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Optimizing Text Messaging to Improve Adherence to Web-Based Cessation Treatment: A Randomized Control Trial Protocol

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Roles and Responsibilities

ALG, MAJ, AMC, SC, LA, and GDP participated in study concept, study design, and obtaining funding. ALG, MAJ, and SC participated in acquisition of data. ALG and GDP participated in statistical analysis. All authors participated in drafting of the manuscript.

The sponsor will have no involvement in any aspect of the conduct of this trial.

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ABSTRACT

Introduction: Millions of smokers use the Internet for cessation assistance each year; however, most smokers engage minimally with even the best designed websites. The ubiquity of mobile devices and their effectiveness in promoting adherence in other areas of health behavior change make them a promising tool to address adherence in web-based cessation interventions. Text messaging is used by most adults, and messages can proactively encourage continued exploration of a web-based intervention. Text messaging can also be integrated with an Internet intervention to facilitate the use of core Internet intervention components. **Methods and Analysis:** We have identified four aspects of a text message intervention that may enhance its effectiveness in promoting adherence to a web-based cessation program: personalization, integration, dynamic tailoring, and message intensity. Phase I will use a 2-level full factorial design to test the impact of these four experimental features on adherence to a web-based intervention. The primary outcome is a composite metric of adherence that incorporates website logins, time on site, page views, and use of interactive site components shown to predict abstinence. Participants will be N=860 adult smokers that register on an established Internet cessation program and enroll in its text message program. Phase II will be a 2-arm randomized trial to compare the efficacy of the web-based cessation program alone and in conjunction with the optimized text messaging intervention on 30-day point prevalence abstinence at 9 months. Phase II participants will be N=600 adult smokers that register to use an established Internet cessation program and enroll in text messaging. Secondary analyses will explore whether adherence mediates the effect of treatment condition on outcome. **Ethics and Dissemination:** This protocol was approved by Chesapeake IRB. We will disseminate study results through peer reviewed manuscripts and conference presentations related to the methods and design, trial outcomes, and exploratory analyses.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study will improve adherence to proven web-based cessation interventions, which is critical to leveraging the potential public health impact of this “broad reach” treatment modality.
- The proposed study is innovative in its use of an optimized text messaging intervention as an adherence strategy.
- Study findings will add to the growing knowledge base about the overall effectiveness of Internet cessation programs and mechanisms through which their population impact on smoking prevalence can be improved.
- The potential scientific and public health impact of this study is likely to extend beyond web-based cessation programs to other health-risk behaviors.

- A limitation of this study is that it examines a limited number of factors related to adherence. Although multiple factors influence use of web-based cessation programs, we cannot examine all factors relevant to adherence, but will measure theory-driven constructs to inform our interpretation of results.
- This study also does not specifically target individuals with certain psychiatric or medical comorbidities known to impact smoking cessation rates. If findings are supported, future studies will further refine text message protocols to focus on sub-groups at greater risk of smoking relapse.

INTRODUCTION

Background and Rationale

Tobacco use is the leading cause of preventable death in the United States, causing 480,000 premature deaths among adults and nearly $289 billion in total economic burden each year.[1] Reducing population smoking prevalence can save more lives and money than almost any other preventive intervention. Internet interventions are a promising delivery channel for cessation treatment that have potential for enormous public health impact.[2] The reach of web-based cessation programs is unparalleled. Millions of smokers search online for quit smoking information each year[3] and hundreds of thousands register on web-based cessation programs offered by quitlines in 51 U.S. states and territories and Canada,[4] by hundreds of employers and health plans throughout the U.S.,[5] or on publicly available, high-volume web-based cessation programs around the globe.[6-8] Quit rates in Internet programs range from 18-20% at 1 year[9-11] and greater intensity of use yields higher quit rates.[12-17]

However, most smokers engage minimally with even the best designed cessation websites, visiting only one to two times and not using many of the interactive tools or community support that promote abstinence.[15, 18-21] As a result, the full potential of Internet cessation programs to reduce smoking prevalence and save lives is yet to be realized. Poor adherence has been extensively documented across dozens of Internet studies,[18, 22-35] systematic reviews,[36-40] reviews of systematic reviews,[41] and meta-analyses [42] across a range of health behaviors, and is so pervasive it has been described as a "fundamental methodological challenge in the evaluation of eHealth applications" (p. 2).[30] This is not a phenomenon unique to one or two websites or to smoking cessation. Adherence is traditionally defined as "the extent to which a person's behaviour corresponds with agreed upon recommendations from a health care providers."[43] Since many Internet interventions have no specified prescriptions for use,[38] adherence may best be defined as "the extent to which individuals experience the content of the intervention"[24] or simply "use of the eHealth intervention over time".[44] Adherence is typically measured by utilization metrics such as number of visits to a website, page views, interactive features used, and time on site.[42, 44, 45]

Periodic prompts and automated reminders can boost intervention adherence.[46, 47] Several studies have examined the effectiveness of email prompts on website engagement[23, 25, 35, 48-50] finding that email contacts generally yield more logins[36] but only among a small proportion of study participants.[49, 50] Other elements that improve adherence to web-based cessation programs include multiple modes of delivery[51] and individually tailored communications.[22, 52] Together these studies support the use of 1) frequent automated reminders, 2) supplemental modes of communication, and 3) a tailored approach to increase adherence to a web-based cessation program. These converging lines of evidence inform the intervention design of this protocol.

Given the reach of mobile phones, text messaging is an ideal form of supplemental communication for prompts and reminders to promote adherence.[35, 53, 54] As of October 2014, 90% of U.S. adults own a mobile phone.[55] The vast majority of mobile phone owners (81%) use text messaging, including those most likely to smoke: 80% of African Americans, 78% with household income <$30,000/year, and 75% with a high school degree send and receive text messages.[56] Mobile phone owners over age 18 send and receive an average of 42 texts/day.[57] Text message interventions have been shown to increase medication adherence[58-60] and appointment attendance,[61-66] and to promote smoking cessation in both the short-term[67-69] and long-term.[70] However, few studies have included both web and text programs components[21, 71, 72] and those that have included both modalities offered them in parallel with little to no integration between the two platforms, potentially missing powerful synergies. To our knowledge, no studies have examined text messaging to promote adherence to web-based cessation treatment or potential mechanisms of effectiveness.[70]

The mechanisms through which text messages influence behavior are understudied, and no studies have systematically varied characteristics of text message programs.[73] Based on communication and behavior change theories, the empirical literature, and prior work, we identified four aspects of a text message intervention that may enhance its effectiveness in promoting adherence to a web-based cessation program: *personalization*, *integration*, *dynamic tailoring*, and *message intensity*.

Personalization: According to the Elaboration Likelihood Model,[74] people are more likely to actively process information if they perceive it to be personally relevant. Personally relevant messages may stimulate more thorough consideration of a proposed behavior change.[75] Personalization uses person-specific elements, such as gender, age, first name, nickname, etc., to enhance the perceived relevance of a message.[76] Prior studies show that personalization can increase smokers' attention to written information and the perceived quality of that information.[77, 78] Across a range of health behaviors, personalized text message and web-based interventions have been found to be more efficacious than generic interventions.[42, 79] Personalization is also important to and desired by text users.[80, 81]

Integration: A meta-analysis by Webb et al.[51] found that the effectiveness of Internet interventions for a variety of health behaviors was enhanced by text message (d=.81, k=4). However, in the 4 studies reviewed, the Internet interventions were used simply to gather data needed to tailor the text message program; the Internet and text programs operated in parallel with little to no integration. Similarly, a more recent study by Borland et al.[21] tested the combined effects of web and text for smoking cessation, but there was little integration between the two. To date, no studies have examined the effectiveness of a truly integrated web and text intervention in improving treatment adherence and cessation outcomes.[72, 82-84] Addressing these questions has great practical relevance given the number of existing web-based cessation programs that currently offer text messaging as an adjunct service.[4] The Webb et al.[51] meta-

analysis provides an empirical basis for the current study, in which a fully-integrated, multi-modal intervention using evidence-based components of a web-based intervention is facilitated via interactive text messages. The goal is to enable users to engage with the components of a web-based intervention anywhere a cell phone can be used. The ability to interact with and use the tools of a web-based program via interactive text messages may be more effective in promoting treatment adherence than delivering static text messages that simply refer to a web-based program.

Dynamic Tailoring: Whereas personalization targets more superficial and often unchanging elements of a message (i.e., name, gender, age), tailored communications target theory-driven constructs related to a specific desired outcome.[85] Decades of research on tailored interventions – including tailored text message interventions[79] – have yielded positive effects on health behavior change and participation in health promotion programs.[79, 86, 87] Consistent with the Elaboration Likelihood Model,[74, 88] tailored messages are thought to be more effective due to the greater degree of cognitive processing they elicit; tailored messages are more likely to be read, understood, recalled, rated highly, and perceived as credible.[88] However, tailored interventions most often rely on a *static* assessment of variables used for tailoring. Indeed, most automated text messaging programs are static in nature, tailored only to baseline variables. Few studies have dynamically tailored communications to deliver ipsative feedback (within-subject change).[88] With the advent of mobile devices and the ability to gather "real-time" data, there is exciting potential to tailor communications to incorporate *changes* in an individual's behavior to provide a "smart" intervention that adapts as the needs of the individual change.[89] Dynamic text message interventions that change over time in response to a user's interaction with the program and progress in quitting are a promising target for next generation, scalable systems for behavior change.[90] The current study will mimic a face-to-face treatment approach in which participants are given feedback about their treatment progress, reminded about intervention features/content they have not yet used, and encouraged to remain engaged with treatment.[38] Tailoring text messages based on a participant's previous pattern of engagement with treatment and recommending "next steps" may be more efficacious than requiring users to find their own way through a web-based intervention.

Message Intensity: Lastly, text message programs typically involve an automated program of messages based around a self-selected quit day.[67] For example, in the txt2stop study, Free et al.[91] delivered an intensive protocol of 35 messages/week for 5 weeks with an abrupt stop to 3 messages/week for the remaining 26 weeks. A meta-analysis by Head et al.[79] of text message interventions across a range of health behaviors found that intervention efficacy varied by message intensity, with the largest effect size observed for programs with decreasing intensity (d=.52, 95% CI .44, .61). Decreasing text message protocols tend to taper the intervention from one phase to the next to gradually decrease content delivery. To date, no study has explicitly examined the impact of various levels of message intensity or identified the optimal intensity for a smoking cessation text message intervention. Decreasing message intensity – especially in

conjunction with personalization, interactivity, and/or dynamic tailoring – may be more salient and impactful than unchanging intensity.

Findings from this study will yield important insights into improving adherence for web-based cessation programs offered by quitlines in 51 U.S. states and territories and Canada,[4] by hundreds of employers and health plans throughout the U.S.,[5] and other high-volume web-based cessation programs around the globe[6-8] whose combined reach is unparalleled by any other cessation modality. Many of these programs offer text messaging as an adjunct service alongside a web-based program, but none to date that integrate Web and text programs so that they seamlessly and dynamically work together. Results from this study will identify strategies for integrating these services to promote adherence and improve quit rates, and will identify specific features and functionality to include in a text program.

The potential scientific and public health impact of this study is likely to extend beyond web-based cessation programs. Millions of adults use the Internet for assistance with addictions and other health behaviors.[92] Across healthcare, adherence is a problem that plagues numerous therapies.[43] Results from this study may inform advances in intervention design to better engage users and sustain their involvement across a range of evidence-based programs. Given the demonstrated use of web-based interventions among hundreds of thousands of minimally-engaged smokers who want to quit, it is critical to advance scientific understanding about how to better engage users so they receive the optimal dose of treatment necessary for abstinence. The need to improve adherence is clear: even the best treatments will have little impact if they are not used.

Objectives

The overarching goal of this study is to more effectively engage the hundreds of thousands of minimally engaged smokers already using the Internet to quit smoking. As shown in Figure 1, this two-phase study will: 1) Identify the factors in a text message intervention that yield optimal adherence to a web-based smoking cessation intervention (Phase I), and 2) Examine the comparative effectiveness of a web-based cessation intervention alone (WEB) and in conjunction with the optimal-adherence text messaging intervention (WEB+TXT; Phase II).

Specifically, in Phase I, the study will examine the impact of four experimental features of a text message intervention on a composite metric of adherence to a web-based cessation intervention. We hypothesize that personalization, integration, dynamic tailoring, and decreasing message intensity will have positive effects on adherence. Phase II will address two aims. Aim 1 will examine the comparative effectiveness of a web-based cessation intervention alone (WEB) or in conjunction with an optimized text messaging intervention (WEB+TXT) with regard to 30-day point prevalence abstinence at 9 months post-randomization (primary outcome) and adherence metrics (secondary outcomes). We hypothesize that WEB+TXT will yield higher rates of abstinence and adherence than WEB. Aim 2 will examine whether the impact of treatment

assignment on cessation is mediated by adherence. We hypothesize treatment group differences in 30-day point prevalence abstinence at 9 months will be mediated by greater levels of adherence at 3 months to a web-based cessation program.

< Figure 1 >

Trial Design: This two phase study will be conducted with registered users on BecomeAnEX.org, an established and widely used smoking cessation website run by Truth Initiative. Phase I involves the initial development and optimization of the text message intervention. We will examine the impact of four experimental text message intervention features on smokers' adherence to a web-based cessation intervention during the first three months of program enrollment. We will utilize a full factorial design where participants will be randomized to 1 of 2 levels of each of the following features: 1) personalization (yes/no), 2) integration (yes/no), 3) dynamic tailoring (yes/no), and 4) message intensity (standard vs. decreasing). The primary outcome in Phase I will be a composite metric of website adherence. Phase II involves a 2-arm randomized trial that compares WEB alone to WEB plus the text message intervention from Phase I that yields optimal adherence (WEB+TXT). The randomized trial will use a repeated measures design, with assessments at baseline, 3, 9, and 15 months post-randomization. Follow-ups at 3, 9, and 15 months correspond to 0, 6, and 12 months post-treatment. The primary outcome is 30-day point prevalence abstinence (ppa) at 9-months. Other outcomes include motivation to quit smoking, number of quit attempts, and continuous abstinence.

