PROTOCOL TITLE: Addressing Rural Cancer Disparities via Proactive Smoking Cessation Treatment within Primary Care: A Hybrid Type 1 Effectiveness-Implementation Trial of a Scalable Smoking Cessation Electronic Visit

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1.0 Objectives / Specific Aims

We will conduct a Hybrid Type I effectiveness-implementation trial to comprehensively assess effectiveness of a proactive electronic visit (e-visit) for smoking cessation relative to treatment as usual (TAU) while simultaneously evaluating implementation when delivered across rural primary care settings. In Aim 1, we will conduct a stepped-wedge, cluster-randomized clinical trial (N=288) to examine the effectiveness of the smoking cessation e-visit vs. TAU for smoking cessation across seven rural (Rural-Urban Commuting Area codes 4-10) primary care practices in South Carolina. In Aim 2, we will evaluate e-visit implementation outcomes across rural South Carolina primary care settings at patient, provider, and organizational levels. Main outcomes include: 1) biochemically verified 7-day PPA (point prevalence of abstinence) at six-month follow-up, 2) reduction in cigarettes per day, and 3) evidence-based smoking cessation treatment utilization (medication, psychosocial cessation counseling). We hypothesize that rural smokers randomized to the e-visit condition will have significantly better cessation outcomes relative to TAU.

2.0 Background

Rural residents are both more likely to smoke cigarettes and less likely to quit than their urban counterparts. Consequently, individuals in rural areas have a 7% higher incidence of tobacco-associated cancers. Comprehensive smoking cessation treatment dissemination strategies are needed to increase utilization of evidence-based treatment, improve cessation outcomes, and ultimately decrease cancer incidence among rural smokers. Primary care providers (PCPs) see 70% of smokers annually, and rural residents are more likely than urban residents to have a usual source of health care. As such, primary care offers a ripe opportunity to deliver cessation treatment to rural smokers. All primary care practices that qualify for Centers for Medicare and Medicaid Services reimbursement are required to maintain electronic health records (EHRs) with coded smoking status data for adult patients. These data can be utilized to proactively identify smokers and deliver remote treatment. Our team recently completed a pilot study to develop, refine, and preliminarily evaluate a proactive asynchronous smoking cessation electronic visit (e-visit) delivered via the EHR. The goal of the e-visit is to automate best practice guidelines for cessation treatment via primary care to ensure that all smokers receive an evidence-based intervention. An initial baseline e-visit gathers information about smoking history and motivation to quit, followed by an algorithm to determine the best FDA-approved cessation medication to prescribe. A one-month follow-up e-visit assesses progress toward cessation. Clinical outcomes of our pilot (N=51 followed for three months) were promising. Among rural participants who received the e-visit (n=6), 17% reported 7-day point prevalence abstinence (PPA), 67% reduced their cigarettes per day (CPD) by >50%, and 50% used a cessation medication. E-visit participants, relative to treatment as usual (TAU), were 4.2 times more likely to report 7-day PPA, 4.1 times more likely to have reduced their CPD by >50%, and 4.7 times more likely to have used a cessation medication. Acceptability outcomes were strong, with 100% of rural e-visit participants reporting that they would use an e-visit again in the future. These data suggest that the e-visit may be a feasible, efficacious approach to extend the reach of evidence-based cessation treatment via rural primary care. We now propose a Hybrid Type I effectiveness-implementation trial to comprehensively assess e-visit effectiveness relative to TAU while simultaneously evaluating implementation when delivered across rural primary care settings. Effectiveness outcomes will be assessed through 6-months of follow-up and include: 1) biochemically verified 7-day PPA, 2) reduction in CPD, and 3) evidence-based cessation treatment utilization. Implementation outcomes will be assessed at patient, provider, and organizational levels. This trial has the potential to expand cessation treatment access in a manner scalable across rural healthcare systems and ultimately reduce rural cancer disparities.

3.0 Intervention to be studied

Smoking Cessation E-Visit. The goal of the e-visit is to automate the 5As (Ask, Advise, Assess, Assist, Arrange) to ensure that all smokers receive treatment. After completing screening and consent, adult smokers recruited from clinics assigned to the e-visit condition will be automatically linked to initiate an asynchronous cessation e-visit via MyChart. The baseline e-visit will gather information about smoking history and motivation to quit, followed by an algorithm to determine the best FDA-approved cessation medication (i.e., NRT, varenicline, bupropion). This algorithm is based on our team's prior research[1-3] and evidence-based guidelines[4]. It uses branching logic to prioritize the most efficacious medications (varenicline and combination NRT), while tailoring recommendations based on contraindications and patient preference. The outcome is a medication recommendation displayed to the patient with a personalized rationale. All medication recommendations are provided in conjunction with a referral to the quitline for psychosocial counseling. The patient can agree with the recommendation or request a different treatment. E-visit results are automatically sent to the PCP's in-basket, who will have 48 business hours to respond. If the e-visit is not responded to within this timeframe, it will be routed to MUSC's e-visit care team for review and response. Providers will open the e-visit from their in-basket, review the e-visit and its algorithm outcome (e.g., medication recommendation), review the chart for contraindications to that outcome, agree or disagree with the recommendation, respond to the patient via MyChart with instructions, and e-prescribe (if indicated) medication. Varenicline, a class C medication, may be provided as a result of the e-visit. Because risks during pregnancy related to Varenicline are unknown, all females of childbearing potential will subsequently be asked if they would be willing to complete a pregnancy test that will be mailed to them. Females of childbearing potential who report a positive pregnancy test will not be prescribed Varenicline. All medications will be prescribed on label to the patient's pharmacy of record, consistent with procedures from our pilot, and will be billed as in usual practice (i.e., to the patient's insurance if insured). Participants are not required to obtain their prescribed medication from their pharmacy or to take the medication as part of their participation in this study. In addition to the quitline referral for psychosocial counseling, all responses from providers to patients will also include a digital copy of NCI's *Clearing the Air: Quit Smoking Today*[5]. In a recent trial, smokers who were provided with *Clearing the Air* had a 12% abstinence rate at 6 months[6]. **There will be direct contact between the PCP and patient prior to prescription, either via secure MyChart messaging or telephone, depending on the provider's preference and need for information.** If contraindications are present (e.g., a contraindicated medication is noted in the EHR) or if the patient reports untreated health concerns requiring attention (e.g., cough with blood), electronic contact will be supplemented with phone and/or in person contact.

All participants will be scheduled for a follow-up e-visit one month later. The purpose of the 1-month e-visit is to assess progress toward cessation and troubleshoot barriers consistent with 5As guidelines to Arrange follow-up. This e-visit will begin by assessing current smoking status, quit attempts in the last month, and quit duration. Subsequently, the participant will report: 1) whether they received a cessation medication following baseline, 2) whether they are currently taking the medication, and 3) whether they have any questions/concerns. Participants will be asked if they are interested in any other treatment options, including a medication refill. Results will be sent to providers and reviewed and responded to in the same manner as the baseline e-visit.

IRB approved investigators (e.g., Drs. Dahne, Diaz, and Player) will provide training on the smoking cessation e-visit to all PCPs at the beginning of each division's e-visit period. All MUSC Regional Health Network (RHN) providers already respond to e-visits. Within the last year alone, MUSC PCPs have responded to 3,412 e-visits. Thus, additional training herein will focus on the specific use of the smoking cessation e-visit and its decision-support algorithm. All RHN clinics have monthly all-staff meetings, during which training will occur. Trainings will be recorded and distributed following meetings. Drs. Dahne, Diaz, and Player will also develop a brief video describing the workflow and tip sheets with overviews of e-visit functionality. These tip sheets will include information on smartphrases developed to improve the ease with which e-visits can be responded to (e.g., with information regarding dosing and links to additional information). These procedures are consistent with MUSC's current training approaches which have been successful in promoting new workflow adoption. For example, this approach was used to train providers in the use of virtual check-ins and video visits during the COVID-19 pandemic and resulted in primary care providing 75.1% of historical in-person volume virtually within two weeks of implementation. Training recordings and tip sheets will be provided to new hires in clinics active within the e-visit condition upon onboarding. Similar training will be provided at study start to MUSC's e-visit care team, which will be responsible for responding to e-visits not responded to within 48-hours by a patient's PCP. It is important to note that this same training approach has been taken by Drs. Diaz and Player to train MUSC's PCPs and the e-visit care team in delivery of all other e-visits currently available in MUSC's e-visit primary care menu (e.g., for back pain, nosebleed, etc.). Because the workflow for this e-visit mirrors that of other e-visits, we believe it can likely be adopted with minimal training.

