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1.0 ABSTRACT

Adult smoking prevalence in the United States (US) is approximately 14% nationwide, yet significant disparities persist, including among adults with annual household incomes <$35,000 (21.3%), Medicaid recipients (23.9%), and the uninsured (23.9%). These populations are also less likely to receive smoking cessation assistance and to use evidence-based cessation interventions. Many public health agendas emphasize addressing these inequalities to reduce smoking related morbidity and mortality. To do this, we need to increase accessibility to cessation services among these populations. Community health centers (CHCs) are ideal settings to reach smokers who are socioeconomically disadvantaged as they provide care to 29 million patients, the majority of whom are uninsured or publicly insured. Integrating Quitline referrals into these settings has the potential to reach a large number of smokers. Bidirectional eReferral systems, which allow providers to send a referral directly to the Quitline from the electronic health record (EHR) and Quitlines to send information about the patient's disposition back into the patient's individual EHR, provide a platform for more efficient and standardized referral systems. This method has increased Quitline reach compared to faxed or indirect referral methods; however, the Centers for Disease Control and Prevention's goal for Quitlines to reach 8% of all tobacco users annually has not been met. A critical knowledge gap exists in how best to implement Quitline eReferral systems into health care settings to maximize the reach and effectiveness of cessation services. Enhanced academic detailing, which includes educational outreach and performance audit and feedback, can increase the use of best practices and the uptake of new processes and procedures among health care providers; however, enhanced academic detailing is infrequently used for Quitline referral implementation. Almost half of all US states report no staff training related to their provider referral programs. This cluster-randomized trial will recruit 20 Oregon CHCs (n~10,000 patients who smoke). Half of the clinics will be randomized to receive the Quitline eReferral system with enhanced academic detailing (intervention condition; n=10 clinics) and half to receive the Quitline eReferral system without enhanced academic detailing (comparison condition; n=10 clinics). This pragmatic trial will use EHR and Quitline data to assess rates of smoking cessation assistance reach and effectiveness among patients in the intervention clinics compared with rates among patients in the comparison clinics. We will also evaluate the cost-effectiveness of the eReferral system, both with and without enhanced academic detailing. This scalable intervention has high potential to increase accessibility to smoking cessation treatment through the collaboration between state Quitlines and CHCs that serve large numbers of socioeconomically disadvantaged smokers. This study addresses the National Cancer Institute's research priority of developing targeted and scalable interventions to reduce smoking among this vulnerable population.

2.0 BACKGROUND / RATIONALE

Adult smoking prevalence in the United States is approximately 14% nationwide,[1] yet significant disparities persist, including among adults with annual household incomes <$35,000 (21.3%), Medicaid recipients (23.9%), and the uninsured (23.9%).[1] These socioeconomically disadvantaged individuals are also less likely to receive smoking cessation advice and assistance[2-6] and to use evidence-based cessation interventions.[7,8] Many public health agendas emphasize addressing these inequalities to reduce smoking related morbidity and mortality.[9,10] To do so, we must improve the availability of and accessibility to cessation services among these populations. Community health centers (CHCs) serve >28 million people, most of whom are publicly insured or uninsured;[11] thus, provision of cessation services to CHC patients is critical to reducing population-level smoking rates.

Quitlines are effective, evidence-based smoking cessation interventions.[12] Integrating Quitline referrals into primary care settings has the potential to reach a large number of smokers, as approximately 70% of smokers report seeing a physician annually;[13] however, Quitline referrals remain low. This is due in part to inefficient, unstandardized referral methods. Electronic health records (EHR) can support bi-directional eReferrals – referrals are sent directly to the Quitline and information from the Quitline is sent back to the EHR. As of June 2018, 25 states had implemented eReferrals with ≥1 health care partner.[14] EHR-based

referrals increase reach compared to other referral modes (fax, print),[15,16] but Quitline reach of all tobacco users remains well below the CDC's goal of 8%.[17] A critical knowledge gap is how best to introduce Quitline eReferral systems into health care settings to maximize the reach and effectiveness of cessation services among patients who smoke. One approach is enhanced academic detailing (AD). Enhanced AD, which involves educational outreach, technical assistance and performance audit and feedback, can increase the use of best practices[18] and the uptake of new processes and procedures among health care providers;[18-22] however, only about 50% of state Quitlines report any staff training around provider referral programs.[23]

In this study, we partner with OCHIN, a nonprofit health information technology organization that provides an Epic EHR system to CHCs nationwide (e.g. Federally Qualified Health Centers (FQHCs), FQHC lookalikes, and county clinics). We also partner with Oregon Health Authority (OHA), which includes the state's public health division and funds Optum, Oregon's Quitline provider, to conduct a pragmatic hybrid type III effectiveness-implementation[24] cluster-randomized trial in 20 Oregon CHCs (n~10,000 smokers). A Quitline eReferral system with a best practice advisory (BPA) that prompts and enables Quitline referrals for tobacco users will be built into the EHR of the study clinics. We will examine the reach and effectiveness of implementing the eReferral system using enhanced AD strategies designed to educate and train providers on Quitline services, eReferral workflows and evidence-based tobacco treatment guidelines (intervention condition) compared to implementation without this detailing (comparison condition). We will also evaluate the cost-effectiveness of the eReferral system in CHCs, both with and without enhanced AD.