METHODS AND ANALYSIS

This clinical trial protocol was prepared in accordance with the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) checklist.[93, 94]

Phase I Methods

Participants. In Phase I, participants will be N=860 adult U.S. smokers that are new registered users on BecomeAnEX (i.e., no prior use of the site as determined by IP address and registration data) and that fully enroll in the BecomeAnEX text messaging program. During registration, participants must indicate current smoking (every day or some days), age 18 or older, and U.S. zip code as determined by IP address.

Enrollment. New BecomeAnEX members that meet eligibility criteria will be automatically randomized to 1 of 16 arms of the factorial. Study enrollment will be conducted in 10 months. Based on our prior work, we conservatively estimate that N=3/day (~90/month) new members of BecomeAnEX will enroll in text messaging. This estimate accounts for the slower enrollment of males and racial/ethnic minorities that we anticipate.

Sequence generation. Randomization will be stratified by whether participants access the

Internet on their cell phone (yes/no), since access to BecomeAnEX via mobile site may influence adherence. Randomization will be automated using a computer algorithm.

Interventions

Web-Based Cessation Program (WEB). BecomeAnEX is an evidence-based cessation program that was launched in 2008 by Truth Initiative (formerly the American Legacy Foundation).[19, 95] Based on the Clinical Practice Guideline for Treating Tobacco Dependence[96] and consistent with Social Cognitive Theory,[97] the site educates smokers and provides the tools necessary to enhance self-efficacy for quitting. BecomeAnEX guides and supports smokers through the following *interactive* components: (1) a *Quit Date* tool that assists users in selecting a quit date; (2) *Cigarette Tracker* exercise to identify smoking triggers; (3) *Beat Your Smoking Triggers* exercise to identify strategies to dissociate cigarettes from triggers; (4) *Build Your Support System* exercise to identify helpful supporters; (5) *Choose a Quit Smoking Aid* exercise, in which users indicate their plans for pharmacotherapy use; and (6) *Community*, a large online network of current and former smokers who communicate via personal messages sent directly between members, public "wall posts" (comments on a user's profile page), and blog posts/replies. Sign-up for text messaging occurs during registration, and involves providing a mobile number and affirming "Please send me text messages about quitting smoking." A mobile web version includes the full functionality of the site.

Text Messaging (TXT). Truth Initiative has developed a fully-automated text messaging program that is available via BecomeAnEX. Users can set a quit date and receive 8 weeks of daily scheduled messages tailored to their quit date (2 weeks prior and 6 weeks post-quit date); quit dates may be changed or cleared an infinite number of times. Messages tailored to quit date encourage use of evidence-based cessation methods (e.g., nicotine replacement therapy, peer support), praise success, inform users about addiction, and reinforce benefits of quitting. Users who do not set a quit date receive 2 weeks of daily scheduled messages tailored to their enrollment date. These messages prompt users to set a quit date, use evidence-based resources, reinforce benefits of quitting and harms of continuing to smoke. Three keywords ('COPE,' 'SLIP,' and 'MOOD') allow users to request on-demand support related to cravings, relapse, and negative affect. The existing text message intervention will be modified slightly to serve as the base case (Arm 1) in Phase I. The intervention will not be personalized, integrated with BecomeAnEX, or dynamically tailored, and will use a standard message intensity delivery schedule (see Study Arm 1 in Figure 1). For Study Arms 2-16, we will modify at least half the messages to ensure adequate differentiation between factor levels, while preserving a coherent user experience. We will user-test messages prior to the launch of Phase I to obtain feedback about their persuasiveness, relevance, likelihood of stimulating a response, and appeal. We will also obtain user feedback about message intensity (e.g., desired message frequency, duration of text intervention) and integration between Web and text via interactive messages.

Factor 1: Personalization. Personalization has been implemented in varying ways in text message studies, ranging from participant name only[55] to name plus numerous pieces of personal information.[56] We will personalize text messages using the participant's first name or BecomeAnEX username, and gender.

Factor 2: Integration. Interactive messages will facilitate engagement via text with the 6 interactive intervention components of the BecomeAnEX website listed above. ***Set Quit Date*** is already a feature of the text message program; the system tailors messages around a quit date. Unlike most other text message programs that require a quit date – and consistent with our aim to improve adherence to a web-based intervention among all users – we will deliver 3 months of text messages regardless of whether a user sets a quit date. When a user sets a quit date via the website, it will trigger text messages tailored to that quit date; likewise, if a user sets a quit date via the text system, this date will be automatically populated on the website and will reinforce the user experience online. To enable participants to interact with the *Cigarette Tracker*, *Beat Your Smoking Triggers*, *Build Your Support System*, and *Choose a Quit Smoking Aid* exercises via text message, an initial text message will query the user for a response. Subsequent messages will elicit additional user input (e.g., other triggers), highlight relevant content on BecomeAnEX (e.g., how to cope with boredom), and reinforce use of the site. To facilitate interaction in the *Community* via text message, we will develop a new Community feature called "QuickTips" that will enable BecomeAnEX members to submit text message-sized tips to help support other members. We will enable BecomeAnEX members to submit QuickTips via website, mobile site, or text message. Submissions will undergo review/approval by the BecomeAnEX Administrator before being distributed via text message. The Administrator will augment the QuickTips library as needed, excerpting community content to craft "user-generated" tips. Text users can also request QuickTips for on-demand "peer support".

Factor 3: Dynamic Tailoring. The general principle guiding implementation of this feature is that messages will be individually tailored to remind/reinforce users about BecomeAnEX information/tools they have already used, or to prompt users to take actions they have not yet taken. Although BecomeAnEX and the text message system are separate systems, they will communicate via an application programming interface (API) which will allow BecomeAnEX to alert the text message system of site utilization. Real-time site utilization data will trigger text messages that encourage the participant to use components of the website they have not yet used or to reinforce ongoing use.

Factor 4: Message Intensity. The text message intervention will be 12 weeks in duration. For the standard intensity protocol, participants will receive 7 messages per week (1/day) for 5 weeks and 1 message/week for the remaining 7 weeks (*"adherence messages"*) irrespective of quit date status. If a participant sets a quit date, they will receive additional messages to match the Free protocol [91] (i.e., 35 messages/week for 5 weeks, 3 messages/week for 7 weeks). The decreasing intensity protocol mimics this standard intensity protocol, but with additional tapering

steps designed to mirror the declines in cravings and withdrawal typically experienced by a smoker after quitting.[98] *"Adherence messages"* will be 7 messages/week for 4 weeks, 5 messages/week for 4 weeks, 3 messages/week for 2 weeks, and 1 message/week for 2 weeks. If a participant sets a quit date, s/he will receive additional messages to reach 35/week for 4 weeks, 19/week for 4 weeks, 10/week for 2 weeks, and 3/week for 2 weeks. We will examine the relationship between "dose" of text messages received and our composite adherence metric.

Measures

Phase I will rely on data from 4 sources: (1) BecomeAnEX registration data, (2) automated tracking data gathered through Adobe Analytics[99] software, (3) automated tracking data stored in unified event logs, and (4) text message utilization data. Use of the following components of BecomeAnEX will be extracted from unified event logs: *Set Quit Date, Cigarette Tracker, Beat Your Smoking Triggers, Choose your Quit Smoking Aid, Build Your Support System, and Community* (e.g., # wall posts made/received, blog posts/replies, messages sent/received, QuickTips submitted). From our text message system, we will extract replies to interactive text messages including engagement with the 6 interactive features of BecomeAnEX, unsubscribe rates, modal day of unsubscribe, number of days enrolled, messages received, and keyword requests. All text interactions are date/time stamped.

Primary outcome. The primary outcome of Phase I will be a composite metric of adherence for each Phase I participant created using a weighted sum of their total number of website visits, as well as of their page views, time on site, and use of the 6 interactive components of the site per visit during 3 months post-enrollment. The weights for these utilization metrics will be given by the regression coefficients of a logistic regression model that we have already developed to measure the effects of website engagement on 3-month abstinence rates in the control arm of a prior ongoing web-based cessation study.[100] The resulting composite adherence metric has the advantage that it is continuously distributed, even if some of the original utilization metrics are binary or count data. Therefore, it can be analyzed as the primary outcome for Phase I using standard linear regression techniques, possibly after a normalizing transformation. Treatment duration of 3 months will provide sufficient time to examine the impact of the text message intervention on adherence, since most non-usage attrition happens within the first 3 months.[19]

Phase I Data Analysis Plan and Sample Size Calculations

Analysis Plan. Our weighted adherence metric will be the primary outcome. We expect it to be continuously distributed, although it may require a symmetrizing transformation to reduce skewness. Given our prior experience with these data, we expect to find a few outliers that represent heavy website users. Rather than discard such valid data points, we will reduce their impact by winsorization (similar to trimming).[101] Once we are satisfied about the adequacy of the normal approximation, we will analyze the data from our factorial designs using the approach detailed in Chakraborty et al.[102]

Sample Size Calculations. To be conservative, we used a sample size for Phase I that allows us to detect small main effects of any of the 4 factors of interest (d=.25) or moderate 2-way interactions (d=.50) with power 80% at a 2-sided significance level of alpha=.05/10 (multiplicity adjustment based on 4 main effects and 6 two-way interactions in the model). Effect sizes for interactions were chosen to be such that they could nullify the presumed beneficial main effects of the factors involved. The sample size required is N=430 per factor level, or N=860 overall. These calculations were not adjusted for attrition since we will have adherence data on all participants.

Phase II Methods

Subjects. We will recruit a separate sample of N=600 adult smokers who register on BecomeAnEX and sign up for text messaging during registration. To be invited, participants must be adult current smokers (every day/some days) that register on BecomeAnEX and enroll in the text message program. Invited participants will complete a separate screening process to confirm eligibility. To maximize generalizability, we have no inclusion criteria related to motivation for cessation.

Recruitment and Enrollment. Phase II participants will not be enrolled automatically as in Phase I, but must respond to a study invitation and complete online eligibility screening, informed consent, and a baseline assessment, and fully enroll in the text messaging program. Study enrollment occurs online via our web-based clinical trials management system. Randomization will only occur after a potential study participant has completed the online enrollment process (completed baseline survey) and replied 'OK' to the welcome text message to confirm text message enrollment. Randomization will be stratified by gender, age (≤30, 30+), and whether participants access the Internet on their cell phone (yes/no) since age and access to BecomeAnEX via mobile site may influence adherence. A computer algorithm will automate random allocation. Recruitment will be conducted over 14 months.

Interventions. ***WEB:*** Participants will have full access to BecomeAnEX. They will not receive any intervention via text message. Informed consent will explain the possibility of being randomized to a non-text treatment arm. ***WEB+TXT.*** Participants will have full access to BecomeAnEX and the optimal-adherence text intervention developed in Phase I.

Retention. We expect at least 70% follow-up at 9 months. To maximize follow-up we will: (1) provide clear information about the study at the outset, including expectations for follow-up; (2) reimburse participants $50 per follow-up; and (3) emphasize the importance of survey completion regardless of smoking status. If follow-up rates are lower than expected early in the trial, we will consider shortening the 9-month follow-up to gather only abstinence outcomes.

Measures

Assessments will occur at baseline, 3, 9, and 15 months post-randomization. The baseline survey will be conducted online and hosted on a secure server. Mixed-mode follow-up (email, phone, text) will be employed. Telephone surveys will be conducted by research staff blind to treatment. Text messages have demonstrated moderately high reliability (k=.66) compared with web-based surveys in assessing smoking outcomes[103] and will be used as a final means of gathering abstinence data from non-responders. Most measures listed below are standard instruments used in cessation studies, and are reliable when administered via the Internet.[104, 105]

Baseline Variables. To characterize the sample and examine moderators, we will gather information on: *demographics* (age, sex, marital status, race, ethnicity, employment, and education); *current smoking behavior and smoking history* (smoking frequency and rate; quitting history, including quit methods; current and past use of other tobacco products); *nicotine dependence* assessed by the Heaviness of Smoking Index[106]; *motivation to quit smoking* measured with the Readiness Ladder[107]; *mobile phone type/use* (average number of text messages sent/received each day, cell phone use to access the Internet, send or receive email,[56] data plan on phone,[108] and where, how, and how often they access the Internet); and *smoking cessation self-efficacy* measured with the short form of the Smoking Situations Confidence Questionnaire.[109]

Outcome Measures. The *primary outcome* is self-reported 30-day ppa at 9 months post-randomization but we will gather abstinence data at all follow-ups. *Other smoking-related outcomes* will include change in motivation to quit, quit attempts, 7-day ppa, and continuous abstinence measured at each follow-up. *Intervention satisfaction* in both conditions will be measured with items about overall satisfaction, perceived helpfulness, whether the intervention met their expectations (1=not at all, 5=very much), and whether they would recommend the intervention to a friend (1=definitely not, 5=definitely would). Satisfaction with frequency/duration of text messages and perceptions about Internet and text message integration will also be measured.[71] To assess *perceived message relevance*, participants will be asked whether text messages "were written personally for you"[22] and "were directed at you personally" (1=not at all, 7=very much).[76]

Mediating Variables. We will examine the same website utilization metrics as in Phase I from Adobe Analytics[99] and unified event logs. Adobe Analytics will provide metrics for contact time (total time spent logged into the website), number of website sessions (number of return visits to the website), use of the static content on the site (number of page views), and number of videos watched. Unified event logs will provide data on use of the 6 interactive components of BecomeAnEX and the platform on which they were used (i.e., website or mobile site). We will extract replies to interactive text messages including engagement with the 6 interactive features of BecomeAnEX and number of keyword requests from the text message system. Unsubscribe

rates, modal day of unsubscribe, number of days enrolled, and messages received will be extracted. All text message interactions are date and time stamped.

Phase II Data Analysis Plan and Sample Size calculations

The distributional properties of continuously scaled variables will be examined to determine the need for normalizing transformations. Next, we will determine whether the groups show large standardized mean differences at pre-treatment on demographic characteristics, psychosocial variables, or smoking variables. Although the large sample size should preclude finite sample randomization imbalances, should such between-group differences be found, we will correct for them via regression adjustment.