TAU. TAU mimics existing standard care and follows procedures from our pilot trial. Participants recruited during TAU steps will be linked to a screen that includes information on the state quitline, education about quitting,

and a recommendation to contact their PCP to discuss cessation. TAU enrollment will precede e-visit enrollment for all divisions, which will prevent treatment contamination. Participants enrolled during a division's TAU step will not be eligible for re-enrollment after the division transitions to the e-visit.

4.0 Study Endpoints (if applicable)

Primary outcome variables include:

- Experience using technology and internet access (home broadband, access via mobile device) will be assessed via questions from Pew Research Center's technology adoption survey[7].
- Digital literacy will be assessed at baseline via the Mobile Device Proficiency Questionnaire (MDPQ-16)[8] and the Computer Proficiency Questionnaire (CPQ-12)[9]. Both questionnaires are valid, reliable measures of device (mobile, computer) proficiency and have been used to facilitate digital literacy training within research contexts.[8,9]
- Cigarette smoking, use of other tobacco products (e.g., e-cigarettes), and quit attempts/quit duration will be assessed at each follow-up using a timeline followback for the last 6-months at baseline and since prior follow-up for each subsequent assessment[10,11]. Nicotine dependence will be assessed at baseline via the Fagerström Test of Nicotine Dependence[12]. Participants will report motivation to quit and confidence in quitting using a modified Contemplation Ladder[13]. Self-reported smoking will be biochemically verified via breath CO, with abstinence defined as CO of ≤ 4ppm[14]. Self-report and CO data will be utilized together to determine 7-day PPA.
- Treatment utilization will be assessed via self-report and EHR data. At each follow-up, all participants regardless of intervention will be queried for: 1) use of a cessation treatment (medication or psychosocial counseling) since the last assessment, 2) how the medication was obtained, and 3) receipt of the 5As from their PCP[15]. Self-report data will be supplemented with treatment utilization data pulled from the EHR coinciding with each follow-up. Specifically, we will capture: 1) cessation medication prescriptions, 2) if prescribed, whether cessation medications were filled, 3) whether the participant was referred to counseling, and 4) whether the participant attended a counseling session.
- Confounders of CO including combustible cannabis use, secondhand smoke exposure, and environmental CO exposure within the last 24 hours will be assessed at all timepoints to account for factors that may falsely inflate CO.
- Additional data from the EHR will be captured to describe the sample including information on: 1) medical and psychiatric comorbidities, 2) medications, 3) tobacco-related billing codes, and 4) insurance type.

5.0 Inclusion and Exclusion Criteria/ Study Population

Participants will complete a REDCap survey to be screened for eligibility and we will use cold-contact recruitment approaches herein.

Inclusion criteria:

a) Current cigarette smoking, defined as smoking 5+ cigarettes per day, for 20+ days out of the last 30, for the last 6+ months
b) Age 18+
c) Enrolled in Epic's MyChart program or willing to enroll
d) Possess a valid e-mail address that is checked daily to access study assessments and MyChart messages
e) Owner of an iOS or Android compatible smartphone to provide remote CO readings
f) Have a valid address at which mail can be received (for mailing iCO™)
g) English fluency

Exclusion criteria:

a) Current engagement in cessation treatment, defined as use of an FDA-approved cessation medication within the last 30 days

6.0 Number of Subjects

We will recruit up to 288 subjects.

7.0 Setting

Research will be conducted remotely via REDCap and MyChart. Study participants will be recruited from rural South Carolina primary care clinics affiliated with MUSC's Regional Health Network (RHN). The RHN is divided into four divisions: 1) Florence, 2) Marion, 3) Lancaster, and 4) Chester. At the time of this submission, 7 MUSC RHN primary care clinics are located in federally designated rural areas, **defined as RUCA codes of 4-10**. Among these seven clinics, three are affiliated with the Florence division, three with Marion, and one with Lancaster (no rural clinics are affiliated with Chester).

8.0 Recruitment Methods

Participants will be recruited in the following ways:

1) Cold-contact Recruitment: We will submit a research data request to obtain a recruitment report of MUSC patients who potentially meet eligibility criteria. We will not cold-contact any patients who have chosen to opt-out of receiving contact about research or who have met the maximum number of contact attempts at the time of recruitment. We will use the following methods to contact participants: 1) e-mail , 2) phone, 3) text messaging, 4) MyChart.
2) Via advertisements (e.g. flyers) and online postings
3) Participants for key informant interviews will be recruited for interviews via targeted e-mail and phone messages.

Note, that while we include the options to recruit via advertisements, these will be used as backup options should cold-contact recruitment be slow and /or result in an insufficient number of participants recruited.

Recruitment of Minority Smokers

Minorities will be included in the R01 trial. All participants will be recruited from rural MUSC Regional Health Network (RHN) primary care practices, which primarily serve residents of Florence, Marion, and Lancaster, South Carolina. Data from the 2019 American Community Survey reveal that the population within these areas is 67.2% White, 26.8% Black, 2.1% American Indian/Alaskan Native, Asian, or Pacific Islander, 2.3% reporting two or more races, and 5.7% are Hispanic or Latinx. Compared to overall area demographics, members of racial and/or ethnic minority groups tend to be overrepresented among adult smokers treated via MUSC's rural RHN primary care practices. Roughly half of adult smokers treated via these clinics are members of a racial or ethnic minority group and 49.8% of participants enrolled in our e-visit pilot study identified as Black. We will monitor closely our minority recruitment goals on an ongoing basis. If the recruitment of minorities is lower than expected (less than 80% projected enrollment for each minority group), efforts will be made to improve recruitment of minorities into the study through oversampling.

9.0 Consent Process

After determination of eligibility, a study team member will complete remote electronic informed consent (e-consent) with the participant via REDCap. Participants will receive a link to an electronic consent form, available via REDCap, that they can review and sign. Review of the consent form will be paired with a phone call with a member of the research team to ensure that all questions are answered prior to enrollment. This remote consent procedure is currently utilized by Dr. Dahne in both her K23 and R21 awards and has been used with success with smokers residing in rural areas. As smartphone ownership is an inclusion criterion (to provide remote CO), all participants will have internet access and thus access to the electronic consent form.

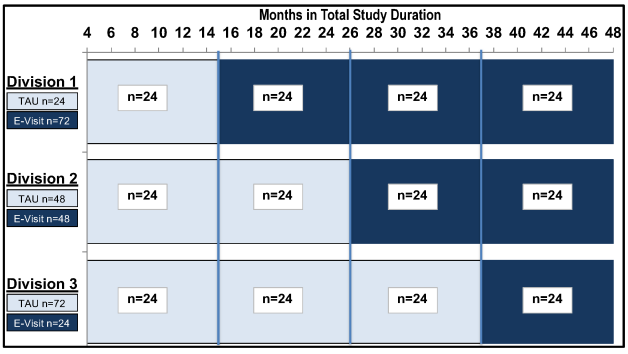
All participants will be provided with a hard copy and/or an electronic copy of the consent form. Participants will be informed that participation in this research is strictly voluntary. Informed consent will include a detailed description of the purpose and the procedure of the study emphasizing our policy regarding privacy and confidentiality and an opportunity for the individual to ask any questions or voice concerns.

10.0 Study Design / Methods

Aim 1: Effectiveness Trial of Smoking Cessation E-Visit vs. TAU in Rural Southern Primary Care.

We will conduct a stepped-wedge, cluster-randomized clinical trial to comprehensively evaluate effectiveness of the smoking cessation e-visit within rural SC primary care clinics. Consistent with a Type I Hybrid effectiveness-implementation design, we will assess implementation concurrently with effectiveness. Adult smokers will be recruited proactively across rural MUSC RHN clinics and assigned based on their clinic division's current step to either e-visit or TAU (***see Figure***). Implementation will be assessed consistent with an adaptation of Proctor's framework[16,17] proposed by Hermes et al.[18] for digital interventions.