This pragmatic study fills a critical knowledge gap of optimal implementation strategies to increase Quitline reach and tobacco cessation assistance in health care settings. This scalable intervention has high potential to increase accessibility to cessation treatment through the collaboration between state Quitlines and CHCs that serve large numbers of socioeconomically disadvantaged smokers. Our team has the experience and expertise to conduct this innovative study that addresses the National Cancer Institute's research priority of developing targeted and scalable interventions to reduce smoking among this vulnerable population.[25]

3.0 OBJECTIVES

Aim 1. Implement a Quitline eReferral system with enhanced AD (intervention; n=10 CHCs) and without enhanced AD (comparison; n=10 CHCs) to compare rates of eReferral *offers,* eReferral *acceptance* **(primary study outcome)**, Quitline *enrollment*, *orders* for cessation medication, and receipt of in-clinic *counseling* among patients identified as current users of tobacco.

Aim 2. Assess the effectiveness of implementing a Quitline eReferral system with enhanced AD (intervention) versus without enhanced AD (comparison) on self-reported tobacco quit rates among all patients identified as users of tobacco using EHR data.

Aim 3. Estimate the total annual costs and incremental cost-effectiveness of a Quitline eReferral system, with and without enhanced AD.

Baseline Exploratory Analysis. Examine rates of tobacco use and assessment in OCHIN primary care clinics prior the intervention start date, including if this varies by telehealth vs in-person visits.

4.0 STUDY POPULATION

Our study population for Aims 1-3 will include adult patients (≥18 years of age) who are identified as a tobacco user (combustible tobacco products and smokeless tobacco products) during ≥1 ambulatory or telehealth visit during the study period to one of the 20 OCHIN CHCs recruited for the study. We will

include all users of tobacco in our primary analyses as the Quitline provides services to support quitting all forms of tobacco. Given differences in FDA-approved medications for combustible vs. non-combustible tobacco use, and the fact that the majority of tobacco users are smokers, we will conduct additional analyses limited to those patients who smoke, and if sufficient sample size, among a subset of smokeless tobacco users.

Baseline analyses may be conducted to understand the rates of tobacco-related care prior to the intervention, which will include adult patients (≥18 years of age) who are identified as a tobacco user (combustible tobacco products and smokeless tobacco products) during ≥1 ambulatory visit from all OCHIN CHCs prior to the intervention start date (1/1/2019 to 1/1/2023).

5.0 INCLUSION/EXCLUSION CRITERIA

Study clinics. Eligible clinics are 1) in Oregon, 2) on the OCHIN Epic EHR for ≥1 year, 3) willing to be randomized to the intervention or comparison condition, and 4) willing to recruit a provider to serve as a clinic champion (to share monthly performance audit and feedback at all-staff meetings, determine desired content of booster sessions with clinic team members, and complete a survey at the completion of the intervention period) and a clinic manager to coordinate training and booster sessions.

Study patients. We include adult patients (≥18 years of age) identified as current tobacco users during ≥1 ambulatory and/or telehealth visit to one of the eligible study clinics over the intervention study period. Patients are asked by clinical staff about tobacco use during routine clinical practice and use is documented in either the vital signs or social history; over 95% of patients in the OCHIN network have current tobacco use assessments defined as a change in the tobacco use status field or by a checked box indicating status was reviewed. If identified as a current tobacco user during an office visit, a BPA will be triggered to remind the clinic team member to assess if the patient is ready to quit using tobacco and the patient is now considered a study participant; patients are not recruited for this study.

Baseline analysis. For baseline analyses, we include all OCHIN clinics and all adult patients (≥18 years of age) identified during ≥1 ambulatory and/or telehealth visit to any OCHIN primary care clinic during our baseline period (1/1/2019 to 1/1/2023). We include all patients and all clinics for our baseline period to better understand rates of assessment and changes in type of visit given disruptions to standard care procedures throughout the COVD-19 pandemic.

6.0 METHODOLOGY

This pragmatic study uses a parallel, two-arm, cluster-randomized controlled trial to assess cessation assistance reach and effectiveness of a bidirectional Quitline eReferral system in 20 Oregon community health centers (n~10,000 smokers total) on the OCHIN network randomly assigned to receive one of two eReferral implementation strategies: enhanced academic detailing (AD) (intervention) or standard practice (comparison) over anintervention period. We use a hybrid type III effectiveness-implementation design, with the primary aim to determine the impact of enhanced AD implementation strategy on Quitline reach and the secondary aims to assess the impact of implementation on clinical outcomes and cost-effectiveness of the intervention. [24,26] [24,26] Our primary analyses will be among patients who use any tobacco product; however, we will conduct additional analyses to examine reach and effectiveness limited to those identified as currently smoking at the time of visit, if sufficient sample size, among a subset of smokeless tobacco users. Randomization will be conducted at the clinic level.

Comparison Condition (n=10 clinics). The implementation strategy for clinics in this condition is designed to mimic how the Quitline referral systems are commonly implemented in the U.S., with little to no on-site training or enhanced AD activities. Clinics in this group will have the Quitline eReferral system implemented at the same time as clinics in the intervention CHCs. Prior to the eReferral being activated, the comparison clinics will be notified via email that the eReferral system is available with a link to an online publication on OCHIN's Learning Management System website. This is standard practice when OCHIN introduces a new functionality in the EHR system to their member clinics. It includes an online overview of Quitline services, information on Quitline effectiveness, and a detailed eReferral workflow with corresponding EHR screenshots, including how to identify eligible patients, create an eReferral, and access Quitline follow-up data in the EHR. As with any new functionality provided to clinics on the OCHIN network, clinics will have remote access to technological assistance, as needed.

