseness, thrush, pneumonia, hyperglycemia, bone loss (osteopenia/osteoporosis).
- Azithromycin: diarrhea, nausea, abdominal pain, loose stools, dyspepsia, hearing loss, prolonged QTc.
- Roflumilast: nausea, vomiting, diarrhea, weight loss, headache, back pain, insomnia, decreased appetite, dizziness.

Patients with more severe COPD may also be referred for additional clinically indicated therapies that can have known side effects that include:

- Side effects of pulmonary rehabilitation: Fainting, dizziness, chest pain, lower extremity claudication, mental confusion.
- Side effects of oxygen therapy for hypoxemia: Burns (from smoking while using O2, using O2 around flame or sparking equipment, frost buildup on liquid systems), nosebleed or dry nose, musculoskeletal injury from tripping over oxygen cords

Patients who have inhaled or other therapies discontinued because they do not have clinical indications for them may experience side effects that include:

- Worsening of respiratory symptoms

A pharmacist is part of the intervention team to review medication lists. Common drug interactions between specific antiretrovirals and inhaled medications include:

- Ritonavir and all protease inhibitors (PIs), and elvitegravir (Integrase strand transfer inhibitor [INSTI]), can interact with Inhaled corticosteroids (ICS), particularly fluticasone and budesonide. Beclomethasone is thought to have the least interaction. The interaction can result in hypercortisolism (Cushing's syndrome).

17 Stopping rules.

Given that the intervention is a variant of normal care and that the likelihood for unanticipated adverse events is low, formal stopping rules for safety, efficacy, and futility are not proposed. However, rules may be established per recommendations of the DSMB following the funding of the grant. Evidence of extremely low rates of provider participation, extremely high rates of

provider drop-out, and/or a marked difference in the rates of AEs will trigger further consideration by the DSMB to decide whether the trial should continue.

18 Data quality monitoring and handling procedures.

To ensure all elements of the study protocol are followed and that study goals are met, the project manager will conduct bi-weekly meetings with project staff to review study procedures and status, barriers encountered, and develop responses to any identified issues. To ensure data accuracy, either Dr. Crothers, Dr. Feemster, Dr. Donovan, Dr. Spece or Dr. Au will review accuracy of chart abstractions, data collection sheets, and template recommendations with a 5% full-audit review each month. Results will be reviewed at regular staff meetings and study coordinators will receive individualized feedback to correct any error patterns. Double data entry and data field validation rules for structured fields will be used as quality control measures. The study manager will prepare quarterly reports for review by the research team to identify any potential concerns regarding data accuracy and completeness. All members of the research team will complete and maintain required human subjects, good clinical practice, and HIPAA training, including training in data handling and confidentiality. All electronic and non-electronic data will be stored and handled as described earlier. All breaches of confidentiality will be reported and resolved according to IRB, VA Privacy, and Information Security regulations.

Data Collection**:** To ensure rigor and reproducibility, we will review accuracy of chart abstractions, data collection sheets, and template recommendations with monthly audits. Double data entry and field validation rules for structured fields will be used as quality control measures.

Qualitative interviews. Dr. George Sayre will train and oversee research assistants to interview participating providers and HIV+ COPD patients who receive the intervention (see Figure 2). We will use guides adapted from our ongoing study to de-implement inappropriate ICS (see Appendices A-C). Interviews will be recorded using VA approved recording devices or software applications. Interviewers will complete field notes (context of the interview, emerging themes or issues, areas for clarification).

11.0 Privacy and Confidentiality

This study will use PHI. We will not disclose the PHI outside the VA.

To ensure the data are secure, the study team will code study data with a unique study code. The researchers will maintain data on the VA HSR&D network in password protected and permission specific directories and databases. Our network has multiple levels of protections and access is restricted to IRB-approved staff. If a staff member leaves the study, we will remove his/her permissions to access the data. We will follow all VA HSR&D data security policies.

Paper copies will be stored in a secure office suite in locked files accessible by approved study staff only. The ISO and Privacy Officer will be notified within one hour of the improper use or disclosure, as well as any other local policies.

All study information is accessible only by IRB approved study staff on a need-to-know basis.

