PROTOCOL TITLE: Development and Testing of an Electronic Visit for COPD Early Detection and Smoking Cessation

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1.0 Objectives / Specific Aims

The goal of this work is to develop, refine, and pilot test an electronic visit (e-visit) to: 1) deliver smoking cessation treatment to adults at risk for COPD and 2) to improve rates of COPD early detection and accurate diagnosis. We will conduct a pilot RCT (N=100, up to 120 assuming 20% attrition) of the COPD/smoking cessation e-visit as compared to treatment as usual (TAU), with primary objective to provide effect size estimates for a larger RCT. Specific aims are twofold:

Aim 1: Conduct usability testing of the smoking cessation/COPD e-visit with patients (N=5, up to 10 to account for attrition) followed by iterative refinements consistent with participant feedback.

Aim 2: Conduct a pilot, small-scale randomized controlled trial to examine COPD and smoking cessation outcomes associated with the E-Visit as compared to treatment as usual (TAU; i.e., no e-visit). Outcomes will include those related to: e-visit feasibility (i.e., time to complete e-visit, time for provider to review e-visit, % completed e-visits, qualitative feedback), COPD (early diagnosis rates as a function of treatment condition, emergency department visits for respiratory infection), smoking cessation outcomes (self-reported quit attempts/quit duration and biochemically verified cessation via carbon monoxide), and cessation medication utilization.

We hypothesize that participants randomized to the e-visit condition as compared to those randomized to the TAU condition will have higher (numerically, if not statistically significant) rates of COPD early diagnosis, cessation treatment utilization (medications, counseling), and superior cessation-related outcomes.

2.0 Background

More than 16 million Americans have COPD and millions more suffer from COPD but have not yet been accurately diagnosed or treated[1]. Nationwide healthcare costs associated with COPD exceed $36 billion annually and are projected to reach $49 billion by 2020[1]. COPD is now concentrated within rural communities and those who reside in rural areas as compared to those who reside in large metropolitan areas have both higher COPD incidence (8% vs. 5%) and higher COPD-related death rates (55 per 100,000 vs. 32 per 100,000)[2]. Telehealth strategies to implement evidence-based best practice for COPD may be particularly impactful among rural communities as such treatment modalities can extend the reach of traditional COPD prevention, diagnosis, and treatment strategies.

In light of the significant public health impact of COPD, the National Heart Lung and Blood Institute (NHLBI) issued a COPD National Action Plan in 2017. A key goal within this national action plan is to improve the diagnosis, prevention, treatment, and management of COPD by improving the quality of care delivered across the health care continuum. Informed by this federal national action plan, and with the guidance of HRSA, our team will undertake a 22-month planning and pilot intervention period to identify how telehealth modalities might be optimally leveraged to improve the quality of care and outcomes among patients at risk for COPD. Because COPD is most commonly caused by cigarette smoking, we will focus our planning and intervention period specifically on COPD early detection among cigarette smokers and on leveraging telehealth to extend the reach of evidence-based smoking cessation treatment (i.e., medications and counseling for smoking cessation) for those at risk for COPD. This work will build upon and extend our team's ongoing efforts to develop a smoking cessation electronic visit (e-visit) that can be proactively delivered to all adult MUSC patients who have been identified via the electronic health record as cigarette smokers. E-visits are embedded into the most common electronic health record (EHR) systems (e.g., Epic, Allscripts, and others) and offer a secure platform through which patients can

remotely supply providers with health information. Providers in turn can deliver personalized instructions and/or treatment to the patient. Prior studies of asynchronous e-visits for chronic condition treatment have found high satisfaction among both patients and providers and that such e-visits can be delivered efficiently (average time for patient to complete e-visit = 8.3 minutes, average time for provider to review and respond to e-visit = 3.6 minutes)[3].

Our team received a pilot award (PIs: Dahne and Diaz) from the South Carolina Telehealth Alliance in July 2018 to begin development of a smoking cessation e-visit for implementation within MUSC primary care. Preliminary e-visit development is now complete and a pilot trial to examine smoking cessation outcomes associated with e-visit receipt is underway. Herein, we will leverage this proactive, scalable platform to: 1) deliver smoking cessation treatment to adults at risk for COPD and 2) to improve rates of COPD early detection and accurate diagnosis. The ultimate goal of this line of work is to improve the quality of care and associated outcomes among patients at risk for COPD.

