PROTOCOL TITLE: Development and Testing of a Depression-Specific Behavioral Activation Mobile App Paired with Nicotine Replacement Therapy Sampling for Smoking Cessation Treatment Via Primary Care

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1.0 Objectives / Specific Aims

The goal of this work is to develop, systematically evaluate, and clinically test an integrated cessation intervention comprised of a depression-specific Behavioral Activation (BA) for cessation mobile app ("Goal2Quit") packaged with nicotine replacement therapy (NRT) sampling. This integrated intervention will address the need for an easily disseminable, evidence-based, depression-specific cessation intervention for delivery via primary care.

Aim 1: We will first develop Goal2Quit consistent with the BA for smoking cessation manual(1) and will complete usability testing of the app with depressed smokers (N=10) engaged with primary care.

Aim 2: We will then refine the app and preliminarily test the integrated intervention via a single-arm feasibility test (N=10) followed by individual interviews to address potential pitfalls. Goals of feasibility testing include assessment of: 1) access, 2) user feasibility/acceptability, 3) engagement and retention, 4) adherence, and 5) NRT utilization.

Aim 3: Upon further refinement, we will then conduct an RCT (N=150, followed for 12 weeks) of Goal2Quit+NRT Sampling as compared to treatment as usual (TAU) among primary care engaged adults with primary objective to provide effect size estimates for a larger RCT.

Hypotheses: Participants randomized to Goal2Quit+NRT Sampling, compared to TAU, will have greater (numerically, if not statistically) decreases in depressive symptoms as well as superior cessation-related outcomes (motivation to quit, confidence in quitting, quit attempts/quit duration). Secondary outcomes include all those listed in Aim 2.

2.0 Background

Cigarette Smoking is a Major Public Health Problem, Highly Prevalent Among those with Depressive Symptoms. Over the last 50 years, the United States has seen substantial declines in cigarette smoking among the general population, with smoking prevalence dropping from 43% in 1965 to 18% today(2). Despite these general population declines, smoking prevalence remains astonishingly high among certain vulnerable subgroups. One such subgroup is the 20 million adults in the US with depressive symptomatology(3-5). Nearly half of all adults with elevated depressive symptoms are smokers(6-9), and these symptoms are a robust risk factor for the etiology of tobacco use across the lifespan(10-12).

Despite similar levels of motivation to quit(13, 14) and incidence of quit attempts(15) as their non-depressed counterparts, depressed smokers are 30-50% less likely to be abstinent one-month post-quit(15), regardless of depression severity(16). These disproportionate smoking and cessation rates in turn confer heightened risk for tobacco-related mortality(17). Consistent with the transdiagnostic emotional vulnerability framework for smoking(18), the relationship between depressive symptomatology and cigarette smoking is bidirectional, as depressive symptoms confer risk across stages of smoking and continued smoking in turn leads to worsening of depression over time. To significantly reduce the continued public health burden of cigarette smoking, it is necessary to address tobacco use among those with depressive symptoms(19).

Integrated Treatments that Target Smoking Cessation and Depressive Symptoms Improve Outcomes. Numerous intervention studies have integrated psychosocial depression components into cessation treatment. A recent Cochrane review identified 33 randomized clinical trials (RCTs) comparing cessation interventions with specific psychological components targeting depression to standard evidence-based cessation programs and found that the addition of depression-specific psychological treatment increased long-term quit rates 50% among those with current depressive symptoms(20). Thus, off-the-shelf interventions are insufficient to meet the needs of this population and tailored cessation treatments

incorporating depression-specific psychological treatment are necessary for smokers with depressive symptoms to quit.

Available Depression-Specific Cessation Treatments Have Limited Reach and are Unlikely to Significantly Impact Cigarette Smoking. The predominant delivery method for depression-specific psychological cessation treatments is in-person individual or group psychotherapy(20). In-person psychotherapy has been widely criticized as unlikely to reach the majority in need(21-24) and a recent nationally representative study from our group found that only 4.0% of smokers who attempted to quit in the last year utilized individual or group psychotherapy to quit(25). There is clear need to reach depressed smokers through other outlets.

Primary care is the most important point of healthcare contact for current smokers as there are established procedures for depression and smoking screening within primary care(26, 27) and at least 70% of smokers visit a primary care physician (PCP) annually(27). US Public Health Service clinical practice guidelines advise PCPs to utilize the 5As/AAR model (Ask, Advise, Assess, Assist, Arrange/Ask, Advise, Refer) for cessation treatment(28). Beyond documented problems with compliance(29-32), this model lacks depression-specific treatment and is unlikely to help depressed smokers quit. Barriers to adding depression-specific treatment to the 5As/AAR include: 1) lack of training among PCPs in the delivery of evidence-based depression-specific cessation treatment, 2) lack of time to acquire such training and to deliver such interventions, and 3) lack of confidence among PCPs in their ability to deliver psychological interventions(33). Thus, there is a need to improve dissemination of depression-specific cessation treatment from the point of contact with a PCP.