Intervention Condition (n=10 clinics). In addition to the standard online materials that the comparison clinics receive and access to remote technological assistance, intervention clinics will also receive the enhanced AD intervention. The enhanced AD intervention includes 1) group training of clinic staff prior to activation of the eReferral system and 12 months post-activation, 2) follow-up booster sessions and; 3) monthly performance audit and feedback. The medical director at each intervention clinic will recruit a clinical provider to serve as a clinic champion to share the monthly audit and feedback reports at all-staff clinic meetings, determine desired content of booster sessions, and complete a follow-up survey at the end of the intervention period. The medical director also will recruit a clinic manager to coordinate trainings and booster sessions, as described below.

7.0 STUDY PROCEDURES AND SCHEDULE OF EVENTS

All study clinics will be notified of the eReferral system in the EHR through an online publication on OCHIN's Learning Management System website with online training materials around the eReferral workflow; this is standard for release of a new functionality in the OCHIN system. Clinics will also have remote technical support from OCHIN, as needed. Clinics will agree to either be randomized to have the Quitline eReferral implemented with enhanced academic detailing strategies (intervention condition; n=10 clinics) or without enhanced academic detailing (comparison condition; n= 10 clinics). The study staff will not have contact with clinical staff at the comparison clinics. In exchange for participation in the CONNECT study, participating clinics will receive an impact fee of $1,000 for the control condition, and $1,800 in the intervention condition.

Enhanced academic detailing will be provided to the intervention clinics, which will include trainings of clinic providers and staff once in Year 2 and once in Year 3, booster sessions six months after the enhanced academic detailing, and monthly performance audit and feedback reports. Dr. Bailey and/or another trained OHSU team member will deliver the group trainings on the eReferral workflow, education on Quitline services, and best practices for tobacco treatment in primary care at each intervention clinic at a time that is convenient for the clinic. Booster sessions will be delivered by members of the OHSU research team, and will be conducted via webinar. At each intervention clinic, the medical director will recruit a clinical provider to serve as a clinic champion, and a clinic manager to help coordinate training and booster sessions. The OCHIN research assistant will provide intervention clinics with monthly reports on the percent of patients who were assessed for tobacco use among all adults seen, the number who were asked if they were ready to quit using tobacco among those identified as tobacco users, and the number who were offered an eReferral among those who were ready to quit. This emailed report will include these data for the other intervention clinics for comparison; reports will not include identifying information for comparison clinics. The report will also include monthly total numbers of patients seen, asked about tobacco use, using tobacco, assessed for readiness to quit, offered eReferral and

eReferral ordered for their clinic only. The clinic champion will share these at monthly all-staff meetings, both via verbal and written communication. The clinic champion will also discuss the desired content of the booster sessions with the clinical staff and convey this information to the OHSU study team. The clinic manager will aid in coordinating the two group trainings and the two booster sessions. To evaluate the training and the potential for scalability of the AD intervention, brief post-training surveys will be completed immediately following the initial and 12-month group trainings to assess the content, quality, and effectiveness of the training, as well as anticipated barriers or facilitators to use of the eReferral system. The 12-month survey will also collect information on prior session attendance (initial, booster), reason for not attending initial training, if applicable (e.g., new hire, not in office, too busy), as well as feedback on experiences with the eReferral system post-implementation. In addition, each clinic champion will be asked to complete a separate 15-20-minute survey at the end of the intervention period to provide an overall evaluation of each intervention component (e.g., training sessions, booster sessions, audit and feedback) and suggestions on how to improve the enhanced AD intervention around tobacco cessation assistance, in general, and the eReferral workflow, specifically. Each clinic champion will receive a $30 gift card for completion of the brief 15-20 minute survey at the end of the intervention period. Providers and staff (including the clinic champions) in the intervention clinics can choose not to complete the surveys.

The cost-effectiveness analysis will be conducted in Year 5 and will use data from a variety of sources, including: clinic staff time for tobacco cessation delivery (e.g., eReferrals, cessation medications, cessation counseling, review of Optum information in the EHR, reporting, ongoing staff training), retail costs of Quitline services for referred tobacco users (e.g., counseling time and costs of cessation medications), OCHIN resource costs used to implement and deliver the eReferral system including decision-support implementation and maintenance, and intervention components (cost of training materials, generating audit and feedback reports, OHSU study team time for training and travel, and clinic champion/clinic manager training and time spent coordinating/delivering intervention components).