Stepped-Wedge Design and Enrollment



Enrollment will begin in month 4 and will continue for a total of 44 months, ending at the end of Year 4. Final assessments will occur between months 48-54. With planned enrollment of 288, we fully expect to enroll 6-7 participants per month (~2 per week) and recruit our full sample within 44 months. In our prior work, 20% of study invitations resulted in an enrolled participant, and engagement rates were similar across rural and urban patients. As such, we will send 35 invitations per month (35 * 0.2 = 7 enrolled participants) and 1,540 study invitations in total to meet recruitment milestones. Study invitations will be equally distributed across divisions with ~12 study invitations sent per division per month. Within divisions, study invitations will be sent proportional to the total patient volume of each individual clinic. Enrollment will be capped at 24 patients per division per step, and each step will last 11 months.

Recruitment will occur proactively and remotely via cold-contact methods. We will submit a research data request to obtain a recruitment report of MUSC patients who potentially meet eligibility criteria. The study team will not cold-contact any patients who have chosen to opt-out of receiving contact about research or who have met the maximum number of contact attempts at the time of recruitment. Participants will be contacted via the following methods: 1) e-mail, 2) phone, 3) text messaging, and 4) MyChart.

Following the initial study invitation, if the patient does not complete the screening within 72-hours, our team will contact the patient via automated phone calls and/or text messages. If interested, participants will complete an online screening within REDCap to determine eligibility. After determination of eligibility, a study team member will complete remote electronic informed consent (e-consent) with the participant via REDCap[19]. Participants will receive a link to an electronic consent form, available via REDCap, that they can review and sign. Review of the consent form will be paired with a phone or video call with a member of the research team to ensure that all questions are answered prior to enrollment. This remote consent procedure is currently utilized by Dr. Dahne in both her K23 and R21 awards and has been used with success with smokers residing in rural areas. As smartphone ownership is an inclusion criterion (to provide remote CO), all participants will have internet access and thus access to the electronic consent form. Regarding potential impact of the digital divide on recruitment, 80% of rural residents[20] and 85% of the general population[21] now own smartphones. Notably, this gap has decreased considerably in just two years—in 2019, 71% of rural residents[7] and 81% of the general population[21] owned smartphones. Thus, we do not believe that sample representativeness or trial access will be substantially reduced by requiring smartphone ownership. We considered providing smartphones with internet access to otherwise eligible participants but decided against it because this approach is unlikely to be adopted by healthcare systems if the e-visit is scaled in the future.

This Hybrid Type I trial is designed to optimize external validity while assessing implementation. A stepped-wedge, cluster-randomized clinical trial (N=288 participants) will test e-visit effectiveness vs. TAU. This trial will involve three clinical divisions (Florence, Marion, Lancaster) and thus three wedges. At trial outset, divisions will be randomized to active intervention (e-visit) start as first, second, or third. All divisions will begin the trial assigned to TAU and will transition to e-visit according to randomization order (***see Figure***). Individual clinics (seven total) will

be assigned to treatment based on their divisional affiliation. Participants will be recruited within clinics. After completing consent, participants will complete baseline assessments and receive the intervention currently assigned to their clinic/division (based on their last primary care visit). Women who indicate during the e-visit that they are currently pregnant or are planning to become pregnant within the next 6 months will not receive a medication recommendation/prescription as a result of the e-visit. These women will receive NRT, Bupropion, and/or a counseling referral. Any female of childbearing potential will be asked to complete a pregnancy test. Females of childbearing potential will be mailed a pregnancy test by study staff and will receive a REDCap form within 3 days to verify (with signature) that they completed the test and their pregnancy test results. If the participant reports a positive pregnancy test to the study team, they will not receive varenicline as a result of the e-visit. These women instead will either receive NRT, bupropion and/or counseling based on other contraindications and medication preferences indicated throughout the e-visit. All participants will complete follow-up research assessments at 1-, 3-, and 6-months post-enrollment.

Following enrollment, participants will be mailed an iCO™ Smokerlyzer. Prior to mailing, all iCO™ devices will be tested against a fixed concentration CO cannister and only devices that test within the manufacturer's stated accuracy range ($\pm$15%) will be sent to participants. All participants will receive their iCO™ prior to their 1-month follow-up, and we anticipate having CO readings for all follow-ups.

In addition to CO readings, participants will be text messaged and/or emailed (based on preference) a REDCap link to complete follow-up assessments at 1-, 3-, and 6-months post-enrollment. The 1-month research assessments and 1-month e-visit invitations will be sent at the same time, as baseline research assessments and the baseline e-visit are both completed at the same time. All participants (e-visit and TAU) will complete research assessments via REDCap (i.e., assessments are not embedded in the MyChart e-visit). We will require that participants complete follow-ups via their smartphone so that CO collection is seamlessly integrated with assessments.

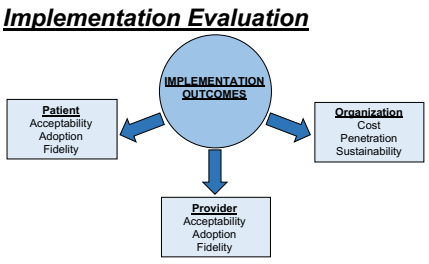
Assessments are estimated at 20 minutes. All compensation for this study will be provided with electronic gift card codes (e.g., Amazon). Participants will be compensated $20 in electronic gift codes for completion of each assessment, $20 for submission of CO at each follow-up timepoint, and will receive a $100 bonus if all follow-up assessments are completed. Procedures for remote remuneration are well-established through our prior trials[22]. At baseline, participants will self-report basic demographics including home address which will be used to determine degree of rurality. Experience using technology and internet access (home broadband, access via mobile device) will be assessed via questions from Pew Research Center's technology adoption survey[7]. Digital literacy will be assessed at baseline via the Mobile Device Proficiency Questionnaire (MDPQ-16)[8] and the Computer Proficiency Questionnaire (CPQ-12)[9]. Both questionnaires are valid, reliable measures of device (mobile, computer) proficiency and have been used to facilitate digital literacy training within research contexts.[8,9] Cigarette smoking, use of other tobacco products (e.g., e-cigarettes), and quit attempts/quit duration will be assessed at each follow-up using a timeline followback for the last 6-months at baseline and since prior follow-up for each subsequent assessment[10,11]. Nicotine dependence will be assessed at baseline via the Fagerström Test of Nicotine Dependence[12]. Participants will report motivation to quit and confidence in quitting using a modified Contemplation Ladder[13]. Self-reported smoking will be biochemically verified via breath CO, with abstinence defined as CO of $\leq$ 4ppm[14]. Self-report and CO data will be utilized together to determine 7-day PPA. Treatment utilization will be assessed via self-report and EHR data. At each follow-up, all participants regardless of intervention will be queried for: 1) use of a cessation treatment (medication or psychosocial counseling) since the last assessment, 2) how the medication was obtained, and 3) receipt of the 5As from their PCP[15]. Self-report data will be supplemented with treatment utilization data pulled from the EHR coinciding with each follow-up. Specifically, we will capture: 1) cessation medication prescriptions, 2) if prescribed, whether cessation medications were filled, 3) whether the participant was referred to counseling, and 4) whether the participant attended a counseling session. Confounders of CO including combustible cannabis use, secondhand smoke exposure, and environmental CO exposure within the last 24 hours will be assessed at all timepoints to account for factors that may falsely inflate CO. Additional data from the EHR will be captured to describe the sample including information on: 1) medical and psychiatric comorbidities, 2) medications, 3) tobacco-related billing codes, and 4) insurance type.

Interviews with key informants are estimated at 30-45 minutes and will be audio and video recorded. Participants will be compensated $20 in electronic gift card codes to Amazon upon completion of the interview. Interviews will be held with patients (n = 30), PCPs (n = 10), and stakeholders (n = 5). Drs. Dahne and Sterba will guide these interviews using the Consolidated Framework for Implementation Research (CFIR).