Mobile Health Technologies Can Be Leveraged to Disseminate Depression-Specific Cessation Treatment. Mobile health (mHealth) technologies offer an ideal strategy to disseminate evidence-based depression-specific cessation treatment while eliminating the above barriers(34). Smartphones and mobile applications (apps) are ubiquitous, with recent estimates suggesting more than 75% of U.S. adults own a smartphone(35), 77% of smartphone owners download apps(36), and 56% of physicians already utilize apps in their practices(37). Hundreds of apps marketed for cessation are available for iOS and Android, many with downloads exceeding 1 million per month(38-40). Recent content analyses of these apps reveal that the majority do not adhere to clinical practice guidelines, and none incorporate evidence-based depression-specific treatment(38-40). Further, having an app and using an app are not synonymous as apps lose, on average, 70% of their users within the first week(41). By leveraging the trusted patient-physician relationship to reach depressed smokers, we can both broadly disseminate treatment and promote continued utilization(34, 42, 43). Taken together, despite clear interest among smokers in utilizing mobile apps to quit, extant cessation apps are insufficient to address the need for an evidence-based depression-specific cessation app. An ideal depression-specific cessation treatment to adapt for mHealth delivery must be: 1) evidence-based, to promote PCP buy-in and 2) simple/straightforward, so that the treatment can be easily recommended to and understood by patients. A logical next step is to tailor an evidence-based depression-specific cessation treatment for delivery via mHealth and primary care.

Behavioral Activation is an Ideal Depression-Specific Cessation Treatment for mHealth in Primary Care. Behavioral Activation (BA) is an evidence-based depression intervention that focuses on regular self-monitoring to 1) examine already occurring activities and 2) facilitate the incorporation of new activities consistent with individualized values/goals across life areas. BA specifically targets the anhedonic component of depression, identified by the transdiagnostic emotional vulnerability framework as central to the comorbidity of depression and smoking(18). BA has an extensive literature-base for the treatment of depression (including both Major Depressive Disorder and sub-threshold elevated depressive symptoms)(44-52) as well as demonstrated promise for cessation(53, 54). In one seminal study, MacPherson and colleagues(53) developed a modified version of BA for cessation and conducted an RCT comparing BA for cessation to standard cessation counseling among smokers with elevated depressive symptoms. Smokers attended weekly in-person group therapy for 8-weeks and completed measures of smoking cessation outcomes (7-day verified point prevalence abstinence) and depressive symptoms at 1, 4,

16, and 26 weeks post quit date. Across 26 weeks of follow-up, BA participants were 3.6 times more likely to maintain abstinence and had significantly greater reductions in depressive symptoms than those randomized to standard treatment. While this study demonstrates treatment efficacy, effectiveness remains unknown. There is clear interest in BA for cessation, with four currently NIH-funded studies (R01CA206058, R43CA206682, R01CA184211, R34DA037391) and two recently completed, but not yet published studies (K23HL10739, I01CX000560) to examine BA for cessation. None of these studies are examining BA for smoking cessation with depressed smokers based within the real-world (e.g., primary care), delivered using mobile technologies. The present study fills this gap.

A Mobile App Alone is Insufficient to Promote Quitting; Pairing with Pharmacotherapy is Needed. In light of physiological withdrawal associated with quitting smoking(55), an app would likely have maximum benefit when integrated with pharmacotherapy for quitting. Provision of pharmacotherapy for smoking cessation is a first line treatment recommendation for all smokers treated in primary care(28). Thus, another feature of the current study is to integrate BA with pharmacotherapy (specifically nicotine replacement therapy; NRT). NRT products, both alone and in combination, have significant benefits on quitting smoking(56, 57) (see C.2. for additional rationale). Medication sampling (i.e., provision of a two-week NRT starter kit including nicotine patch and lozenge) is a highly disseminable and translatable medication delivery strategy, well-suited to primary care. NRT sampling is inexpensive, can be delivered briefly (i.e., 1-2 minutes), and is an immediately actionable cessation catalyst, regardless of motivation to quit. Longer duration of NRT might be better, but this would require smokers to return for frequent visits for re-supply, which has limited feasibility. NRT sampling is disseminable in ways that both a full NRT course and a prescription treatment are not. Most importantly, sampling is associated with significantly higher incidence of 24-hour quit attempts relative to control (43% vs. 34%)(58), while also increasing motivation to quit(59) and self-efficacy(60), which in turn are predictive of sustained cessation(61, 62).