Outcomes and Covariates for Study Aims (Independent Variable: Clinic-Level Enhanced AD vs. No Enhanced AD)

Aim 1. Implement a Quitline eReferral system with enhanced AD (intervention) and without enhanced AD (comparison) to compare rates of eReferral offers, eReferral acceptance, Quitline enrollment, orders for smoking cessation medication, and receipt of in-clinic counseling among patients identified as current tobacco users.		
	Numerator	**Denominator**
Primary Study Outcome (Reach)		# of unique patients identified as tobacco users in the EHR during the study period (BPA triggered)
Accepted eReferral to Quitline	# of unique patients who accepted the Quitline eReferral	
Secondary Study Outcomes (Reach)		
Quitline eReferral offered	# of unique patients who accepted or declined the eReferral	
Quitline enrollment	# of unique patients who enrolled in Quitline services	
Receipt of in-office counseling	# of unique patients with an indication in the EHR of receipt of counseling during an office visit	
Smoking cessation medication ordered	# of unique patients with a smoking cessation medication in the 'medication orders' list of the EHR	
Aim 2. Assess the effectiveness of implementing a Quitline eReferral system with enhanced AD (intervention) versus without enhanced AD (comparison) on self-reported smoking quit rates among all patients identified as current tobacco users using EHR data.		
	Numerator	**Denominator**
Secondary Study Outcomes (Effectiveness)		
Tobacco cessation	# of unique patients with EHR status change from current to former tobacco user	# of unique patients identified as current tobacco users in the EHR during the study period (BPA

		triggered)
Tobacco cessation among Quitline enrollees	# of unique patients with EHR status change from current to former tobacco use	# of unique patients who enrolled in Quitline services
Aim 3. Estimate the total annual costs and incremental cost-effectiveness of a Quitline eReferral system, with and without enhanced AD.		
Annual intervention costs	Mean total annual costs in years 1-4 to implement the eReferral into the EHR and maintain eReferral system, with and without enhanced academic detailing	Difference in life-years saved for tobacco users seen in intervention and comparison clinics, annually, and overall for Years 1-4
Cost-effectiveness	Mean total annual costs over years 1-4 by study arm, overall and for patients enrolled in the Quitline	# of tobacco users; # of eReferrals; # of Quitline enrollees; # of quitters (EHR documented, Optum survey sample); life-years saved
Incremental cost-effectiveness ratio	Difference in total costs by study arm, overall and for patients enrolled in Quitline	Difference in quit rates (and LYS) between enhanced and standard detailing, overall and by those enrolled in Quitline
Patient, Provider and Clinic Covariates from EHR		
Age: Age at time of visit; *Sex*: Male, Female, Other; *Ethnicity*: Hispanic, Latino (yes/no); *Household Income / Poverty Level*: % FPL, overall income; *Insurance coverage:* insurance status at visit; *Clinic factors*: number of patients, *rural/urban; Provider factors:* number of providers, number of provider types; *Language Preference*: English, Spanish, Other; *Psychiatric Conditions*: Diagnosis of mood (depressive, bipolar), anxiety, post-traumatic stress, psychotic disorders; *Medical Conditions*: Diagnosis of hypertension, diabetes, coronary artery disease, asthma/chronic obstructive pulmonary disease, cancer, substance use disorder other than tobacco use disorder; *Quitline services*: medication (8-week NRT), telephone counseling, web-based support, unreachable		

Note. AD=academic detailing; EHR=electronic health record

SCHEDULE OF EVENTS

Overall study timeline

	Y1			Y2					Y3			Y4			Y5		
	2021-2022			2022-2024					2024-2025			2025-2026			2026-2027		
	Jul-Oct	Nov-Feb	Mar-Jun	Jul '22-Oct	Nov-Feb	Mar-Jun	Jul '23-Oct	Nov-Feb' 24	Mar-Jun	Jul-Oct	Nov-Feb	Mar-Jun	Ju'25-Oct	Nov-Feb	Mar-Jun	Jul-Oct	Nov-Feb
Regulatory paperwork including registration in Clinicaltrials.gov	x																
NaRCAD academic detailing training		x															
Develop AD training materials		x	x	x													
Refinements to eReferral system		x	x	x													
Recruit clinics and randomize			x	x	x												
Online eReferral material sent via email (both arms)						x											
Remote technical assistance (both arms)						x	x	x	x	x	x	x	x				
eReferral activated in all study clinics						x											
Intervention Condition Only																	
Remote group training							x			x							
Booster sessions								x			x						
Performance audit & feedback							x	x	x	x	x	x	x				
Post-training survey							x			x							
Clinic champion survey													x				
EHR data on first subject							x	x									

EHR data on 25% of study sample (n~2500 current tobacco users)									x								
EHR data on 50% of study sample (n~5000 current tobacco users											x						
EHR data on 75% of study sample (n~7500 current tobacco users)													x				
EHR data on 100% of study sample (n~10,000 current tobacco users)															x		
EHR data pull to ensure data integrity							x		x		x		x		x		
Data pull and preparation for transfer													x	x			
Primary and secondary data analysis														x	x	x	
Cost-effectiveness data collection	x	x	x	x				x				x	x	x	x		
Cost-effectiveness analysis														x	x	x	
Annual in-person research team meetings			x				x				x						x
Present at regional/national conferences								x	x	x	x	x	x	x	x	x	x
Prepare and submit manuscripts									x	x	x	x	x	x	x	x	x
Results reported in Clinicaltrials.gov																x	x

Study timeline of enhanced academic detailing (Intervention clinics only): Year 2 Qtr 3-Year 4 Qtr 2

Component	Months												
	Y2									Y3			
	Jun 2023	Jul 2023	Aug 2023	Sep 2023	Oct 2023	Nov 2023	Dec 2023	Jan 2024	Feb 2024	Mar 2024	Apr 2024	May 2024	Jun 2024
eReferral activated for all clinics	x												
Remote group training		x	x										
Booster sessions								x	x				
Performance audit and feedback from OCHIN				x	x	x	x	x	x	x	x	x	x
Post- training evaluation		x	x					x	x				