Outcome analyses: Our primary outcome for Aim 1 is self-reported 30-day ppa. Differences in abstinence rates between the two treatment conditions will be evaluated at our primary endpoint of 9 months post-randomization, as well as the secondary endpoint of 3 months post-randomization. To account for within-subject correlation due to the repeated-measures aspect of our study, we will employ the Generalized Estimating Equation (GEE), which extends generalized linear model methodology to correlated data in PROC GENMOD of SAS/STAT (SAS Inc., Cary, North Carolina, USA). Analyses will be conducted first using an Intention- to-treat (ITT) principle, analyzing data from all subjects randomized to treatment and counting as smokers those lost to follow-up (missing = smoking).

Moderator analyses: We will examine potential moderators of the intervention-smoking cessation relationship (for example, gender, baseline stage of motivational readiness, nicotine dependence). Effect modification will be conducted by analyzing interactions between treatment and selected variables.

Mediator analyses: Primary Aim 2 hypothesizes that adherence mediates the intervention-cessation relationship. We will establish mediation using the MacKinnon approach.[110] As explained in Cerin and MacKinnon[111] and implemented by Papandonatos et al.,[112] behavioral researchers ought to determine whether: (a) the intervention successfully acted upon the putative mediator (that is, 'Action Theory test'); (b) changes in the mediator were indeed predictive of changes in the target behavior suggested by the conceptual framework underpinning the intervention over and above any direct treatment effects (that is, 'Conceptual Theory test'); and (c) these conditions held simultaneously for each mediator of interest, indicating that the corresponding mediational pathway accounted for at least part of the relationship between the intervention and the target behavior (that is, 'Mediation test').

Missing data: We expect less than 25% missing data at any time. If a participant refuses follow-up, we will censor the data at the point of loss of contact. Under an ITT approach, participants who had been considered non-smokers up to the point of loss will be considered smokers at future data points. One concern is that this approach is sensitive to differential

attrition across study arms and tends to overestimate precision of estimates of treatment effects.[113] Therefore, we will supplement ITT analyses with a multiple imputation procedure that assumes the odds of missingness vary for smokers and non-smokers lost to follow-up. This model falls under the missing-not-at-random (MNAR) characterization of missingness mechanisms by Little and Rubin[114] and requires knowledge of the odds ratio (OR) relating missingness to smoking. Since this OR is in practice unknown, we will conduct a sensitivity analysis to assess its impact on the estimate and significance of the intervention effect.[115, 116]

Sample Size. We conservatively estimate that the ITT 30-day ppa rate at 9 months will be 9% for WEB alone vs. 16.5% for WEB+OA_TXT, corresponding to an intervention OR=2.0 which can be detected with 80% at 2-sided alpha=.05 using N=300 per study arm (N=600 total).

Study Monitoring

At the start of the study, a Data Safety Monitoring Committee will be established, comprised of the Principal Investigator, Data Analyst, Biostatistician, Technical Lead, and Project Manager. This committee will discuss protocol development and will review scientific, safety and ethical issues related to the study design and approve plans for data integrity. The committee will meet every two weeks to review the following information in detail: 1) Participant accrual rate, 2) Participant drop-out and the reasons for drop-out, 3) Targeted enrollment status, and 4) Major and minor problems related to treatment arm assigned.

ETHICS AND DISSEMINATION

Research Ethics Approval

Institutional Review Board approval for the study was provided by Chesapeake Institutional Review Board.

Consent

New registrants on BecomeAnEX.org will be automatically enrolled in Phase I following BecomeAnEX registration if they meet the eligibility criteria and complete BecomeAnEX text message enrollment by replying ‘OK” to the welcome message. To register on BecomeAnEX, individuals must agree to the site’s Terms of Use and Privacy Policy. The Privacy Policy makes explicit that 1) Truth Initiative automatically collects information about its users and their use of the site, 2) information is used for research and quality improvement purposes only and, 3) personal information is kept confidential. Eligible individuals will be automatically randomized to 1 of 16 arms of the factorial design. Their use of the BecomeAnEX website and text messages will be tracked for 3 months. No additional screening information will be requested or obtained and no separate informed consent will be solicited as the registration process makes it clear that

Truth Initiative may monitor all regististered users' use of the website and that they are explicity agreeing to receive text messages.

In Phase II, new registered users on BecomeAnEX are presented the informed consent page and provided detailed information about the study. Randomization will only occur after an eligible study participant has completed the online enrollment process (confirmed eligibility, indicated informed consent, confirmed contact information, and completed baseline survey) and replied 'OK' to the welcome text message to confirm text message enrollment (for participants randomized to WEB+TXT).

Confidentiality

Confidentiality will be protected at all times and potential risks minimized systematically. During BecomeAnEX registration, participants create a username and password that they use to log in to the website. Each use of BecomeAnEX involves a session ID unique to the user and the date and time of access. BecomeAnEX uses industry standard security protocols. Users are automatically logged out of BecomeAnEX after 30 minutes of inactivity. The BecomeAnEX Privacy Policy will be in effect for all participants enrolled in the project. Transactional data from the site are loaded on a daily basis into a local data warehouse which is subject to both physical and electronic protection. Confidentiality of data will be maintained by numerically coding all data, by keeping identifying information separate from research data, and by keeping all data electronically protected. Identifying information will not be reported.

Declaration of Interests

ALG, MAJ, AMC, SC are employees of Truth Initiative (formerly American Legacy Foundation), a non-profit public health foundation that runs the BecomeAnEX smoking cessation website.

Access to Data

For Phase I and II, the Principal Investigator, Data Analyst, Project Manager, software development team, and telephone survey staff will have access to individually identifiable information about human subjects. Electronic data files with identifiable information will be maintained separately from other data files and will only be used for administrative purposes (e.g., tracking follow-up completion, managing subject payment). All personnel will receive certification in human subjects protection from the NIH Office of Human Subjects Research prior to beginning work on this project.

Dissemination Policy

We will disseminate results of this study through peer reviewed manuscripts and conference presentations related to the methods and design, outcomes from the randomized trial, and the

exploratory analyses planned for the project. Once appropriate, a completely de-identified data set will be created that obfuscates any variable that might potentially be used to identify an individual study participant. To facilitate sharing, a member of our investigative team will be required to participate as an investigator on any sub-project requiring data sharing. We will review our data sharing plan throughout the trial to ensure that appropriate strategies are developed to cover all interested audiences.

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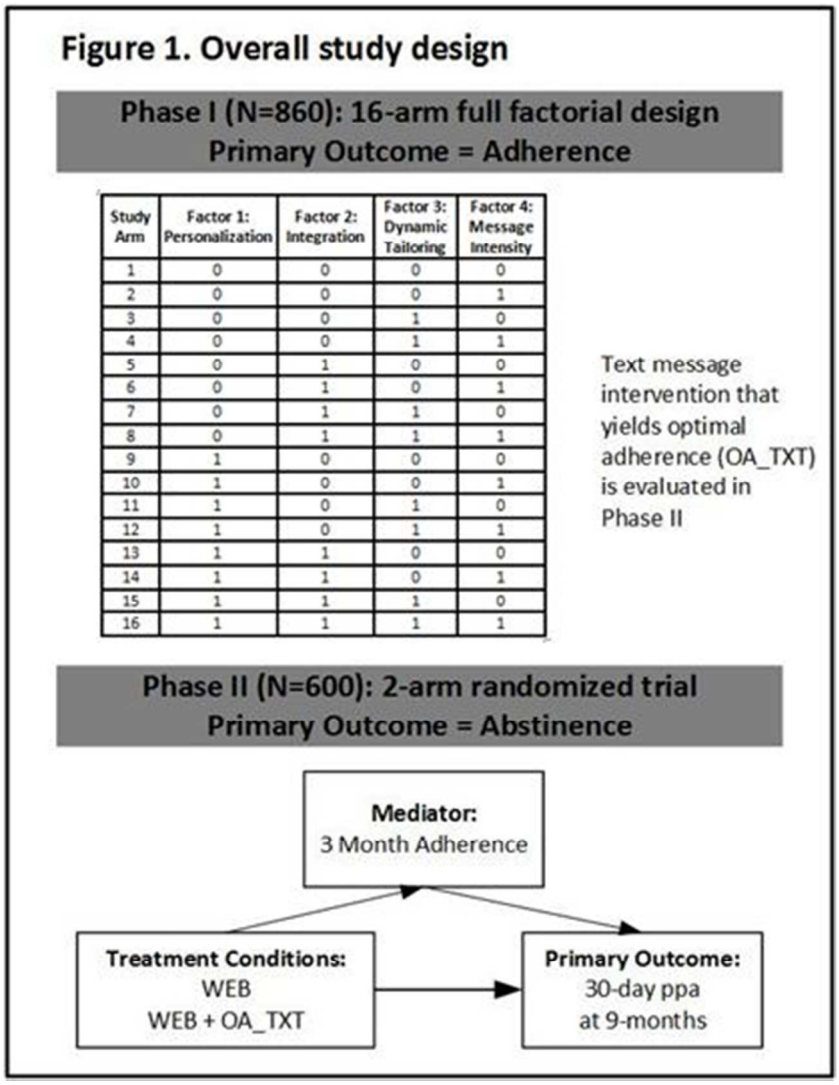

Figure 1. Overall Study Design
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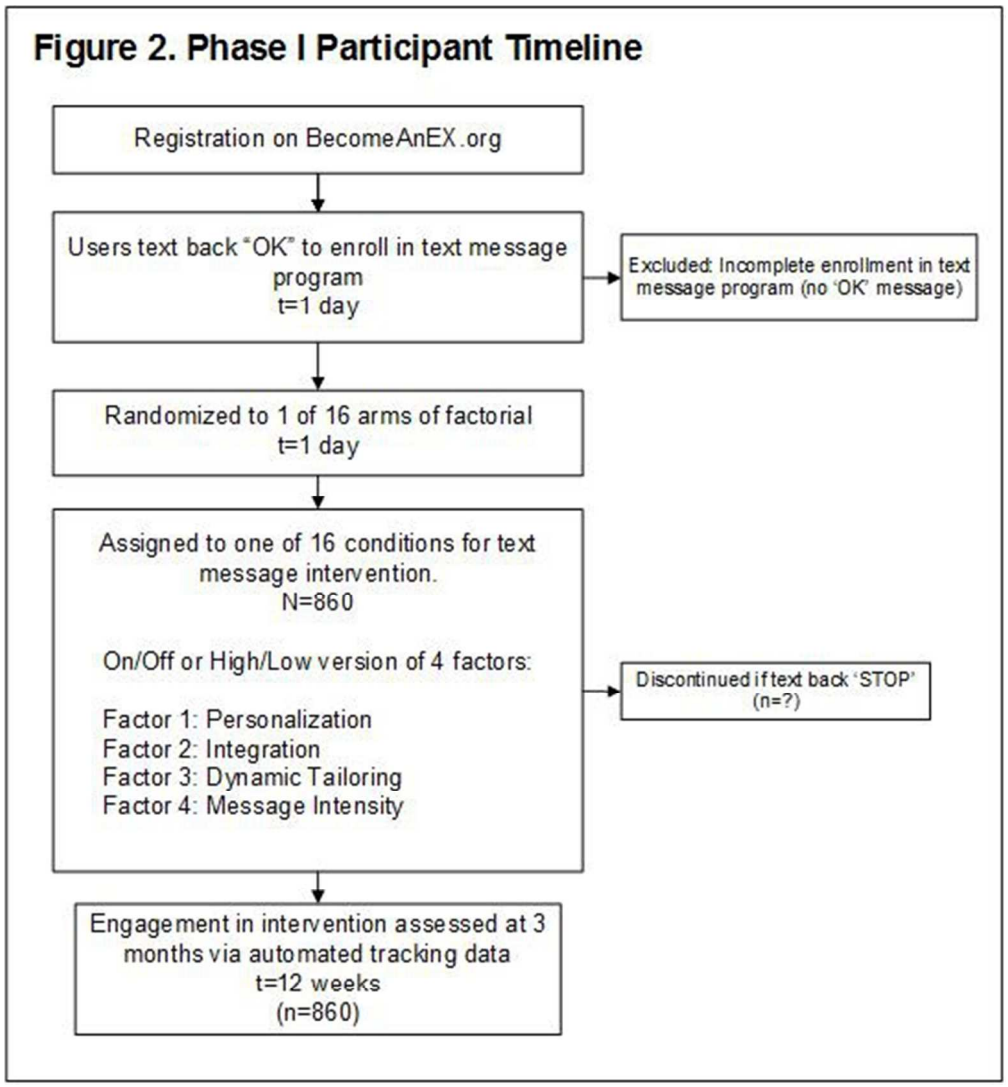

