DETAILED PROTOCOL

TITLE: A Text Messaging Intervention for Smoking Cessation Among Community Health Center Patients

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I. BACKGROUND SIGNIFICANCE

a. Historical Background

Smoking is the leading preventable cause of death in the US, responsible for over 480,000 deaths per year.[1,2] Among US smokers, 52% try to quit each year[3] but less than one-third use medication or counseling in their quit attempt.[4] Text messaging shows promise as a way to assist smokers to quit. Over 90% of Americans own mobile phones[5] and 72% of adult cell phone owners text.[6] Text message interventions for smokers have increased tobacco abstinence rates by 36 to 70% compared to non-health related text messages and/or self-help materials.[7-17] However, most prior studies of text messaging recruited smokers from the community who were planning to quit in the next month. There is little prior work evaluating text messaging for smokers in healthcare systems. Of the three prior text messaging studies that recruited smokers from healthcare settings, all targeted particularly motivated smokers including those already enrolled in a tobacco treatment program[18], pregnant smokers,[19] and patients with coronary disease.[20] The effectiveness of delivering tobacco cessation assistance by text message for the broader population of smokers in primary care, including both those who are "ready to quit" now and those "not ready to quit", is unknown.

Healthcare systems are well-positioned to promote smoking cessation because 70% of smokers visit a physician each year[21] and, although physicians often recommend quitting during these visits, competing priorities and time constraints prevent them from offering further assistance such as referral to counseling or medication.[22] To address this treatment gap, new chronic disease management models of care delivery are being developed for tobacco users. These models supplement clinicians' efforts during office visits by offering assistance including counseling, medication support and care coordination between visits. In these programs, smokers in a healthcare system are identified using the electronic health record (EHR).[23] The program then reaches out to smokers independent of office visits to offer them help to quit. Prior studies of chronic disease management models for tobacco have used mailings and telephone calls between visits to engage smokers in tobacco cessation treatment. These studies reported an increase in use of treatment and tobacco abstinence.[24-30] However, at a health system level, repeated mailings or phone calls are costly. Text messaging may be a less costly way to reach out to help smokers. Outreach by text message may also overcome barriers[27,31] faced by low socioeconomic status (SES) smokers who have well-documented disparities in receipt of treatment.[4,32,33]

Text messaging has been used in healthcare systems to promote medication adherence in other conditions including HIV, cardiac disease, mental illness, and for family planning.[34-37] Adherence to smoking cessation medications is at least modestly associated with cessation[38-41] and measures of adherence to smoking cessation medications suggest overall low adherence, both in terms of medication execution (total dose of medication) and persistence (duration of use) of medication use outside of clinical trials.[42-47] Offering nicotine replacement therapy along with the medication adherence advice in the text messaging intervention will allow us to

evaluate of the effect of adherence messages on medication use. Little work has been done to explore whether text messaging can effectively promote smoking cessation medication adherence in primary care.

Chronic disease models also allow health systems to reach out to all smokers, not just those who are seeking treatment and ready to quit. In the US, 80% of smokers are "not ready to quit" in the next 30 days.[48] From a public health standpoint, an effective intervention for this group may have an even greater impact than programs targeting the minority of smokers who are ready to quit.[49] Furthermore, few evidence-based treatments are available to help "not ready to quit" smokers.[21,50,51]

b. Preliminary work supporting the proposed study

In prior work, I developed a text message program called the getReady2Quit program (R2Q) and pilot-tested its feasibility among CHC patients. We recruited smokers at MGH Revere and Charlestown using a proactive recruitment process which consisted of sending a letter from the subject's PCP notifying them of the study, followed by a single text message invitation to opt-in to R2Q. Among 1,603 smokers, 1,279 (80%) had a mobile number in the EHR and 949 were approved by their PCP for the study. 9% (88 of 949) of smokers opted in to R2Q following the letter and single recruitment text and this included both ready to quit (68%) and not ready to quit smokers (32%). The R2Q pilot model had two components. Part 1 targeted smokers who were ready to quit in the next 30 days by proactively recruiting them to a text message program with content to support them through a quit attempt. Part 2 targeted smokers who were not ready to quit. They were sent novel motivational messages and advice to try a 'Practice Quit Attempt'. This work demonstrated the feasibility of delivering a text messaging program to primary care patients. Subjects in the feasibility study are being recruited to participate in qualitative interviews to further improve the program design and content prior to the current trial.

c. Study rationale

The data summarized above demonstrate several issues that motivate the current study: 1) despite the availability of effective treatments, primary are patients who smoke rarely use assistance when they try to quit, 2) text messaging interventions have been effective in helping smokers to quit in the community or school-based settings but have not been well studied in clinical populations, 3) text messaging has been used to promote medication adherence in other conditions and medication adherence is sub-optimal among smokers and 3) few treatments are available for smokers who are not ready to quit and mobile health interventions may be a way to nudge these smokers to act. These observations suggest a need for new interventions that reach primary care smokers outside of the busy office visit using a convenient low-cost communication modality.

I propose to conduct a 4-arm randomized controlled trial testing the effect of a text messaging intervention and mailed nicotine medication, alone and in combination to a control condition consisting of brief advice and usual care. These intervention modalities have shown promise in non-clinical populations of smokers and there are several advantages of using text messaging interventions in healthcare systems:

1) Text messaging programs originating from the physicians' office may leverage the influence physicians have on smokers' motivation to quit. Simple advice to quit smoking from a physician is a predictor of cessation and smokers' cite advice from a doctor as an important motivation to

quit.[21] Individuals most often look to their own healthcare systems for health information [52] and this trust in their healthcare providers may make health promoting advice more potent if it is coming from local healthcare providers

2) Integrating text messaging within healthcare systems also offers the opportunity to feedback patient information to PCPs to keep them informed of changes in patients' smoking. Integrating text messaging within the healthcare system provides opportunities to coordinate with pharmacotherapy. Effective evidence-based treatment combines behavioral support and pharmacotherapy.[21]

The PI for this study is on faculty in the MGH Division of General Internal Medicine and is a staff physician at MGH Revere. The proposed trial will be funded by the PI's Career Development (K23) Award from the National Institute on Drug Abuse at the National Institutes of Health, and by a grant to the PI from the MGH Executive Committee on Research Claflin Distinguished Scholars Award.

II. Specific Aim

Research Aim 1: To test, in a 4 arm pilot randomized controlled trial (*N=50/group*), the effect of delivering behavioral smoking cessation content by text message and mailed nicotine replacement therapy on self-reported quit attempts (intentional non-smoking for ≥24 hours), pharmacotherapy adherence, and smoking abstinence at the end of treatment.

Hypothesis 1: A 12 week text messaging intervention (up to 30 days pre-quit through 8 weeks post-quit) providing behavioral support will increase the proportion of smokers making a quit attempt compared to smokers receiving no text messaging.

Hypothesis 2: A 12 week text messaging intervention will increase adherence to NRT compared to subjects receiving only 2 weeks of NRT as measured by: (a) duration of NRT use in days and (b) total mg of NRT used.

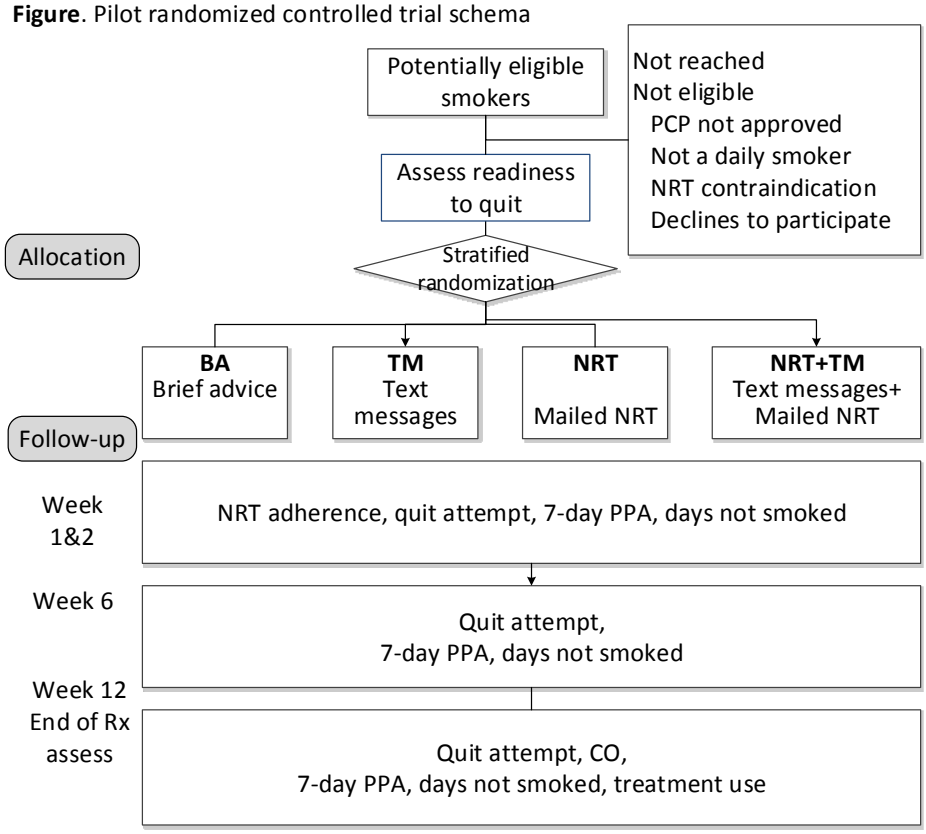
Hypothesis 3: A 12 week text messaging intervention will increase the rate of *biochemically confirmed* past 7-day point prevalent tobacco abstinence at end of treatment compared to subjects receiving no text messaging intervention.