To report study results, we will use only aggregated data or otherwise unidentifiable data (e.g., any identifiers will be redacted when reporting illustrative quotes from interviews).

The study team considers all participant information confidential. We will share information with participants' physicians only as needed to protect participants' safety. We inform the participant of this practice as part of the informed consent process.

A certificate of confidentiality will be granted by NIH, and is described in the patient Information Statement.

12.0 Communication Plan

To ensure all elements of the study protocol are followed and that study goals are met, the project manager will conduct regular meetings with project staff to review study procedures and status, barriers encountered, and develop responses to any identified issues.

13.0 Information Security and Data Storage/Movement

ACHIEVE staff will store paper-recorded data in secure, locked file cabinets within HSR&D secure office suite, and electronic data in password protected files on secure VA network servers or VA Office of Information and/or Technology (OI&T) managed archived back-up media, according to VA data security policy. Our network has multiple levels of protections and access is restricted to IRB-approved staff. Limited analytic datasets are shared between authorized study personnel via secure transmission and/or via a secure virtual private network employing industry-standard password protection and data encryption. Study information is not disclosed to any third party except as required by law.

Once the study is closed, we will retain these research data for the minimum period required for records retention in accordance with the National Archives and Records Administration (NARA) VHA Record Control Schedule (RCS). The VAPSHCS 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 research data records in the possession of VAPSHCS will be destroyed. At this same time, we will also work with VINCI staff to destroy these records from any VINCI server(s) and archived tape backups/media. 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 by a method to be determined by the VAPSHCS Information Security Officer (ISO) in a manner that is compliant with VA Handbook 6500.1 and National Institute of Standards and Technology NIST SP 800-88.

A de-identified data set will be submitted to the NHLBI study Program Official no later than 3 years after the end of the clinical activity (final patient follow-up, etc.) or 2 years after the main paper of the trial has been published, whichever comes first. Data are prepared by the study coordinating center and sent to the PO for review prior to release.

Study staff will enter all study data into SQL databases housed within HSR&D. All data entry systems will employ automatic, real-time range, logic, and missing value checks. We will employ double data entry and logic controls to minimize data entry error. We will maintain one official copy of all the study data and a master data dictionary.

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ACHIEVE – Data analysis and sample size

SA1 Data analysis: Our two-arm parallel cluster randomized controlled trial design, through its randomized intervention allocation, offers several advantages to validity compared to observational approaches. The clustered design also requires additional analytic evaluation compared to a simple two-arm randomized trial. We will perform an intention-to-treat analysis as we have done in previous studies;[48] and will include all patients for providers assigned to the intervention arm, even if the patient does not show for their scheduled visit or adhere with the recommendations (e.g., completing spirometry).

For our primary outcome, we will assess quality of COPD care at 6 months using a mixed-effects logistic regression model that explains variation in log odds of accepting a given COPD care recommendation. The primary analysis model will include a fixed effect indicator of treatment arm to allow testing for a non-zero treatment effect and random effects to account for clustering of outcomes within provider. The secondary analysis model will additionally adjust for observed variables that (1) are known to have an association with the outcome, and (2) are imbalanced across treatment arm with respect to mean (continuous variable) or proportions (dichotomous and categorical variables).

Our SF12 PCS score secondary outcome will be modeled using mixed-effects linear regression. Covariate adjustment in SF12 PCS primary and secondary analysis models will be handled similarly to the approach used in modeling the primary outcome.

For the proportion of recommendations for COPD care that providers accept (sign), we will determine outcomes through the EHR and anticipate a high degree of outcome completion. For the analyses of SF12 scores, we estimate our response rate on the surveys from our prior work to be about 50% (conservatively 150 responders out of 400 patients surveyed). We will perform sensitivity analysis to assess for the effect of missing data. We will compare information from the EHR on those that complete and do not complete the survey. “Imputation using chained equations” will be used for patients who were lost to follow up or those who had any missing covariate information.[94, 117, 118] The sensitivity of findings to missing data approach will be assessed through comparisons of complete-case analyses to analyses of data completed through multiple imputation.