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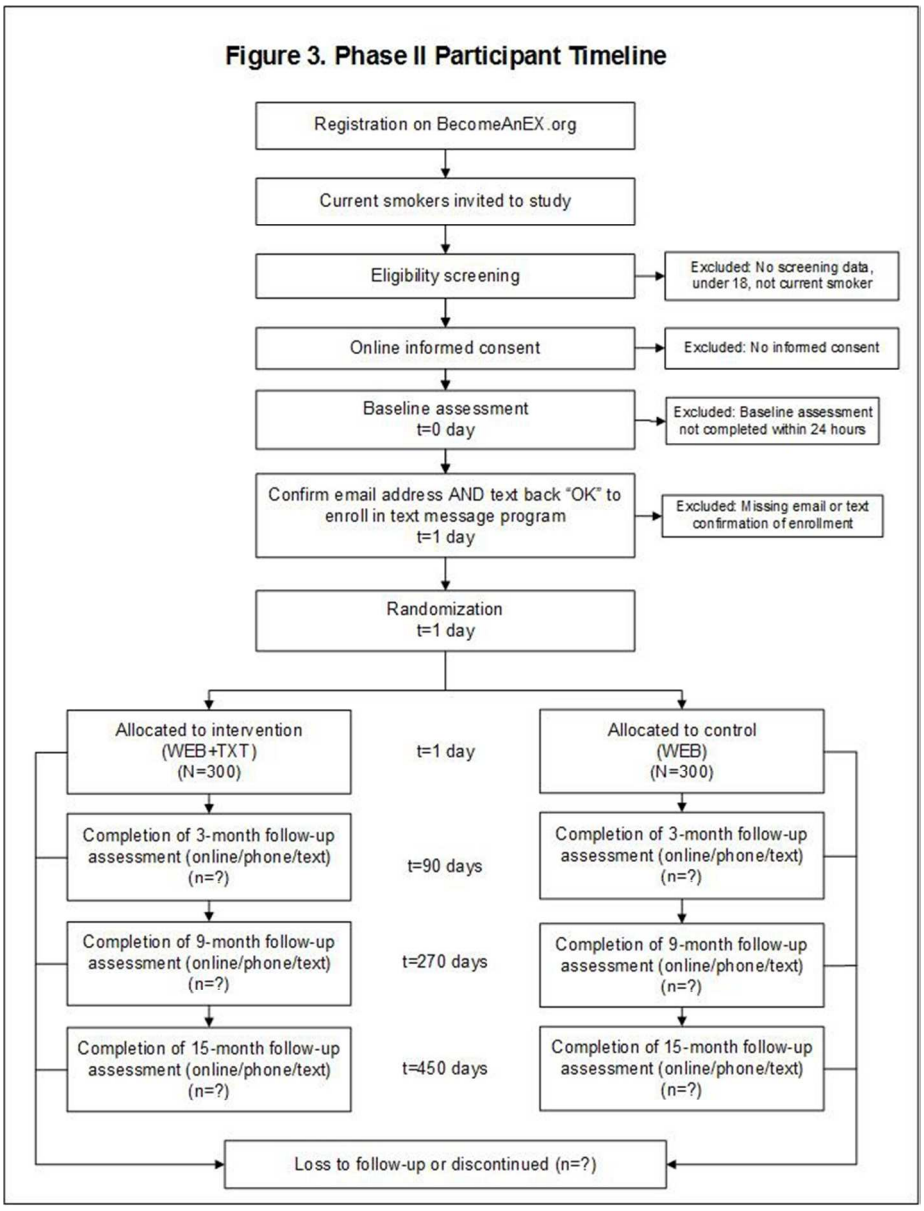

184x241mm (96 x 96 DPI)

APPENDIX A. RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	Optimizing Text Messaging to Improve Adherence to Web-Based Cessation Treatment
PROTOCOL NO.:	R01 DA038139-01A1
SPONSOR:	National Institute on Drug Abuse
INVESTIGATOR:	Amanda L. Graham, PhD Schroeder Institute for Tobacco Research & Policy Studies 900 G St NW Fourth Floor Washington DC 20001
SITE(S):	Truth Initiative Schroeder Institute for Tobacco Research & Policy Studies 900 G St NW Fourth Floor Washington DC 20001
STUDY-RELATED PHONE NUMBER(S):	202-709-8587

INFORMED CONSENT

ABOUT THE STUDY

You are invited to participate in a research study. The study is called *Optimizing Text Messaging to Improve Adherence to Web-Based Cessation Treatment.* The research is sponsored by the National Institute on Drug Abuse of the National Institutes of Health (NIH) and is being conducted at the Truth Initiative, which is located at 900 G St NW Fourth Floor, Washington DC 20001. Dr. Amanda Graham is the Primary Investigator.

WHAT IS INFORMED CONSENT?

The purpose of this consent form is to help you decide if you want to be in the study. Please scroll through and read this entire consent form carefully. To join a research study you must give your informed consent. "Informed consent" includes: (1) reading this consent form and (2) asking questions about anything that is not clear. You should not join this research study until all of your questions are answered.

If you have any questions, please contact the study investigator, Dr. Amanda Graham, at EX_Study@truthinitiative.org or 202-709-8587.

Things to know before deciding to take part in a research study:

- Taking part in the study is entirely your choice - if you choose not to join the study, you can continue to use the BecomeAnEx website however you wish;
- Personal benefit to you may or may not result from taking part in the study, but knowledge may be gained from your participation that will benefit others;
- You may withdraw from the study at any time.

If you decide to take part in this research study, you will be able to print or save a copy of this consent form.

WHY IS THE STUDY BEING DONE?

The purpose of this study is to investigate the effectiveness of a smoking cessation website called BecomeAnEx.org when it is used alone, and when it is used along with social network support and/or nicotine replacement therapy (nicotine patch, gum, or lozenge). The study also hopes to identify ways to improve the effectiveness of the BecomeAnEx.org website in helping smokers to quit smoking.

About 600 subjects are expected to enroll in this study.

WHAT IS INVOLVED IN THE STUDY?

Joining the Study: If you agree to take part in this study, here's what will happen. First, you will sign this Informed Consent page by entering your initials at the bottom of the page and clicking "I Want to Participate." This page must be signed before any study-related procedures are performed. Second, you will be asked to provide some basic contact information, including your name, email, and mobile telephone number. Third, you will asked to complete an online survey that includes questions about your use of the Internet and your cell phone, your smoking habit, and your health in general. This survey should take about 5-8 minutes to complete. Fourth, we will send you a text message at the phone number you provided to confirm your enrollment in the study. To fully enroll in the study, you must text back "OK" this welcome text message.

Being in the Study: Once the survey is completed, you will be "randomized" into one of the study groups. Randomization means that you are put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researchers will choose what group you will be in. If you are randomized to Group 1, you will have full access to the BecomeAnEX.org website to use as you desire. If you are randomized to Group 2, you will also have full access to the BecomeAnEx.org website and you may receive text messages over the next month. You will have an equal chance of being assigned to either Group.

Follow-Up Surveys: You will be contacted by email at three different time points by study staff to complete follow-up Internet surveys. If we are not able to reach you by email to complete the surveys, a research assistant will attempt to reach you to complete them over the phone. These follow-up surveys will occur at 3, 9, and 15 months after you join the study. The surveys will ask about your smoking, your health in general, and your feedback about being in the study. Each follow-up survey will take about 12-15 minutes to complete.

The follow-up surveys are a critical part of the study – we need to hear from everyone, even if you are still smoking and/or have not used the website or the text message program.

Your participation will last about 15 months, if you complete the study.

RISKS AND DISCOMFORTS

Quitting Smoking: If you decide to quit smoking, you may experience mood changes, anxiety, irritability, decreased concentration, restlessness, increased hunger or trouble sleeping. These symptoms usually last for about 1 to 2 weeks after quitting.

NEW INFORMATION

You will be told about any new information that might change your decision to be in this study. You may be asked to read and submit a new online consent form if this occurs.

POSSIBLE BENEFITS

By taking part in this study, you may quit smoking or cut down the number of cigarettes that you smoke which will improve your health, but this cannot be guaranteed.

COSTS

There is no cost to you to join the study or to participate in the study.

PAYMENT FOR PARTICIPATION

You will not be paid for completing the baseline survey. You will be paid $50 via Amazon gift card emailed to you for completing each of the three follow-up surveys. If you do not complete all follow-up surveys, you will be paid for the surveys you complete.

ALTERNATIVE TREATMENTS

You do not have to participate in this study. You can continue to use BecomeAnEx.org however you wish. There are also other quit smoking programs available, such as telephone support available at 1-800-QUIT-NOW and community agencies such as the American Lung Association.

CONFIDENTIALITY

All information collected from you for the study will be kept confidential to the extent of the law. Confidentiality will be protected at all times and several steps will be taken to reduce any risks to confidentiality. Complete confidentiality cannot be guaranteed. All information collected via the Internet will be kept secure using the Secure Socket Layer (SSL) Protocol, the same technology used to encrypt credit card numbers during transmission over the Internet. You will be asked to designate a username and password to access the website. All data will be stored in a database subject to both physical and electronic protection. All participants will be assigned an identification number that will be used to link responses, but no identifying information will be kept with those responses.

Please note that study staff involved in processing your payment for participation will be aware of your identity.

The results of the research study will be shared with other people and will be published in scientific reports; however, your name and the fact that you were in the study will be kept confidential.

The funding agency, the National Cancer Institute, may see your information if it is audited. The federal auditors can use this audit information only for audit or evaluation of the program.

COMPENSATION FOR INJURY

We do not expect any injuries to result from this research study. If an unexpected injury occurs as a result of your participation in this study, you will receive treatment that Truth Initiative considers to be fair and appropriate for that injury, without charge to you. Truth Initiative does not intend to provide you with any other money or payment if this happens. Agreeing to participate in this study does not change any of your legal rights. For more information regarding this provision, please contact Ryan Desrosiers in the Office of Grants Management at Truth Initiative at 202-454-5555.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

The decision whether to be in this study is entirely up to you. Participation is voluntary. Also, if you decide now to participate, you can to change your mind later and withdraw from the study.

There will be no penalty if you decide not to participate, or if you withdraw from the study. The research team may choose to end your participation in this study at any time prior to the completion of the study for any reason.

The researcher will provide you with additional information as it becomes available that may affect your decision to continue in the research study.

SOURCE OF FUNDING FOR THE STUDY

This study is funded by the National Institute on Drug Abuse of the National Institutes of Health (NIH).

QUESTIONS

Please contact the study investigator, Dr. Amanda Graham, for any of the following reasons:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury, or
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns, input or complaints about the research, you may contact:

Chesapeake IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, MD 21046-3403
Telephone: 410-884-2900
http://www.chesapeakeirb.com/

Chesapeake IRB is a group of people who independently review research.

Chesapeake IRB will not be able to answer some study-specific questions. However, you may contact Chesapeake IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not agree to participate in this study unless you have had a chance to ask questions and have gotten satisfactory answers.

CONSENT

I have read this consent form. All my questions about the study and my part in it have been answered. By entering my initials in the box below, I freely consent to be in this research study.

By agreeing to participate in this study, I have not given up any of my legal rights.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **Page number:** 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **Page number:** 2
	2b	All items from the World Health Organization Trial Registration Data Set **Page number:** N/A
Protocol version	3	Date and version identifier **Page number:** 2
Funding	4	Sources and types of financial, material, and other support **Page number:** 2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Page number:** 2
	5b	Name and contact information for the trial sponsor **Page number:** 2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **Page number:** 2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **Page number:** 2
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Page number:** 5-10
	6b	Explanation for choice of comparators **Page number:** 5-10

Objectives	7	Specific objectives or hypotheses **Page number:** 8-9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Page number:** 9
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Page number:** 9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Page number:** Phase I: 11; Phase II: 15
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Page number:** Phase I:11-13; Phase II: 15
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **Page number:** Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Page number:** Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **Page number:** Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Page number:** Phase I: 13-14; Phase II: 15-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **Page number:** Phase I: 18; Phase II: 18-19
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Page number:** Phase I: 14; Phase II: 16-18

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **Page number:** 9, 13

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Page number:** Phase I: 11; Phase II: 15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Page number:** Phase I: 11; Phase II: 15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Page number:** Phase I: 11; Phase II: 15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **Page number:** Phase I: 11; Phase II: 15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **Page number:** Not applicable

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Page number:** Phase I: 13-14; Phase II: 15-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **Page number:** Phase I: Not applicable, automatic data collection only; Phase II: 15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **Page number:** 18

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Page number:** Phase I: 14; Phase II: 17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **Page number:** Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **Page number:** Phase I: Not applicable, automatic data collection only; Phase II: 17
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **Page number:** 18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **Page number:** 18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **Page number:** 18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Page number:** 18
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Page number:** 19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **Page number:** 19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **Page number:** 19-20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **Page number:** Not applicable

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **Page number:** 20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **Page number:** 20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **Page number:** 20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **Page number:** Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **Page number:** 20-21
	31b	Authorship eligibility guidelines and any intended use of professional writers **Page number:** 20-21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **Page number:** 21
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **Page number:** Appendix A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **Page number:** Not applicable.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Optimizing Text Messaging to Improve Adherence to Web-Based Smoking Cessation Treatment: A Randomized Control Trial Protocol

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Optimizing Text Messaging to Improve Adherence to Web-Based Smoking Cessation Treatment: A Randomized Control Trial Protocol

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ABSTRACT

Introduction: Millions of smokers use the Internet for smoking cessation assistance each year; however, most smokers engage minimally with even the best designed websites. The ubiquity of mobile devices and their effectiveness in promoting adherence in other areas of health behavior change make them a promising tool to address adherence in Internet smoking cessation interventions. Text messaging is used by most adults, and messages can proactively encourage use of a web-based intervention. Text messaging can also be integrated with an Internet intervention to facilitate the use of core Internet intervention components. **Methods and Analysis:** We identified four aspects of a text message intervention that may enhance its effectiveness in promoting adherence to a web-based smoking cessation program: personalization, integration, dynamic tailoring, and message intensity. Phase I will use a 2-level full factorial design to test the impact of these four experimental features on adherence to a web-based intervention. The primary outcome is a composite metric of adherence that incorporates general utilization metrics (e.g., logins, page views) and specific feature utilization shown to predict abstinence. Participants will be N=860 adult smokers that register on an established Internet cessation program and enroll in its text message program. Phase II will be a 2-arm randomized trial to compare the efficacy of the web-based cessation program alone and in conjunction with the optimized text messaging intervention on 30-day point prevalence abstinence at 9 months. Phase II participants will be N=600 adult smokers that register to use an established Internet cessation program and enroll in text messaging. Secondary analyses will explore whether adherence mediates the effect of treatment condition on outcome. **Ethics and Dissemination:** This protocol was approved by Chesapeake IRB. We will disseminate study results through peer reviewed manuscripts and conference presentations related to the methods and design, outcomes, and exploratory analyses.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study will improve adherence to proven web-based cessation interventions, which is critical to leveraging the potential public health impact of this "broad reach" treatment modality.
- The proposed study is innovative in its use of an optimized text messaging intervention as an adherence strategy.
- Study findings will add to the growing knowledge base about the overall effectiveness of Internet cessation programs and mechanisms through which their population impact on smoking prevalence can be improved.
- The potential scientific and public health impact of this study is likely to extend beyond web-based cessation programs to other health risk behaviors.
- A limitation of this study is that it examines a limited number of factors related to adherence. Although multiple factors influence use of web-based cessation programs, we cannot

examine all factors relevant to adherence, but will measure theory-driven constructs to inform our interpretation of results.