Assessments:

Measure	Screening	Baseline	1-month	3-month	6-month
Screening	x				
Demographics		x			
PRC Technology Survey		x			
MDPQ-16		x			
CPQ-12		x			
TLFB		x	x	x	x
FTND		x			
Contemplation Ladder		x	x	x	x
MTQ Saliency		x	x	x	x
Use of Other Tobacco Products			x	x	x
Use of Cessation Treatment			x	x	x
Brief Physician Advice			x	x	x
EHR data (e-visit group)				x	
AIM (e-visit group)				x	
E-Visit Feedback (e-visit group)			x	x	x
Confounders/Validity of CO			x	x	x
Adverse Events			x	x	x

Aim 2: Implementation Evaluation



We will use mixed methods to assess implementation during our effectiveness trial at patient, provider, and organizational levels. Our framework is guided by the Consolidated Framework for Implementation Research (CFIR), which provides a comprehensive, pragmatic approach to understand implementation barriers, facilitators and processes[23]. The goal is to provide an in-depth understanding of implementation acceptability, adoption, and capacity for sustainability. Specific implementation outcomes will be assessed according to Proctor's guidance[17], which has recently been adapted by Hermes et al. for digital intervention evaluation[18]. These models suggest the evaluation of key implementation factors including: acceptability, adoption, fidelity, cost, penetration, and sustainability. All self-report

assessments will be administered to patients in the e-visit condition during the 3-month research assessment, following completion of baseline and 1-month e-visits. Provider questionnaires will be administered via REDCap to MUSC RHN PCPs affiliated with the rural clinics involved in the trial who have at least one patient enrolled in the e-visit condition. Provider questionnaires will be sent at 6 weeks following each site's start in the e-visit arm and again at the end of Year 4. Systems-level evaluation will utilize aggregate analytics supplemented with qualitative data. We will conduct key informant interviews with patients, PCPs, and stakeholders to enhance quantitative data. No studies to our knowledge have specifically examined implementation outcomes of proactive EHR-facilitated cessation treatments. As such, for each implementation factor, we have identified benchmarks that would be indicative of meaningful uptake. These benchmarks have been selected based on prior documented rates of cessation treatment acceptance and medication receipt within primary care[24], *Healthy People 2020*'s goals for cessation treatment in ambulatory settings[25], and prior uptake rates in response to proactive, automated cessation intervention delivery in primary care[26,27].

Acceptability

Acceptability refers to the extent to which an innovation is agreeable, palatable, or satisfactory to a stakeholder. We will measure acceptability at patient and provider levels via the 4-item Acceptability of Intervention Measure (AIM)[28]. Items are scored on a 5-point Likert scale, and the resulting scale score is the mean of responses. The e-visit will be considered acceptable if the average score within each group across respondents is greater than or equal to 4 (scale range = 1-5).

Adoption

Adoption refers to the intention, decision, or initiation of use for an evidence-based practice and will be characterized at patient and provider levels via EHR data. At the patient level, we will capture the percent of: 1) e-visits opened, 2) e-visits completed and forwarded to the PCP, and 3) prescribed medications obtained. Using EHR data, we will also compare demographics of patients who enroll in the trial vs. do not to determine whether a demographic-related adoption gap exists. At the provider level, we will assess the percent of e-visits: 1) opened by a patient's PCP, 2) responded to by a patient's PCP, and 3) that result in a prescription from a patient's PCP. The same metrics will be captured for e-visits responded to by the ED e-visit team. The e-visit will be characterized as having high adoption potential among patients if >80% of e-visits are opened, completed, and forwarded to the PCP and >70% of patients prescribed a medication obtain their medication. The e-visit will be characterized as having high adoption potential among PCPs if >80% of completed e-visits are opened and responded to by a patient's own PCP and if >80% of e-visits in which contraindications are not present result in medication prescription. Similar evaluation metrics will be applied to e-visits routed to the ED e-visit team.

Fidelity

Fidelity refers to the extent to which an intervention is used/delivered as intended. Fidelity evaluation herein will focus on protocol adherence, which will be assessed at patient and provider levels. We will utilize an implementation tracking checklist in REDCap to monitor completion of each step of the e-visit process for patients and providers. Research assistants will complete the checklist for each e-visit and we will evaluate the percentage of total steps completed. Across e-visits, we will assess which steps are most often skipped and why, which will be probed during key informant interviews and will guide refinements. For example, if across e-visits we find that PCPs are e-prescribing medications but are not responding to patients electronically with treatment plans, this would suggest needed intervention modifications to augment and facilitate this process.

Cost Impact of Implementation

Health systems may be more likely to implement the e-visit if it is established as either 1) cost-saving or 2) providing benefit cost-effectively. To examine cost-savings from the budgetary perspective, we will first calculate the net benefit of the e-visit: cost-savings = $[(\text{Expenditures}_{pre} - \text{Expenditures}_{post})_{e\text{-}visit} - (\text{Expenditures}_{pre} - \text{Expenditures}_{post})_{TAU}] - \text{Cost}_{e\text{-}visit} + \text{Revenues}_{e\text{-}visit}$. Healthcare utilization expenditures will be obtained from MUSC RHN billings. E-visit implementation cost will be provided by MUSC's BMIC, who will provide ranges of e-visit development and distribution costs. Cessation medication costs will be based on actual billing data. We will conduct sensitivity analyses using medication cost ranges from the National Average Acquisition Cost data, and e-visit revenue ranges from $15.52 to $50.16 (current Medicare e-visit reimbursement rate).

There is also a compelling case for adoption if the e-visit improves outcomes cost-effectively. We will follow gold standard procedures[29] to calculate the incremental cost effectiveness ratio (ICER), or the additional cost per additional desired outcome. Here, $\text{ICER} = (\text{Cost}_{e\text{-}visit} - \text{Cost}_{TAU}) / (\text{7-day PPA Prevalence}_{e\text{-}visit} - \text{7-day PPA Prevalence}_{TAU})$. If differences in baseline patient characteristics between e-visit and TAU are evident, a generalized

linear model will be used to adjust outcomes and costs for these differences. We will conduct probabilistic sensitivity analyses to test results robustness across ranges of costs, revenues and treatment effectiveness[30]. Effectiveness ranges will be based on confidence intervals estimated in Aim 1. Ranges in cost and revenues will be captured as described above. All costs and revenues will be converted to net present value at standard discount rates of 3% and 5%. We will also construct an acceptability curve to demonstrate the probability of the e-visit being cost-effective under different levels of willingness to pay.

Penetration

Penetration refers to the integration of a practice within a service setting. Provider-level penetration will be assessed during the effectiveness trial. We will determine the total number of unique PCPs employed by MUSC's rural RHN primary care clinics who reviewed a study e-visit and divide this number by the total number of PCPs employed by those clinics. High penetration will be indicated by >75% of providers reviewing an e-visit during the study. Patient-level penetration will be assessed during the sustainability evaluation period and will be defined as the total number of unique patients who complete a smoking cessation e-visit during Year 5 divided by the total number adult patients who are current smokers with MyChart access that have a primary care appointment in a rural RHN clinic during Year 5. High patient-level penetration will be defined as >20% of eligible patients completing a smoking cessation e-visit during the sustainability period. A 20% benchmark is similar[31] or higher[26,27] than other proactive cessation trials within the primary care setting.

Sustainability

Effectiveness trial enrollment will conclude by the end of Year 4, and e-visit sustainability will be evaluated in Year 5. During the final three months of Year 4, Dr. Dahne will work with MUSC's BMIC team to ready the e-visit for clinical implementation across rural RHN clinics. Drs. Dahne, Diaz, and Player will provide additional training to all providers and clinic staff regarding how to invite patients to complete the e-visit. MUSC's BMIC will create patient lists, available to each provider, of patients that are e-visit eligible. Trainings will focus on accessing these lists, inviting patients to complete the e-visit, and review of procedures for responding to e-visits. As with trainings provided during the effectiveness trial, we will match as closely as possible training procedures that would occur in usual practice if a new e-visit were to be released. Billing procedures will be identical between the effectiveness trial and the sustainability evaluation (i.e., as in usual practice). At the beginning of Year 5, the e-visit will become available for clinical utilization. During this period, providers will be able to invite their own patients to complete the e-visit. During Year 5, we will track adoption, fidelity, and penetration via EHR analytics data. These metrics will be calculated and interpreted in the same manner as above.