Hypothesis 4: A 12 week text messaging intervention will increase the number of days not smoking compared to subjects receiving no text messaging intervention.

Hypothesis 5: A 12 week text messaging intervention will decrease the number of cigarettes smoked compared to subjects receiving no text messaging intervention

Study Design

Figure. Pilot randomized controlled trial schema



III. SUBJECT SELECTION

Study staff will identify subjects through three methods: patients in the MGH Primary Care Practice Based research network listed as smokers in the electronic health record, patients responding to an advertisement on the Partners clinical trials website, patients seen by the MGH inpatient Tobacco Treatment Service. The Massachusetts General Primary Care Practice Based Research Network's (MGPC-PBRN) linkage cohort. An existing smoking algorithm will be applied to this cohort, which will identify smokers seen at MGH Primary Care practices during the past two years, identified as a current smoker (as reported within the calendar year based upon structured field in the EHR), and who have a listed telephone number. These patients will be eligible for recruitment by PCP approval or documented Research Opportunities Direct to You (RODY) consent. For PCP approval, PCPs at participating practices will receive an email from study staff describing the study and asking permission to contact their patients who are smokers (see PCP Permission Email). A list of potentially eligible smokers will be included in the email and the PCP will be asked to check-off any patient they do not want study staff members to contact. All approved patients will receive a letter (see Opt Out Letter) signed by the PCP and PI explaining the study and offering a way to opt out of proactive outreach by telephone and email. RODY consent patients will receive a letter from the PI only. Patients who do not opt out will receive a proactive call from the study research coordinator to recruit them for the study. Patients responding to an advertisement on the Partners Clinical Trials website will be contacted by phone and/or email. These subjects will have the same eligibility criteria except that MGH PCP will not be required, patients with a Partners PCP and an MGH medical record number are eligible. The MGH inpatient Tobacco Treatment Service counselors qualify as

specialty providers who can give approval for their patients to be contacted for research purposes, introduce the study to the patient, and verbally obtain the patient's permission to be contacted by study staff. Patients referred by the TTS counselors will be sent letters from the study team and contacted proactively by telephone.

To be eligible to participate, individuals must meet **all** of the following criteria:

- Adults (≥18 years)

  Rationale: We wish to focus only on adult smokers since adolescent smokers present unique issues that merit separate consideration.

- Smoking status of current smoker in structured field of EHR

  Rationale: Using the EHR to identify and reach out to smokers leverages smoking status documentation promoted by federal Meaningful Use standards and makes the intervention potentially scalable to any healthcare system with smoking status documented in their EHR.

- Language listed as English in EHR

  Rationale: We do not have the resources to develop intervention materials in languages other than English at this time.

- PCP within Partners Healthcare system and MGH medical record number

  Rationale: This intervention is designed to target patients engaged in primary care. Patients undergo chart review by PI as part of eligibility screening for possible contraindications to NRT and this is possible only with Partners primary care patients. Subjects require an MGH MRN because some patients will be randomized to NRT prescribed through MGH Epic and sent through the MGH pharmacy. Subjects who report cessation will also be asked to come to MGH for an exhaled carbon monoxide assessment to confirm tobacco abstinence at the end of the 12 week study.

- PCP visit in the past 2 years

  Rationale: We want to include patients who are actively engaged in primary care.

- Mobile telephone number listed in EHR

  Rationale: We need an active mobile number for the patient to receive text messages.

- Potential TSS referred subjects who have been recently hospitalized for a heart attack or chest pain may participate in the study with approval from their primary care physician.

  Rationale: Smokers who have been hospitalized for a recent heart attack or chest pain may likely use nicotine replacement therapy during their admittance. If there are no contradictions with other medications and their primary care physician approves of nicotine replacement therapy usage then it will be safe to enroll them.

Individuals meeting **any** of the following criteria will be excluded from the study:

- Not a current daily smoker defined as not having smoked ≥100 cigarettes in lifetime or not having smoked in the last 30 days

Rationale: EHR smoking status of current smoking will be verified by self-report using the CDC's definition of current smoking. We exclude non-daily smokers because our primary outcome of self-reported quit attempts has not been well-studied among non-daily smokers.

- Unwilling or unable to receive and participate with a text message program for up to 12 weeks.

  Rationale: We will not require that users have unlimited text messaging in their telephone plan, rather we will provide payment at baseline that should offset any costs incurred by sending or receiving text messages for the intervention.

- Pregnant, planning to become pregnant in the next 3 months, or breastfeeding.

  Rationale: The use of nicotine replacement therapy in pregnant smokers requires close monitoring, and the treatment of pregnant smokers more generally presents unique challenges that go beyond the scope of the present study.

  Past 30 day use of nicotine replacement therapy, bupropion, or varenicline. For TTS referred patients: Use of nicotine replacement therapy in the 30 days prior to hospital admission

  Rationale: In order to better isolate treatment effects for the proposed interventions, we wish to focus on individuals who are not currently using medications to try to quit smoking.

- Past 30-day use of Massachusetts state quitline, QuitWorks or SmokefreeTXT programs. For TTS referred patients: Use of Massachusetts state quitline, QuitWorks or SmokefreeTXT programs in the 30 days prior to hospital admission.

  Rationale: In order to better isolate treatment effects for the proposed interventions, we wish to focus on individuals who are not currently receiving behavioral interventions for smoking cessation.

- Prior serious adverse reaction to the nicotine patch or lozenge defined as any reaction that was life-threatening, required hospitalization, or other clinical evaluation

  Rationale: Nicotine replacement therapy is a component of both arms of the study.

- Weight < 100 pounds

  Rationale: Nicotine replacement therapy is a component of both arms of the study and requires clinical consultation for individuals under 100 pounds.

- New or increasing chest pain or heart attack in the past 30 days.

  Rationale: Although likely safer than smoking cigarettes, use of nicotine replacement therapy might pose a risk to individuals with unstable cardiac conditions.

- Ever been told by a doctor that patient has an irregularly fast, abnormal heartbeat

  Rationale: Although likely safer than smoking cigarettes, use of nicotine replacement therapy might pose a risk to individuals with unstable cardiac conditions.

- Ever been told by a doctor that patient has dementia, psychosis or schizoaffective disorder.

  Rationale: This intervention is primarily conducted by telephone and we do not believe it is appropriate for patients with these conditions which may affect cognition and thought processes.

For patients who are eligible by these criteria will be invited to participate in the study and complete verbal informed consent. Following verbal informed consent, the PI will review their medical chart for contraindications to nicotine replacement therapy and diagnoses of dementia, psychosis, schizophrenia, Alzheimer's disease, delirium, or schizoaffective disorders. Any subjects with contraindications to NRT or these diagnoses will be notified that, following

review of their medical record they are not eligible and they will be provided with information about the MGH tobacco cessation counseling services, the state quitline, and National Cancer Institute's smokefreeTXT. Subjects without contraindications will be randomized.

a. Source of subjects and recruitment methods

Smokers will be recruited through four methods. The primary method is through proactive outreach to individuals who receive primary care at MGH and are identified in the health record as smokers. We will first ask PCPs to review their patients meeting inclusion criteria per electronic health records and designate any patients who they do not want us to contact for the study. We will then send letters, signed by the study PI and signed with secretarial notation by the PCP, to patients meeting the inclusion criteria to introduce the study. The letter will notify patients that they will be receiving a call about the study at their home or mobile telephone number as listed in their clinic registration. Patients will be provided with a number which they can call if they do not want to receive the telephone call or if they want to update their mobile telephone number. The letter will also include a study fact sheet. One week after the letter, participants who do not opt-out will then be contacted by telephone by a study RC to enroll and consent the patient to participate in the randomized trial. The RC will attempt to contact the patient up to 5 times (either 3 times leaving messages or 5 times if unable to leave messages) at the home or mobile phone number listed in their Epic registration data. At the recruitment phone call, the RC will assess patients for exclusion criteria.