3.0 Intervention to be studied

We are currently in the process of modifying our existing asynchronous smoking cessation e-visit to incorporate COPD early detection with MUSC's BMIC Epic development team. The smoking cessation component of the e-visit is based on USPHS guidelines[4] and serves to automate much of the 5As (i.e., Ask, Advise, Assess, Assist, Arrange) process. Smokers are proactively invited via electronic message (e.g., via MyChart) to initiate an asynchronous smoking cessation e-visit. The e-visit is a questionnaire administered via MyChart. The initial asynchronous e-visit gathers information about smoking and quit histories, followed by questions to assess motivation to quit and an algorithm to determine the best smoking cessation medication to prescribe for each patient by assessing contraindications and preferences for FDA-approved first line cessation medications (i.e., nicotine replacement therapy, varenicline, bupropion). The e-visit will be sent to an attending physician (study physicians included on the IRB protocol), who will review the recommendations, inform study staff of which medication to provide to participants, make referrals to additional smoking cessation resources (e.g., state quitline), and schedule a follow-up e-visit. Varenicline, a class C medication, may be provided as a result of the e-visit. Because risks during pregnancy related to Varenicline are unknown, women under the age of 55 who receive a recommendation for Varenicline as a result of the e-visit algorithm will subsequently be asked if they would be willing to complete a pregnancy test that will be mailed to them. Women under the age of 55 who are respond "No" to this item will not be prescribed Varenicline. The follow-up e-visit will assess tobacco use, medication adherence, side effects, and determine if further cessation treatment is needed (e.g., an additional follow-up e-visit, referral to counseling). All patients will be scheduled for at least one follow-up e-visit within a month after the initial e-visit. E-visits will also include a SmartSet (i.e., a group of orders and other elements that are commonly used together to document a specific type of visit) to streamline provider documentation and treatment plans. E-visits typically delivered for clinical purposes via Epic at MUSC cost $25, but this cost will be waived for participants in this study.

For the purpose of this trial, this initial asynchronous e-visit will also include an assessment of COPD symptoms via the COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE)[5]. Those who score $\geq$ 2 on the CAPTURE will be considered symptomatic and will be invited to complete additional COPD screening measures. These individuals will be mailed a home spirometer and will be asked to complete an additional e-visit during which they will upload a video of themselves completing home spirometry via the device. The home spirometer will measure peak expiratory flow (PEF), forced expiratory volume (FEV1 and FEV6), and forced vital capacity (FVC). These videos will be reviewed by a study attending physician and follow-up care will be provided consistent with best clinical practices. In addition to home spirometry, all patients who screen positive on

the CAPTURE during the baseline e-visit will be referred to an in person appointment for spirometry/bronchodilation consistent with best practices.

Participants enrolled in the present study who are randomized to the TAU condition will be provided information about the state quitline and about the importance of quitting smoking and it will be recommended that they contact their PCP to schedule a medical visit to discuss quitting smoking.

4.0 Study Endpoints (if applicable)

Primary outcome variables include:

- Evidence-based cessation treatment utilization will be assessed via participant self-report. At each follow-up assessment, participants in both groups will be queried for: 1) use of a smoking cessation medication since the last assessment, 2) how the medication was obtained (e.g., via the study or another outlet such as MUSC's existing smoking cessation service), and 3) receipt of the 5As from their PCP[6].
- Cessation-related outcomes will be assessed via participant self-report. 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[7,8].
- COPD diagnosis will be assessed both via established metrics captured via home spirometry and via chart review.

Secondary outcome variables include:

- E-visit acceptability and feasibility will be assessed both by examining the percentage of patients who complete the initial and follow-up e-visits, and by participant self-report during follow-up assessments. Participants will respond to items assessing ease of use, satisfaction, and pros/cons of the e-visit. Analytics data (e.g., amount of time it takes to complete the e-visit, amount of time it takes the provider to review the e-visit) will also be collected as will data on provider fidelity to e-visit recommendations (captured by reviewing within Epic whether the provider administered treatment consistent with e-visit recommendations).

We will also assess:

- Nicotine dependence will be assessed at baseline via the Fagerstrom Test of Nicotine Dependence[9].
- Motivation to quit and confidence in quitting will be assessed via participant self-report using a modified Contemplation Ladder[10].