Qualitative Data Collection

Quantitative data collection will be supplemented with key informant interviews with patients (n=30, or until saturation), PCPs (n=20, or until saturation), and organizational stakeholders (n=5). This mixed methods approach was chosen because, while quantitative data can identify implementation outcomes, qualitative data provide guidance regarding implementation barriers and facilitators faced and methods for optimization in rural practices and among rural patients. Diverse patients and PCPs in terms of clinic location, demographics, time in practice, and cessation outcomes will be recruited for interviews. For patient interviews, we will specifically recruit patients who were invited to enroll in the trial, but opted not to (n=10), patients who enrolled but did not complete either the baseline or 1-month e-visit (n=10), and patients who enrolled and completed both the baseline and 1-month e-visits (n=10). A key focus of these interviews will be on the potential impact of the digital divide on trial/intervention access and uptake to determine which patients are most likely to access the e-visit, should it be scaled. Similarly, we will recruit PCPs with high e-visit adoption (i.e., responded to >80% of e-visits completed by their patients; n=10) and low e-visit adoption (i.e., responded to <20%; n=10). Organizational stakeholders will include IT support staff from the RHN, the RHN's Chief Quality Officer, practice managers and medical directors, clinical pharmacists, the co-Director of MUSC's BMIC, and the Chief Executive Officer of Palmetto Care Connections. PCPs and stakeholders will be recruited for interviews via targeted e-mail and phone messages. Interviews (~30-45 minutes) will be conducted by IRB approved members of the investigative team (e.g., Drs. Sterba and Dahne) in person or by telephone with a structured interview guide developed using the CFIR[23]. Interviews will focus on each implementation factor described above with the goal to enhance quantitative data within each domain and guide best practices for implementation in rural settings. Interviews will be conducted until theme saturation is achieved[32,33] and will be audio-taped and transcribed for analysis. All audio and video recordings will be destroyed within 12 months of completion of the entire study. Methods to ensure trustworthiness of qualitative data collection and analysis (e.g., audit trails, prolonged engagement with data) will be used[34].

11.0 Data Analysis and Data Management

Aim 1 (Effectiveness RCT) Statistical Design

Power. Our primary effectiveness outcome is cessation, defined as 7-day CO-verified PPA at 6-months. Preliminary data from our e-visit pilot demonstrated 7-day PPA rates at 3-months of 21.7% and 6.3% for e-visit and TAU groups, respectively. We expect similar group differences at 6-months and use these rates for power and sample size estimation. In addition, we expect some degree of intra-clinic/intra-division correlation (i.e., intraclass correlation (ICC)), where patients who attend the same clinic are not completely independent from each other and allow for the possibility that they are correlated with each other. We assume this to be relatively low and estimate it at 0.013, based on our prior site-randomized NRT sampling study[35,36]. A complete stepped-wedge cluster-randomized design with three clusters (divisions), four time periods (including a baseline period), three steps (one for each division to switch from TAU to e-visit), and an average of 72 patients per division (18 patients per division per time period), provides a total sample size of 216. Using a Wald Z-Test, with an ICC of 0.013 and a significance level of 0.05, N=216 has more than 80% power to detect a difference in 7-day CO-verified PPA at 6-months of 21.7% (e-visit) vs. 6.3% (TAU). To account for 25% possible attrition based on our previous studies[35,37], the sample size is inflated to **a total of 288 participants** (96 patients per division, with 24 patients per division per time period).

Other outcomes for this trial include treatment utilization and reduction in CPD of >50%. In our e-visit pilot, treatment utilization rates at 3-months were higher in the e-visit group (60.9%) compared to the TAU group (25%); similarly, reduction in CPD of >50% was higher in the e-visit group (65.2%) compared to the TAU group (31.3%). Using a complete stepped-wedge cluster-randomized design (as above with three clusters, four time periods, and three steps with a total sample size of N=288), we will have more than sufficient power to see similar differences, and in fact smaller differences. For example, a stepped-wedge cluster-randomized trial (as defined herein) would have >80% power to see differences as small as 27% (Treatment Utilization: 52% e-visit, 25% TAU) and 29% (Reduction in CPD: 60% e-visit, 31% TAU).

Cessation treatment utilization and cessation outcomes. Simple descriptive statistics will be summarized overall and within division and intervention group for baseline demographic variables, such as sex, age, race, ethnicity, digital literacy, insurance type, income, marital status, medical and psychiatric comorbidities (as indicated in the EHR), nicotine dependence, motivation to quit, and other household members who smoke. These baseline variables will also be summarized within division (between intervention groups) to evaluate balance within a division and between intervention groups and identify potential selection bias or time effects. Comparisons within clusters (i.e., TAU vs. e-visit within divisions) will be initially compared via paired testing such as paired-t-tests, Wilcoxon signed-rank tests (continuous variables), or McNemar's tests (categorical variables). To evaluate the possibility of time effects, generalized linear mixed models (GLMMs) will then be used including all patients from all divisions and all time periods. These models allow for examining baseline differences while accounting for random effects for division as well as fixed effects of time (for each step in the design). The fixed effect of time is important to include in order to verify that any potential intervention effects are not a function of a temporal trend outside of the intervention. This will allow for confidence in identifying any effects due to the intervention. A larger GLMM will then be used that incorporates all patients from all divisions to evaluate baseline differences between intervention groups (while accounting for division and time effects).

Descriptive statistics (e.g., frequencies, percentages) will be calculated for the primary smoking-related outcomes (self-reported and biochemically verified 7-day PPA, reduction in CPD >50%, treatment utilization) overall, by division, by treatment group, and by treatment group within division. For analysis of these primary outcomes, GLMMs with logit links for binary outcomes will be used to examine between group (intervention) differences while accounting for division clustering effects and fixed time effects (for each step). To examine group differences adjusted for relevant covariates based on baseline differences, GLMMs will also be used by adding baseline effects to models in addition to a random effect for division and a fixed effect of time (for each step).

Secondary subgroup analyses. While digital platforms have the potential to increase treatment access by decreasing barriers, they may be more readily accessed by more advantaged groups. Thus, it is critical to understand for which groups of rural smokers the e-visit is most/least beneficial. GLMMs including main effects of treatment group and specific subgroup variables of interest (e.g., education, race, income, degree of rurality, mental health comorbidities,

digital literacy, insurance type) along with an interaction term between treatment and the subgroup will be used to evaluate for which groups of smokers the e-visit is most beneficial. Each subgroup will be evaluated individually. All models will include a random division effect to account for clustering as well as a fixed effect for time. As this is an exploratory analysis, the focus will be on effect sizes rather than solely on statistical significance, with no adjustment for multiple comparisons. Statistical significance of interaction terms will be interpreted in conjunction with the effect size and will not solely define a significant, observed effect.

Missing data and dropout. All enrolled participants will be included in analyses (intent-to-treat approach). We will examine dropout as function of treatment group, division, and time to examine whether treatment is associated with differential study retention. A sensitivity analysis will be used to assess the potential effect of missing outcome data on parameter estimates. Parameters will be estimated using: 1) all available data, 2) missing outcome data imputed to baseline, and 3) methods of multiple imputations. Imputation of missing data in smoking cessation trials to the baseline condition is often used as it is conservative[38], does not necessitate the missing and random assumption, and allows for correlation between missing status and smoking status[39].

Aim 2 Qualitative Data Analysis

Qualitative data will be analyzed using NVivo software[40] with a deductive/inductive template analysis approach[41,42] using an initial CFIR-derived codebook but also allowing additional codes to be generated directly from the data. Two coders will independently review and code data using an iterative, team-based process to refine the codebook with discrepancies resolved by the study team. After completing qualitative and quantitative data analysis independently, data from each source will be synthesized using graphical matrix configurations for data triangulation[43]. Qualitative themes will be supplemented by patterns identified in quantitative results. Findings will characterize needs, concerns, and impressions of our key informants and guide implementation strategies for disseminating the e-visit intervention widely in rural settings.

Data Management

Regarding questionnaire data, data will be obtained for research purposes only. All data will be collected, stored, and managed via REDCap, which is a secure, web-based application designed exclusively to support data capture for research studies. REDCap includes real time validation rules with automated data type and range checks at the time of entry. The underlying database is hosted in a secure data center at MUSC and includes redundancy, failover capability, backups and extensive security checks. The system has several layers of protection including user/group account management, "Data Access Groups" which allow data to be entered by multiple groups in one database with segmented user rights for entered data, audit trails for all changes, queries and reports, and Secure Sockets Layer (SSL) encryption. Name and relevant contact information will be obtained to provide compensation and every effort will be made to maintain subject confidentiality, in accordance with HIPAA. All data will be identified only by code numbers (participant IDs). Participant IDs will be linked to participants' names in a password-protected file that is accessible only to the PI and trained research staff. Audio and video recordings from key informant interviews will be destroyed within 12 months of completion of the entire study.