In addition to the primary recruitment method described above, we will recruit subjects through three other methods. 1)Potentially eligible MGH patients who have agreed to be contacted for research studies under the hospital's [Partners/ MGH] Research Options Direct to You (RODY) program. We will draw a list of names based on the same eligibility criteria that has been initially used throughout the recruitment process. Once potential subjects have been identified, we will send them an Opt Out letter describing the study and explaining how they can either obtain more information or how they can be removed from our list within 1 week of letter receipt. After 1 week, we will call these patients for prescreening to assess eligibility and interest.

2) We will advertise the study by posting an online advertisement on the Partners Clinical Trials website (https://clinicaltrials.partners.org/). Subjects who respond by email or telephone to this advertisement will be contacted by telephone or email by the clinical research coordinator. Interested subjects will be sent an informational letter and the study fact sheet.

3) The MGH Inpatient Tobacco Treatment Service counselors can serve as specialty healthcare providers who can give approval for patients to be contacted for research purposes, briefly introduce the study to patients who smoke and verbally obtain the patients permission to be contacted by study staff. They will provide study pamphlets with the same information as is included in the online advertisement to interested patients. TTS counselor referred patients will be sent an informational letter and study fact sheet and called by telephone by the study RC.

At time of the recruitment call, the RC will review the potential cost of the text messaging program which we expect to be up to 60 messages or a maximum cost of $15 per month. The RC will explain that we will pay research subjects $0.25 per message sent or received by the program up to 50$ or 200 messages. This is based on the amount of text messages sent between the most engaged participants and the program in our pilot study. In addition,

payments will be offered for each telephone assessment including $20 for completion of baseline assessment, $10 at weeks 1, 2 and 6 for telephone assessment, $40 for completion of the 12 week end of treatment assessment, $20 fo CO measurement for those reporting abstinence, and $10 for those selected for an exit survey. Subjects randomized to the NRT or TM+NRT arms will be offered 2 weeks of nicotine patch and/or lozenge if they are daily smokers who are planning to quit in the next 30 days or one box of nicotine lozenges to use in a practice quit attempt for those not planning to quit in the next 30 days. Subjects who have ever had an allergy to adhesive tape, such as bandaids, or medical tape or who have not tolerated nicotine patches in the past will be offered lozenges only if randomized to the NRT or TM+NRT arms.

Participants who decline to enroll will be given advice to quit and encouraged to talk to their doctor, call the MGH tobacco cessation counseling office, enroll in National Cancer Institute's smokefreeTXT or call the state quitline.

IV. SUBJECT ENROLLMENT

a. Methods of enrollment, including procedures for patient registration and/or randomization

This will be a 4 arm randomized controlled trial among 206 smokers who are patients at Massachusetts General Hospital and who receive primary care from a Partners primary care provider. Patients will be proactively recruited from MGH primary care practices. Patients will also be recruited from online advertisements on the Partners Clinical Trials website, from among MGH primary care patients who consent to participate in Research Offers Direct to You, and by referral from the MGH inpatient Tobacco Treatment Service counselors. We will recruit both smokers who are ready to quit smoking in the next 30 days and those who are not planning to quit in the next 30 days. The text message program is tailored to readiness to quit. For those ready to quit in the next 30 days, they will be sent messages based on the SmokeFreeTXT content. For those not ready to quit, we have developed content including motivational advice and tips to try a practice quit attempt for a few hours or days.[53] The text message program will also include medication adherence support text messages based on the Information-Motivation-Behavioral Skills model of adherence.[54] Combination NRT is first-line therapy which is more effective than nicotine patch alone and will be offered to daily smokers, dosed per package instructions.[21] Smokers who are not ready to quit and who are randomized to one of the two nicotine medication arms will be offered one box of lozenges to try in a practice quit attempt.[53]

The RC will not be blinded to treatment assignment because he/she will register subjects randomized to the text messaging arms in the text messaging program during the enrollment telephone call to verify receipt of an enrollment confirmation text message ("Hi [First name] Welcome to getReady2Quit (R2Q). Your messages and ratings will start soon. Reply STOP to quit, HELP for info. Msg&DataRatesMayApply"). Randomization will be done by a computer generated random sequence.

b. Procedures for obtaining informed consent (including timing of consent process)

Permission from primary care providers (PCP) or MGH inpatient Tobacco Treatment Service counselors will be obtained before making any patient contact unless the patient participates in 'Research Oppertunities Direct to You' or proactively contacts the study in response to online advertisements. For PCP approval, providers will be given a list of smokers identified for the study and asked to identify any individuals who should not be (see "PCP Permission Email") contacted. Patients whose PCP's consider them to be inappropriate or ineligible for the study will be excluded from participation regardless of RODY status or self-selection. MGH inpatient

Tobacco Treatment Service counselors will introduce the study to interested patients they deem appropriate during a counseling visit. Patients who are considered eligible will be sent a letter from their PCP and a letter from the study PI if PCP approved, from the PI only if RODY consented, or the PI only if TTS counselor referred. The letter notifies patients that they will be receiving a telephone call inviting them to participate at the mobile telephone number listed in their clinic registration. The letters will include a copy of a study information fact sheet with informed consent content.

Patients sent study introduction letters will be provided with a number which they can call in the letter if they do not want to receive the telephone call or if they want to update their mobile telephone number. Approximately one week after the letter, smokers who do not opt out will be contacted by telephone by a study RC who will screen for eligibility.

Patients who proactively contact the study will be sent more information on the study via mail and email. Patients with MGH MRNs and a Partners PCP will be considered eligible to proceed.

Eligible subjects who are interested in enrolling will be offered a call back the next day to allow 24 hours to consider enrollment. For those that decline this additional time or at the time of the call the next day, the study RC will complete verbal informed consent (see "Consenting call script"). For those subjects who complete verbal informed consent but report they no longer have a copy of the study information fact sheet that was mailed with the Opt Out Letter, a new copy of the study information fact sheet will be mailed. Following verbal informed consent, the PI will screen the medical chart of consented subjects for NRT contraindications or diagnoses in the exclusion criteria (dementia, psychoses, and schizoaffective disorder). Subjects without contraindications will undergo baseline survey and then be randomized.

Rationale: There is a precedent for mailing nicotine replacement therapy to smokers after telephone screening for contraindications to the medication. The precedent is based on the methods used by the Massachusetts State quitline, we include screening questions used by the quitline in our eligibility screener. Our approach to screening for medical contraindications is more robust than that used by the quitline in that the PI-Dr. Kruse will also conduct a chart review for medical contraindications or psychiatric diagnoses that may make a remotely conducted study inappropriate. Finally, Partners has approved at least two other randomized controlled trials that mailed nicotine replacement therapy following verbal consent and telephone screening (protocol 2009-P-001137/3 and 2011-P-000644/1).

c. Treatment assignment, and randomization

Those who consent and enroll will be randomly assigned to one of 4 groups:

1. Brief advice (BA): Brief advice to quit smoking
   Rationale: All subjects will receive brief advice from a trained RC. All primary care subjects also have access to guideline-concordant tobacco treatment [21] through their primary care provider (PCP). Their PCP can refer them to in-person or telephone counseling and can prescribe medications. This constitutes a scientifically and ethically appropriate standard against which to measure the experimental interventions.

2. Nicotine replacement therapy (NRT): Brief advice + 2 weeks of nicotine patches and/or lozenges mailed to subject

Rationale: In order to test the effect of text messaging on medication adherence, we need to have treatment groups receiving medication and medication plus text messaging. To deliver medication, mailed NRT, like text messaging, reaches patients outside of the busy office visit. Mailed NRT alone has also been shown to increase cessation [55] and may itself be an effective intervention compared to standard care.