Component	Months												
	Y3								Y4				
	Jul 2024	Aug 2024	Sep 2024	Oct 2024	Nov 2024	Dec 2024	Jan 2025	Feb 2025	Mar 2025	Apr 2025	May 2025	Jun 2025	Jul/Aug 2025
Remote group training	x	x											
Booster sessions							x	x					
Performance audit and feedback from OCHIN	x	x	x	x	x	x	x	x	x	x	x	x	x
Post- training evaluation	x	x					x	x					
Clinic champion survey												x	x

8.0 TIME LINE AND MILESTONES

	YEAR 1				YEAR 2				YEAR 3				YEAR 4				YEAR 5			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
EHR data on first subject						x														
EHR data on 25% of study sample (n~2,500 current tobacco users)								x												
EHR data on 50% of study sample (n~5,000 current tobacco users)										x										
EHR data on 75% of study sample (n~7,500 current tobacco users)												x								
EHR data on 100% of study sample (n~10,000 current tobacco users)														x						
Data analysis																	x	x	x	

9.0 BIOSTATISTICAL CONSIDERATIONS

Specific Aim 1 (Reach). The primary goal of Aim 1 is to establish whether implementing a Quitline eReferral system with enhanced AD (intervention) improves reach (odds of accepted eReferral to Quitline) compared to implementation without enhanced AD (comparison) among tobacco users. To compare the effect of the intervention on reach in the context of a cluster-randomized design, we will utilize Generalized Linear Mixed Models (GLMMs).[27] For our primary outcome, we will use a logistic mixed effects model that addresses the following design features of the study: 1) we will include a random intercept for clinic to account for clustering of patients within clinics; 2) we will perform an intent-to-treat analysis; 3) hypothesis tests will be two-sided. The general model is: (1) $\mathbf{logit}(\boldsymbol{Y_{ik}}|\boldsymbol{b_k}) = \boldsymbol{\beta_0} + \boldsymbol{\beta_1 I_{int}} + \boldsymbol{b_k}$ where $\boldsymbol{Y_{ik}}$ is a binary variable denoting if a patient accepted the eReferral to the Oregon Quitline, $\boldsymbol{I_{int}}$ is an indicator variable where $\boldsymbol{I_{int}} = \mathbf{1}$ if patient *i* sought care in an intervention clinic and $\boldsymbol{I_{int}} = \mathbf{0}$ if the patient was seen at a comparison group clinic. Lastly $\boldsymbol{b_k}$ denotes a random effect term for clinic *k*. The parameter of interest will be $\boldsymbol{\beta_1}$ as it denotes the log odds ratio of accepted eReferral to Quitline between intervention and comparison clinics. This model is general but can be adapted to account for scenarios where significant differences in key clinic, provider or patient characteristics remain post-randomization. If we observe differences at baseline, we will use multilevel propensity score methods to reduce observed bias, to minimize external threats to the results' validity.[28-30] For secondary outcomes (e.g. Quitline eReferral offered, Quitline enrollment, etc.), we will construct similar logistic mixed effects models as in the primary outcome model. In all disseminated products, we will caution the reader that there are multiple secondary analyses, and report the unadjusted p-values as well as the significance given an overall p-value of 0.05 divided by the number of secondary analyses—for transparency. For our primary outcome, we assessed the ability to detect ≥80% power of a 2-sided significance test with $\boldsymbol{\alpha = 0.05}$. Given the following conditions: 1) pre-specified total sample size of 20 CHCs; 2) cluster randomized design of 10 clinics in each of the two arms; 3) ~10,000 tobacco users anticipated will be seen at these 20 OCHIN clinics; 4) two-sided 0.05 significance level; 5) starting average clinic-level Quitline eReferral acceptance prevalence of 8%, based on a preliminary OCHIN data pull of the 5 clinics that implemented the eReferral system without enhanced AD and informed by data from studies that included control clinics without AD,[31,32] and 6) an intracluster correlation (ICC) of

patients within clinics of 0.03 based on the preliminary OCHIN data pull, we will have ≥80% power to detect ≥7.5% difference in absolute change between study arms.

Specific Aim 2 (Effectiveness). Final EHR data extraction for Aim 2 will occur 6 months after the end of the intervention period to ensure capture of tobacco cessation via EHR documentation among patients seen in the last month of the intervention period. Given the similar structure of data for primary and secondary outcomes (binary indicators denoting tobacco cessation), we will utilize similar GLMM modeling as described in the Aim 1 statistical analysis approach to estimate the impact of the intervention on cessation outcomes. For our Aim 2 outcome that examines quit rates among all unique patients identified as current tobacco users in the EHR, given similar criteria as in Aim 1 power estimation and with the additional information that baseline quit rates (based on similar algorithms) in OCHIN clinics is around 15%, we will have 80% power to detect ≥11.5% difference in absolute change between study arms when the ICC=0.045 (as estimated from a preliminary OCHIN data pull). Our estimated ICC is in line with a cluster-randomized study of 15 primary care clinics examining performance coaching for tobacco treatment that reported a clinic ICC of 0.03 for smoking cessation.