Recruitment projects are housed in REDCap. Only IRB-approved study personnel listed on this application will have access to the recruitment project database. The research team will only have access to the REDCap recruitment project while actively enrolling for the study. This recruitment project will be stored separately from the project containing research data.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

This section is based on the recommendations in NCI's "Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute" as well as NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan".

Summary of the Protocol

This R01 application consists of a 2-Aim proposal. In Aim 1, we will conduct a stepped-wedge, cluster-randomized clinical trial (N=288) to examine the effectiveness of the smoking cessation e-visit vs. TAU for smoking cessation across seven rural (Rural-Urban Commuting Area codes 4-10) primary care practices in South Carolina. In Aim 2, we will evaluate e-visit implementation outcomes across rural South Carolina primary care settings at patient, provider, and organizational levels. See "Protection of Human Subjects" for inclusion/exclusion criteria and C.4.g within the "Research Strategy" for sample size justification.

Trial Management

The study will be managed from the Addiction Sciences Division within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina (MUSC). Recruitment, data collection, data management, and treatment provision will be coordinated and centrally managed at our research lab at MUSC and will be implemented within rural primary care clinics that are part of MUSC's Regional Health Network (RHN). The target population is described under "Protection of Human Subjects" and below in the adjoining Planned Enrollment Table. Participant enrollment for Aim 1 will occur during months 4-48 (months within total study duration).

Data Management and Analysis

Participants will enter data in REDCap, a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. These procedures are effective in minimizing data entry errors (e.g., missing or errant data). All data from the iCO™ Smokerlyzer (personal breath CO monitor) will also be entered and stored in REDCap. Data analytic plans are outlined in section C.4.h of the Research Strategy as well as in the Statistical Design and Power attachment.

Quality Assurance

Accuracy and completeness of the data collected will be ensured by weekly review. The REDCap system does not accept outliers, illogical response patterns, etc. The PI and research assistants will have weekly meetings to discuss any qualitative comments received during data collection and any problems in data collection. The PI will examine the database for potential irregularities monthly. Initial data analyses will examine distributions of variable scores and comparability of baseline characteristics across conditions in case analyses need to be adjusted for these. Confidentiality procedures are outlined above.

Regulatory Issues

This study will be registered on clinicaltrials.gov. The study does not require an IND from the FDA. All serious AEs will be reported to the MUSC Committee on Human Research within 48-hours. Follow-up of all unexpected and serious AEs will also be reported. All AEs will be reviewed weekly by the PI and yearly by the IRB. Any significant actions taken by the local IRB and protocol changes will be relayed to the funding agency. We estimate the significant AE rate to be 5% or less. If monthly monitoring indicates the rate is above this, we will convene a meeting of the DSMB. Potential conflicts of interest (COI) will be reported using the Society for Research on Nicotine and Tobacco's rules for disclosure as well as the rules of MUSC's COI committee.

Trial Safety

The potential risks and benefits and methods to minimize these risks are outlined in the "Protection of Human Subjects" section. AEs will be tracked and rated by the participant as mild, moderate or severe and as related or unrelated to cessation medications received as part of the e-visit. We will determine if any AEs result in dropouts or are serious according to FDA guidelines. The PI (Dr. Dahne) will serve as the Program Manager for AEs. All unexpected AEs will be monitored while they are active to determine if treatment is needed. We anticipate that AEs will be rare as only FDA-approved medications for cessation will be used and all medications will be used on label. Nonetheless, any AEs will be coded on a weekly basis using the FDA's COSTART rules[44] and entered into a database. For each weekly study meeting, the research assistant will prepare a summary of all AEs, including their severity, whether they caused a dropout, required treatment and presumed relation to drug intake. The PI will review this at the weekly study meeting (or before if more urgent). At the weekly meeting (or before if urgent), the research assistant will report any premonitory symptoms to suggest emergence of a serious psychiatric condition (e.g., major

depression, suicidality). Drs. Diaz and Player, board-certified Family Medicine physicians, will be available on an ad-hoc basis for on-site medical supervision for any issues that cannot be resolved by Dr. Dahne.

Study procedures will follow as much as possible the FDA's Good Clinical Practice Guidelines and our research team has found Spilker's comprehensive text on conducting clinical trials to be useful[45]. We will encourage participants to notify their physicians that a) they are in a randomized controlled research study examining a treatment for smoking cessation, and b) the physician should contact the PI directly if the physician has any questions.

The research assistants will be instructed not to reveal whether a person is a participant in the study and will report to the PI any outside requests for information about a participant or any breaches in confidentiality. All requests by participant's physicians and other medical providers will be referred directly to the PI.

Trial Efficacy
The Data and Safety Monitoring Board (see below) may request a blinded interim efficacy report (blinded to the PI and research team) for review while the trial is ongoing. Final (fully unblinded) efficacy analysis will occur after all participants have completed all follow-ups.

Data and Safety Monitoring Plan Administration
The PI will be responsible for monitoring the trial, with additional oversight provided by study co-Investigators. The PI will examine monthly the outcomes database for missing data, unexpected distributions or responses, and outliers. The PI will check weekly the AE database prepared by the research assistant immediately prior to the lab meeting to a) see if any particular COSTART categories are being endorsed more frequently than normal and b) determine if any side-effect symptom checklist scores are higher than expected. A DSM report will be filed with the IRB and funding agency on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report efficacy at the end of the trial.

Data and Safety Monitoring Board Plan
We will create a Data and Safety Monitoring Board (DSMB), comprised of three clinicians with expertise in rural health, smoking cessation treatment, and smoking cessation clinical trials, and a statistician. The DSMB will meet annually (more frequently as needed for emergent situations) to review any AEs related to the study, as well as review any data management related errors. The board may be called at any point if needed for unexpected, serious AEs, etc. If necessary, modifications will be made to the procedures and/or the protocol based on the findings of the board.

13.0 Risks to Subjects

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 than those ordinarily encountered in daily life or during performance of routine physical or psychological examinations or tests. The potential risks in this study include those related to: a) smoking cessation medications, b) confidentiality, c) frustration, d) risks during pregnancy, e) randomization, and f) uknown risks.

a) Smoking cessation medications: Participants assigned to the smoking cessation e-visit may receive an FDA-approved smoking cessation medication recommendation and prescription as an outcome of the e-visit. Medication options include: nicotine replacement therapy (NRT; prescribed either as a single or combination therapy, e.g., patch+lozenge/gum), varenicline, and/or bupropion. Participants will be educated about their smoking cessation medication as part of the e-visit, which will include education about potential medication side effects. The e-visit will assess contraindications for each FDA-approved cessation medication and medication will only be prescribed if the participant does not have contraindications for that medication. Contraindications for NRT include: 1) recent ($\leq$ 2 weeks) myocardial infarction, 2) serious underlying arrhythmias, and 3) serious/worsening angina pectoris. Contraindications for varenicline include: 1) severe renal impairment, 2) pregnancy, and 3) breastfeeding. Contraindications for bupropion include: 1) severe renal impairment, 2)

concomitant therapy with medications/conditions known to lower the seizure threshold, 3) hepatic impairment, 4) seizure disorder, 5) current or prior diagnosis of bulimia or anorexia nervosa, 6) simultaneous abrupt discontinuation of alcohol or sedatives/benzodiazepines, 7) use of MAO inhibitors within the last 14 days or concurrent use of reversible MAO inhibitors, 8) pregnancy, and 9) breastfeeding. Participants will be provided with our study phone number and instructed to call our study personnel should they experience AEs or if they have questions/concerns about medication use. Given the relatively benign risk profiles of these medications, we expect AEs, which will be assessed across follow-up timepoints via REDCap, to be rare and mild. Participants will be encouraged to contact Dr. Dahne as soon as possible for serious AEs and for those conditions that labeling suggests seeing a provider. We will withdraw participants who have a serious AE. For other AEs, if the participant wishes it, the participant will be withdrawn from the study.