- This study also does not specifically target individuals with certain psychiatric or medical comorbidities known to impact smoking cessation rates. If findings are supported, future studies will further refine text message protocols to focus on sub-groups at greater risk of smoking relapse.
- Although text messaging is nearly ubiquitous in 2016 at the start of the trial, we are aware of early reports that the number of text messages sent has declined recently, potentially due to the adoption of instant multimedia messaging applications such as Snapchat and WhatsApp. With the increasing use of smartphone and growing use of instant messaging applications, the use of text messaging may continue to decline. However, the number of text messages sent each year remains in the billions, ensuring that this technology will remain relevant for the foreseeable future. In addition, the lessons learned from this trial about how best to use text messaging to facilitate intervention engagement will be relevant to smartphone apps.

INTRODUCTION

Background and Rationale

Tobacco use is the leading cause of preventable death in the United States, causing 480,000 premature deaths among adults and nearly $289 billion in total economic burden each year.[1] Reducing population smoking prevalence can save more lives and money than almost any other preventive intervention. Internet interventions are a promising delivery channel for cessation treatment that have potential for enormous public health impact.[2] The reach of web-based cessation programs is unparalleled. Millions of smokers search online for quit smoking information each year[3] and hundreds of thousands register on web-based cessation programs offered by quitlines in 51 U.S. states and territories and Canada,[4] by hundreds of employers and health plans throughout the U.S.,[5] or on publicly available, high-volume web-based cessation programs around the globe.[6-8] Quit rates in Internet programs range from 18-20% at 1 year[9-11] and greater intensity of use yields higher quit rates.[12-17]

However, most smokers engage minimally with even the best designed cessation websites, visiting only one to two times and not using many of the interactive tools or community support that promote abstinence.[15 18-21] As a result, the full potential of Internet cessation programs to reduce smoking prevalence and save lives is yet to be realized. Poor adherence has been extensively documented across dozens of Internet studies,[18 22-35] systematic reviews,[36-40] reviews of systematic reviews,[41] and meta-analyses [42] across a range of health behaviors, and is so pervasive it has been described as a "fundamental methodological challenge in the evaluation of eHealth applications" (p. 2).[30] This is not a phenomenon unique to one or two websites or to smoking cessation. Adherence is traditionally defined as "the extent to which a person's behaviour corresponds with agreed upon recommendations from a health care providers."[43] Since many Internet interventions have no specified prescriptions for use,[38] adherence may best be defined as "the extent to which individuals experience the content of the intervention"[24] or simply "use of the eHealth intervention over time".[44] Adherence is typically measured by utilization metrics such as number of visits to a website, page views, interactive features used, and time on site.[42 44 45]

Periodic prompts and automated reminders can boost intervention adherence.[46 47] Several studies have examined the effectiveness of email prompts on website engagement[23 25 35 48-50] finding that email contacts generally yield more logins[36] but only among a small proportion of study participants.[49 50] Other elements that improve adherence to web-based cessation programs include multiple modes of delivery[51] and individually tailored communications.[22 52] Together these studies support the use of 1) frequent automated reminders, 2) supplemental modes of communication, and 3) a tailored approach to increase adherence to a web-based cessation program. These converging lines of evidence inform the intervention design of this protocol.

Given the reach of mobile phones, text messaging is an ideal form of supplemental communication for prompts and reminders to promote adherence.[35 53 54] As of October 2014, 90% of U.S. adults own a mobile phone.[55] The vast majority of mobile phone owners (81%) use text messaging, including those most likely to smoke: 85% of African Americans, 78% with household income <$30,000/year, and 77% with a high school degree send and receive text messages.**[56]** Mobile phone owners over age 18 send and receive an average of 42 texts/day.[57] Text message interventions have been shown to increase medication adherence[58-60] and appointment attendance,[61-66] and to promote smoking cessation in both the short-term[67-69] and long-term.[70] However, few studies have included both web and text programs components[21 71 72] and those that have included both modalities offered them in parallel with little to no integration between the two platforms, potentially missing powerful synergies. To our knowledge, no studies have examined text messaging to promote adherence to web-based cessation treatment or potential mechanisms of effectiveness.[70]

The mechanisms through which text messages influence behavior are understudied, and no studies have systematically varied characteristics of text message programs.[73] Based on communication and behavior change theories, the empirical literature, and prior work, we identified four aspects of a text message intervention that may enhance its effectiveness in promoting adherence to a web-based cessation program: *personalization*, *integration*, *dynamic tailoring*, and *message intensity*.

Personalization: According to the Elaboration Likelihood Model,[74] people are more likely to actively process information if they perceive it to be personally relevant. Personally relevant messages may stimulate more thorough consideration of a proposed behavior change.[75] Personalization uses person-specific elements, such as gender, age, name, etc., to enhance the perceived relevance of a message.[76] Prior studies show that personalization can increase smokers' attention to written information and the perceived quality of that information.[77 78] Across a range of health behaviors, personalized text message and web-based interventions have been found to be more efficacious than generic interventions.[42 79] Personalization is also important to and desired by text users.[80 81]

Integration: A meta-analysis by Webb et al.[51] found that the effectiveness of Internet interventions for a variety of health behaviors was enhanced by text message (d=.81, k=4). However, in the 4 studies reviewed, the Internet interventions were used simply to gather data needed to tailor the text message program; the Internet and text programs operated in parallel with little to no integration. Similarly, a more recent study by Borland et al.[21] tested the combined effects of web and text for smoking cessation, but there was little integration between the two. To date, no studies have examined the effectiveness of a truly integrated web and text intervention in improving treatment adherence and cessation outcomes.[72 82-84] Addressing these questions has great practical relevance given the number of existing web-based cessation programs that currently offer text messaging as an adjunct service.[4] The Webb et al.[51] meta-

analysis provides an empirical basis for the current study, in which a fully-integrated, multi-modal intervention using evidence-based components of a web-based intervention is facilitated via interactive text messages. The goal is to enable users to engage with the components of a web-based intervention via interactive text message. The ability to interact with and use the tools of a web-based program via interactive text messages may be more effective in promoting treatment adherence than delivering static text messages that simply refer to a web-based program.

Dynamic Tailoring: Whereas personalization targets more superficial and often unchanging elements of a message (i.e., name, gender, age), tailored communications target theory-driven constructs related to a specific desired outcome.[85] Decades of research on tailored interventions – including tailored text message interventions[79] – have yielded positive effects on health behavior change and participation in health promotion programs.[79 86 87] Consistent with the Elaboration Likelihood Model,[74 88] tailored messages are thought to be more effective due to the greater degree of cognitive processing they elicit; tailored messages are more likely to be read, understood, recalled, rated highly, and perceived as credible.[88] However, tailored interventions most often rely on a *static* assessment of variables used for tailoring. Indeed, most automated text messaging programs are static in nature, tailored only to baseline variables. Few studies have dynamically tailored communications to deliver ipsative feedback (within-subject change).[88] With the advent of mobile devices and the ability to gather "real-time" data, there is exciting potential to tailor communications to incorporate *changes* in an individual's behavior to provide a "smart" intervention that adapts as the needs of the individual change.[89] Dynamic text message interventions that change over time in response to a user's interaction with the program and progress in quitting are a promising target for next generation, scalable systems for behavior change.[90] The current study will mimic a face-to-face treatment approach in which participants are given feedback about their treatment progress, reminded about intervention features/content they have not yet used, and encouraged to remain engaged with treatment.[38] Tailoring text messages based on a participant's previous pattern of engagement with treatment and recommending "next steps" may be more efficacious than requiring users to find their own way through a web-based intervention.

Message Intensity: Lastly, text message programs typically involve an automated program of messages based around a self-selected quit day.[67] For example, in the txt2stop study, Free et al.[91] delivered an intensive protocol of 35 messages/week for 5 weeks with an abrupt drop to 3 messages/week for the remaining 26 weeks. A meta-analysis by Head et al.[79] of text message interventions across a range of health behaviors found that intervention efficacy varied by message intensity, with the largest effect size observed for programs with decreasing intensity (d=.52, 95% CI .44, .61). Decreasing text message protocols tend to taper the intervention from one phase to the next to gradually decrease content delivery. To date, no study has explicitly examined the impact of various levels of message intensity or identified the optimal intensity for a smoking cessation text message intervention. Decreasing message intensity – especially in

conjunction with personalization, interactivity, and/or dynamic tailoring – may be more salient and impactful than unchanging intensity.

Findings from this study will yield important insights into improving adherence for web-based cessation programs around the globe. Many of these programs offer text messaging as an adjunct service alongside a web-based program, but none to date that integrate Web and text programs so that they seamlessly and dynamically work together. Results from this study will identify strategies for integrating these services to promote adherence and improve quit rates, and will identify specific features and functionality to include in a text program.

The potential scientific and public health impact of this study is likely to extend beyond web-based cessation programs. Millions of adults use the Internet for assistance with addictions and other health behaviors.[92] Across healthcare, adherence is a problem that plagues numerous therapies.[43] Results from this study may inform advances in intervention design to better engage users and sustain their involvement across a range of evidence-based programs. Given the demonstrated use of web-based interventions among hundreds of thousands of minimally-engaged smokers who want to quit, it is critical to advance scientific understanding about how to better engage users so they receive the optimal dose of treatment necessary for abstinence. The need to improve adherence is clear: even the best treatments will have little impact if they are not used.

Objectives

The overarching goal of this study is to more effectively engage the hundreds of thousands of minimally engaged smokers already using the Internet to quit smoking. As shown in Figure 1, this two-phase study will: 1) Identify the factors in a text message intervention that yield optimal adherence to a web-based smoking cessation intervention (Phase I), and 2) Examine the comparative effectiveness of a web-based cessation intervention alone (WEB) and in conjunction with the optimal-adherence text messaging intervention (WEB+TXT; Phase II).

Specifically, in Phase I, the study will examine the impact of four experimental features of a text message intervention on a composite metric of adherence to a web-based cessation intervention. We hypothesize that personalization, integration, dynamic tailoring, and decreasing message intensity will have positive effects on adherence. Phase II will address two aims. Aim 1 will examine the comparative effectiveness of a web-based cessation intervention alone (WEB) or in conjunction with an optimized text messaging intervention (WEB+TXT) with regard to 30-day point prevalence abstinence at 9 months post-randomization (primary outcome) and adherence metrics (secondary outcomes). We hypothesize that WEB+TXT will yield higher rates of abstinence and adherence than WEB. Aim 2 will examine whether the impact of treatment assignment on cessation is mediated by adherence. We hypothesize treatment group differences in 30-day point prevalence abstinence at 9 months will be mediated by greater levels of adherence at 3 months to a web-based cessation program.

< Figure 1 >

Trial Design

This two phase study will be conducted with registered users on BecomeAnEX.org, an established and widely used smoking cessation website run by Truth Initiative. Phase I involves the initial development and optimization of the text message intervention. We will examine the impact of four experimental text message intervention features on smokers' adherence to a web-based cessation intervention during the first three months of program enrollment. We will utilize a full factorial design where participants will be randomized to 1 of 2 levels of each of the following features: 1) personalization (yes/no), 2) integration (yes/no), 3) dynamic tailoring (yes/no), and 4) message intensity (standard vs. decreasing). The primary outcome in Phase I will be a composite metric of website adherence. Phase II involves a 2-arm randomized trial that compares WEB alone to WEB plus the text message intervention from Phase I that yields optimal adherence (WEB+TXT). The randomized trial will use a repeated measures design, with assessments at baseline, 3, 9, and 15 months post-randomization. Follow-ups at 3, 9, and 15 months correspond to 0, 6, and 12 months post-treatment. The primary outcome is 30-day point prevalence abstinence (ppa) at 9-months. Other outcomes include motivation to quit smoking, number of quit attempts, and continuous abstinence.

Design Considerations

Text messaging vs. smartphone app: We chose a text message intervention over a smartphone app for several reasons: 1) A majority of mobile phone owners across most demographic groups use text messaging (excepting those age 65+), especially young adults ages 18-29 and minority groups such as African Americans and Hispanics;[93] 2) 80% of mobile users send/receive text messages compared to only 43% who download apps;[93] 3) Text messaging is a proven cessation modality whereas smartphone apps are not; 4) App installation may feel intrusive: 57% of app users uninstall/decline to install apps due to privacy concerns.[94] Text programs require minimal personal data and may feel less intrusive; 5) Smartphone penetration (56%) lags behind high rates of mobile use.[95]

Use of full vs. fractional factorial design: Fractional factorial designs for evaluating multicomponent interventions have become popular[96 97] and have been used in several web-based cessation trials.[98-100] Their popularity is partly based on the ability to rapidly screen a large number of intervention components for main effects using a fraction of the treatment component combinations required for a full factorial design. A potential downside of fractional factorial designs is that they require a formal refinement phase to resolve interactions aliased with main effects and to evaluate the optimal dose of factors with more than 2 levels. The addition of a refinement phase makes the total sample size and study duration for Phase I hard to estimate in advance, since the exact nature of follow-up experiments to be conducted is highly dependent on the screening phase. Given only N=4 factors and their binary nature – and the fact that we incur no costs for participant recruitment and have an ample pool to recruit from – we

will use a full factorial design that makes use of all 2^4=16 combinations of intervention components. Since we have no aliasing issues to resolve and no need to conduct additional experiments to determine optimal factor doses, we can finalize our text intervention based on Phase I results whose sample size and duration can be fixed in advance.