3. Text messaging (TM): Brief advice + 12 week personalized, tailored text messaging program.
   Rationale: Text messaging shows promise as an intervention to help smokers to quit.[8,56] However, it has not been well tested among primary care patients. Text messaging may connect those primary care smokers who do not access currently available treatment services like telephone counseling or prescribed medication with assistance outside of the clinic office.

4. Text messaging and nicotine replacement therapy (TM+NRT): Brief advice + 12 week personalized, tailored text messaging program + 2 weeks of nicotine patches and/or lozenges mailed to subject.
   Rationale: As above, in order to test the effect of text messaging on medication adherence, we need to have treatment groups receiving medication and medication plus text messaging. Text messaging has been shown to increase medication adherence in other conditions [34-37] and medication adherence is suboptimal among users of smoking cessation medications. [38,39,41] Integrating text messaging within healthcare systems offers opportunities to coordinate with pharmacotherapy and this 4 group design allows us to test the effect of text messaging alone on smoking outcomes and the effect of text messaging on NRT use.

We will use stratified block randomization. We will stratify by practice and readiness to quit in the next 30 days. We will use variable block sizes. Subjects will be randomized 1:1:1:1.

After verbal consent and chart review by the PCP. Randomized enrollees will be asked to complete a baseline telephone survey. After completion of the baseline survey, participants will be mailed a $20 gift card.

Following the telephone survey, smokers randomized to the text messaging arms (TM and TM+NRT) will have their mobile numbers, and first names entered into the MobileCommons web-based platform. The program will be tailored to readiness to quit and user-entered quit date and personalized with individual's first name.

Participants randomized to NRT or TM + NRT arms will be offered nicotine patches and/or nicotine lozenges in a two-week allotment. Daily smokers with a quit date will be offered patch and lozenge. Smokers not ready to quit will be encouraged to use lozenges when not smoking during practice quit attempts[53]. Patches will be dosed according to reported cigarette consumption per day and lozenges will be dosed according to time to first cigarette as per package instructions. Smokers with a previous allergy to skin adhesives with an unknown tolerance of or known intolerance to nicotine patches will only be offered lozenges if randomized to the NRT or TM+NRT arms. The prescriptions will be sent to the MGH outpatient pharmacy by printing and faxing the prescription with a cover sheet which lists the study fund to bill or by e-prescription with the study information and study fund to bill in the comments to pharmacy section. The MGH pharmacy will then mail the 2 week supply of medication directly to the study subject.If the pharmacy discovers any issues with mailing they will notify us and we will attempt to notify IRB within 1 working day. For any issues with subjects not receiving

medications that are discovered at the week 1 and 2 telephone surveys, we will notify IRB within 5 working days.

V. STUDY PROCEDURES

The following interventions and procedures will be applied to 6 pre-test subjects (3 in each treatment arm) and then we will aim for 200 subjects in the randomized trial.

a. Text messaging intervention

Patients randomized to the text messaging program are offered a 12-week text messaging program (up to 4 weeks pre-quit, and 8 weeks post-quit attempt). The text messaging intervention will use content from the National Cancer Institute's SmokeFreeTXT library[57], content for smokers not ready to quit from SmokeFreeTXT and our pilot feasibility study, and new messages supporting nicotine replacement medication adherence. SmokeFreeTXT content is tailored to smokers with a quit date in the next 30 days. It includes messages with tips for behavioral tips for cessation, motivational and encouraging messages, and fact-based messages about smoking including health risks (see attached Text Message Campaign). Smokers are also periodically asked how they are feeling. Their response to this message triggers a tailored motivational message in response. Messages will refer patients to the local tobacco counseling service. Smokers can also request specific advice to deal with cravings, mood symptoms, or slips by texting keywords "CRAVE", "MOOD", or "SLIP". Participants will have access to a study telephone line for the duration of the intervention.

The content for smokers who do not have a quit date in the next 30 days will include advice to try making a practice quit attempt and motivational messages. This idea of practicing quitting is based on the idea of quit induction. Pre-quit activities that increase self-efficacy and motivation and move a smoker towards action and a serious quit attempt. [53] We developed some content promoting practice quit attempts and motivational advice and pilot tested it (see "Preliminary work supporting the proposed study" above). The National Cancer Institute has also developed content for smokers not ready to quit which includes advice to try a practice quit attempt. This content was shared with the PI and was released February 2016 as part of SmokeFreeTXT (see attached Text Message Campaign).

The novel content encouraging NRT use and promoting adherence will include advice for proper use of NRT, education about medication safety [58,59], reminders to use the patch every day, reminders to use lozenges at the first sign of craving, and motivational messages about the effectiveness of these medications. These messages are based on the Information-Motivation-Behavioral Skills theoretical model of medication adherence (Fisher 2006).

Finally, the text messaging program will be tailored to the individual and MGH. Text messages will include the telephone number for the MGH tobacco cessation counseling services LivingTobacco-Free which accept self-referrals as well as the number for the Massachusetts state quitline.

Smokers receiving the intervention will be sent from 0 and 5 text messages per day. This is the message volume used by most smoking cessation text messaging programs.[60] Smokers are asked to enter a quit date in the first 30 days after enrollment. Those without a quit date will be sent the practice quit attempt messages. At the end of the practice quit attempt messages subjects will be asked again if they have a quit date in the next 30 days. For those who are ready to quit at time of enrollment, or those who become ready to quit after the practice attempt, up to 5 messages per day are delivered in the 2 weeks leading up to the self-designated quit

date and the 2 weeks after the quit date when they are at greatest risk for relapse.[61] Messages then decrease to 3 messages per week for 8 weeks after the attempt.

b. Drugs used

Subjects randomized to the NRT or TM + NRT arms will be offered nicotine replacement therapy dependent on their smoking patterns and readiness to quit.

Daily smokers planning to quit in the next 30 days will be offered combination nicotine replacement therapy including nicotine patches and nicotine lozenges. Daily smokers will be offered nicotine patches (14 or 21 mg patches) and lozenges (2 or 4 mg lozenges). Smokers who smoke ≥10 cigarettes per day will be offered 21 mg patches, those who smoke <10 cigarettes per day will be offered 14 mg patches. Daily smokers who smoke within 30 minutes of awakening will be also offered the 4 mg lozenges. Daily smokers who smoke >30 minutes of awakening will be offered 2 mg lozenges. Daily smokers with a prior reaction to adhesives from bandaids or the nicotine patch will be offered lozenges only.

Smokers not planning to quit will be offered one box of lozenges (72 count box of 4 mg or 2 mg lozenges based on time to first cigarette as above per package instructions) to use when they are not smoking during their practice quit attempt [53].

The efficacy and safety of mailing nicotine replacement therapy to general population has recently been demonstrated [55].

NRT prescriptions will be entered into the EHR and signed by the study PI (Gina Kruse), printed and faxed to the MGH Outpatient pharmacy. The MGH Outpatient pharmacy will send the NRT by mail to the subject.

NRT will be distributed in a two-week allotment. The RC will screen participants for any self-reported contraindications to NRT use or other exclusion criteria before enrollment. High-risk comorbidities (e.g. cardiovascular disease, uncontrolled hypertension) will also be assessed but will not be grounds for withholding NRT since the risks of continued smoking outweigh the potential risks of using NRT in these conditions. After verbal consent, the PI will screen medical records of subjects randomized to NRT for contraindications or exclusion criteria prior to randomization. Participants will be instructed not to use the patch or lozenges while smoking, but rather to commence use when/if they make a quit attempt or practice quit attempt (lozenges only). The most common side effect of transdermal NRT is skin irritation. Other possible but rare side effects of all forms of NRT include cardiovascular (chest pain, hypertension, tachycardia, palpitations), metabolic (hot flashes, sweats), gastrointestinal (diarrhea, dyspepsia, nausea/vomiting, flatulence/gas, hiccups), musculoskeletal (arthralgia, myalgia), neurologic (headaches, dizziness), ophthalmic (lacrimation, nystagmus), respiratory (coughing), oropharyngeal (dry mouth, alteration of taste) and psychiatric (sleep disturbance, vivid dreams) manifestations.[62] The most common side effects of nicotine lozenges include mouth irritation or ulcers, nausea, vomiting, hiccups, abdominal pain, diarrhea, headaches and palpitations. Randomized trials of combination nicotine replacement therapy have shown increased report of adverse events but not more serious adverse events or study withdrawal among subjects receiving combination therapy compared with subjects receiving NRT monotherapy. The risk of nicotine toxicity is rare in clinical trials. Among trial subjects who achieve higher cotinine levels with nicotine therapy than with smoking alone, the most common symptoms reported were nausea, vomiting, palpitations, dizziness, and headaches and all occurred in 0.5% or fewer trial subjects.[63]

All study subjects will be asked about adverse reactions to the nicotine patch or lozenge at weeks 1, 2 and 6.

c. Devices

We will attempt to obtain exhaled carbon monoxide samples from study participants who self-report 7 day point prevalent abstinence at end of treatment using the coVita | Bedfont Micro+ Smokerlyzer carbon monoxide monitor. The device will be used, maintained, and calibrated in accordance with the manufacturer's instructions.