Summary of Scientific Premise. Cigarette smoking remains a public health priority and is highly prevalent among those with depressive symptoms. Depression-specific cessation interventions, particularly disseminable treatments that can be applied within primary care, are necessary but currently lacking. Tailoring a simple, straightforward evidence-based depression-specific cessation intervention, such as BA, for delivery via a mobile app holds the potential to overcome treatment barriers and reach large numbers of depressed smokers who are not currently receiving necessary treatment. The integration of such an app with pharmacologic treatment with similar translational potential, such as NRT sampling, offers a dual-pronged approach targeting both psychological and physical dependence risk factors for relapse. Herein, we propose to develop, systematically evaluate, and clinically test an integrated cessation intervention comprised of a depression-specific BA for cessation smartphone mobile app (Goal2Quit) and NRT sampling that will meet this unmet need for an easily disseminable, evidence-based, depression-specific cessation intervention for delivery via primary care.

3.0 Intervention to be studied

The intervention to be studied herein is an integrated cessation intervention comprised of Goal2Quit paired with NRT sampling (Goal2Quit+NRT Sampling), which will be compared to a TAU condition. Each component of the integrated intervention is described below, as is the TAU condition.

Goal2Quit. Goal2Quit treatment content (outlined below) will follow treatment content from the BA for cessation manual(1), including integrated BA and standard smoking cessation components. Interactive functionality (e.g., videos, quizzes, animations) will be incorporated throughout. Goal2Quit will prioritize user autonomy (i.e., how to use the app/what to use in the app, tracked as study outcomes), which is key to retention and engagement(63).

BA components will include: 1) Psychoeducation highlighting the connection between mood and smoking, the BA model for cessation, and description of Goal2Quit treatment components, 2) Activity

monitoring including rating of enjoyment and importance associated with each activity and number of cigarettes smoked (or craving after quitting) during each activity, 3) Identification of values and activities within six life areas including relationships, daily responsibilities, recreation, career/education, health, and being smoke-free, 4) Activity planning, consisting of scheduling in and monitoring new, value-driven, smoke-free activities, and 5) Enlisting social support to obtain help completing difficult activities and remaining smoke-free.

Standard smoking cessation components will include: 1) Reinforcement and support for quitting, including education about the benefits of quitting and suggested lifestyle changes, 2) Guided and interactive questions to identify past quit experiences in order to determine what hindered past quit attempts and how to avoid pitfalls, 3) Setting a quit date, suggested to be no later than three weeks after treatment initiation, 4) Identification of triggers and high risk situations and development of coping strategies (i.e., avoid, alter, substitute) to target these situations and limit the abstinence violation effect, 5) Information about alcohol use and suggestion to refrain from or limit alcohol use while trying to quit, and 6) Education about medications for quitting smoking including guidance on NRT use, potential side effects, tracking of NRT use, and suggestions for obtaining additional NRT.

NRT Sampling. We will provide a 2-week supply of combination nicotine patch and lozenge in uniform doses (14mg patch and 4mg lozenge; the standard minimum dose for this population). We considered a tailored dosing (e.g., with 21mg patch), but believe this diminishes the translational potential of the intervention and is not clinically indicated given adjunctive lozenge use. Goal2Quit will educate participants about nicotine withdrawal/intoxication, with suggested dosage alterations and guidance on where to obtain NRT. Participants will be instructed to use the NRT however they wish (e.g., to get started quitting, to reduce, to practice quitting).

TAU Condition. Participants randomized to the TAU condition will receive NCI's "Clearing the Air" booklet, which includes information on quitting smoking.

4.0 Study Endpoints

Outcome variables include:

- Cigarette smoking, use of other tobacco products (e.g., e-cigarettes), and quit attempts/quit duration
- Nicotine dependence
- Motivation to quit and confidence in quitting
- Depressive symptoms
- Activation
- Environmental reward
- Treatment adherence
- Feasibility
- Acceptability

5.0 Inclusion and Exclusion Criteria/ Study Population

Participants will complete a REDCap survey to be screened for eligibility. Inclusion criteria for usability testing (Aim 1), feasibility testing (Aim 2), and the subsequent pilot RCT (Aim 3) include: 1) current elevated depressive symptoms defined as a score of $\geq$ 10 (at least mild depression) on the Patient Health Questionnaire-8 (PHQ-8); if a participant reports a Beck Depression Inventory-II (BDI- II) score < 10 during baseline the PHQ from screening will be repeated with the particicpant over the phone (64), 2) current smoking, defined as smoking 5+ cigarettes/day, for 25+ days out of the last 30, for the last 6+ months, 3) ownership of an Android or iOS smartphone compatible with Goal2Quit, 4) age 18+, 5) a

valid e-mail address that is checked daily to access follow-up assessments, 6) English fluency, and 7) has been seen by a primary care physician within the last year. Exclusion criteria include: 1) contraindications for NRT (pregnancy/intention to become pregnant/breastfeeding, recent cardiovascular trauma/uncontrolled hypertension), 2) severe visual impairment, which may limit ability to utilize an app, and 3) household member currently enrolled in the study.