5.0 Inclusion and Exclusion Criteria/ Study Population

Participants will complete a survey within MyChart to be screened for eligibility. Inclusion criteria for patients across aims include: 1) current smoking, defined as smoking 5+ cigarettes/day, for 20+ days out of the last 30, for the last 6+ months, 2) age 40+, 3) enrolled in Epic's MyChart program or willing to sign up for MyChart, 4) possess a valid e-mail address that is checked daily to access follow-up assessments and MyChart messages, 5) English fluency, and 6) owner of an iOS or Android-compatible smartphone and a webcam-enabled device (necessary for providing carbon monoxide readings). As an aim of this study is to facilitate COPD early diagnosis, participants will be excluded if they have COPD on their problem list within Epic. Inclusion criteria for providers for usability testing include: 1) medical provider at MUSC and 2) treat adult patients.

6.0 Number of Subjects

We will recruit up to 10 patients for usability testing and 120 subjects for the pilot RCT.

7.0 Setting

Research will be conducted remotely via REDCap and MyChart. Participants will be recruited remotely and will be MUSC patients.

8.0 Recruitment Methods

Participants will be recruited in the following ways:

1) Via MyChart: MUSC patients who have previously been identified as smokers will be sent a secure message via MyChart inviting them to complete a preliminary eligibility screening. **These patients will have either agreed to research contact within MyChart or their attending physician will have agreed to contact their patients who smoke cigarettes via MyChart.** Within the message, potential participants will be invited to click a link to complete an eligibility screening via MyChart.
2) In Clinic: Participants may be recruited in clinic either after being identified as a smoker by research personnel listed on this application.
3) Via advertisements (e.g., flyers) and online postings

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

<u>Recruitment of Minority Smokers</u>

Minority smokers will be included in this trial. All participants will be recruited from MUSC practices, which primarily serve residents of Charleston County, South Carolina. United States Census data from 2015 (the most recent Census year available) reveal that the population within Charleston County is 68.2% White, 28.1% Black, 2.2% American Indian/Alaskan Native, Asian, or Pacific Islander, 1.5% reporting two or more races, and 5.0% are Hispanic or Latino. Compared to Charleston County demographics, members of racial and/or ethnic minority groups tend to be overrepresented among smokers treated via MUSC's clinics. Roughly half of smokers treated via these clinics are members of a racial or ethnic minority group. We will monitor closely our minority recruitment goals on an ongoing basis. If the recruitment of minorities is lower than expected (< 10% projected enrollment), efforts will be made to improve recruitment of minorities into the study through oversampling.

9.0 Consent Process

Signed informed consent will be obtained from study participants. The consent process will take place via one of the following modalities: 1) Remote or in person electronic consent (e-consent) via REDCap (if remote, e-consent will be facilitated with a discussion over the phone or via video), 2) Remote consent via doxy.me facilitated with either a discussion over the phone or video connection via doxy.me, 3) Mailed (paper) consent facilitated with a discussion over the phone, or 4) in person consent (e.g., in clinic).

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. Signatures on the consent form may be obtained with paper and pen OR electronically via REDCap/doxy.me. Participants who do not have access to the required technology to complete consent remotely via REDCap or doxy.me will be given the option to complete consent via mail facilitated with a

discussion over the phone. For participants consented via doxy.me, we will track software analytics anonymously, while using the platform, for potential future secondary data analysis examining usability of remote electronic consent. We have discussed this with doxy.me developers, who have assured us that we can get this data for a given protocol in an anonymous way. We are only interested in times it takes individuals to accomplish given tasks within doxy.me. For example, track the time it takes them to navigate through the online document and time it takes them to sign the consent form electronically.

10.0 Study Design / Methods

Usability Testing

Following initial development of the modified e-visit, we will complete usability testing of the e-visit with 5 patients (up to 10 to account for attrition). Usability testing participants will complete all study procedures as outlined below for the pilot RCT, but will also be asked to provide additional feedback as they complete the e-visits so that the investigative team can iteratively refine and improve the e-visits. Inclusion/exclusion criteria for usability testing participants will be the same as criteria for pilot RCT participants (see section 5.0 above). As participants complete the e-visits remotely, research staff will be connected in real time to the participant via audio and/or video. As participants complete the e-visits, we will follow the Concurrent Think Aloud method to elicit real-time feedback and research staff will take notes on emotional reactions, task completion, task time, and errors[11]. The compensation schedule for participants included in initial usability testing will be the same as for participants enrolled in the RCT. Following usability testing, Dr. Dahne will then prioritize refinements which will be implemented by the BMIC Epic development team in preparation for the subsequent pilot trial.