Specific Aim 3 (Cost-effectiveness). We will use data collected during the intervention delivery and evaluation period to project annual cost and cost-effectiveness results over four years. We will assess mean total annual, and overall intervention costs using an opportunity cost approach from a health system/insurer perspective,[33,34] capturing all resource costs used to implement and deliver the bidirectional eReferral system with and without the enhanced AD intervention. This will include decision-support implementation and maintenance, provider in-office counseling, cessation medication orders, and eReferral recommendations, Quitline counseling, cessation medication received from the Quitline, clinic reporting and review, and ongoing staff training. Costs will be adjusted across years to a single year (e.g., 2021 dollars) using a 3% social discount rate.

Assuming the eReferral system is effective, the incremental cost per additional quit will be calculated for tobacco users in the intervention arm compared to patients identified as using tobacco in the comparison arm, and incremental costs per life-years saved (LYS). We will estimate LYS using remaining life expectancy data, by age, sex, and race/ethnicity, obtained from the Census, and adjusted for tobacco status using tobacco-attributable risks of death from the Cancer Prevention Study II.[35] The general model is: $(TC_{EAD} - TC_{SD})/(QR_{EAD}-QR_{SD})$, which reflects the difference in mean total costs (TC) per participant divided by differences in quit rates (QR), for enhanced academic detailing (EAD) and standard detailing (SD). The models will be rerun using mean LYS in the denominator. Separate analyses will be conducted using documented quitting in the OCHIN EHR for all adult tobacco users seen during the intervention period, and for the subgroup of Quitline enrolled patients (assuming an intent-to-treat approach where patients lost to follow-up are assumed to be tobacco users). We will collect individual-level cost data from the OCHIN EHR and Optum, which enables variance estimation for the average annual cost estimates and supports sub-analyses for patient population subgroups (amount of tobacco use, age group, sex, race/ethnicity, insurance plan type, etc.). A previous cost study of AD[36] suggests we have ≥.80 power ($\alpha = 0.05$) to detect differences in mean total costs of $500 or more for 10 intervention and 10 comparison clinics[37], while effect sizes meeting the Aim 2 power assumptions will provide sufficient power to detect differences in quit rates within each group. Estimating incremental cost-effectiveness ratios can be subject to statistical problems if the ranges include zeroes. If this occurs, we will rerun the analyses using an incremental net benefit approach.

10.0 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Protocol Review

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute (Knight) Clinical Research Review Committee (CRRC) and appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

10.2 Informed Consent

Clinic Recruitment. OCHIN has agreed to integrate the eReferral into the EHRs of 16 of its member clinics. The Clinic Recruitment and Engagement Coordinator at OCHIN will be responsible for coordinating the recruitment of 16 OCHIN member clinics, under the supervision of the PI and the OCHIN site-PI. Recruitment strategies will include announcements via OCHIN newsletters and at the Primary Care Clinical Operations Review Committee bi-weekly meetings, as well as emails and letters to clinic medical directors from the OCHIN Clinic Recruitment and Engagement Coordinator. The Oregon Health Authority (OHA) will collaborate on these outreach efforts via targeted emails to only OCHIN-member county service areas. These clinics will sign a Memorandum of Understanding (MOU) that provides details of the study and the roles and responsibilities of the research staff and the study clinic as part of participation. Additional outreach will be done by OHA through the Oregon Medical Association's monthly newsletter, sent to clinics and clinicians across the state. Interested parties can reach out directly or fill out a secure survey with name, email, and position to screen for their eligibility. None of the information collected will be used in analysis.

Clinic staff. As the risks to clinic staff, including the medical director, clinic champion and clinic manager are minimal, we will request IRB approval to provide study information sheets. As part of the MOU, the medical director at each intervention clinic will recruit a clinic champion and clinic manager. The study staff will provide the clinic champion and clinic manager with a study information sheet and answer any questions about the study, their role in the study, and will obtain verbal consent to serve in their respective roles. Each clinic champion will complete a brief 15-20 minute survey at the end of the intervention period. The survey will contain an information sheet that does not require a signature (in order to protect respondent identities). Any identifying information will be collected solely for disbursement of incentives (i.e. gift cards) and will be removed from documents used for analysis. No identifying information will be collected on any other clinic staff.

Patients. Patients are not recruited for study participation and study staff will have no direct contact with patients; thus, neither verbal or written consent will be obtained. Patients sign a consent form with the clinic when establishing care that allows for their data to be used for research purposes. Each clinic has business use agreements with OCHIN to utilize their EHR data for research purposes, including proper handling and managing of PHI from their clinical data. We will request an IRB approval for a waiver of authorization and a waiver of informed consent because it is not feasible to consent all of the patients whose EHR data will be included and the use or disclosure of the PHI involves no more than minimal risk to the privacy of the subjects as a result.

10.3 Changes to Protocol

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the patient. In that event, the investigator must notify the CRRC and IRB in writing within 5 working days after the implementation. Investigators holding the IND must notify FDA of substantive changes to the protocol.

10.4 Privacy, Confidentiality, and Data Security

Study Staff Training. All study staff involved with the design or conduct of research involving human subjects will complete all required human subjects' protection training as per OHSU's IRB. All researchers are trained and follow federal HIPAA regulations, which require specific protocols for the transferring, storage, and reporting of protected health information. The study PI, Dr. Bailey, will be responsible for ensuring that all individuals have satisfied this requirement and will monitor completion of any renewals or additional trainings over the course of the study.