6.0 Number of Subjects

We will recruit 10 participants for usability testing, 10 participants for feasibility testing, and 150 participants for the pilot RCT (Total number of participants = 170, up to 240 assuming 20% attrition).

7.0 Setting

Research will be conducted remotely via REDCap as well as in clinics affiliated with MUSC's Department of Family Medicine (DFM) and MUSC Health Primary Care. The DFM operates three family medicine clinics across the Charleston County area: 1) MUSC Family Medicine located on James Island, 2) East Cooper Family Medicine located in Mount Pleasant, and 3) Rutledge Tower Family Medicine located downtown on the Charleston peninsula. The DFM also has a community residency site at the Trident Regional Medical Center in North Charleston.

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 informing them of this research study. 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 after being identified as a smoker by research personnel listed on this application.
3) Via advertisements (e.g., flyers) and online postings such as Craigslist.

9.0 Consent Process

For all components of this project, signed informed consent will be obtained from study participants. The consent process may take place either in person (e.g., in clinic) or remotely utilizing electronic consent or mailed consent paired with a video/telephone connection to an IRB-approved member of the study team. 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. Our study team has laptops and tablets that may be used for the eConsent and all eligible participants will own a smartphone on which eConsent may also be obtained. No information will be stored locally on study team laptops or tablets; all information will be stored securely in REDCap if captured electronically.

10.0 Study Design / Methods

Study Overview. We will develop, refine, and iteratively test Goal2Quit+NRT Sampling. Through an established partnership with MountainPass Technology LLC (MPT; developer of prior app interventions to be expanded and refined herein), we will develop Goal2Quit consistent with the BA for smoking cessation manual(1). Usability testing will guide app refinements prior to a small, single arm feasibility trial of Goal2Quit+NRT Sampling. Following participant interviews, the intervention will be further refined. We will then conduct a 2-group RCT of 1) Goal2Quit+NRT Sampling vs. 2) TAU.

Goal2Quit Development. We have an established partnership with MPT and will expand on this relationship to develop Goal2Quit. MPT has expertise in developing HIPAA-compliant mobile apps. We will develop Goal2Quit for both iOS and Android. In order to customize BA for smoking cessation for mHealth delivery, we will utilize an iterative, patient-centered, agile software development approach(65). See above for Goal2Quit functionality.

Usability Testing and Refinements. We will recruit 10 participants (up to 12 assuming 20% attrition, the standard number for usability testing(66)) for usability testing. Smoking status is assessed for every Family Medicine/Primary Care patient, consistent with MUSC's best practice guidelines. Patients identified as smokers will be asked either in person or remotely (e.g., via MyChart or REDCap) if they are interested in participating in a study examining a mobile app for the treatment of depressive symptoms and smoking. If interested, the participant will subsequently complete an eligibility screening via MUSC's REDCap system, a secure, HIPAA-compliant data management system.

All patients, whether study eligible or not, will continue with standard care as provided by their PCP. Eligible participants will be contacted by Dr. Dahne's research team to schedule a usability testing visit. At the beginning of the usability visit, participants will be provided with a copy of the consent form and the consent document will be described to them by a member of the research team. Upon informed consent, we will follow the Concurrent Think Aloud (CTA) method(67), which elicits real-time feedback. Participants will be videotaped while completing user-specific tasks (e.g., create a new value, schedule a new activity, set a quit date, learn about NRT). During the CTA process, research staff will take notes to report emotional reactions, task time, errors, and if the participant successfully completes the assigned tasks. Participants will be compensated $40 for participation.

Feasibility Testing. We will recruit 10 participants (up to 12, assuming 20% attrition) for a single-arm feasibility test of the integrated Goal2Quit+NRT Sampling intervention. The goal of feasibility testing is to preliminarily test the integrated Goal2Quit+NRT Sampling intervention to target any potential pitfalls prior to larger-scale testing. Interested participants will be recruited either via MUSC's primary care/family medicine clinics or online and will first complete an eligibility screening via REDCap. If eligible, participants will review study procedures and proceed with completing informed consent, detailed above. Participants will be provided with a code to download Goal2Quit by a member of the reserch team and the staff member will ensure the participant successfully downloads the app and will allow them to use the app for ~10 minutes and ask questions regarding functionality. Subsequently, participants will be mailed: 1) A two-week "starter kit" sample of NRT (14mg patch and 4mg lozenge, both in original packaging; the standard minimum dose for daily smokers smoking at least 5 cigarettes per day), 2) Educational material suggesting that participants utilize Goal2Quit regularly, at least daily, and the provided NRT in an attempt to quit smoking, 3) A handout detailing subsequent assessments and payment schedule for assessments, and 4) NCI's "Clearing the Air" booklet, which includes information on quitting smoking. The follow-up assessment schedule and compensation will be the same for feasibility testing participants as for participants enrolled in the RCT (see below).