SA1 Sample size: To estimate sample size, we rigorously considered a range of scenarios . Using an informed estimate for number of providers at our 5 sites, an average number of patients per provider, an average number of recommendations per patient, and an mmax (maximum number of recommendations per provider), we present one such reasonable estimate to illustrate the magnitude of effect we could detect with a power of 80%: We assume that, among enrolled sites, we will have (X1=55) providers seeing an average of (X3=5) patients each. Patients are assumed to have an average of (X2=4) recommendations each, implying (X6=1,100) total recommendations among (X4=276) patients. Based on a significance level of 0.05, 80% power, provider cluster sizes not exceeding 50 recommendations, and intracluster correlation (ICC) of 0.134 (estimated from our preliminary data from Dr. Au’s InCasE study), we conservatively estimate having the ability to detect Cohen’s h effect sizes greater than 0.47 as statistically significant. If we assume that the control arm percentage of patients receiving recommended, high-quality COPD care at 6 months is 25%, then intervention arm percentages of either $\leqslant$8.2% or $\geqslant$47.1% will lead to rejecting the null hypothesis of zero effect size. With all else unchanging, if we instead assume that ICC is equal to twice our data-driven estimate of 0.134, our minimum detectable effect size increases from 0.47 to 0.64, with intervention arm

percentages ⩽4.2% and ⩾55.6% leading to null hypothesis rejection given a 25.0% control arm percentage. If ICC is equal to half our data-driven estimate, our minimum detectable effect size decreases from 0.47 to 0.35, with intervention arm percentages ⩽11.7% and ⩾41.3% leading to null hypothesis rejection given a 25.0% control arm percentage.

SA2 Data analysis: Qualitative data analysis. We will use a rapid qualitative analytic process120 to analyze interview data at the site level in order to provide formative feedback to the intervention team. Immediately after interviews, the qualitative team will review and revise interview notes. Within two weeks of the interview, the team will compile all interview notes, and create tables summarizing and categorizing key barriers, facilitators and recommendations by provider type and site. This will allow us to immediately produce structured summary findings to the E-Consult intervention team about potential changes to consider for the formative evaluation, while retaining more detailed notes for subsequent analyses related to our more theoretically oriented analysis of CFIR constructs to contribute to implementation science. Interview guides will be adapted iteratively during data collection to better understand themes as they emerge. Following rapid analysis the audio and notes will be analyzed using simultaneous deductive content analysis guided by CFIR and inductive content analysis.121 Data management and analysis will be performed using Atlas.ti ® software.

Mixed methods process. We will also conduct mixed-methods analyses with interview and survey data to triangulate, and compare the survey (quantitative) analyses and interview (qualitative) datasets.122, 123 This will provide more robust findings by combining qualitative findings (rich but from a small number of interviews) with quantitative findings from surveys (from a larger sample but limited numbers of question with constrained responses). We will specifically code interviews for constructs assessed in the survey, such as awareness of COPD guidelines and potential harms from suboptimal care such as inappropriate ICS prescriptions.

Sampling and non-response bias and missing data: We will purposively sample PCPs from each site, and will attempt to interview the same PCPs in each wave. If there is turnover or unanticipated difficulty obtaining provider participation we may have to interview different providers after the intervention than at baseline. This could introduce bias comparing baseline and follow-up interview themes, with differences potentially emerging due to the individuals differing and not an effect of the intervention. We will compare findings for just interview participants that we have at baseline and follow-up to see if themes differ.

SA2 Sample size: In accordance with usual qualitative procedures, we will conduct interviews until we reach theoretical saturation, that is, when no new or novel insights (no new themes) are provided.[124, 125] We will conduct an additional 3 interviews after no new themes emerge to ensure that saturation has been reached. We anticipate conducting a minimum of 30 interviews each with patients and with providers. For post-intervention interviews, we will interview providers after a least two of their patients have received intervention recommendations. We will survey all providers participating in the study; the study is not powered on provider survey findings and we anticipate using survey findings primarily in the mixed methods analysis.

AdvanCing High-quality COPD care for people with immune dysfunction by Implementing EVidence-based management through proactive E-consults (ACHIEVE)

Researchers:

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Researchers' Statement

We are inviting you to participate in a research study. The purpose of this Information Statement is to give you information you will need to help you decide whether to be in the study. Please read this form carefully. You may ask questions about the purpose of the research, what we are asking you to do, the possible risks and benefits, your rights, as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not.

