DETAILED PROTOCOL

TITLE: A Text Messaging Intervention for Smoking Cessation Among Primary Care 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 an audiotaped qualitative interviews to further improve the program design and content prior to the current trial.

c. Study rationale

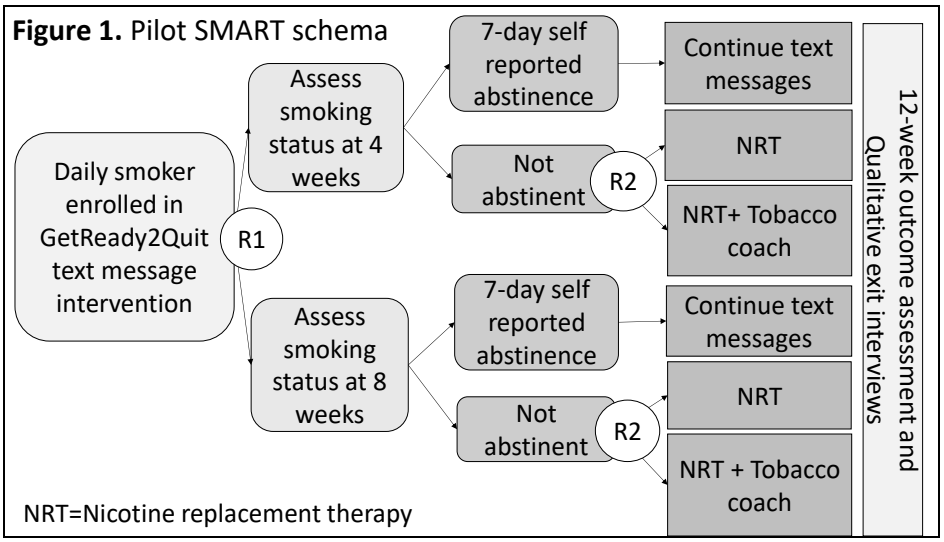
The data summarized above demonstrate several issues that motivate the current study: 1) despite the availability of effective treatments, primary are patients who smoke rarely use assistance when they try to quit, 2) text messaging interventions have been effective in helping smokers to quit in the 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.

To further understand how to optimally use text messages for smokers in primary care, we will establish the feasibility of a sequential multiple assignment randomized trial (SMART) comparing different timing for assessing response to text messages and different treatment intensifications for smokers who fail to quit with text messages alone.

3) A pilot SMART will ascertain the feasibility of conducting a larger SMART to understand when smokers should be contacted about response to the text messages and whether treatment intensification should include medications or medications plus telephone coaching.

Research Aim: To assess the feasibility of a sequential multiple assignment randomized trial (SMART) of a proactively offered text message intervention for smokers in primary care that

compares early (4 weeks) versus late (8 weeks) assessment of treatment response and the addition of nicotine replacement therapy (NRT) alone or with telephone coaching for non-responders and to understand primary care patients' experiences with the text message intervention and the adaptive treatment sequence and timing.



This is a pilot Sequential multiple assignment randomized trial (SMART) among 35 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 and from among MGH primary care patients who consent to participate in Research Offers Direct to You. 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.

Smokers will be offered a choice of lozenges and/ or patches if they are medically eligible and have not quit at their allocated assessment timepoint.

The research coordinator will not be blinded to treatment assignment because he/she will register subjects in the text message 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 at time of enrollment and again at time of assessment (4- vs. 8-weeks). The second computer generated random sequence is used among patients reporting continue smoking at 4- or 8-weeks.

Those who consent and enroll will be enrolled in our tailored text message program:

- Text messaging (TM): Brief advice + 12-week personalized, tailored text messaging program.
    - Rationale: We use the same text message intervention tested in aim 1. Text messaging shows promise as an intervention to help smokers to quit. However, it has not been well tested among primary care patients and it is not understood how it should be optimally combined with other smoking cessation treatments. It has potential to engage primary care

smokers who do not access currently available treatment services like telephone counseling or prescribed medication with assistance outside of the clinic office.