Pilot RCT

A two-arm pilot RCT (N=100, up to 120 assuming 20% attrition) will test cessation treatment utilization, smoking cessation outcomes, and COPD diagnosis rates as a function of smoking cessation e-visit vs. TAU. Recruitment will primarily occur proactively and remotely via the EMR. We will conduct an automated EMR search via established procedures for all patients treated within MUSC DFM clinics during the past 12 months who: 1) smoke, 2) are $\geq$ 40, 3) have MyChart accounts, and 4) do not have COPD on their problem list. **These patients will be sent a MyChart message from a member of their care team inviting them to participate in a research study for cigarette smokers. These messages will only be sent to patients of PCPs who have agreed that their patients may be contacted for the purpose of this study. This invitation will include clear opt out procedures should the patient not wish to be contacted in the future for the purpose of this study. Clinical providers included in the Usability Testing phase of the project will not be asked to directly refer their own patients to the study. However, their patients may still be recruited via the EMR.** After sending these automated e-mail messages via MyChart, the study team may also call, e-mail, and/or text message potential participants to notify them that a message was sent to them via MyChart. Again, such contact will only be made to patients of PCPs who have agreed that their patients may be contacted for the purpose of this study. If interested, participants will complete a screening online via MyChart to determine study eligibility (see above for inclusion criteria). After completing determination of eligibility, if eligible and interested in participating in the study, participants will be scheduled for a time to complete informed consent (see 9.0 Consent Process). After consent is obtained, participants will be randomized 2:1 to receive either the smoking cessation e-visit or TAU. If randomized to the e-visit condition, participants will be sent a link to initiate the e-visit. All e-visit medication recommendations will be reviewed by physicians included on this IRB protocol. Medications will be e-prescribed to a mail order pharmacy (e.g., MUSC's mail order pharmacy) and then mailed to participants, with all costs covered by the study. Note

that only FDA approved cessation medications will be recommended, which include nicotine replacement therapy (patch, gum, lozenge), varenicline, or bupropion. Medications will only be recommended if a participant does not have a contraindication for that medication. 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 a counseling referral. Any woman under the age of 55 who receives a varenicline recommendation as a result of the e-visit will subsequently be asked within the e-visit if she is willing to complete a pregnancy test that will be mailed to her at no cost to verify that she is not pregnant prior to taking varenicline. Women under the age of 55 who respond "Yes" to this item will be mailed a pregnancy test by study staff and will be required to verify (with signature) that they completed the test and are not pregnant via REDCap. Women under the age of 55 who respond "No" to this item 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. Participants will be scheduled for a follow-up e-visit one month following their initial e-visits. The follow-up e-visit may also result in a medication recommendation that will be e-prescribed and mailed to the participant as outlined above for the baseline e-visit. If randomized to the TAU condition, participants will be provided information on quitting smoking, including information about the state quitline, and will be provided a recommendation to contact their PCP to schedule a medical visit to discuss quitting smoking.
For participants randomized to the e-visit condition, the baseline e-visit will include a 5-item questionnaire (the CAPTURE) to assess COPD symptoms. Participants who score ≥ 2 on this measure will be invited to complete home spirometry. These participants will be mailed a home spirometer and will be invited to complete an additional e-visit after receiving the home spirometer at which time they will be instructed regarding how to use the device and will upload a video of themselves completing home spirometry. Participants will also be asked to enter into the e-visit metrics available via the spirometer including FEV1 and peak expiratory flow. These videos will be reviewed by a study attending physician and follow-up care will be provided consistent with best clinical practices. In addition to home spirometry, all patients who screen positive on the CAPTURE during the baseline e-visit will be referred to an in person appointment for spirometry/bronchodilation consistent with best practices. Costs related to in person spirometry testing will be paid for by the study for appointments completed by the time of the 3-month assessment. Although the medical order for spirometry testing may remain active following the 3-month assessment, any testing completed after the date of the 3-month assessment will not be paid for by the study.