We will utilize app analytics to examine indicators of user engagement and retention including: 1) Access, defined as the number of users who download Goal2Quit divided by the number provided with a download code, 2) User feasibility and acceptability, assessed both during and following treatment

utilization, 3) App engagement and retention (i.e., "stickiness"), with engagement defined as the percentage of participants with ≥ 10 app sessions during a month and retention defined as the percentage returning to the app within 2 weeks of their first session, and 4) Treatment adherence, measured via Goal2Quit's activity selection and scheduling component (score calculated by dividing number of activities completed/number scheduled). We will assess NRT sampling utilization weekly including use of NRT products, additional NRT purchase, and perception of NRT products.

Small-Scale RCT. A two-arm RCT (N=150) will test the efficacy of Goal2Quit+NRT Sampling vs. TAU. See above for inclusion/exclusion criteria. After completing determination of eligibility, reviewing study procedures, completing informed consent, and completing baseline assessments, if eligible, the participant will be randomized 2:1 to either Goal2Quit + NRT sampling or TAU. Participants randomized to Goal2Quit + NRT sampling will be provided with their intervention in the same manner as feasibility testing participants. TAU participants will be mailed a package that includes only 1) NCI's "Clearing the Air" booklet, which includes information on quitting smoking, and 2) Information on study participation, including the schedule of follow-up assessments and compensation. Participants will subsequently be e-mailed a REDCap link (accessible via smartphone, tablet, or computer) to complete follow-ups weekly for 8 weeks, with an additional follow-up at Week 12.

Assessments: Assessments are estimated at 20 minutes each and will be administered remotely via REDCap through our established procedures. Participants will be sent an email and/or SMS text each week with a link to access their REDCap surveys. SMS text messaging is possible via Twilio, embedded within our RedCap system, which allows participants to complete a survey directly from their phone, without having to access a webpage. Note that surveys are not completed via texting, just prompted via text with link to RedCap. Participants can choose to receive their weekly surveys via email if they wish, again with a link to a secure RedCap survey. Participants will be compensated $10 in cash and/or electronic gift codes (e.g., Amazon) for completion of each and will receive a $20 bonus if at least 2/3 are complete. Participants will also receive a second bonus of $20 for completing all follow up surveys. To help with retention, the last 20-25 participants enrolled will receive a signed letter from the study team and a few small items with the study's logo (e.g., pen, flash drive, coaster, t-shirt) from the study team at random time points throughout their participation as a thank you for joining. 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(71, 72). Nicotine dependence will be assessed at baseline via the Fagerstrom Test of Nicotine Dependence(73). Participants will report motivation to quit and confidence in quitting using a modified Contemplation Ladder(74). Depressive symptomatology will be assessed via both the PHQ-8(64) and the Beck Depression Inventory-II (BDI-II)(75). The PHQ-8 is briefer than the BDI-II, and thus will determine study eligibility. The BDI-II will be administered at all time points to determine change in symptoms. We will assess and track psychiatric medication use over time and will stratify randomization based on medication use. Adequate procedures are in place to assess for and protect against the potential for suicidal ideation (see Protection of Human Subjects). Process-related variables including activation, assessed via the activation subscale of the Behavioral Activation for Depression Scale(76), and environmental reward, assessed via the Reward Probability Index(77) will be assessed at baseline and all follow-ups to examine potential treatment mechanisms. Treatment adherence will reflect both Goal2Quit and NRT utilization. Regarding Goal2Quit, adherence will be measured based on 1) download of Goal2Quit (yes/no) and 2) analytic data including: number of logins, duration of sessions (average per session and cumulative), rolling retention, number of activities scheduled, and percent completed activities. Regarding NRT utilization, participants in both groups will be queried at all follow-ups for: 1) use of NRT since the last assessment, 2) purchase of NRT since the last assessment, and 3) perception of NRT products via the Attitudes Toward NRT Scale(78). Engagement in other cessation (other medications, behavioral treatment, quitlines) and mental health (medications, therapy) treatments will also be assessed. Feasibility and acceptability will be assessed for those in the Goal2Quit+NRT Sampling condition during each assessment. Participants will be prompted to

respond to questions querying their experiences with the intervention including: 1) ease of use, 2) barriers to utilization, and 3) suggested improvements to the treatment.