Enrolled patients will also be randomly assigned at baseline to early or late assessment of response to text messages:

- Early Assessment: After 4 weeks of text messages, Early Assessment smokers are asked at week 4 about cigarette use in the past 7 days by text message, email or telephone.

- Late Assessment: After 8 weeks of text messages, Late Assessment smokers are asked at week 8 about cigarette use in the past 7 days by text message, email or telephone.
    - *Rationale*: In order to test the timepoint at which additional support should be offered to text message users, we need to compare groups who are assessed for response (i.e. smoking cessation) at different time points.

Patients who report continued smoking defined as cigarette use in the past 7 days at the early or late assessment will be randomized to one of two interventions:

- Nicotine replacement therapy (NRT): 4 weeks of nicotine patches or lozenges mailed to subject

- NRT and proactive telephone coaching: 4 weeks of nicotine patches or lozenges mailed to subject and proactive telephone coaching for smoking cessation.
    - Rationale: For non-responders in an adaptive treatment model it is not clear whether treatment should be intensified by adding mailed medication to the behavioral text messages or if patients who fail to respond (continue to smoke) need more help with both medications, text messages and telephone coaching. To deliver medication, mailed NRT and telephone coaching reaches patients outside of the busy office visit.

After verbal consent and screening by the RC. 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 will have their mobile numbers, and first names entered into the web-based messaging 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 telephone counseling + NRT arms will be offered nicotine patches or nicotine lozenges in a four-week allotment. 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 telephone counseling + NRT arms. The prescriptions will be sent by mail by study staff to the patient.

Subjects randomized to the NRT or NRT + coaching arms will be offered nicotine replacement therapy dosed per package instructions. Smokers will be offered nicotine patches (14 or 21 mg patches) or 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.

All study subjects will be asked about adverse reactions to the nicotine patch or lozenge at all surveys after they are sent medication, at week 8 and week 12 if they are in the early assessment group or at week 12 if they are in the late assessment group.

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, Fagerström 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:

4-week telephone outcome assessment

- 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?

8-week telephone outcome assessment

- Have you received text messages since last assessment.
- 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 No→Have you smoked cigarettes, even a puff in the past 7 days?
- If early assessment and non-responder
    - 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?
    - Have you experienced any side effects in the past 30 days from quit smoking medications?
    - Have you received a call from a tobacco coach

12-week telephone outcome assessment

- Have you received text messages since last assessment.
- 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 No→Have you smoked cigarettes, even a puff in the past 7 days?
- If non-responder
    - 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?
    - Have you experienced any side effects in the past 30 days from quit smoking medications?
    - Have you received a call from a tobacco coach

Statistical Analysis

Uptake will be calculated as proportion of potentially eligible patients reached and randomized. Characteristics of patients randomized will be compared with those who declined using t-tests and chi-square tests to identify predictors of intervention uptake. Retention will be measured as LTFU at 12 week assessment and will be compared across treatment groups to assess non-differential LTFU. Fidelity will be measured as number of text messages sent divided by the total number intended and proportion of patients reached by the coach, proportion of coaching sessions completed, and NRT uptake and adherence (days of NRT used). Qualitative interviews will be analyzed using Nvivo 11 using a grounded theory approach and the constant comparative method[74]. Two coders will independently code a subset of interviews then compare resulting themes. Discrepancies will be discussed and reconciled iteratively during data collection to produce a final coding structure. Intercoder agreement will be measured by kappa statistic.

Sample size

This sample size is based on having enough patients in all six treatment subgroups (see Figure 1) to assess the feasibility of a larger-scale SMART. With 30 patients randomized 1:1 in R1 and 20% response, we expect 3 patients in the smallest subgroup. However, using a method by Almirall et al., the probability of reaching this minimum subgroup size by randomization is only 59%, therefore we will randomize 35 patients to have a 70% probability of at least 3 patients per subgroup[73]. We anticipate screening up to 90 patients to reach our target randomization of 35 patients.

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