PURPOSE OF THE STUDY

The purpose of this research study is to find better ways to care for patients with an immune system condition who have chronic obstructive pulmonary disease (COPD). If this study is successful, we hope other hospitals will use our methods so other patients with an immune system condition and COPD may benefit as well.

This is a multisite research study, sponsored by the National Institutes of Health. VA Puget Sound Health Care System (VA Puget Sound) will join seven other VA sites for this study (Atlanta, DC, Denver, Los Angeles, West Haven, Philadelphia, Nashville). The VA Puget Sound has approved the enrollment of 150 providers and 600 patients into this study. We will approach 200 providers and 600 patients to participate. If you are interested and eligible to participate, your participation will take about one hour. All study procedures will take place by mail or over the phone, whichever is more convenient for you.

STUDY PROCEDURES

Our research team is reviewing the clinical care of patients with an immune system condition who have COPD. Our team is working with infectious disease providers to prepare a care plan for patients with COPD and related problems prior to their appointments. We have randomly selected providers to receive care suggestions from our research team, so your provider may or may not have received plan suggestions from our research team at the time of your recent scheduled appointment. To protect study validity, we cannot tell you if your provider received any care suggestions or not.

Qualitative interview

We will ask a small number of patients to participate in an interview, which should take about 30-45 minutes to complete. The purpose of these interviews is to better understand patients' experiences with access to and satisfaction with their COPD care.

For research purposes, we will audio-record the interviews for documentation, data analysis, and potential use in research publications and presentations. Once the study recordings are transcribed (written down word for word), we will include the transcripts as part of the data collected for the study.

If we ask you to participate in an interview, you may decline to answer any question. You may stop the interview at any time.

Structured survey(s)

We will ask all patients who enroll in the study to answer some survey questions, which will take you about 20 minutes to complete. You may choose to complete them by mail or over the phone. The questions will be related to your recent medical care and your health. You may decline to answer any question. We will not share your answers with your provider.

To complete the surveys, we will mail you the survey packet and a self-addressed, stamped envelope for returning the surveys once they are completed. Your feedback is important to us. By receiving feedback from patients with COPD, we hope to learn whether it is beneficial for primary and specialty care providers to work together on care plans, such as yours.

If you do not want us to call you regarding this study, please check "Please do NOT contact" on the enclosed pre-paid postcard and drop it in the mail. Otherwise, if we do not receive a response from you, a member of this study team will call you to discuss the study with you. At this time, you may ask any questions to help you decide if you want to take part in this research study.

POTENTIAL RISKS AND DISCOMFORTS

Survey questions and qualitative interview: If you are asked to take part in an interview, you may be uncomfortable answering some of the questions. You can skip any question you do not want to answer. You may stop the interview and/or survey at any time.

Privacy: There is a risk of loss of privacy (confidentiality) by participating in this study. We will protect all identifying health care information with great care. We have extensive measures in place to keep this from happening and expect these measures to protect your personal information. Although there are many procedures in place to protect your privacy, there is the potential risk that your information could be released by mistake. For details on the steps we will take to protect your confidentiality, please refer to the Confidentiality section below.

Audio-recording (if applicable): If you are asked to take part in an interview, we will not place your name or any identifying information on the audio-recording. However, please note that your voiceprint is considered a "personal identifier" according to the patient privacy rules, so the research team will ensure the security of these recordings. We will record the interview directly to a secure VA server using a VA-approved conference line. Our methods of securing your privacy and confidentiality are described in in the Confidentiality section below.

POSSIBLE BENEFITS

There may be no direct benefit to you by participating in this study, although you will contribute to information that may potentially improve care for patients with an immune system condition and COPD in the future.

CONFIDENTIALITY

Your research information will be kept confidential. However, some data will be shared, communicated, or stored during or after this research study.