OCHIN EHR Data. All data from the study clinics are stored on secure servers at OCHIN. OCHIN staff will remove all personal identifiers from the limited data set and will assign each patient a unique identification number. Limited datasets will only be shared by OCHIN with OHSU and the Kaiser Center for Health Research (CHR) once data use agreements are fully executed. OCHIN's compliance officer will supervise all processes for obtaining data. These datasets will be securely exported to password protected HIPAA-compliant computers under the direct supervision of Dr. Bailey and co-investigators. The research team will meet at regular intervals to identify and discuss any data collection and management issues that may arise. Our protocol and procedures for using the data ensures no patients are individually identifiable for data transfers and analyses. We have previous experience in conducting these types of data transfers and data sharing between OHSU and OCHIN.

Regulatory compliance. We will follow all federal, state, and institution regulations relevant to the type of research we are conducting. All data work will be done on password-protected, HIPAA-compliant computers.

10.5 Maintenance of Records

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to OHSU Knight Cancer Institute Clinical Research Management. Records must be maintained according to sponsor or FDA requirements.

Many safeguards are in place to protect the OCHIN EHR data. All data from the study clinics are stored on secure servers at OCHIN. OCHIN staff will remove all personal identifiers from the limited data set and will assign each patient a unique identification number. OCHIN staff work with patient data from their member clinics on a regular basis and are appropriately trained in data security. Limited datasets will only be shared by OCHIN with OHSU and the Kaiser Center for Health Research (CHR) once data use agreements are fully executed. OCHIN's compliance officer will supervise all processes for obtaining data. These datasets will be securely exported to password protected HIPAA-compliant computers under the direct supervision of Dr. Bailey and co-investigators. All data will be stored and backed up on password-protected secure servers.

All survey responses will be stored on secure servers at OHSU. An information sheet explaining the study will be provided to participants prior to the AD and surveys. Surveys will be done anonymously and stored on secure servers at OHSU. All findings will be reported in aggregate.

All printouts required for the purposes of analysis will be kept in locked storage containers belonging to Dr. Bailey or Dr. Marino (OHSU) and Dr. Fellows (CHR) and will be destroyed after use. Analysts will maintain an analytical data file for a period of two years following the end of the study to permit appropriate ongoing analysis. After two years from the study conclusion date, the files will be destroyed. In the latter instance, Dr. Bailey will file a new application for IRB approval.

10.6 OHSU IRB Reporting of Reportable New Information and Adverse Events

This is considered a minimal risk study. Minimal risk means the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves other than those ordinarily encountered in daily life or during performance of routine physical or psychological examinations or tests. Dr. Bailey will be informed by the medical director or the clinic champion of any adverse events related to the implementation and use of the eReferral system or participation of clinic staff in components of the enhanced academic detailing protocol.

This intervention may increase the provision of medications to treat tobacco use disorder, either through the patient's provider recommending or prescribing smoking cessation medications, the patient obtaining over-the-counter nicotine replacement therapy (NRT), or as part of the services provided by the Quitline (if eligible, the patient can receive up to an 8-week supply of nicotine replacement gum and/or patch). As this is a highly pragmatic trial that involves no direct contact with patients, adverse events related to use of tobacco cessation medications will not be monitored by study staff.

Reportable New Information (RNI) and Adverse Events (AE) will be reported to IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site:

- Reportable New Information is submitted through OHSU eIRB and will be reviewed by OHSU Knight Cancer Institute and IRB.

10.8 OHSU Knight Cancer Institute Data and Safety Monitoring Plan

In addition to complete study and pharmacy files, complete records must be maintained on each patient treated on this protocol. OHSU Knight Cancer Institute (the Knight), KCTO shared resource is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies. The Data and Safety Monitoring Committee (DSMC) is responsible for conducting Quality Assurance audits on Knight approved protocols according to the Data and Safety Monitoring Plan policies and procedures available on the Data Safety and Monitoring Committee Bridge page. Locally initiated observational and low risk interventional studies may be audited by an OHSU Knight DSMC audit team any time after enrollment begins. The Quality Assurance audit process provides assurance that the reported data accurately reflects the data in the primary patient record and that regulatory requirements are met.

Regulatory Issues. This study will be registered on clinicaltrials.gov. The study does not require an IND from the FDA. Any significant actions taken by the local IRB and protocol changes will be relayed to the funding agency.

Monitoring Data Quality. All study outcome data will come from the OCHIN EHR. In the year prior to the activation of the eReferral system in the EHR, OCHIN IT will ensure the eReferral system is working correctly. This will include test cases that will be shared with Optum to ensure the bidirectional eReferral system is transferring data as intended. Once the eReferral system has been activated, back-end checks (for missing data fields and logical inconsistences) will be conducted to ensure accurate collection and transfer of data between EHR to Optum. These checks will be conducted by the OCHIN research analyst monthly for the first 3 months of the study and then every six months for the remainder of the intervention period.