Decision to power for interactions vs. main effects: As shown by Chakraborty et al.,[97] 2^k factorial designs are grossly underpowered for detecting simple effects (i.e., changes in individual factors while keeping all remaining factors fixed). Rather, they gain power by focusing on main effects (i.e., averages of all 2^{k-1} simple effects obtained by varying an individual factor at fixed levels of the remaining factors). For example, a simple effect of personalization would correspond to comparisons of arms 1 vs. 9 in **Figure 1**, whereas its main effect would correspond to a comparison of arms 1-8 (personalization=no) with 9-16 (personalization=yes). A focus on main effects is acceptable during a screening experiment to identify inactive components rather than in evaluating the usefulness of a particular treatment combination compared to the effects of each component alone. Intervention components with null effects will be dropped from further consideration, while optimum levels for the remaining factors will be set based on their signs in the regression model, with levels having positive signs being associated with higher engagement. In principle, one could observe a situation in which the joint effect of two protective factors is lower in magnitude than the sum of their main effects; such subadditivity is not a concern given the negligible cost of offering additional intervention components, as long as the joint effect of the two factors exceeds each of their main effects considered alone. Failure of the latter condition would correspond to a strongly antagonistic interaction that manifests itself in some pharmacological trials, but which we consider unlikely to occur in a web intervention. We have chosen a sample size that allows us to identify and explain any such strongly antagonistic 2-way interactions.

METHODS AND ANALYSIS

This clinical trial protocol was prepared in accordance with the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) checklist.[101 102]

Phase I Methods

Participants: In Phase I, participants will be N=860 adult U.S. smokers that are new registered users on BecomeAnEX (i.e., no prior use of the site as determined by IP address and registration data) and that fully enroll in the BecomeAnEX text messaging program. During registration, participants must indicate current smoking (every day or some days), age 18 or older, and U.S. zip code as determined by IP address.

Enrollment: New BecomeAnEX members that meet eligibility criteria will be automatically randomized to 1 of 16 arms of the factorial. Study enrollment will be conducted in 10 months.

Based on our prior work, we conservatively estimate that N=3/day (~90/month) new members of BecomeAnEX will enroll in text messaging.

Allocation and Blinding: Randomization will be stratified by whether participants access the Internet on their cell phone (yes/no), since access to BecomeAnEX via mobile site may influence adherence. Randomization will be automated using a computer algorithm. The allocation sequence for the full factorial will be generated by the study statistician at study start-up and uploaded into the web-based clinical trials management system that will automate its implementation. All investigators and research staff will remain blinded to treatment assignment throughout the conduct of the study.

Interventions

Participants are free to use the interventions described below for as long as they desire. Proactive emails from the WEB program can be stopped at any time, and users can unsubscribe from the text message program at any time. There are no restrictions on use of other cessation interventions during the study period.

Web-Based Cessation Program (WEB): BecomeAnEX is an evidence-based cessation program that was launched in 2008 by Truth Initiative (formerly the American Legacy Foundation).[19 103] Based on the Clinical Practice Guideline for Treating Tobacco Dependence[104] and consistent with Social Cognitive Theory,[105] the site educates smokers and provides the tools necessary to enhance self-efficacy for quitting. BecomeAnEX guides and supports smokers through the following *interactive* components: (1) a *Quit Date* tool that assists users in selecting a quit date; (2) *Cigarette Tracker* exercise to identify smoking triggers; (3) *Beat Your Smoking Triggers* exercise to identify strategies to dissociate cigarettes from triggers; (4) *Build Your Support System* exercise to identify helpful supporters; (5) *Choose a Quit Smoking Aid* exercise, in which users indicate their plans for pharmacotherapy use; and (6) *Community*, a large online network of current and former smokers who communicate via personal messages sent directly between members, public "wall posts" (comments on a user's profile page), and blog posts/replies. The site can be browsed anonymously but to save information, visitors must register. Registration includes smoking status, gender and age, email, username/password, and request for email messages. Sign-up for text messaging occurs during registration, and involves providing a mobile number and affirming the request. A mobile web version includes the full functionality of the site.

Text Messaging (TXT): Truth Initiative has developed a fully-automated text messaging program that is available via BecomeAnEX. Users can set a quit date and receive scheduled messages tailored to their quit date; quit dates may be changed or cleared as frequently as a user desires. Messages tailored to quit date encourage use of evidence-based cessation methods (e.g., nicotine replacement therapy, peer support), praise success, inform users about addiction, and reinforce benefits of quitting. Users who do not set a quit date receive scheduled messages

tailored to their enrollment date. These messages prompt users to set a quit date, use evidence-based resources, reinforce benefits of quitting and harms of continuing to smoke. Keywords (e.g.,'COPE,' 'SLIP,' 'MOOD') allow users to request on-demand support related to cravings, relapse, and negative affect. 'STOP' terminates the program at any time. The existing text message intervention will be modified to serve as the base case (Arm 1) in Phase I. The intervention will not be personalized, integrated with BecomeAnEX, or dynamically tailored, and will use a standard message intensity delivery schedule (see Study Arm 1 in Figure 1). For Study Arms 2-16, we will modify approximately half the messages to ensure adequate differentiation between factor levels, while preserving a coherent user experience. We will user-test messages prior to the launch of Phase I to obtain feedback about their persuasiveness, relevance, likelihood of stimulating a response, and appeal. We will also obtain user feedback about message intensity (e.g., desired message frequency, duration of text intervention) and integration between Web and text via interactive messages.

Factor 1 – Personalization: Personalization has been implemented in varying ways in text message studies, ranging from participant name only[106] to name plus numerous pieces of personal information.[107] We will personalize text messages using the participant's BecomeAnEX username and gender.

Factor 2 – Integration: Interactive messages will facilitate engagement via text with the 6 interactive intervention components of the BecomeAnEX website listed above. ***Set Quit Date*** is already a feature of the text message program; the system tailors messages around a quit date. Unlike most other text message programs that require a quit date – and consistent with our aim to improve adherence to a web-based intervention among all users – we will deliver 3 months of text messages regardless of whether a user sets a quit date. When a user sets a quit date via the website, it will trigger text messages tailored to that quit date. All participants, regardless of randomization assignment, will be able to set their quit date via text message and have this information reflected on the website. To enable participants to interact with the *Cigarette Tracker*, *Beat Your Smoking Triggers*, *Build Your Support System*, and *Choose a Quit Smoking Aid* exercises via text message, an initial text message will query the user for a response. Subsequent messages will elicit additional user input (e.g., other triggers), highlight relevant content on BecomeAnEX (e.g., how to cope with boredom), and reinforce use of the site. To facilitate interaction in the *Community* via text message, we will develop a new Community feature called "QuickTips" that will enable BecomeAnEX members to submit text message-sized tips to help support other members. We will enable BecomeAnEX members to submit QuickTips via website, mobile site, or text message. Submissions will undergo review/approval by the BecomeAnEX Administrator before being distributed via text message. The Administrator will augment the QuickTips library as needed, excerpting community content to craft "user-generated" tips. Text users can also request QuickTips for on-demand "peer support".

Factor 3 - Dynamic Tailoring: The general principle guiding implementation of this feature is that messages will be individually tailored to remind/reinforce users about BecomeAnEX information/tools they have already used, or to prompt users to take actions they have not yet taken. Although BecomeAnEX and the text message system are separate systems, they will communicate via an application programming interface (API) which will allow BecomeAnEX to alert the text message system of site utilization. Real-time site utilization data will tailor text messages to encourage the participant to use components of the website they have not yet used or reinforce ongoing use.

Factor 4 - Message Intensity: The text message intervention will be 12 weeks in duration. For the standard intensity protocol, participants will receive a consistent number of messages each day. The decreasing intensity protocol will deliver approximately the same total number and content of messages as the standard intensity protocol, but with additional tapering steps designed to mirror the declines in cravings and withdrawal typically experienced by a smoker after quitting.[108] The decreasing protocol will gradually reduce the number of daily messages, rather than sharply decrease as in the standard intensity protocol. We will examine the relationship between "dose" of text messages received and our composite adherence metric.

Measures

Phase I will rely on data from 4 sources: (1) BecomeAnEX registration data, (2) automated tracking data gathered through Adobe Analytics[109] software, (3) automated tracking data stored in unified event logs, and (4) text message utilization data. Use of the following components of BecomeAnEX will be extracted from unified event logs: *Set Quit Date, Cigarette Tracker, Beat Your Smoking Triggers, Choose your Quit Smoking Aid, Build Your Support System, and Community* (e.g., # wall posts made/received, blog posts/replies, messages sent/received, QuickTips submitted). From our text message system, we will extract replies to interactive text messages including engagement with the 6 interactive features of BecomeAnEX, unsubscribe rates, modal day of unsubscribe, number of days enrolled, messages received, and keyword requests. All text interactions are date/time stamped.

Primary outcome: The primary outcome of Phase I will be a composite metric of adherence for each participant created using a weighted sum of general measures of engagement (e.g., visits, page views, time on site) and specific feature utilization shown to predict abstinence during 3 months post-enrollment. The weights for these utilization metrics will be given by the regression coefficients of a logistic regression model that we have already developed to measure the effects of website engagement on 3-month abstinence rates in the control arm of a prior ongoing web-based cessation study.[110] The resulting adherence metric has the advantage that it is continuously distributed, even if some of the original utilization metrics are binary or count data. Therefore, it can be analyzed as the primary outcome for Phase I using standard linear regression techniques, possibly after a normalizing transformation. Treatment duration of 3

months will provide sufficient time to examine the impact of the text message intervention on adherence, since most non-usage attrition happens within the first 3 months.[19]

Phase I Data Analysis Plan and Sample Size Calculations

Analysis Plan: We expect the primary outcome to be continuously distributed, although it may require a symmetrizing transformation to reduce skewness. Given our prior experience with these data, we expect to find a few outliers that represent heavy website users. Rather than discard such valid data points, we will reduce their impact by winsorization (similar to trimming).[111] Once we are satisfied about the adequacy of the normal approximation, we will analyze the data from our factorial designs using the approach detailed in Chakraborty et al.[97]

Sample Size Calculations: To be conservative, we used a sample size for Phase I that allows us to detect small main effects of any of the 4 factors of interest (d=.25) or moderate 2-way interactions (d=.50) with power 80% at a 2-sided significance level of alpha=.05/10 (multiplicity adjustment based on 4 main effects and 6 two-way interactions in the model). Effect sizes for interactions were chosen to be such that they could nullify the presumed beneficial main effects of the factors involved. The sample size required is N=430 per factor level, or N=860 overall. These calculations were not adjusted for attrition since we will have adherence data on all participants.

Phase II Methods

Subjects: We will recruit a separate sample of N=600 adult smokers who register on BecomeAnEX and sign up for text messaging during registration. To be invited, participants must be adult current smokers (every day/some days) that register on BecomeAnEX and enroll in the text message program. Invited participants will complete a separate screening process to confirm eligibility. To maximize generalizability, we have no inclusion criteria related to motivation for cessation.

Recruitment and Enrollment: Phase II participants will not be enrolled automatically as in Phase I, but must respond to a study invitation and complete online eligibility screening, informed consent, and a baseline assessment, and fully enroll in the text messaging program. Study enrollment occurs online via our web-based clinical trials management system. Randomization will only occur after a potential study participant has completed the online enrollment process (completed baseline survey) and replied 'OK' to the welcome text message to confirm text message enrollment. Randomization will be stratified by gender, age (≤30, 30+), and whether participants access the Internet on their cell phone (yes/no) since age and access to BecomeAnEX via mobile site may influence adherence and gender may influence cessation outcomes. A computer algorithm will automate random allocation. Recruitment will be conducted over 14 months.

Interventions. ***WEB:*** Participants will have full access to BecomeAnEX. They will not receive any intervention via text message. Informed consent will explain the possibility of being randomized to a non-text treatment arm. ***WEB+TXT:*** Participants will have full access to BecomeAnEX and the optimal-adherence text intervention developed in Phase I. Participants are free to use the interventions for as long as they desire. Proactive emails from the WEB program can be stopped at any time, and users can unsubscribe from the text message program at any time. There are no restrictions on use of other cessation interventions during the study period. Use of other quit methods will be assessed at all follow-up intervals.

Retention: We expect at least 70% follow-up at 9 months. To maximize follow-up we will: (1) provide clear information about the study at the outset, including expectations for follow-up; (2) reimburse participants $50 per follow-up; and (3) emphasize the importance of survey completion regardless of smoking status. If follow-up rates are lower than expected early in the trial, we will consider shortening the 9-month follow-up to gather only abstinence outcomes.

Measures

Assessments will occur at baseline, 3, 9, and 15 months post-randomization. The baseline survey will be conducted online and hosted on a secure server. Mixed-mode follow-up (email, phone, text) will be employed. Telephone surveys will be conducted by research staff blind to treatment. Text messages have demonstrated moderately high reliability (k=.66) compared with web-based surveys in assessing smoking outcomes[112] and will be used as a final means of gathering abstinence data from non-responders. Most measures listed below are standard instruments used in cessation studies, and are reliable when administered via the Internet.[113 114]

Baseline Variables: To characterize the sample and examine moderators, we will gather information on: *demographics* (age, sex, marital status, race, ethnicity, employment, and education); *current smoking behavior and smoking history* (smoking frequency and rate; quitting history, including quit methods; current and past use of other tobacco products); *nicotine dependence* assessed by the Heaviness of Smoking Index[115]; *motivation to quit smoking* measured with the Readiness Ladder[116]; *mobile phone type/use* (average number of text messages sent/received each day, cell phone use to access the Internet, send or receive email,[93] data plan on phone,[117] and where, how, and how often they access the Internet); and *smoking cessation self-efficacy* measured with the short form of the Smoking Situations Confidence Questionnaire.[118]

Outcome Measures: The *primary outcome* is self-reported 30-day ppa at 9 months post-randomization but we will gather abstinence data at all follow-ups. *Other smoking-related outcomes* will include change in motivation to quit, quit attempts, 7-day ppa, and continuous abstinence measured at each follow-up. *Intervention satisfaction* in both conditions will be measured with items about overall satisfaction, perceived helpfulness, whether the intervention met their expectations (1=not at all, 5=very much), and whether they would recommend the

intervention to a friend (1=definitely not, 5=definitely would). Satisfaction with frequency/duration of text messages and perceptions about Internet and text message integration will also be measured.[71] To assess *perceived message relevance*, participants will be asked whether text messages "were written personally for you"[22] and "were directed at you personally" (1=not at all, 7=very much).[76]

Mediating Variables: We will examine the same website utilization metrics as in Phase I from Adobe Analytics[109] and unified event logs. Adobe Analytics will provide metrics for contact time (total time spent logged into the website), number of website sessions (number of return visits to the website), use of the static content on the site (number of page views), and number of videos watched. Unified event logs will provide data on use of the 6 interactive components of BecomeAnEX and the platform on which they were used (i.e., website or mobile site). We will extract replies to interactive text messages including engagement with the 6 interactive features of BecomeAnEX and number of keyword requests from the text message system. Unsubscribe rates, modal day of unsubscribe, number of days enrolled, and messages received will be extracted. All text message interactions are date and time stamped.