Measure	Screening	Baseline	1	2	3	4	5	6	7	8	12
PHQ-8	x										
BDI-II		x	x	x	x	x	x	x	x	x	x
Current use of Psychotropic Meds		x	x	x	x	x	x	x	x	x	x
Demographics	x	x									
Smoking History, Including History of Previous Quit Attempts and NRT Use		x									
BADS		x	x	x	x	x	x	x	x	x	x
RPI		x	x	x	x	x	x	x	x	x	x
SHAPS		x	x	x	x	x	x	x	x	x	x
SF-12		x				x					x
Tech Comfort		x									
Utilization of Goal2Quit /Other smoking cessation apps in the last week			x	x	x	x	x	x	x	x	x
Cigarettes per smoking day	x										
Fagerstrom Test of Nicotine Dependence		x									
TLFB (cigarettes, quit attempts, NRT)		x	x	x	x	x	x	x	x	x	x
Contemplation Ladder		x	x	x	x	x	x	x	x	x	x
MTQ Saliency		x	x	x	x	x	x	x	x	x	x
NRT Use			x	x	x	x	x	x	x	x	x
App Feedback (only for those who receive Goal2Quit)			x	x	x	x	x	x	x	x	x

Goal2Quit Usability Scale						x					
Attitudes Toward NRT		x	x	x	x	x	x	x	x	x	x
NRT AEs			x	x	x	x	x	x	x	x	x
Payment		$10	$10	$10	$10	$10	$10	$10 +$20 bonus (completing 6 out of 9 surveys	$10	$10	$10 + $20 bonus (all surveys completed)

11.0 Data Management

As this is a pilot trial, our primary goal is to determine feasibility/acceptability and estimate an intervention effect size. To estimate an effect size for the Goal2Quit+NRT Sampling intervention, we will randomize participants 2:1 (active:control), with 100 participants in the active condition and 50 in the control condition. Assuming a quit attempt rate (point prevalence) of 40% in the active condition and 15% in the control(59), with 2:1 randomization we will have 60% power to detect an effect; again our intent is not a fully powered trial. To further account for attrition (assumed to be 20% across groups), we will recruit 180 participants total. For this pilot RCT, with a 22-month enrollment period, subtracting three months for final study participants, we fully expect to feasibly recruit 9-10 participants per month (180 participants/19 months).

Data analysis will focus on descriptive analysis of changes over time in depressive symptoms and cigarette smoking by condition. Considering the relatively small sample, possible missing data, and repeated measures, we will fit the longitudinal data with Hierarchical Linear Modeling (HLM) to fully use available data(80). With HLM, we can estimate and model the degree of relatedness of our observations within the same treatment condition and within the same individual, thereby correctly estimating standard errors and eliminating the problem of inflated Type I error(81). First, we will assess patterns of missing data, research dropout, and distributional properties of all measures. Then, effects of the Goal2Quit+NRT Sampling intervention as compared to TAU on cigarette smoking (motivation to quit, confidence in quitting, and quit attempts/quit duration) and depressive symptoms over time will be examined using HLM. Planned covariates will include sex and baseline levels of depression and nicotine dependence as well as the main effect of time.

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

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

This application consists of a 3-aim proposal. In Aim 1, participants (N=10) will complete usability testing of a depression-specific smoking cessation mobile app, Goal2Quit. Usability testing data will subsequently be utilized to refine Goal2Quit. In Aim 2, the refined Goal2Quit app will be integrated with NRT Sampling (14mg patch and 4mg lozenge, both in original packaging; the standard minimum dose for daily smokers smoking at least 5 cigarettes per day) and examined via a single-arm feasibility test of the integrated intervention (N=10). The goal of feasibility testing is to preliminarily test the integrated Goal2Quit+NRT Sampling intervention to target any potential pitfalls prior to larger-scale testing. In Aim 3, we will conduct a small-sale RCT (N=180) of Goal2Quit + NRT Sampling vs. TAU to provide effect size estimates for a larger RCT.

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.

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 (for Aim 3) 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 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 NRT 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. Since a maximum two-week supply of OTC NRT will be provided, AEs will be rare. Nonetheless, they will be coded on a weekly basis using the FDA's COSTART rules(82) 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). At the weekly meeting (or before if urgent), research assistants will report any premonitory symptoms to suggest emergence of a serious psychiatric condition (e.g., major depression, suicidality). See "Risks to Subjects" for procedures in place for handling significant clinical deterioration/suicidality. Dr. Diaz, a board-certified Family Medicine physician, will be available on ad-hoc basis for on-site medical supervision for any issues that cannot be resolved by Drs. Dahne and Carpenter.