Monitoring Data Confidentiality. Many safeguards are in place to protect the OCHIN EHR data. All data from the study clinics are stored on secure servers at OCHIN. OCHIN staff will remove all personal identifiers from the limited data set and will assign each patient a unique identification number. OCHIN staff work with patient data from their member clinics on a regular basis and are appropriately trained in data security. Limited datasets will only be shared by OCHIN with OHSU and CHR once data use agreements are fully executed. OCHIN's compliance officer will supervise all processes for obtaining data. Any data transferred between institutions will be done so under a data use agreement and will be exported, stored, and backed up on password protected HIPAA-compliant computers under the direct

supervision of Dr. Bailey and co-investigators. The research team will meet at regular intervals (at least monthly) to identify and discuss any data collection and management issues that may arise. All printouts required for the purposes of analysis will be kept in locked storage containers belonging to Dr. Bailey or Dr. Marino (OHSU) and Dr. Fellows (CHR) and will be destroyed after use. Analysts will maintain the analytical data file for a period of two years following the end of the study period to permit appropriate ongoing analysis. After two years from the study conclusion date, the files will either be destroyed, or will be used for ongoing research. In the latter instance, Dr. Bailey will file a new application for IRB approval. Our protocol and procedures for using the data ensures no patients are individually identifiable for data transfers and analyses. We have previous experience in conducting these types of data transfers and data sharing between OHSU and OCHIN. All research staff are highly trained and appropriately certified in data security and confidentiality, and the current protection measures represent the cutting edge of electronic protection.

Monitoring Adverse Events Related to the Study Protocol. This is considered a minimal risk study. Minimal risk means the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves other than those ordinarily encountered in daily life or during performance of routine physical or psychological examinations or tests. Dr. Bailey will be informed by the medical director or the clinic champion of any adverse events related to the implementation and use of the eReferral system or participation of clinic staff in components of the enhanced academic detailing protocol. This intervention may increase the provision of medications to treat tobacco use disorder, either through the patient's provider recommending or prescribing cessation medications, the patient obtaining over-the-counter nicotine replacement therapy (NRT), or as part of the services provided by the Quitline (if eligible, the patient can receive up to an 8-week supply of nicotine replacement gum and/or patch). As this is a highly pragmatic trial that involves no direct contact with patients, adverse events related to use of cessation medications will not be monitored by study staff.

Monitoring study progress. Dr. Bailey (PI) is responsible for routine monitoring of the study progress, including recruitment and retention of study clinics. Based on previous OCHIN trials, the proposed 9-month timeframe during Year 1 is sufficient to recruit 20 clinics. Based on a conservative estimate of a 23% smoking prevalence, approximately 10,000 smokers will be included in the dataset by the end of the intervention period. At the end of the first year of the intervention, the OCHIN analyst will extract preliminary data on the number of smokers seen within the year, and the percent of smokers offered the eReferral in both the intervention and comparison clinics combined. These aggregated data will be shared with the PI and research team to determine if the patient numbers are consistent with the planned enrollment numbers by the end of first intervention year and to compare eReferral rates to existing literature. If eReferral rates are significantly lower than anticipated, our team will consult with OCHIN IT staff and Optum to ensure this is not related to technical issues; however, this would be extremely unlikely given the frequent data quality checks. Given the pragmatic nature of the trial, low eReferral rates will not result in termination of the trial. Finally, within the intervention condition, the PI will work with both the clinic champion and medical director, as needed, to ensure fidelity to the protocol (e.g. monthly sharing of OCHIN reports during all-staff meetings).

Data and Safety Monitoring Plan Administration. The PI is responsible for monitoring the data, protocol compliance, and safety of the study with additional oversight provided by study co-investigators. Due to the low risks associated with participation in this study, study-related adverse events are expected to be rare. Dr. Bailey will monitor and respond accordingly to any reported adverse events that arise and notify the IRB per protocol. A report will be filed with the IRB and funding agency on a yearly basis or as requested. In the unlikely occurrence of an adverse event (AE) or serious adverse event (SAE) which is severe, unexpected, and possibly related to the protocol, the PI will notify NIH and the OHSU IRB in a timely manner (consistent with IRB and NIH policies). During the review process, the PI will evaluate whether the study should continue unchanged, require modification/amendment, continue or close.

10.9 Inclusion of Women, Minorities and Children

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No subject will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied.

The projected gender, racial and ethnic composition of the study will represent that of the Oregon population of patients seen in the OCHIN CHC study clinics who are identified as currently smoking during the study period because we are not recruiting patients for this pragmatic trial.

Table 2: Projected Accrual for the Present Study - Estimated using total unique patients seen in an Oregon OCHIN clinic with current smoking status at any point during 7/1/17-6/30/20 time frame

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	409	394		8.0
Not Hispanic or Latino	4870	4328		92.0
Unknown				
Ethnic Category: Total of all subjects*	52.8	47.2		100.0
Racial Category				
American Indian or Alaskan Native	100	70		1.70
Asian	14	21		0.35
Black or African American	39	47		0.86
Native Hawaiian or other Pacific Islander	12	17		0.29
White	4920	4380		93.0
More than one race	193	187		3.80
Unknown	0	0		0
Racial Category: Total of all subjects*	52.8	47.2		100*

Source: Adapted from U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.

10.10 Inclusion of Children

In accordance with NIH guidelines on the inclusion of children as participants in research involving human subjects, children under the age of 18 years must be included in all human subjects' research, conducted or supported by the NIH, unless there are clear and compelling reasons not to include them. Therefore, proposals for research involving human subjects must include a description of plans for the inclusion of children.

This protocol does not include children for the following reasons: 1) the number of children with this type of cancer (lung) is limited as smoking rates and patterns (including length of time smoking) are different for children compared with adults; 2) as part of the intervention (enhanced academic detailing), training

will be provided on provision of pharmacotherapy for smoking cessation as evidence-based treatment; there are no FDA-approved cessation medications for persons under 18 years of age.

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