The following list of people or groups may know that you are in this study. They may have access to your research records, which may include your medical records:

- Research team members
- Seattle Institute for Biomedical and Clinical Research (the nonprofit institute that works with VA Puget Sound to conduct research)
- Federal agencies including, but not limited to, the Food and Drug Administration (FDA), the Office for Human Research Protection (OHRP), the VA Office of Research Oversight (ORO), the VA Office of the Inspector General (OIG), and the Government Accountability Office (GAO)
- VA committees that oversee research, including the Institutional Review Board that oversees the safety and ethics of VA studies
- A Data and Safely Monitory Board (DSMB) who may review study information for patient safety purposes

Certificate of Confidentiality

We have been given a Certificate of Confidentiality from NIH. The researchers will use the Certificate to resist any demands, even by a court of law, for information that would identify you. You may still share information about yourself or your part in this research as you see fit.

The Certificate of Confidentiality does not protect us from:

- Disclosing information to the National Institutes of Health, the Sponsor of the study.
- Disclosing information to law enforcement authorities if we get any information that suggests the occurrence of child abuse, elder abuse, or your intent to immediately and substantially harm yourself or others.
- Giving the VA Puget Sound office that manages payments to subjects your name, social security number, address, and the name of this study.
- Giving your name to state, federal, and institutional offices involved in auditing or compliance of research, risk management, patient safety, and financial controls.

Study code and link

If you agree to participate in our study, we will assign you a study code number. We will not include your name or other identifying information on any of the information that we collect from you. Only your study code number will be used. We will keep a master list that links study participants' names to code numbers separate from the study data in a secure VA database with restricted access. Once this study is completed, we will keep the study data and code numbers in a secure database until VA receives authorization to destroy them in accordance with federal records regulations, (which will be a minimum of 6 years after the study has been completed).

Safekeeping and storage
We will store all study data on VA secure-password protected computers and/or locked files in secure offices that are accessible only to VA study research staff at each of the study sites.

If you participate in the qualitative interview, we will store the transcription of the recording with all other study data on the secure VA network. Therefore, the transcription will be labeled with your study code and will not contain your name, social security number, or other identifying information. In addition, we will not transcribe any personal identifiers if any are mentioned during the interview.

After study completion
In the future, researchers may write about the information collected from this research study. Any future publications or articles will not include any identifying information about you without your approval in writing.

Once this study is completed, we will keep your data and code in a secure database in accordance with the VA records retention policy (which will be a minimum of 6 years after the study has been completed). Future studies may use some of your coded study data. At the conclusion of ACHIEVE, we may send your data to a publicly available data repository sponsored by the National Heart, Lung, and Blood Institute. Researchers not affiliated with ACHIEVE can use this data for future research to address new questions.

OTHER INFORMATION

Your provider is fully in charge of your care. Any suggestions the research team may make will be approved or disapproved by your provider based on his or her best clinical judgment about your condition.

You do not have to take part in this study. If you are in this study, you can withdraw at any time. If you decide not to participate or to withdraw, no action will be taken against you; for instance, you will not lose your VA benefits. If you decide to withdraw from the study, no new information will be collected from you; however, data already collected will continue to be part of the analyses. To withdraw from the study, you may call our study line at <removed> and indicate you wish to withdraw.

COMPENSATION

To compensate you for your time and effort, we will pay you $20 for completing the set of surveys. If you are among the patients we ask to interview, we will pay you $50 for the interview once completed. In total, the maximum amount you can receive by participating in this study will be $70. It may take up to 10 weeks to receive a check in the mail.

To comply with Internal Revenue Service (IRS) guidelines, we will collect your social security number. You may receive an IRS Form 1099.

QUESTIONS OR CONCERNS RELATED TO THE STUDY

If you have questions about the study, you may contact the study team at <removed>. You may also contact the VA Institutional Review Board (IRB) Office at <removed> if you:

- Would like to speak with a neutral party who is not involved with this study.
- Have questions, concerns, or complaints about the research.
- Would like to verify the validity of the study.
- Have questions about your rights as a research subject.

An IRB is an independent body made up of medical, scientific, and non-scientific members, who ensures the protection of the rights, safety, and well-being of subjects involved in research.

RESEARCH SUBJECT'S RIGHTS

If you have any questions about the study purpose, procedures, risks, discomforts, possible benefit, choices available to you, or your rights as a research subject after reading this Information Statement, please discuss them with one of the researchers listed above prior to agreeing to participate in this research activity.

We very much appreciate your consideration
in participating in this study. Thank you!