Subjects randomized to the TM and TM + NRT arms will have their mobile telephone number, first name and PCP's name entered into the MobileCommons web-based text messaging platform. Their name will be used to personalize text messages.

d. Study visits and parameters to be measured

This study will be primarily conducted by telephone contact, email if the participant chooses, and mailings with a single in-person contact for subjects reporting abstinence from smoking at the end of treatment to collect an exhaled carbon monoxide sample to confirm abstinence. Subjects will be contacted by telephone and data collected by self-report at time of enrollment (baseline assessment interview), and by telephone or email for 1, 2, and 6 weeks after enrollment (follow-up outcome assessments), and end of treatment (primary outcome).

We will also offer a qualitative exit interview to be completed by phone for 10 participants per intervention arm (TM, TM+NRT, and NRT).

Baseline assessment:

Variables obtained from the EHR:

- Demographic factors: age, sex, health insurance (commercial, Medicare, Medicaid, no insurance or other), name, and address
- Medical history: coronary heart disease, COPD, diabetes, hypertension, cancer
- Practice characteristics: PCP, practice, number of visits to practice in past year

Variables obtained from baseline telephone interview:

- Smoking patterns: daily or non-daily, years smoked, Fagerstrom test for nicotine dependence (includes time to first cigarette after waking and cigarettes smoked per day)[64], number of previous quit attempts defined as any serious quit attempt lasting ≥24 hours [65] ever and in the last 12 months, during the past 30 days, on how many days did you have at least one cigarette, and do you ever use menthol cigarettes.
- Demographic factors: ethnicity, race (white, black, Native American, Asian, Native Hawaiian or other Pacific Islander, other, unknown), and education
- Any prior use of smoking cessation medication (nicotine patch, lozenge, gum, inhaler or nasal spray, varenicline, or buproprion)
- Any prior use of behavioral treatment for smoking cessation (clinic or class, in-person counseling, telephone counseling, text messaging, alternative therapy, self help materials, or online communities and applications)
- Past month use of other tobacco products-cigars, cigarillos, smokeless tobacco, hookah, or e-cigarette

Motivation to quit, confidence to quit, and perceived 2-week distress measured using single-item instruments with 11-item likert scale

- Readiness to quit [66]
- Measures of psychosocial mechanisms targeted by the text messaging
- PHQ-2 and GAD-2 screening for depression and anxiety
- Single item alcohol[67] and substance use disorder[68] screening questions and past month illegal use of drugs[69]
- On an average day, about how many text messages do you send and receive on your cell phone?
- Cell phone carrier, type (smartphone) and plan details (pay per text or unlimited text messaging).
- Email for subjects that want the follow up surveys emailed
- Social security number for payment purposes

Outcome assessments:

Medication use outcomes will be assessed by telephone interview at week 1 and 2 by a second research coordinator blinded to treatment assignment: number of days patch was used in the last week and number of lozenges used each of the last two days. These will be used to calculate total duration of medication.[70].

1 &2 week telephone outcome assessments

- Have you used nicotine patch in the past 7 days?
  - How many days in the past week did you use a nicotine patch?
- Have you used nicotine lozenges in the past 7 days?
  - How many days in the past 7 days did you use a nicotine lozenge?
  - On days when you use lozenge, how many do you use on average?
- Since starting the study, have you stopped smoking cigarettes for 1 day or longer because you were trying to quit smoking?
  - If yes→On how many of the past 7 days did you have at least one cigarette?
    If 0→Have you smoked cigarettes, even a puff in the past 7 days?
- Have you experienced any side effects in the last 7 days from quit smoking medications?
- Receipt of text messages since last assessment.
- *Only Week 2*→ Would you like more nicotine medication? A refill request would be sent to your PCP and it will be billed through your regular insurance.

6 week telephone outcome assessments

- Have you used nicotine patch in the past 7 days?
  - How many days in the past week did you use a nicotine patch?
- Have you used nicotine lozenges in the past 7 days?
  - How many days in the past 7 days did you use nicotine lozenges?
  - On days when you use lozenge, how many do you use on average?
- Since starting the study,have you stopped smoking cigarettes for 1 day or longer because you were trying to quit smoking?
  - If yes→In the past 30 days, how many days did you not smoke cigarettes?
  - If yes→On how many of the past 7 days did you have at least one cigarette?
    If 0→Have you smoked cigarettes, even a puff in the past 7 days?
- Have you experienced any side effects in the past 30 days from quit smoking medications?
- Receipt of text messages since last assessment

12 week end-of-treatment telephone outcome assessment

Quit attempt and smoking cessation outcomes will be assessed by telephone at 12 weeks (end of treatment)
PRIMARY OUTCOME: Self-reported quit attempt in the last 12 weeks defined as intentional not smoking for 24 hours or more ("Since the start of the study, have you quit smoking intentionally for 1 day or longer" in addition to past follow up reports of quit attempts). We recognize that tobacco abstinence for more than one day is the desired outcome but feel this intermediate outcome is appropriate in the context of a pilot study with limited resources.
SECONDARY OUTCOMES:
How many times did you try to quit during the study?
Have you smoked, even a puff, in the past 7 days? (7 day PPA)
In the past 30 days, how many days did you not have a cigarette?
How many cigarettes do you now smoke per day?
Motivation to quit, confidence to quit, and perceived 2-week distress measured using single-item instruments with 11-item likert scale
Use of evidence based treatment and behaviorial treatment in the past 12 weeks (NRT, varenicline, bupropion, clinic or class, in-person counseling, telephone counseling, text messaging, alternative therapy, self help materials, or online communities and applications)
Past month use of other tobacco products including electronic cigarettes
Side effects of quit smoking medications in the past 12 weeks
Satisfaction with treatment
Exhaled CO in ppm among subjects reporting 7 day PPA

Up to 10 attempts will be made to reach study subjects for each outcome assessment (weeks 1, 2, 6 and 12).

Measures of intervention utilization:
Intervention utilization will be obtained from MobileCommons software.

ADHERENCE: length of active time in the text messaging program. At least twice per week a text message will be followed by another text message asking respondents if they found the message useful. Active time will be defined as number of days from enrollment to last reply to these usefulness messages.
ENGAGEMENT: number of messages sent from participant to the server. Messages from the participant could be in response to the periodic questions about how they are feeling or to request specific help with cravings, mood symptoms, or slips. We will exclude responses to the receipt confirmation messages from this total.
COMPLAINTS: due to technical issues or programmatic issues received by the technical helpline.

e. Remuneration
We will pay subjects $0.25 per text message sent or received from the program server up to $50 or 200 text messages. Participants will be issued $20 for completion of the baseline survey and $10 for follow-up surveys at 1, 2 and 6 weeks after enrollment. Participants will be issued another $40 after completion of the outcome telephone interview. Participants will be issued $20 if they complete a CO measurement. A small subset of participants will be issued a $10 gift card for a qualitative exit interview. All payments for surveys and for the CO measurement will be issued by a gift card. Text message reimbursement will be issued by check every 4 weeks.

VI. BIOSTATISTICAL ANALYSIS

At the start of the project, MGH Primary Care Practice Based Research Network staff will identify the target population of documented smokers in MGH primary care practices and create a database that includes baseline variables from the EHR. We will use REDCap to collect baseline self-reported data and outcomes. At the end of the study we will merge the EHR data from the Primary Care Practice Based Research Network, REDCap, and MobileCommons for analysis (see Data Collection sheets).