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(83). We will encourage, but not require, participants to notify their physicians that a) they are in a randomized controlled research study examining a treatment for mood and 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.

Data and Safety Monitoring Plan Administration

The PI will be responsible for monitoring the trial, with oversight provided by the primary mentor, Dr. Carpenter. 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) clinical deterioration, b) suicidality, c) NRT, d) confidentiality, e) potential data breach from the app database, and f) frustration.

a) Clinical deterioration: Depressive symptoms will be monitored via the BDI-II. All participants will complete the BDI-II weekly online and at 12 weeks via a REDCap survey that is accessible via mobile phone, computer, and tablet web browsers. All participants will own an iOS- or Android-compatible smartphone. Thus, all participants will have access to the online BDI-II assessments. Dr. Dahne and her research team will monitor participant BDI-II scores for possible clinical deterioration (i.e., increasing

depressive symptoms) throughout the course of the study as participants complete the BDI-II. Clinical deterioration will be defined as an increase of 10 or more points on the BDI-II from the baseline BDI-II assessment. In the event that a participant evidences clinical deterioration, Dr. Dahne will contact the participant via phone and will provide referrals for local mental health resources and/or instruction to go to the ED or call 911 for immediate depression treatment. Dr. Dahne will suggest that the participant seek treatment and then will follow-up with the participant via phone one week later. In the event that a participant evidences clinical deterioration, the participant will be allowed to continue in the trial, but we will recruit an additional participant for data collection purposes.

b) Suicidality: Dr. Dahne and her research team will monitor participant BDI-II scores for suicidality, defined as a response of "I would like to kill myself" or "I would kill myself if I had the chance" on the suicidal thoughts or wishes item of the BDI-II at any point during the study, including at baseline. In the event that a participant reports suicidal ideation, Dr. Dahne, a licensed clinical psychologist with 8 years of experience conducting risk assessments with high risk populations (e.g., adults in residential and outpatient substance use treatment, patients in a mood disorders clinic), will complete a risk assessment with the participant via phone. Dr. Dahne will query the participant for details regarding the suicidal ideation, including a likelihood of harming oneself imminently and a plan for committing suicide. If the participant reports an imminent likelihood of harming him/herself or a plan for committing suicide, Dr. Dahne will call emergency services and will remain on the phone with the participant until emergency services arrives. In the event that Dr. Dahne makes contact with the participant (e.g., via phone), the participant expresses an imminent likelihood of harming him/herself, and the connection is lost, Dr. Dahne will contact emergency services and will provide emergency services with the participant's contact information, including address. In the event that the participant is not in imminent danger, Dr. Dahne will provide referrals for local mental health resources and/or instruction to go to the ED or call 911 should suicidal ideation worsen. Dr. Dahne will suggest that the participant seek treatment and then will follow-up with the participant via phone one week later. In the event that a participant endorses suicidal ideation but is not responsive to Dr. Dahne's phone call within 48 hours, Dr. Dahne will e-mail the participant a list of local mental health resources and will suggest that the participant seek additional treatment. Dr. Dahne will also ask that the participant respond to Dr. Dahne either via phone or e-mail within 24 hours to confirm receipt of the treatment referrals. Should the participant not respond to Dr. Dahne's email within an additional 48 hours (4 days from completion of the assessment) **and** endorse "I would kill myself if I had the chance" on the BDI-II (score = 3 on BDI-II Item 9) Dr. Dahne will call emergency services and provide emergency services with the participant's name and address. In the event that a participant endorses suicidal ideation, the participant will be allowed to continue in the trial, but an additional participant will be recruited for data collection purposes.

c) NRT: Through brochures delivered as part of the sampling intervention, participants will be educated about lozenge/patch adverse events (AEs) and nicotine intoxication symptoms. We will clearly advise against use of NRT during pregnancy and breast-feeding but we will not require pregnancy tests to be in the study. Female participants will be required to sign a waiver endorsing that: 1) they are not pregnant, 2) they do not plan on becoming pregnant during the study period, and 3) they are using an accepted birth control method. We will not explicitly encourage or discourage use of combined medication (patch+lozenge), though accompanying brochures will advise smokers not to smoke while using NRT product (even though most studies have demonstrated no significant events for combined use). The sampling experience is meant to provide smokers with a real-world opportunity to "test drive" different medications. Our accompanying brochures will discuss the anticipated negative consequences of dual use (nausea, headache) and advise participants to discontinue one or both products should they arise. Participants will be provided with our study phone number and instructed to call our study personnel should they experience such AEs or if they have questions/concerns about NRT use. Given

the 2-week sampling experience, we expect AEs, which will be assessed across follow-up timepoints via REDCap, to be rare and mild. In a prior trial, our group found that 9% of participants who utilized NRT samples in an attempt to quit reported an AE(84). None of these AEs were unexpected, nor did any study participants drop out as a result of an NRT-related AE. Participants will be encouraged to contact Dr. Dahne as soon as possible for serious AEs and for those conditions that OTC 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.