All participants will subsequently be text messaged and/or emailed a REDCap link, accessible via smartphone, tablet, or computer to complete study assessments. These assessments will occur at baseline (following consent), 1-month following study enrollment, and 3-months following study enrollment. Assessments are estimated at 20 minutes each and will be administered remotely via REDCap through our established procedures. Participants will be compensated via electronic gift cards (e.g., Amazon) which will be emailed or texted to participants. Participants will receive $30 for completion of the baseline assessment questionnaire. After completing each follow-up questionnaire within 72 hours of being emailed the link, participants will be compensated $30. Participants will be compensated $30 for each completed carbon monoxide recording. They will be compensated an additional $100 for completion of all three sets of questionnaires and both carbon monoxide samples. E-visit acceptability and feasibility will be assessed both by examining the percentage of patients who complete the initial and follow-up e-visits, and by participant self-report during follow-up assessments. Participants will respond to items assessing ease of use, satisfaction, and pros/cons of the e-visit. Analytics data (e.g., amount of time it takes to complete the e-visit, amount of time it takes the provider to review the e-visit) will also be collected as will data on provider fidelity to e-visit recommendations (captured by reviewing within Epic

whether the provider administered treatment consistent with e-visit recommendations). 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[7,8]. Nicotine dependence will be assessed at baseline via the Fagerstrom Test of Nicotine Dependence[9]. Participants will report motivation to quit and confidence in quitting using a modified Contemplation Ladder[10]. Expired air carbon monoxide will also be captured. Treatment utilization will be assessed via participant self-report. At each follow-up assessment, participants in both groups will be queried for: 1) use of a smoking cessation medication since the last assessment, 2) how the medication was obtained (e.g., via the study or another outlet such as MUSC's existing smoking cessation service), and 3) receipt of the 5As from their PCP[6]. COPD diagnosis will be assessed via participant self-report and via medical records review. At each follow-up time point, participants will be asked whether a clinical provider has given them a COPD diagnosis. Medical records will be reviewed for up to 12-months following completion of the 3-month follow-up survey to identify: 1) whether the participant was referred for in person spirometry, 2) whether the participant attended that appointment, and 3) whether the participant was given a diagnosis of COPD.

11.0 Data Analysis and Data Management

Data Analysis

As this is a pilot trial, our primary goal is to estimate an intervention effect size and out secondary goal is to examine the feasibility/acceptability of the e-visit. Precise parameter estimation can be achieved with 25-30 participants per group[12]. To estimate an effect size for the smoking cessation e-visit intervention, we will randomize participants 2:1 (active:control), with 67 participants in the active condition and 33 in the control condition. Primary smoking-related outcomes for this trial include cessation treatment utilization (e.g., medication) and quit attempts. Assuming a cessation treatment utilization rate of 48% in the active condition and 11% in the control condition, with 2:1 randomization we will have 95% power to detect an effect. For quit attempts, assuming a quit attempt rate of 24% in the e-visit condition and 6% in the TAU condition, we will have 60% power to detect an effect. Our intent here is not a fully powered trial for cessation, but is rather to collect preliminary data to inform future trials.

Data analysis for the primary objective will focus on descriptive analysis of primary smoking-related outcomes. Descriptive statistics (e.g., frequencies, percentages) will be calculated for the primary smoking-related outcomes (treatment utilization, quit attempts). Because rates of these primary outcomes are expected to be low in control group, we will utilize Fisher's exact tests to compare rates between the e-visit and TAU groups. Secondary exploratory analyses for this primary objective will examine changes in these outcomes over time by treatment condition. We will utilize Generalized Estimating Equations (GEEs) with log link functions, which will allow us to account for correlated repeated measures within study participants. Planned covariates include sex and the main effect of time.

Data analysis for the secondary objective to examine treatment feasibility specifically for the smoking cessation e-visit will focus on descriptive analysis of: 1) % of those initiate the baseline e-visit who complete it, 2) % of those who complete the baseline e-visit who subsequently complete the follow-up e-visit, 3) average time to complete the e-visit (for patients), 4) average time to review the e-visit (for providers), 5) provider fidelity to e-visit recommendations, and 6) participant self-report of e-visit ease of use, interest in using an e-visit again in the future, benefits of using the e-visit, and strengths/challenges of completing the e-visit. The e-visit will be considered feasible and acceptable if: 1) >90% of those who initiate the baseline e-visit complete it, 2) >75% of those who complete the baseline e-visit complete the

follow-up e-visit, 3) providers are faithful to e-visit recommendations >80% of the time, and 4) self-report data indicate participant benefits and ease of use (average score for each ≥ 4 on 5-point scale).