Data analysis

The sample of smokers enrolled in the study will be characterized on baseline measures from the EHR and compared to the population of smokers whom we attempted to contact in order to determine the sample's representativeness to the target population. Variables include demographics, medical history, and practice characteristics. We will also compare baseline characteristics collected from the EHR and from baseline interviews between the 4 randomized groups to determine the success of randomization. The primary outcome analysis will be conducted as intention-to-treat, comparing the primary outcome using chi-square analysis or multiple logistic regression analysis if any baseline factor is significantly imbalanced by group ($p<0.05$) as independent variables. The 4 arm design allows for analysis as a factorial design. We will first test for interaction between the NRT and TM interventions and if no interaction is detected we will test the effect of text messaging using both TM and TM+NRT arms compared to BA and NRT arms. If interaction is present, we will compare the TM arm to BA for our primary analysis. We will secondarily compare the groups in terms of self reported 7 day PPA, biochemically confirmed abstinence, number of days not smoked, use of ≥1 evidence based treatments, and cigarettes per day using chi-square or t-tests or logistic or linear regression if groups are imbalanced. We will also compare the TM+NRT group with the NRT group in terms of total days of medication used and total mg of medication used over 2 weeks using linear regression. We will conduct stratified analyses of the primary outcome, 7 day PPA, treatment use and days not smoked by readiness to quit in the next 30 days.

Sample size

Hypothesis 1: A 12 week text messaging intervention (up to 30 days pre-quit through 8 weeks post-quit) providing behavioral support will increase the proportion of smokers making a quit attempt compared to a control group receiving brief advice.

The sample size for this pilot study is selected to adequately estimate recruitment rates, retention, and to get a preliminary estimate of prevalence of clinical outcomes. We anticipate we can recruit 200 patients by proactive outreach over 12 months. With 50 patients per group and 25% loss to follow-up we will have 81% power to detect a relative risk of self-reported ≥24 hour quit attempts of 1.8 for text messaging versus brief advice groups. We base this estimate on meta-analyses of smoking cessation text messaging trials, mostly from community settings or school-based settings, report a relative risk of 1.4 for 7-day point prevalence abstinence and 1.6 for prolonged abstinence measured at six-months.[8,71]

Hypothesis 2: A 12 week text messaging intervention providing personalized, tailored behavioral support and advice about using nicotine replacement therapy (NRT) plus 2 weeks of NRT mailed to the participant will increase adherence to NRT compared to subjects receiving only 2 weeks of NRT as measured by duration of NRT use in days.

For our secondary outcome of medication adherence, we estimate patients randomized to the NRT will use a mean 9 days of medication based on the offer to mail them 2 weeks of medication for free.[72] With this sample size, we also have 80% power to detect an increase in days of NRT use from 9 to 12 days in NRT vs. NRT+TM.

Hypothesis 3: A 12 week text messaging intervention will increase the rate of *biochemically confirmed* past 7-day point prevalent tobacco abstinence at end of treatment compared to subjects receiving no text messaging intervention.

We do not expect to have power to detect cessation in this pilot study. With 100 subjects and 25% loss to follow-up we will have 80% power to detect an increase from 6% among the BA & NRT groups to 22% in TM & TM + NRT groups.

Regardless, this pilot study aims to generate an estimate of effect size on cessation at 12 weeks for further studies.

Hypothesis 4: A 12 week text messaging intervention will increase the number of days not smoking compared to subjects receiving no text messaging intervention.

Assuming α=0.05 and 25% loss to follow-up, leaving 75 patients, we have 68% power to detect an increase in days not smoked from 0.2 in groups receiving no text messaging (BA & NRT) to 1 in groups receiving text messaging (TM & TM + NRT) assuming a standard deviation of 2.

Hypothesis 5: A 12 week text messaging intervention will decrease number of cigarettes smoking compared to subjects receiving no text messaging intervention.

Assuming α=0.05 and 25% loss to follow-up, leaving 75 patients, we have 75% power to detect a decrease in cigarettes smoked per day from 15 among those receiving no text messaging (BA & NRT) to 12 in groups receiving text messaging (TM & TM + NRT) assuming a standard deviation of 7.

VII. RISKS AND DISCOMFORTS

a. Complications of surgical and non-surgical procedures
Not applicable

b. Drug side effects and toxicities
Side effects of the nicotine patch may include itching, burning or tingling when the patch is applied. This usually goes away within an hour, and is a result of nicotine coming in contact with the skin; redness or swelling at the patch site for up to 24 hours; dizziness; headache; upset stomach; vomiting; diarrhea; and palpitations.

Side effects of the nicotine lozenge include mouth irritation or ulcers, in addition to nicotine-related side effects of dizziness; headache; upset stomach; vomiting; diarrhea, and palpitations.

c. Device complications/malfunctions
Errors in the text messaging platform include skipped text messages or failure to respond to a user-initiated text message. While this may affect the fidelity and clarity of the text messaging intervention we do not think this poses a risk to subject health or well-being.

d. Psychosocial (non-medical) risks
i). Psychological discomfort: Quitting smoking can be psychologically stressful and, at times, physically uncomfortable because of cravings and nicotine withdrawal symptoms.

ii). Risks to privacy: Text messages are not a secure messaging platform. Any person using the subject's designated phone can see the messages which may include information about quitting

smoking. It may be psychologically stressful for subjects if other persons see text messages disclosing their smoking status. We will also collect and record identifying information (e.g. name, date of birth and social security number) and ask about potentially sensitive topics (smoking history, depression screening questions, anxiety screening questions, alcohol and substance use disorder screening questions). Name, telephone number, and smoking status will be shared with the text messaging vendor. The vendor underwent risk assessment by Research Information Security to evaluate their data security practices.

e. Radiation risks
Not Applicable

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals
Smoking is the leading preventable cause of death in the U.S. and most individuals make several quit attempts before successfully quitting. A benefit to participating in the trial will be the opportunity to receive tobacco cessation interventions at no financial cost to the participant. This includes brief advice from study staff trained in tobacco cessation treatment. Subjects may receive up to 2 weeks of nicotine patches, nicotine lozenges or combination nicotine replacement therapy for daily smokers. Combination therapy is associated with higher rates of tobacco cessation in comparison to patches alone or unassisted quitting. Participants may also receive behavioral support by text message and medication adherence support to help them navigate their planned quit attempt.

b. Potential benefits to society (e.g., increased understanding of disease process, etc.)
We anticipate that our proposed research program will result in important knowledge contributions. The knowledge gained in mobile interventions will represent an important contribution to the evidence base for addressing tobacco use among primary care patients who suffer from high rates of tobacco dependence and tobacco related illness.

IX. MONITORING AND QUALITY

a. Independent monitoring of source data

All EHR and survey data will be collected using password-protected laptop or desktop computers with full disk encryption. We will use the Partners-hosted Research Electronic Data Capture (REDCap) application for data collection and management. REDCap is a secure, HIPAA compliant web-based application hosted by Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS). Because a Partners username is required for logging in to REDCap, all activity on study documents is electronically logged and therefore traceable. REDCap has built-in functions providing real-time data entry validation to help ensure accuracy and completeness. Data will be collected according to a standardized protocol that will detail which data elements should be collected during each study interaction and the methods for doing so. We will operationalize this protocol by using the calendar function in REDCap to specify which data collection forms to administer on which dates for each participant. Each data collection form will have instructions or prompts for collecting the required data elements, and the response fields for each item will have appropriate ranges and formats to ensure that the data is entered in a valid way.

The PI will review all study data once per week to monitor its integrity. Additionally, the PI, biostatistician, and/or data analyst will download the study data on a weekly basis from the

Partners REDCap server and back it up to the PI's SFA on the Partners network, which is protected by the Partners IS firewall, backed up nightly, and accessible only to authorized study staff. Only the minimum necessary number of study staff will have access to this data. Data analyses will be conducted by authorized study staff on the downloaded data files residing on the PI's Partners SFA. The data will not be transferred to investigators outside the Partners system.

Data will also be collected in the text messaging web-based platform in a database that includes identifiers of first name, telephone number and smoking status. This data will consist of all messages sent to participant from the server and all messages sent by the participant to the server. Once per week the PI will review all messages sent from participants to the server for possible disclosure of urgent or emergent medical information to the server.

b. Safety monitoring (e.g., Data Safety Monitoring Board, etc.)

The PI and her designated research coordinator, working in concert with the Partners IRB, will be responsible for the monitoring of adverse events in study participants.