b) Confidentiality: There is a risk of a loss of confidentiality of the participant's personal information when submitting online questionnaires or breath samples as a result of participation in this study. Participants will be made aware of limits to confidentiality at the beginning of screening and during informed consent which include report of suicidal or homicidal intent or report of abuse or neglect. If the participant reports suicidal or homicidal intent or abuse/neglect during the phone screening or during the trial, Dr. Dahne will take appropriate action as outlined by the MUSC IRB, NIH, and the State of South Carolina, which may include contacting the authorities and/or pursuing involuntary commitment at a mental health facility. If participants present no imminent danger but also need more extensive treatment of mental health concerns, they will be given appropriate referrals and instructed to contact their primary care physician.

c) Frustration: Participants may become frustrated while completing questionnaires or while using the smoking cessation e-visit. Participants will be informed that they may refuse to answer any question(s) that they do not wish to answer and that they may discontinue the e-visit at any time (which will be tracked as a study outcome).

d) Risks During Pregnancy: We do not know if medications that may be prescribed as part of this study will affect mother's milk or an unborn fetus. If a participant is pregnant or becomes pregnant, there may be risks to the embryo or fetus that are unknown at this time. Participants will be made aware during consent that any woman of childbearing potential, as reported on the screening survey, must complete a pregnancy test before completing the e-visit. The pregnancy test will be mailed to her at no cost and the participant will receive a REDCap form within 3 days to verify (with signature) that they completed the test and their pregnancy test results. Once study staff receives this completed REDCap form from the participant, they will be scheduled for consent. Females of childbearing potential who report a positive pregnancy test will not receive varenicline as a result of the e-visit. These women instead will either receive NRT, bupropion and/or counseling based on other contraindications and medication preferences indicated throughout the e-visit.

e) Randomization: Participants are made aware that one treatment method may prove to be more or less effective than the other treatment method provided via the study. Participants are free to discontinue study participation at any time, either prior to or following randomization in order to avoid this risk.

f) **Uknown Risks:** The experimental treatments may have unknown side effects. The researchers will inform participants if they learn anything during the course of the study that might make participants change their mind about participating in the study.

Since patients will all currently be receiving medical care within the MUSC Regional Health Network (RHN), there are no additional risks associated with participation in this study.

Adequacy of Protection Against Risks

Recruitment and Informed Consent

Study participants will be recruited from rural MUSC RHN primary care clinics. Smoking status is assessed for every patient, consistent with MUSC's best practice guidelines. Patients will be idenfitied via cold contact for research recruitment methods and will be sent a message inviting them to participate in a research study. These patients will be sent a message through MyChart to invite them to participate in a research study. Interested patients will complete determination of eligibility via MUSC's REDCap system, a secure, HIPAA-compliant data management system.

Consent will take place remotely via REDCap e-consent paired with a phone call with a member of the research team[19]. This approach allows: 1) live audio contact with an IRB-approved consenter and 2) electronic signed consent. All participants will electronically sign informed consent forms that have been IRB-approved once the study is explained to them in full and they have stated that they understand what is being asked of them. Participants will be given the opportunity to ask questions about their participation throughout the course of the study. A copy of the informed consent will be kept centrally at our study office within locked filing cabinets and a copy will also be given to each study participant. Participants will be given a study phone number and e-mail address to contact for questions.

Protections Against Risk

All screening information will be kept in a password protected REDCap database. Only key study personnel will have access to the database. If an individual is not eligible to participate, his/her screener will include his/her first name and last initial and the reason for disqualification. Eligible participants' full name, telephone number and e-mail address will be recorded in the database. This is the only place where participants' names and subject identification numbers appear together. Eligible participants will be assigned a subject number, will complete informed consent (see procedures above), will be assigned to an intervention based on their clinic division's current step, will complete baseline assessments, and subsequently will receive their randomized intervention.

Upon completing eligibility screening, if study eligible, individuals will be provided with a verbal overview of the study, asked to review a consent form, and asked to provide informed consent. Participants will be informed of limitations of confidentiality (i.e., abuse or neglect, intention to harm self or someone else) both verbally and in writing during the informed consent process. The consent form will include the participant's name, but not his/her subject number. Consent forms will be provided in English. As utilization of the smoking cessation e-visit requires that participants are able to read, participants unable to read the consent form on their own will not be included.

Regarding questionnaire data, data will be obtained for research purposes only. All data will be collected, stored, and managed via REDCap, which is a secure, web-based application designed exclusively to support data capture for research studies. REDCap includes real time validation rules with automated data type and range checks at the time of entry. The underlying database is hosted in a secure data center at MUSC and includes redundancy, failover capability, backups and extensive security checks. The system has several layers of protection including user/group account management, "Data Access Groups" which allow data to be entered by multiple groups in one database with segmented user rights for entered data, audit trails for all changes, queries and reports, and Secure Sockets Layer (SSL) encryption. Name and relevant contact information will be obtained to provide compensation and every effort will be made to maintain subject confidentiality, in accordance with HIPAA. All data will be identified only by code numbers (participant IDs). Participant IDs will be linked to participants' names in a password-protected file that is accessible only to the PI and trained research staff. Audio and video recordings from key informant interviews will be destroyed within 12 months of completion of the entire study.

Protection against risks associated with FDA-approved smoking cessation medications that may be provided as a result of the e-visit includes: 1) review of all medication recommendations by physicians, 2) use of such medications strictly on label, and 3) a Data and Safety Monitoring Plan that includes monitoring of AEs. Participants will not be provided with a medication if they have FDA contraindications for that medication. **There will be direct electronic contact between the participant and the PCP via MyChart prior to prescription. If contraindications are present (e.g., a contraindicated medication is noted in the EHR, but not reported in the e-visit) or if the patient reports untreated health concerns requiring attention (e.g., cough with blood), electronic contact will be supplemented with phone and/or in person contact**. Thus, prescription-related safety concerns are no greater here than in other clinical scenarios. While this direct contact could be viewed as an impediment to scalability, we view it as necessary due to potential safety concerns related to prescription medications. Through informational material provided with the medications and through the e-visit, participants will be educated about potential AEs and nicotine intoxication symptoms. As FDA-approved medications with benign risk profiles, we anticipate very few AEs. AEs will be assessed in research follow-ups as well as in the 1-month follow-up e-visit. During consent and within the e-visit, participants will be provided contact information to use should they experience an AE and need immediate clinical support. AEs will be discussed with Drs. Diaz and Player. We will also form a Data Safety and Monitoring Board (DSMB). If the percent of serious or severe AEs appears to be greater than 5% the DSMB will be notified to make a decision regarding early termination of the study.

14.0 Potential Benefits to Subjects or Others

All rural smokers in this trial will receive at minimum standard smoking cessation care via MUSC's RHN primary care clinics and evidence-based educational information about quitting smoking. We will not augment standard smoking cessation care as provided by the RHN clinics. Participants may also receive an invitation to complete a smoking cessation e-visit. The major benefits to society will be whether this smoking cessation e-visit improves cessation treatment access and cessation outcomes relative to TAU for rural smokers and whether the approach has high implementation potential within rural primary care settings. Potential issues of medication risks, confidentiality, and frustration are a high priority and will be closely monitored throughout the study. Consequently, the risk to benefit ratio in the proposed study appears to be acceptable.

15.0 Sharing of Results with Subjects

Study enrollment and study outcomes will not be shared with medical staff, including the participant's physician.

16.0 Drugs or Devices

This study involves the use of FDA-approved smoking cessation medications. Medications will not be stored or handled by any members of the research team. Medications recommended in the e-visit will be reviewed by the patient's primary care physician before prescription. If no contraindications exist, the primary care physician will e-prescribe the medication to the patient's preferred pharmacy.