Phase II Data Analysis Plan and Sample Size calculations

The distributional properties of continuously scaled variables will be examined to determine the need for normalizing transformations. Next, we will determine whether the groups show large standardized mean differences at pre-treatment on demographic characteristics, psychosocial variables, or smoking variables. Although the large sample size should preclude finite sample randomization imbalances, should such between-group differences be found, we will correct for them via regression adjustment.

Outcome analyses: Our primary outcome for Aim 1 is self-reported 30-day ppa. Differences in abstinence rates between the two treatment conditions will be evaluated at our primary endpoint of 9 months post-randomization, as well as the secondary endpoints of 3 and 15 months post-randomization. To account for within-subject correlation due to the repeated-measures aspect of our study, we will employ the Generalized Estimating Equation (GEE), which extends generalized linear model methodology to correlated data in PROC GENMOD of SAS/STAT (SAS Inc., Cary, North Carolina, USA). Analyses will be conducted first using an Intention- to-treat (ITT) principle, analyzing data from all subjects randomized to treatment and counting as smokers those lost to follow-up (missing = smoking).

Moderator analyses: We will examine potential moderators of the intervention-smoking cessation relationship (for example, gender, baseline stage of motivational readiness, nicotine dependence). Effect modification will be conducted by analyzing interactions between treatment and selected variables.

Mediator analyses: Primary Aim 2 hypothesizes that adherence mediates the intervention-cessation relationship. We will establish mediation using the MacKinnon approach.[119] As explained in Cerin and MacKinnon[120] and implemented by Papandonatos et al.,[121] behavioral researchers ought to determine whether: (a) the intervention successfully acted upon the putative mediator (that is, 'Action Theory test'); (b) changes in the mediator were indeed predictive of changes in the target behavior suggested by the conceptual framework underpinning the intervention over and above any direct treatment effects (that is, 'Conceptual Theory test'); and (c) these conditions held simultaneously for each mediator of interest, indicating that the corresponding mediational pathway accounted for at least part of the relationship between the intervention and the target behavior (that is, 'Mediation test').

Missing data: We expect less than 25% missing data at any time. If a participant refuses follow-up, we will censor the data at the point of loss of contact. Under an ITT approach, participants who had been considered non-smokers up to the point of loss will be considered smokers at future data points. One concern is that this approach is sensitive to differential attrition across study arms and tends to overestimate precision of estimates of treatment effects.[122] Therefore, we will supplement ITT analyses with a multiple imputation procedure that assumes the odds of missingness vary for smokers and non-smokers lost to follow-up. This model falls under the missing-not-at-random (MNAR) characterization of missingness mechanisms by Little and Rubin[123] and requires knowledge of the odds ratio (OR) relating missingness to smoking. Since this OR is in practice unknown, we will conduct a sensitivity analysis to assess its impact on the estimate and significance of the intervention effect.[124 125]

Sample Size: Efficacy estimates for WEB are based primarily on the BecomeAnEX trial[110] and the BecomeAnEX Outcome Evaluation,[19] augmented by results from our iQUITT Study[126] and the American Cancer Society (ACS) trial.[12 127] In our ongoing BecomeAnEX trial,[110] 30-day ppa using ITT at 9 months in the Internet-alone arm is 8.8%. In the BecomeAnEX Outcome Evaluation,[19] 30-day ppa using ITT at 6 months was 9.9%. Quit rates for the web programs in The iQUITT Study ranged from 12.2%-14.4% at 6 months (30-day ppa ITT). In the ACS trial[12] 7-day ppa (ITT) at 13 months was 8-12% across all 5 interactive websites and 10% for the static site. We conservatively estimate that the 30-day ppa rate at 9 months for WEB will be 9% under ITT. Efficacy estimates for WEB+TXT are based on several converging lines of evidence: 1) A meta-analysis by Webb et al.[51] found that the parallel use of text messaging in Internet interventions had large effects on behavior change (d=0.81, k=4); 2) Abstinence rates in the BecomeAnEX Outcome Evaluation[19] at 6 months were roughly doubled among those who used the community (OR=2.22, 95% CI 1.34-3.69, p=.002) and separation exercises (OR= 1.91, 95% CI 1.00-3.65, p=.05) two or more times compared to those with no utilization; increased adherence to these features facilitated by text messages is expected to increase abstinence similarly; 3) Brendryen et al.[72] tested a multi-component cessation intervention that included parallel Internet and text messaging which yielded 12-month repeated ppa of 20% under ITT. We conservatively estimate that the 30-day ppa rate at 9 months for

WEB+TXT will be 16.5% under ITT, corresponding to an intervention OR=2.0 which can be detected with 80% at 2-sided alpha=.05 using N=300 per study arm (N=600 total).

Study Monitoring

At the start of the study, a Data Safety Monitoring Committee will be established, comprised of the Principal Investigator, Data Analyst, Biostatistician, Technical Lead, and Project Manager. This committee will discuss protocol development and will review scientific, safety and ethical issues related to the study design and approve plans for data integrity. The committee will meet every two weeks to review the following information in detail: 1) Participant accrual rate, 2) Participant drop-out and the reasons for drop-out, 3) Targeted enrollment status, and 4) Major and minor problems related to treatment arm assigned.

The overall risk is judged to be very low for both Phase I and Phase II. Study participants who attempt to quit smoking will likely experience some nicotine withdrawal symptoms that may include anxiety, restlessness, anger, irritability, sadness, problems concentrating, appetite change and weight gain, insomnia, and decreased heart rate. There is no reason to believe that participation in this study would worsen nicotine withdrawal symptoms or that symptoms would differ based on randomization assignment in either Phase I or Phase II. Exposure to evidence-based information and support for smoking cessation in both the Internet and text message interventions is expected to attenuate withdrawal symptoms associated with smoking cessation that may occur during Phase I or Phase II. Given the nature of the trial, we do not anticipate the need for interim analyses or stopping guidelines. Serious adverse events are unlikely, but will be reported immediately upon discovery by study staff to the Principal Investigator who will notify the IRB and NIH Project Officer within 24 hours.

Participant Timeline - Phase I and Phase II

The main outcome of interest for Phase I is a composite metric of adherence for each Phase I participant created using a weighted sum of general engagement metrics (e.g., website visits, page views, time on site) and specific feature utilization shown to predict abstinence during 3 months post-enrollment. There is no baseline or follow-up assessment for participants to complete as adherence metrics are collected automatically. Participants will receive the text message intervention for 12 weeks and participants can discontinue any time by texting back "STOP." The timeline for Phase I is depicted in Figure 2.

<Figure 2>

The main outcome of interest for Phase II is 30-day point prevalence abstinence (ppa) at 9 months. Secondary outcomes include 30-day ppa at 3 and 15 months and adherence metrics. Participants will be assessed at baseline to gather demographics; current smoking behavior and smoking history, nicotine dependence assessed by the Heaviness of Smoking Index; motivation

to quit smoking measured with the Readiness Ladder; mobile phone type and use; and smoking cessation self-efficacy measured with the short form of the Smoking Situations Confidence Questionnaire. The intervention period will last for 3 months post randomization. Follow-up surveys will take place for all participants at 3, 9, and 15 months post-randomization, during which they will be assessed on smoking-related outcomes, including change in motivation to quit, quit attempts, 30-day ppa, 7-day ppa, and continuous abstinence; intervention satisfaction; and perceived text message relevance. The baseline survey will be conducted online. Mixed-mode follow-up (email, phone, text) will be employed for all follow-up assessments. The timeline for Phase II is depicted in Figure 3.

<Figure 3>

ETHICS AND DISSEMINATION

Research Ethics Approval

Institutional Review Board approval for the study was provided by Chesapeake Institutional Review Board.

Protocol Amendments

Any protocol modifications will be submitted for approval to Chesapeake IRB and reflected (as needed) in trial registry information available on ClinicalTrials.gov.

Consent

New registrants on BecomeAnEX.org will be automatically enrolled in Phase I following BecomeAnEX registration if they meet the eligibility criteria and complete BecomeAnEX text message enrollment by replying 'OK' to the welcome message. To register on BecomeAnEX, individuals must agree to the site's Terms of Use and Privacy Policy. The Privacy Policy makes explicit that 1) Truth Initiative automatically collects information about its users and their use of the site, 2) information is used for research and quality improvement purposes only and, 3) personal information is kept confidential. Eligible individuals will be automatically randomized to 1 of 16 arms of the factorial design. Their use of the BecomeAnEX website and text messages will be tracked for 3 months. No additional screening information will be requested or obtained and no separate informed consent will be solicited as the registration process makes it clear that Truth Initiative may monitor all regististered users' use of the website and that they are explicity agreeing to receive text messages.

In Phase II, new registered users on BecomeAnEX are presented the informed consent page and provided detailed information about the study. Randomization will only occur after an eligible study participant has completed the online enrollment process (confirmed eligibility, indicated

informed consent, confirmed contact information, and completed baseline survey) and replied 'OK' to the welcome text message to confirm text message enrollment.

Confidentiality

Confidentiality will be protected at all times and potential risks minimized systematically. During BecomeAnEX registration, participants create a username and password that they use to log in to the website. Each use of BecomeAnEX involves a session ID unique to the user and the date and time of access. BecomeAnEX uses industry standard security protocols. Users are automatically logged out of BecomeAnEX after 30 minutes of inactivity. The BecomeAnEX Privacy Policy will be in effect for all participants enrolled in the project. Transactional data from the site are loaded on a daily basis into a local data warehouse which is subject to both physical and electronic protection. Confidentiality of data will be maintained by numerically coding all data, by keeping identifying information separate from research data, and by keeping all data electronically protected. Identifying information will not be reported.

Declaration of Interests

ALG, MAJ, AMC, and SC are employees of Truth Initiative (formerly American Legacy Foundation), a non-profit public health foundation that runs the BecomeAnEX smoking cessation website.

Access to Data

For Phase I and II, the Principal Investigator, Data Analyst, Project Manager, software development team, and telephone survey staff will have access to individually identifiable information about human subjects. Electronic data files with identifiable information will be maintained separately from other data files and will only be used for administrative purposes (e.g., tracking follow-up completion, managing subject payment). All personnel will receive certification in human subjects protection from the NIH Office of Human Subjects Research prior to beginning work on this project.

Dissemination Policy

We will disseminate results of this study through peer reviewed manuscripts and conference presentations related to the methods and design, outcomes from the randomized trial, and the exploratory analyses planned for the project. We will follow the guidelines of the International Committee of Medical Journal Editors in determining authorship. The ICMJE recommends that authorship be based on the following 4 criteria: 1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND 2) Drafting the work or revising it critically for important intellectual content; AND 3) Final approval of the version to be published; AND 4) Agreement to be accountable for all aspects of

the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Once appropriate, a completely de-identified data set will be created that obfuscates any variable that might potentially be used to identify an individual study participant. To facilitate sharing, a member of our investigative team will be required to participate as an investigator on any sub-project requiring data sharing. We will review our data sharing plan throughout the trial to ensure that appropriate strategies are developed to cover all interested audiences.

Roles and Responsibilities: ALG, MAJ, AMC, SC, LA, GDP, RW participated in study concept, study design, and obtaining funding. ALG, MAJ, and SC participated in acquisition of data. ALG and GDP participated in statistical analysis. All authors participated in drafting of the manuscript.