Adverse reactions to nicotine medication: The research coordinator will ask all participants about adverse events at telephone contacts scheduled at week 1, week 2, and week 6 follow up and subjects will also be given a phone number to report any such events between study visits. The PI will review the safety and progress of the trial, including adverse event assessments, biweekly. Mild reactions will be reviewed by the PI and may prompt a dose reduction or cessation of patch or lozenge use. Severe reactions will be referred to emergency medical services. Subjects will be advised not to report events by text message. As above, the PI will also review text messages sent by subjects to the server biweekly in case subjects report adverse events or other health issues by text message. Adverse events will be documented, reviewed by the PI and reported to the IRB at the annual review or sooner based on the severity and nature of the event. All serious adverse events (i.e. hospitalization, death) will be reported within 5 days to the IRB, following institutional guidelines, and carefully reviewed by the PI to assess the likelihood that the event was related to the nicotine patch, lozenges, or text messages. A full written report using the PHRC Adverse Event From will be submitted to IRB within 10 working days/14 calendar days.

Risk to privacy: We will adhere to data management procedures described above to help ensure the safety and integrity of data collected about study participants. All identifying information will be saved securely within the REDCap database and not recorded on paper forms. Only the minimum necessary number of study staff will have access to this data. At the conclusion of the study, personal identifiers will be removed from the dataset and all analyses will occur in a de-identified fashion. To mitigate privacy risks associated with mobile phone use, participants will be instructed to safeguard their phone when not in use and to not leave it laying out in plain view if they do not wish others to see the content of any text messages sent to their phone. Partners Research Information Security reviewed the data security practices of the text messaging vendor. Information shared with the vendor includes name, telephone number and smoking status as well as any data entered by the patient as part of the text messaging program.

c. Outcomes monitoring

Because of the short duration and pilot nature of the proposed study, we will not conduct a formal interim analysis of the data or define rules for early stopping of the trial.

d. Adverse event reporting guidelines

Serious adverse events, defined as adverse events which are life threatening, require hospitalization, cause persistent or significant disability or incapacity, or events otherwise judged to represent significant hazards, which are reported by participants or the clinical staff caring for them will be documented in a serious adverse event report and submitted to the Partners IRB and institutional safety officer within 10 days of notification of the event. The report will include a description of the event, when and how it was reported, and any official chart records or study documents to corroborate the event. Participants will be referred for immediate medical evaluation of any serious adverse events. A summary safety report detailing all adverse events and their handling will be included in annual study progress reports to the Partners IRB and the NIH funding agency. Adverse event reports and annual safety summaries will be documented by study ID number; personal identifiers will not be included in these reports.

e. Protocol adherence

The study coordinators will be trained on the data collection protocols described above. Their understanding of these protocols will be assessed by asking them to demonstrate competency in using the REDCap data collection forms. Additionally, the research coordinator(s) responsible for providing brief advice to study participants will be trained in advance on the protocol to ensure consistency in advice across participants.

During the trial, adherence to the study procedures will be monitored by assessing whether the appropriate data collection modules were administered on the appropriate dates for each participant. Remediation and/or refresher training will be provided to study staff as needed to address any concerns. Additionally, the PI will meet with all study staff once weekly to review the day-to-day workings of the trial and to identify any problems related to the study protocol.

X. REFERENCES

1. US Department of Health and Human Services. The Health Consequences of Smoking--50 years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
2. Carter BD, Abnet CC, Feskanich D, et al. Smoking and mortality--beyond established causes. *N Engl J Med.* 2015;372(7):631-640.
3. Centers for Disease Control and Prevention. Quitting smoking among adults--United States, 2001-2010. *MMWR Morb Mortal Wkly Rep.* 2011;60:1513-1519.
4. Centers for Disease Control and Prevention. Quitting smoking among adults--United States, 2001-2010. *MMWR Morb Mortal Wkly Rep.* 2011;60(44):1513-1519.
5. Brenner J. Pew Internet: Mobile. Washington, D.C.: Pew Internet & American Life Project; 2013.

6. Lenhart A. Cell phones and American adults: They make just as many calls, but text less often than teens. Washington, D.C.: Pew Internet & American Life Project; 2010.
7. Head KJ, Noar SM, Iannarino NT, Grant Harrington N. Efficacy of text messaging-based interventions for health promotion: a meta-analysis. *Soc Sci Med.* 2013;97:41-48.
8. Spohr SA, Nandy R, Gandhiraj D, Vemulapalli A, Anne S, Walters ST. Efficacy of SMS Text Message Interventions for Smoking Cessation: A Meta-Analysis. *J Subst Abuse Treat.* 2015;56:1-10.
9. Whittaker R, Borland R, Bullen C, Lin RB, McRobbie H, Rodgers A. Mobile phone-based interventions for smoking cessation. *Cochrane Database Syst Rev.* 2009(4):CD006611.
10. Free C, Knight R, Robertson S, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. *Lancet.* 2011;378(9785):49-55.
11. Chen YF, Madan J, Welton N, et al. Effectiveness and cost-effectiveness of computer and other electronic aids for smoking cessation: a systematic review and network meta-analysis. *Health Technol Assess.* 2012;16(38):1-205.
12. Abroms LC, Ahuja M, Kodl Y, et al. Text2Quit: results from a pilot test of a personalized, interactive mobile health smoking cessation program. *J Health Commun.* 2012;17 Suppl 1:44-53.
13. Brendryen H, Kraft P. Happy ending: a randomized controlled trial of a digital multi-media smoking cessation intervention. *Addiction.* 2008;103(3):478-484; discussion 485-476.
14. Obermayer JL, Riley WT, Asif O, Jean-Mary J. College smoking-cessation using cell phone text messaging. *J Am Coll Health.* 2004;53(2):71-78.
15. Riley W, Obermayer J, Jean-Mary J. Internet and mobile phone text messaging intervention for college smokers. *J Am Coll Health.* 2008;57(2):245-248.
16. Abroms LC, Boal AL, Simmens SJ, Mendel JA, Windsor RA. A randomized trial of Text2Quit: a text messaging program for smoking cessation. *Am J Prev Med.* 2014;47(3):242-250.
17. Bock B, Heron K, Jennings E, et al. A Text Message Delivered Smoking Cessation Intervention: The Initial Trial of TXT-2-Quit: Randomized Controlled Trial. *JMIR mHealth and uHealth.* 2013;1(2):e17.
18. Naughton F, Jamison J, Boase S, et al. Randomized controlled trial to assess the short-term effectiveness of tailored web- and text-based facilitation of smoking cessation in primary care (iQuit in practice). *Addiction.* 2014;109(7):1184-1193.
19. Naughton F, Prevost AT, Gilbert H, Sutton S. Randomized controlled trial evaluation of a tailored leaflet and SMS text message self-help intervention for pregnant smokers (MiQuit). *Nicotine Tob Res.* 2012;14(5):569-577.
20. Chow CK, Redfern J, Hillis GS, et al. Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With Coronary Heart Disease: A Randomized Clinical Trial. *JAMA.* 2015;314(12):1255-1263.
21. Fiore MC, Jaen CR, Baker T, et al. *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline.* Rockville,MD: U.S. Department of Health and Human Services;2008.

22. Thorndike AN, Regan S, Rigotti NA. The treatment of smoking by US physicians during ambulatory visits: 1994 2003. *American Journal of Public Health.* 2007;97(10):1878-1883.
23. Kruse GR, Chang Y, Kelley JH, Linder JA, Einbinder JS, Rigotti NA. Healthcare system effects of pay-for-performance for smoking status documentation. *Am J Manag Care.* 2013;19(7):554-561.
24. Ellerbeck EF, Mahnken JD, Cupertino AP, et al. Effect of varying levels of disease management on smoking cessation: a randomized trial. *Ann Intern Med.* 2009;150(7):437-446.
25. Murray RL, Coleman T, Antoniak M, et al. The effect of proactively identifying smokers and offering smoking cessation support in primary care populations: a cluster-randomized trial. *Addiction.* 2008;103(6):998-1006; discussion 1007-1008.
26. Tzelepis F, Paul CL, Wiggers J, et al. A randomised controlled trial of proactive telephone counselling on cold-called smokers' cessation rates. *Tob Control.* 2011;20(1):40-46.
27. Haas JS, Linder JA, Park ER, et al. Proactive tobacco cessation outreach to smokers of low socioeconomic status: a randomized clinical trial. *JAMA Intern Med.* 2015;175(2):218-226.
28. Rigotti NA, Bitton A, Kelley JK, Hoeppner BB, Levy DE, Mort E. Offering population-based tobacco treatment in a healthcare setting: a randomized controlled trial. *Am J Prev Med.* 2011;41(5):498-503.
29. Fu SS, van Ryn M, Burgess DJ, et al. Proactive tobacco treatment for low income smokers: study protocol of a randomized controlled trial. *BMC Public Health.* 2014;14:337.
30. Rogers ES, Fu SS, Krebs P, et al. Proactive outreach for smokers using VHA mental health clinics: protocol for a patient-randomized clinical trial. *BMC Public Health.* 2014;14:1294.
31. Duggan M, Rainie L. *Cell Phone Activities 2012.* Washington, D.C.2013.
32. Centers for Disease Control and Prevention. Cigarette smoking among adults--United States, 2007. *MMWR Morb Mortal Wkly Rep.* 2008;57(45):1221-1226.
33. Honjo K, Tsutsumi A, Kawachi I, Kawakami N. What accounts for the relationship between social class and smoking cessation? Results of a path analysis. *Soc Sci Med.* 2006;62(2):317-328.
34. Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. *Cochrane Database Syst Rev.* 2012;3:CD009756.
35. Park LG, Howie-Esquivel J, Chung ML, Dracup K. A text messaging intervention to promote medication adherence for patients with coronary heart disease: A randomized controlled trial. *Patient Educ Couns.* 2013.
36. Montes JM, Medina E, Gomez-Beneyto M, Maurino J. A short message service (SMS)-based strategy for enhancing adherence to antipsychotic medication in schizophrenia. *Psychiatry Res.* 2012;200(2-3):89-95.
37. Castaño PM, Bynum JY, Andrés R, Lara M, Westhoff C. Effect of daily text messages on oral contraceptive continuation: a randomized controlled trial. *Obstet Gynecol.* 2012;119(1):14-20.