REFERENCES

1. Cropsey KL, Jardin BF, Burkholder GA, Clark CB, Raper JL, Saag MS. An Algorithm Approach to Determining Smoking Cessation Treatment for Persons Living With HIV/AIDS: Results of a Pilot Trial. *J Acquir Immune Defic Syndr.* 2015;69(3):291-298.
2. Valera P, McClernon FJ, Burkholder G, et al. A Pilot Trial Examining African American and White Responses to Algorithm-Guided Smoking Cessation Medication Selection in Persons Living with HIV. *AIDS Behav.* 2017;21(7):1975-1984.
3. Cropsey KL, Bean MC, Haynes L, Carpenter MJ, Richey LE. Delivery and implementation of an algorithm for smoking cessation treatment for people living with HIV and AIDS. *AIDS Care.* 2020;32(2):223-229.
4. Fiore MC, Jaen CR, Baker T, et al. *Treating tobacco use and dependence: 2008 update.* Rockville, MD: US Department of Health and Human Services, Public Health Service; 2008.
5. National Cancer Institute. Clearing the air: Quit smoking today. In: National Institutes of Health, US Department of Health and Human Services; 2003.
6. Brandon TH, Simmons VN, Sutton SK, et al. Extended Self-Help for Smoking Cessation: A Randomized Controlled Trial. *Am J Prev Med.* 2016;51(1):54-62.
7. Pew Research Center. Digital gap between rural and nonrural America persists. Pew Internet & American Life Project Web site. https://www.pewresearch.org/fact-tank/2019/05/31/digital-gap-between-rural-and-nonrural-america-persists/. Published 2019. Accessed January 12, 2021.
8. Roque NA, Boot WR. A New Tool for Assessing Mobile Device Proficiency in Older Adults: The Mobile Device Proficiency Questionnaire. *J Appl Gerontol.* 2018;37(2):131-156.
9. Boot WR, Charness N, Czaja SJ, et al. Computer proficiency questionnaire: assessing low and high computer proficient seniors. *Gerontologist.* 2015;55(3):404-411.
10. Sobell L, Sobell M. Timeline followback users guide: A calendar method for assessing alcohol and drug use. *Toronto: Addiction Research Foundation.* 1996.
11. Brown RA, Burgess ES, Sales SD, Whiteley JA, Evans DM, Miller IW. Reliability and validity of a smoking timeline follow-back interview. *Psychol Addict Behav.* 1998;12(2):101-112.
12. Payne TJ, Smith PO, McCracken LM, McSherry WC, Antony MM. Assessing nicotine dependence: a comparison of the Fagerstrom Tolerance Questionnaire (FTQ) with the Fagerstrom Test for Nicotine Dependence (FTND) in a clinical sample. *Addict Behav.* 1994;19(3):307-317.
13. Biener L, Abrams DB. The Contemplation Ladder: validation of a measure of readiness to consider smoking cessation. *Health Psychol.* 1991;10(5):360-365.
14. Perkins KA, Karelitz JL, Jao NC. Optimal carbon monoxide criteria to confirm 24-hr smoking abstinence. *Nicotine Tob Res.* 2013;15(5):978-982.
15. Vijayaraghavan M, Yuan P, Gregorich S, et al. Disparities in receipt of 5As for smoking cessation in diverse primary care and HIV clinics. *Prev Med Rep.* 2017;6:80-87.
16. Proctor E, Silmere H, Raghavan R, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Adm Policy Ment Health.* 2011;38(2):65-76.
17. Proctor EK, Landsverk J, Aarons G, Chambers D, Glisson C, Mittman B. Implementation research in mental health services: an emerging science with conceptual, methodological, and training challenges. *Adm Policy Ment Health.* 2009;36(1):24-34.
18. Hermes ED, Lyon AR, Schueller SM, Glass JE. Measuring the Implementation of Behavioral Intervention Technologies: Recharacterization of Established Outcomes. *J Med Internet Res.* 2019;21(1):e11752.
19. Chen C, Turner SP, Sholle ET, et al. Evaluation of a REDCap-based Workflow for Supporting Federal Guidance for Electronic Informed Consent. *AMIA Jt Summits Transl Sci Proc.* 2019;2019:163-172.

20. Pew Research Center. Some Digital Divides Persist Between Rural, Urban and Suburban America. Fact Tank Web site. https://www.pewresearch.org/fact-tank/2021/08/19/some-digital-divides-persist-between-rural-urban-and-suburban-america/. Published 2021. Accessed November 15, 2021.
21. Pew Research Center. Mobile Fact Sheet. Pew Internet & American Life Project Web site. https://www.pewresearch.org/internet/fact-sheet/mobile/. Published 2021. Accessed November 15, 2021.
22. Dahne J, Tomko RL, McClure EA, Obeid JS, Carpenter MJ. Remote Methods for Conducting Tobacco-Focused Clinical Trials. *Nicotine Tob Res.* 2020;22(12):2134-2140.
23. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci.* 2009;4:50.
24. Fiore MC, McCarthy DE, Jackson TC, et al. Integrating smoking cessation treatment into primary care: an effectiveness study. *Prev Med.* 2004;38(4):412-420.
25. Koh HK, Piotrowski JJ, Kumanyika S, Fielding JE. Healthy people: A 2020 vision for the social determinants approach. *Health Educ Behav.* 2011;38(6):551-557.
26. Haas JS, Linder JA, Park ER, et al. Proactive tobacco cessation outreach to smokers of low socioeconomic status: a randomized clinical trial. *JAMA Intern Med.* 2015;175(2):218-226.
27. Kalkhoran S, Inman EM, Kelley JHK, Ashburner JM, Rigotti NA. Proactive Population Health Strategy to Offer Tobacco Dependence Treatment to Smokers in a Primary Care Practice Network. *J Gen Intern Med.* 2019;34(8):1571-1577.
28. Weiner BJ, Lewis CC, Stanick C, et al. Psychometric assessment of three newly developed implementation outcome measures. *Implement Sci.* 2017;12(1):108.
29. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA.* 1996;276(15):1253-1258.
30. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes.* Oxford university press; 2015.
31. Fu SS, van Ryn M, Sherman SE, et al. Proactive tobacco treatment and population-level cessation: a pragmatic randomized clinical trial. *JAMA Intern Med.* 2014;174(5):671-677.
32. Saunders B, Sim J, Kingstone T, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. *Qual Quant.* 2018;52(4):1893-1907.
33. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field methods.* 2006;18(1):59-82.
34. Korstjens I, Moser A. Series: Practical guidance to qualitative research. Part 4: Trustworthiness and publishing. *Eur J Gen Pract.* 2018;24(1):120-124.
35. Carpenter MJ, Wahlquist AE, Dahne J, et al. Nicotine replacement therapy sampling for smoking cessation within primary care: results from a pragmatic cluster randomized clinical trial. *Addiction.* 2020;115(7):1358-1367.
36. Dahne J, Wahlquist AE, Boatright AS, et al. Nicotine replacement therapy sampling via primary care: Methods from a pragmatic cluster randomized clinical trial. *Contemp Clin Trials.* 2018;72:1-7.
37. Dahne J, Player M, Carpenter MJ, Ford DW, Diaz VA. Evaluation of a Proactive Smoking Cessation Electronic Visit to Extend the Reach of Evidence-Based Cessation Treatment via Primary Care. *Telemed J E Health.* 2021;27(3):347-354.
38. Hall SM, Delucchi KL, Velicer WF, et al. Statistical analysis of randomized trials in tobacco treatment: longitudinal designs with dichotomous outcome. *Nicotine Tob Res.* 2001;3(3):193-202.
39. Barnes SA, Larsen MD, Schroeder D, Hanson A, Decker PA. Missing data assumptions and methods in a smoking cessation study. *Addiction.* 2010;105(3):431-437.
40. *NVivo Software* [computer program]. 2018.

41. Crabtree B, Miller W, Crabtree B, Miller W. Using codes and code manuals: a template organizing style of interpretation. 1999.
42. Brooks J, McCluskey S, Turley E, King N. The Utility of Template Analysis in Qualitative Psychology Research. *Qual Res Psychol.* 2015;12(2):202-222.
43. Guetterman TC, Fetters MD, Creswell JW. Integrating Quantitative and Qualitative Results in Health Science Mixed Methods Research Through Joint Displays. *Ann Fam Med.* 2015;13(6):554-561.
44. Joseph MC, Schoeffler K, Doi PA, Yefko H, Engle C, Nissman EF. An automated COSTART coding scheme. *Drug Inf J.* 1991;25(1):97-108.
45. Spilker B. *Guide To Clinical Trials.* Philadelphia, PA: Lippincott Williams & Wilkins; 2000.