NCT04316260

Protocol Approval Date: 12/6/2018

Development and Testing of a Smoking Cessation E-Visit for Implementation in Primary Care

PROTOCOL TITLE: Development and Testing of a Smoking Cessation E-Visit for Implementation in Primary Care

PRINCIPAL INVESTIGATOR: Jennifer Dahne, Ph.D.

1.0 Objectives / Specific Aims

The goal of this work is to develop, refine, and pilot test a smoking cessation electronic visit (e-visit) for implementation in primary care/family medicine. We will conduct a pilot RCT (n=90, up to 118 assuming 20% attrition) of the smoking cessation e-visit as compared to treatment as usual (TAU), delivered via primary care, with primary objective to provide effect size estimates for a larger RCT. Primary outcomes include: 1) evidence-based cessation treatment utilization as a function of treatment group and 2) cessation-related outcomes (quit attempt incidence, abstinence). 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 cessation treatment utilization (medications, counseling) and superior cessation-related outcomes.

Secondary outcomes will focus on treatment feasibility specifically for the smoking cessation e-visit. Outcomes related to e-visit feasibility will be examined descriptively and include: 1) treatment acceptability (i.e., e-visit uptake and self-reported acceptability) and 2) self-reported treatment satisfaction.

2.0 Background

Cigarette smoking is the leading cause of preventable death nationwide. In South Carolina, 20% of adults smoke, 30% of cancer deaths are caused by smoking, and 7,200 adults die annually from smoking. South Carolina smoking prevalence has plateaued in recent years, decreasing only 3% from 2011 to 2016. Key factors accounting for this are stagnant rates of quit attempts and low use of evidence-based treatment. Engaging smokers in cessation via healthcare resources they already utilize is promising for promoting cessation and decreasing statewide healthcare costs. At least 70% of smokers visit a primary care physician (PCP) annually[1]. Thus, primary care offers a powerful opportunity to identify many smokers and engage them in quitting. United States Public Health Services (USPHS) guidelines advise the 5As model (Ask, Advise, Assess, Assist, Arrange) for cessation treatment, but compliance with this model is modest, leaving many smokers untreated[2]. One recent study of smokers who visited a health professional within the last year (N=10,801) found that 5As compliance dropped precipitously across steps: Ask smoking status (88%), Advise quitting (66%), Assess motivation (43%), Assist with referrals (39%), and Arrange follow-up (6%)[3]. Typical obstacles at the provider level include lack of familiarity with guidelines, lack of confidence to counsel cessation, and inadequate knowledge or skills. It is clear that PCPs need more and better tools to treat smokers. These tools must be brief, easy to implement, and widely accessible to both patients and providers. Telehealth can fill this treatment gap by facilitating a systematic, protocolled, convenient approach to cessation in primary care.

3.0 Intervention to be studied

We are currently in the process of developing an asynchronous smoking cessation e-visit with MUSC's Epic development team. This e-visit is based on USPHS guidelines and serves to automate much of the 5As 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 (for the purposes of the present trial, Drs. Diaz and Player will be the attending physicians), who will review the recommendations, e-prescribe (when indicated) medication, 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 prescribed 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.

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[4].
- 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[5,6].

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[7].
- Motivation to quit and confidence in quitting will be assessed via participant self-report using a modified Contemplation Ladder[8].
- Participation in MUSC's existing smoking cessation service will be assessed via participant self-report. We assume participation in this service will be random across groups and is one component of standard smoking cessation treatment to which both groups have access.

5.0 Inclusion and Exclusion Criteria/ Study Population

Participants will complete a REDCap survey to be screened for eligibility. Inclusion criteria 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 18+, 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, and 5) English fluency. No exclusion criteria will be applied.

6.0 Number of Subjects
We will recruit up to 118 subjects.

7.0 Setting
Research will be conducted remotely via REDCap and MyChart. Participants will be recruited remotely and will be patients of MUSC's Department of Family Medicine (DFM) or MUSC Health Primary Care.

8.0 Recruitment Methods
Participants will be recruited in the following ways:

1) Via MyChart: MUSC DFM and MUSC Health Primary Care 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 REDCap.
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 Department of Family Medicine 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 Department of Family Medicine 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 electronic consent (e-consent) via REDCap facilitated with a discussion over the phone, 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). Because study participants will be recruited remotely, we anticipate that all participants will be consented remotely, but also build in the option for in person consent.