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 provides secure, web-based flexible applications, including 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, a secure environment for data systems and servers on campus, 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.

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

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

Summary of the Protocol
We will develop and iteratively test a comprehensive e-visit for delivery to smokers treated via primary care. Through an established partnership with MUSC Epic developers, we will develop the e-visit consistent with USPHS best practice guidelines for smoking cessation treatment via primary care. Those who self-report symptoms of COPD will be invited to complete home spirometry. We will then complete a randomized pilot trial of 1) e-visit vs. 2) TAU.

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 local MUSC clinics.

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). The data analysis plan is outlined above.

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

All serious AEs will be reported to the MUSC Committee on Human Research within 48 hrs. 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. Potential conflicts of interest (COI) will be reported using the SRNT 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 "Risks to Subjects" section. AEs will be tracked and rated as mild, moderate or severe and as related to medication by the participant. 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. Risk profiles for smoking cessation medications that may be prescribed as an outcome of the e-visit are minimal, with the most common side effects being nausea, headache, and dry mouth. All patients will be active MUSC. As such, we expect AEs will be rare. Nonetheless, they will be coded on a weekly basis using the FDA's COSTART rules[13] and entered into a database. For each weekly study meeting, the research assistant(s) 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). Drs. Diaz and Player, board-certified Family Medicine physicians, will be available 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[14]. 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.

Data and Safety Monitoring Plan Administration

The PI will be responsible for monitoring the trial. 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(s) immediately prior to the lab meeting a) to see if any particular COSTART categories are being endorsed more frequently than normal and b) to 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.

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 in and of themselves other 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, and c) frustration.

a) Smoking cessation medications: Participants in both treatment arms may receive an FDA-approved smoking cessation medication. Participants in the e-visit condition may receive a prescription as an outcome of the e-visit and participants in the TAU condition may receive a prescription if they contact their PCP to discuss quitting smoking. These medications include: nicotine replacement therapy (NRT), varenicline, and/or bupropion. Participants will be educated about their smoking cessation medication as part of the e-visit or during their normally scheduled medical appointment if randomized to the TAU condition. Pregnancy or intention to become pregnant will be assessed during the e-visit. Medication will only be prescribed if a participant does not have contraindications for that medication. 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: Participants will be made aware of limits to confidentiality at the beginning of screening and when reviewing study procedures/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, 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 physician.

c) Frustration: Participants may become frustrated while completing study assessments. 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 study participation at any time.

Since patients will all currently be receiving medical care at MUSC, 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 local MUSC clinics. Smoking status is assessed for every patient, consistent with MUSC's best practice guidelines. Patients identified as smokers via the EMR will be sent a message inviting 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. All participants will review consent documents and will provide informed consent consistent with procedures outlined above. 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 be given to each study participant as well. 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, will be randomized, will complete baseline assessments, and subsequently will receive their randomized intervention.

Upon completing eligibility screening, if study eligible, individuals will be provided with an overview of the study, asked to review study procedures via a consent form, and asked to provide signed consent. Participants will be informed of limitations of confidentiality (i.e., abuse or neglect, intention to harm self or someone else) both verbally and/or 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 provides secure, web-based flexible applications, including 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, a secure environment for data systems and servers on campus, 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.

Protection against risks associated with smoking cessation medications include a Data and Safety Monitoring Plan that includes monitoring of AEs. FDA contraindications for each smoking cessation medication will be factored into the smoking cessation e-visit. Through informational material provided via the e-visit and with standard medication packaging, participants will be educated about potential AEs and nicotine intoxication symptoms (for NRT medications). We anticipate very few AEs. AE's will be discussed with Drs. Diaz and/or Player.

14.0 Potential Benefits to Subjects or Others

All smokers in this trial will receive at minimum standard smoking cessation care and evidence-based educational information about quitting smoking. We will not augment standard smoking cessation care as provided by each patient's primary care physician. The majority of participants will also receive an invitation to complete a smoking cessation e-visit. The major benefit to society will be whether this smoking cessation e-visit will improve cessation outcomes relative to TAU. 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.

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