This study allows smokers to sample individual or combined NRT products, with a suggestion, though not a requirement, to utilize those products in an attempt to quit smoking. Thus, smokers could be using NRT products concurrently (same day) with smoking. This could result in nicotine intoxication; i.e. nausea, dizziness, headache, stomachache, etc.(85). In a prior study conducted by Dr. Carpenter, participants completed a nicotine intoxication scale, and no evidence was found of nicotine intoxication when gum and cigarettes were used concurrently(84). In addition, a review of prior smoking reduction studies indicates that most participants do not have higher than normal cotinine levels with concurrent use of cigarettes and NRT, and few AEs are reported across studies(86).

d) 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.

e) Data breach from app database: Although health information will be collected within Goal2Quit (e.g., daily mood ratings, activities, values, use of NRT, etc.), personally identifiable information will not be collected within the app (e.g., name, phone number, email address, etc.), and thus we will neither collect nor retain protected health information (PHI) within Goal2Quit. Upon app download, all participants will be assigned an anonymous username that does not contain personally identifiable information. In the event of a data breach, it is important to note that health information will not be able to be tracked back to specific individual users. By refraining from collection of PHI within the mobile app, we ensure HIPPA compliance while also protecting the identities of our users. In the event of a data breach, all app users will be notified via email.

f) Frustration: Participants may become frustrated while completing questionnaires or while using Goal2Quit. 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 use of Goal2Quit at any time (which will be tracked as a study outcome).

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 and/or online. Smoking status is assessed for every patient, consistent with MUSC's best practice guidelines. Interested individuals will complete determination of eligibility via MUSC's REDCap system, a secure, HIPAA-

compliant data management system. All participants will 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 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 (see procedures above), will be randomized (Aim 3), will complete baseline assessments (Aims 2 and 3), and subsequently will receive their randomized intervention (or will complete usability testing for Aim 1).

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 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/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 Goal2Quit requires that participants are able to read, participants unable to read the consent form on their own will not be included.

Regarding user privacy while using Goal2Quit, we will store a one-way hashed version of the patient's email address to support password reset and unique identification, but that identification will not be traceable back to the user's true identity. We will not store any personally identifiable information (e.g., first name, last name, email address, phone number) of users in our app database and all participants who receive Goal2Quit will be assigned an anonymous username that does not include personally identifiable information. Our server is protected by industry-standard safeguards to prevent unauthorized access. Since we are not associating patient health information with personally identifiable information within Goal2Quit there would not be a risk of unauthorized release of patient medical data in the event of a security breach. User personal information will be contained behind secured networks and will only be accessible by the investigators, who will have special access rights to such systems. In addition, all sensitive information users supply will be encrypted via Secure Socket Layer (SSL) technology. We will not sell, trade, or otherwise transfer personally identifiable information to outside parties. Our privacy policy will be available within the app for users to view at any time. This plan is consistent with that used by our partnering app development company, MountainPass Technology LLC, in several other previous products with similar protection requirements.

Protection against risk resulting from depressive symptoms/suicidality include the following: Regarding suicidal ideation and broader mental health concerns, Dr. Dahne, a licensed psychologist, 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. As noted above, BDI-II data will be monitored over time in order to detect any possible clinical deterioration. BDI-II data will be monitored using only the participants' subject numbers. Should a participant evidence clinical deterioration, Dr. Dahne will then use the participant database in order to obtain contact information for the participant based on their subject number.

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 NRT (OTC products) include: 1) the short duration for which NRT will be provided—only a 2-week supply and 2) a Data and Safety Monitoring Plan that includes monitoring of AEs. We will exclude individuals based on standard FDA contraindications for NRT use (pregnancy, recent cardiac trauma). Through informational material provided with the NRT samples, participants will be educated about potential NRT AEs and nicotine intoxication symptoms. As an OTC product, given over short duration, we anticipate very few AEs. AE's will be discussed with Dr. Carpenter and, if necessary, consultation with Dr. Diaz, a Family Medicine attending physician and co-investigator on this protocol.

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. The majority of participants in Aim 3 will receive a novel depression-specific smoking cessation mobile app (Goal2Quit) and a two-week sample of NRT, designed to target both affective and physical dependence risk factors for relapse. The major benefit to society will be whether Goal2Quit+NRT Sampling will improve cessation outcomes and depressive symptoms relative to TAU. Potential issues of clinical deterioration/suicidality, NRT risks, confidentiality, data breach, 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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