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.

10.0 Study Design / Methods

A two-arm pilot RCT (N=90, up to 118 assuming 20% attrition) will test cessation treatment utilization and smoking cessation outcomes 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 age 18+, and 3) have MyChart accounts. **These patients will be sent an e-mail via MyChart from their family medicine physician (or from the research team if they have agreed to research contact via Epic) inviting them to participate in a research study for cigarette smokers. These messages will only be sent to patients of PCPs who have agreed to contact their patients for the purpose of this study.** 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 to contact their patients for the purpose of this study. If interested, participants will complete a screening online 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 Drs. Diaz/Player and e-prescribed to the participant's pharmacy of choice. 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 a varenicline prescription as a result of the e-visit. These women instead will either receive a recommendation for 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. 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.

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 $20 in electronic gift codes (e.g., Amazon) for completion of each and will receive a $20 bonus if all 3 assessments are completed. 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[5,6]. Nicotine dependence will be assessed at baseline via the Fagerstrom Test of Nicotine Dependence[7]. Participants will report motivation to quit and confidence in quitting using a modified Contemplation Ladder[8]. 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[4].

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[9]. To estimate an effect size for the smoking cessation e-visit intervention, we will randomize participants 2:1 (active:control), with 60 participants in the active condition and 30 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 56% 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 $\geq$ 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 smoking cessation e-visit for delivery to smokers treated via primary care. Through an established partnership with MUSC Epic developers, we will develop the smoking cessation e-visit consistent with USPHS best practice guidelines for smoking cessation treatment via primary care. We will then complete a randomized pilot trial of 1) smoking cessation 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 Family Medicine/Primary Care clinics that are part of MUSC's Department of Family Medicine.

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 patients in MUSC Family Medicine/Primary Care. As such, we expect AEs will be rare. Nonetheless, they will be coded on a weekly basis using the FDA's COSTART rules[12] 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[13]. 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 a prescription for 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 Family Medicine/Primary Care 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 (i.e., statements of research) and will be invited to contact the study team by phone or e-mail to answer questions about the trial. Consent will be implied by continuing with the study screener. 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 via Family Medicine/Primary Care and evidence-based educational information about quitting smoking. We will not augment standard smoking cessation care as provided by Family Medicine/Primary Care. 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.

REFERENCES

1. Park ER, Gareen IF, Japuntich S, et al. Primary care provider-delivered smoking cessation interventions and smoking cessation among participants in the National Lung Screening Trial. *JAMA internal medicine.* 2015;175(9):1509-1516.
2. 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.
3. Kruger J, O'Halloran A, Rosenthal AC, Babb SD, Fiore MC. Receipt of evidence-based brief cessation interventions by health professionals and use of cessation assisted treatments among current adult cigarette-only smokers: National Adult Tobacco Survey, 2009–2010. *BMC Public Health.* 2016;16(1):141.
4. Vijayaraghavan M, Yuan P, Gregorich S, et al. Disparities in receipt of 5As for smoking cessation in diverse primary care and HIV clinics. *Preventive medicine reports.* 2017;6:80-87.
5. Sobell L, Sobell M. Timeline followback user□s guide: A calendar method for assessing alcohol and drug use. *Toronto: Addiction Research Foundation.* 1996.
6. 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.
7. Payne TJ, Smith PO, McCracken LM, McSherry WC, Antony MM. Assessing nicotine dependence: A comparison of the fagerström tolerance questionnaire (FTQ) with the fagerström test for nicotine dependence (FTND) in a clinical sample* 1. *Addict Behav.* 1994;19(3):307-317.
8. Biener L, Abrams DB. The Contemplation Ladder: validation of a measure of readiness to consider smoking cessation. *Health Psychol.* 1991;10(5):360.
9. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol.* 2012;65(3):301-308.
10. Raudenbush SW, Bryk AS. *Hierarchical linear models: Applications and data analysis methods.* Vol 1: Sage Publications, Incorporated; 2001.
11. McCoach DB. Hierarchical linear modeling. *The reviewer's guide to quantitative methods in the social sciences.* 2010:123-140.
12. 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.
13. Spilker B. *Guide To Clinical Trials.* Philadelphia, PA: Lippincott Williams & Wilkins; 2000.