38. Raupach T, Brown J, Herbec A, Brose L, West R. A systematic review of studies assessing the association between adherence to smoking cessation medication and treatment success. *Addiction.* 2014;109(1):35-43.
39. Shiffman S, Sweeney CT, Ferguson SG, Sembower MA, Gitchell JG. Relationship between adherence to daily nicotine patch use and treatment efficacy: secondary analysis of a 10-week randomized, double-blind, placebo-controlled clinical trial simulating over-the-counter use in adult smokers. *Clin Ther.* 2008;30(10):1852-1858.
40. Lam TH, Abdullah AS, Chan SS, Hedley AJ, Group HKCoSaHSCHCSS. Adherence to nicotine replacement therapy versus quitting smoking among Chinese smokers: a preliminary investigation. *Psychopharmacology (Berl).* 2005;177(4):400-408.
41. Catz SL, Jack LM, McClure JB, et al. Adherence to varenicline in the COMPASS smoking cessation intervention trial. *Nicotine Tob Res.* 2011;13(5):361-368.
42. Johnson RE, Stevens VJ, Hollis JF, Woodson GT. Nicotine chewing gum use in the outpatient care setting. *J Fam Pract.* 1992;34(1):61-65.
43. Bansal MA, Cummings KM, Hyland A, Giovino GA. Stop-smoking medications: who uses them, who misuses them, and who is misinformed about them? *Nicotine Tob Res.* 2004;6 Suppl 3:S303-310.
44. Burns EK, Levinson AH. Discontinuation of nicotine replacement therapy among smoking-cessation attempters. *Am J Prev Med.* 2008;34(3):212-215.
45. Wiggers LC, Smets EM, Oort FJ, et al. The effect of a minimal intervention strategy in addition to nicotine replacement therapy to support smoking cessation in cardiovascular outpatients: a randomized clinical trial. *Eur J Cardiovasc Prev Rehabil.* 2006;13(6):931-937.
46. Ossip DJ, Abrams SM, Mahoney MC, Sall D, Cummings KM. Adverse effects with use of nicotine replacement therapy among quitline clients. *Nicotine Tob Res.* 2009;11(4):408-417.
47. Schmitz JM, Sayre SL, Stotts AL, Rothfleisch J, Mooney ME. Medication compliance during a smoking cessation clinical trial: a brief intervention using MEMS feedback. *J Behav Med.* 2005;28(2):139-147.
48. Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. *J Consult Clin Psychol.* 1983;51(3):390-395.
49. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health.* 1999;89(9):1322-1327.
50. Meredith LS, Yano EM, Hickey SC, Sherman SE. Primary care provider attitudes are associated with smoking cessation counseling and referral. *Medical care.* 2005;43(9):929-934.
51. Sesney JW, Kreher NE, Hickner JM, Webb S. Smoking cessation interventions in rural family practices: an UPRNet study. *J Fam Pract.* 1997;44(6):578-585.
52. Viswanath K, McCloud R, Minsky S, et al. Internet use, browsing, and the urban poor: implications for cancer control. *Journal of the National Cancer Institute Monographs.* 2013;2013(47):199-205.

53. Carpenter MJ, Hughes JR, Gray KM, Wahlquist AE, Saladin ME, Alberg AJ. Nicotine therapy sampling to induce quit attempts among smokers unmotivated to quit: a randomized clinical trial. *Arch Intern Med.* 2011;171(21):1901-1907.
54. Fisher JD, Fisher WA, Amico KR, Harman JJ. An information-motivation-behavioral skills model of adherence to antiretroviral therapy. *Health Psychol.* 2006;25(4):462-473.
55. Cunningham JA, Kushnir V, Selby P, Tyndale RF, Zawertailo L, Leatherdale ST. Effect of Mailing Nicotine Patches on Tobacco Cessation Among Adult Smokers: A Randomized Clinical Trial. *JAMA Intern Med.* 2016;176(2):184-190.
56. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. *Cochrane Database Syst Rev.* 2016;4:CD006611.
57. National Cancer Institute. QuitNowTXT Message Library. 2011.
58. Ferguson SG, Gitchell JG, Shiffman S, Sembower MA, Rohay JM, Allen J. Providing accurate safety information may increase a smoker's willingness to use nicotine replacement therapy as part of a quit attempt. *Addict Behav.* 2011;36(7):713-716.
59. Shiffman S, Ferguson SG, Rohay J, Gitchell JG. Perceived safety and efficacy of nicotine replacement therapies among US smokers and ex-smokers: relationship with use and compliance. *Addiction.* 2008;103(8):1371-1378.
60. Kong G, Ells DM, Camenga DR, Krishnan-Sarin S. Text messaging-based smoking cessation intervention: A narrative review. *Addict Behav.* 2013.
61. Zhu SH, Stretch V, Balabanis M, Rosbrook B, Sadler G, Pierce JP. Telephone counseling for smoking cessation: effects of single-session and multiple-session interventions. *J Consult Clin Psychol.* 1996;64(1):202-211.
62. Mills EJ, Wu P, Lockhart I, Wilson K, Ebbert JO. Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177,390 individuals. *Tob Induc Dis.* 2010;8:8.
63. Tonstad S, Gustavsson G, Kruse E, Walmsley JM, Westin A. Symptoms of nicotine toxicity in subjects achieving high cotinine levels during nicotine replacement therapy. *Nicotine Tob Res.* 2014;16(9):1266-1271.
64. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict.* 1991;86(9):1119-1127.
65. Centers for Disease Control and P. Cigarette smoking among adults and trends in smoking cessation - United States, 2008. *MMWRMorbidity and mortality weekly report.* 2009;58(44):1227-1232.
66. Biener L, Abrams DB. The Contemplation Ladder: validation of a measure of readiness to consider smoking cessation. *Health Psychol.* 1991;10(5):360-365.
67. Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. Primary care validation of a single-question alcohol screening test. *J Gen Intern Med.* 2009;24(7):783-788.
68. Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. A single-question screening test for drug use in primary care. *Arch Intern Med.* 2010;170(13):1155-1160.

69. Humeniuk R, Ali R, Babor TF, et al. Validation of the Alcohol, Smoking And Substance Involvement Screening Test (ASSIST). *Addiction.* 2008;103(6):1039-1047.
70. Raupach T, Shahab L, Neubert K, Felten D, Hasenfuss G, Andreas S. Implementing a hospital-based smoking cessation programme: evidence for a learning effect. *Patient Educ Couns.* 2008;70(2):199-204.
71. Scott-Sheldon LA, Lantini R, Jennings EG, et al. Text Messaging-Based Interventions for Smoking Cessation: A Systematic Review and Meta-Analysis. *JMIR mHealth and uHealth.* 2016;4(2):e49.
72. Cummings KM, Fix B, Celestino P, Carlin-Menter S, O'Connor R, Hyland A. Reach, efficacy, and cost-effectiveness of free nicotine medication giveaway programs. *J Public Health Manag Pract.* 2006;12(1):37-43.