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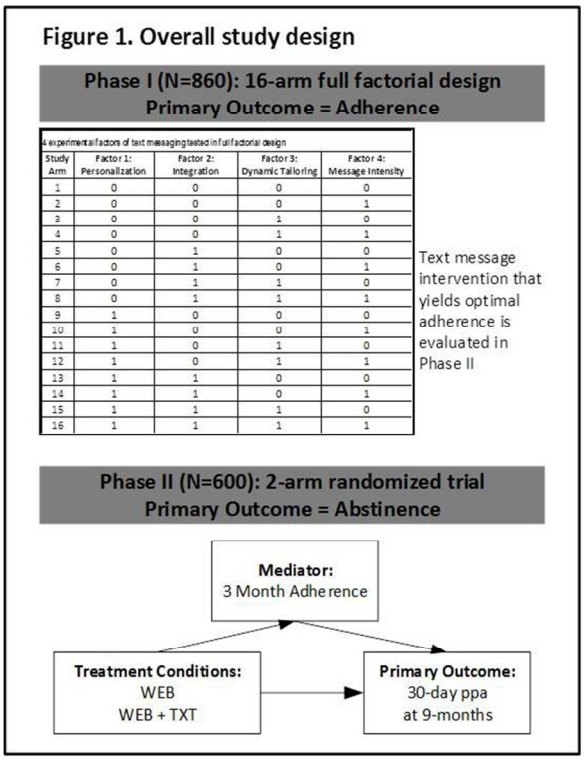

Figure 1. Overall Research Design.
254x190mm (96 x 96 DPI)

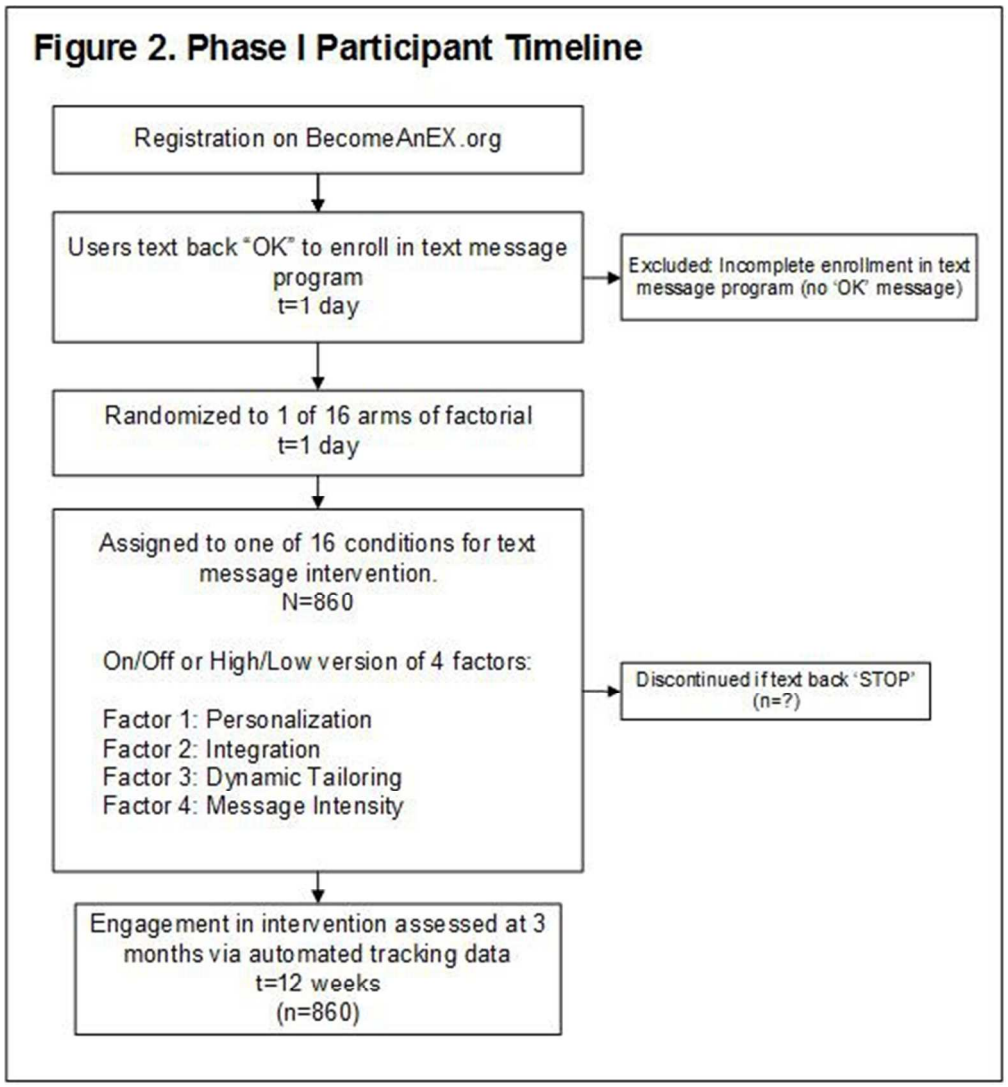

Figure 2. Phase I Participant Timeline
143x155mm (96 x 96 DPI)

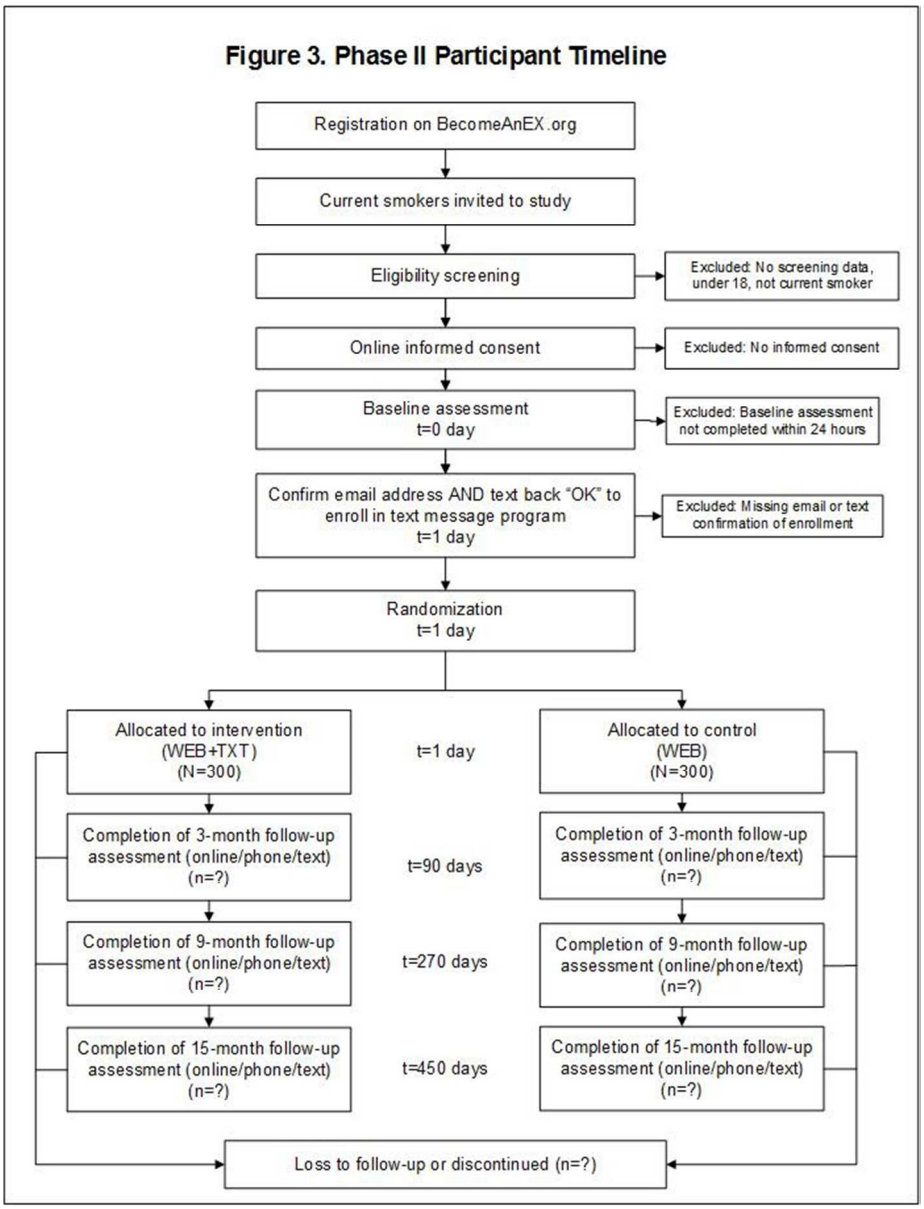

Figure 3. Phase II Participant Timeline
184x241mm (96 x 96 DPI)

APPENDIX A. RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	Optimizing Text Messaging to Improve Adherence to Web-Based Cessation Treatment
PROTOCOL NO.:	R01 DA038139-01A1
SPONSOR:	National Institute on Drug Abuse
INVESTIGATOR:	Amanda L. Graham, PhD Schroeder Institute for Tobacco Research & Policy Studies 900 G St NW Fourth Floor Washington DC 20001
SITE(S):	Truth Initiative Schroeder Institute for Tobacco Research & Policy Studies 900 G St NW Fourth Floor Washington DC 20001
STUDY-RELATED PHONE NUMBER(S):	202-709-8587

INFORMED CONSENT

ABOUT THE STUDY

You are invited to participate in a research study. The study is called *Optimizing Text Messaging to Improve Adherence to Web-Based Cessation Treatment.* The research is sponsored by the National Institute on Drug Abuse of the National Institutes of Health (NIH) and is being conducted at the Truth Initiative, which is located at 900 G St NW Fourth Floor, Washington DC 20001. Dr. Amanda Graham is the Primary Investigator.

WHAT IS INFORMED CONSENT?

The purpose of this consent form is to help you decide if you want to be in the study. Please scroll through and read this entire consent form carefully. To join a research study you must give your informed consent. "Informed consent" includes: (1) reading this consent form and (2) asking questions about anything that is not clear. You should not join this research study until all of your questions are answered.

If you have any questions, please contact the study investigator, Dr. Amanda Graham, at EX_Study@truthinitiative.org or 202-709-8587.

Things to know before deciding to take part in a research study:

- Taking part in the study is entirely your choice - if you choose not to join the study, you can continue to use the BecomeAnEx website however you wish;
- Personal benefit to you may or may not result from taking part in the study, but knowledge may be gained from your participation that will benefit others;
- You may withdraw from the study at any time.

If you decide to take part in this research study, you will be able to print or save a copy of this consent form.

WHY IS THE STUDY BEING DONE?

The purpose of this study is to investigate the effectiveness of a smoking cessation website called BecomeAnEx.org when it is used alone, and when it is used along with social network support and/or nicotine replacement therapy (nicotine patch, gum, or lozenge). The study also hopes to identify ways to improve the effectiveness of the BecomeAnEx.org website in helping smokers to quit smoking.

About 600 subjects are expected to enroll in this study.

WHAT IS INVOLVED IN THE STUDY?

Joining the Study: If you agree to take part in this study, here's what will happen. First, you will sign this Informed Consent page by entering your initials at the bottom of the page and clicking "I Want to Participate." This page must be signed before any study-related procedures are performed. Second, you will be asked to provide some basic contact information, including your name, email, and mobile telephone number. Third, you will asked to complete an online survey that includes questions about your use of the Internet and your cell phone, your smoking habit, and your health in general. This survey should take about 5-8 minutes to complete. Fourth, we will send you a text message at the phone number you provided to confirm your enrollment in the study. To fully enroll in the study, you must text back "OK" this welcome text message.

Being in the Study: Once the survey is completed, you will be "randomized" into one of the study groups. Randomization means that you are put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researchers will choose what group you will be in. If you are randomized to Group 1, you will have full access to the BecomeAnEX.org website to use as you desire. If you are randomized to Group 2, you will also have full access to the BecomeAnEx.org website and you may receive text messages over the next month. You will have an equal chance of being assigned to either Group.

Follow-Up Surveys: You will be contacted by email at three different time points by study staff to complete follow-up Internet surveys. If we are not able to reach you by email to complete the surveys, a research assistant will attempt to reach you to complete them over the phone. These follow-up surveys will occur at 3, 9, and 15 months after you join the study. The surveys will ask about your smoking, your health in general, and your feedback about being in the study. Each follow-up survey will take about 12-15 minutes to complete.

The follow-up surveys are a critical part of the study – we need to hear from everyone, even if you are still smoking and/or have not used the website or the text message program.

Your participation will last about 15 months, if you complete the study.

RISKS AND DISCOMFORTS

Quitting Smoking: If you decide to quit smoking, you may experience mood changes, anxiety, irritability, decreased concentration, restlessness, increased hunger or trouble sleeping. These symptoms usually last for about 1 to 2 weeks after quitting.

NEW INFORMATION

You will be told about any new information that might change your decision to be in this study. You may be asked to read and submit a new online consent form if this occurs.

POSSIBLE BENEFITS

By taking part in this study, you may quit smoking or cut down the number of cigarettes that you smoke which will improve your health, but this cannot be guaranteed.

COSTS

There is no cost to you to join the study or to participate in the study.

PAYMENT FOR PARTICIPATION

You will not be paid for completing the baseline survey. You will be paid $50 via Amazon gift card emailed to you for completing each of the three follow-up surveys. If you do not complete all follow-up surveys, you will be paid for the surveys you complete.

ALTERNATIVE TREATMENTS

You do not have to participate in this study. You can continue to use BecomeAnEx.org however you wish. There are also other quit smoking programs available, such as telephone support available at 1-800-QUIT-NOW and community agencies such as the American Lung Association.

CONFIDENTIALITY

All information collected from you for the study will be kept confidential to the extent of the law. Confidentiality will be protected at all times and several steps will be taken to reduce any risks to confidentiality. Complete confidentiality cannot be guaranteed. All information collected via the Internet will be kept secure using the Secure Socket Layer (SSL) Protocol, the same technology used to encrypt credit card numbers during transmission over the Internet. You will be asked to designate a username and password to access the website. All data will be stored in a database subject to both physical and electronic protection. All participants will be assigned an identification number that will be used to link responses, but no identifying information will be kept with those responses.

Please note that study staff involved in processing your payment for participation will be aware of your identity.

The results of the research study will be shared with other people and will be published in scientific reports; however, your name and the fact that you were in the study will be kept confidential.

The funding agency, the National Cancer Institute, may see your information if it is audited. The federal auditors can use this audit information only for audit or evaluation of the program.

COMPENSATION FOR INJURY

We do not expect any injuries to result from this research study. If an unexpected injury occurs as a result of your participation in this study, you will receive treatment that Truth Initiative considers to be fair and appropriate for that injury, without charge to you. Truth Initiative does not intend to provide you with any other money or payment if this happens. Agreeing to participate in this study does not change any of your legal rights. For more information regarding this provision, please contact Ryan Desrosiers in the Office of Grants Management at Truth Initiative at 202-454-5555.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

The decision whether to be in this study is entirely up to you. Participation is voluntary. Also, if you decide now to participate, you can to change your mind later and withdraw from the study.

There will be no penalty if you decide not to participate, or if you withdraw from the study. The research team may choose to end your participation in this study at any time prior to the completion of the study for any reason.

The researcher will provide you with additional information as it becomes available that may affect your decision to continue in the research study.

SOURCE OF FUNDING FOR THE STUDY

This study is funded by the National Institute on Drug Abuse of the National Institutes of Health (NIH).

QUESTIONS

Please contact the study investigator, Dr. Amanda Graham, for any of the following reasons:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury, or
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns, input or complaints about the research, you may contact:

Chesapeake IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, MD 21046-3403
Telephone: 410-884-2900
http://www.chesapeakeirb.com/

Chesapeake IRB is a group of people who independently review research.

Chesapeake IRB will not be able to answer some study-specific questions. However, you may contact Chesapeake IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not agree to participate in this study unless you have had a chance to ask questions and have gotten satisfactory answers.

CONSENT

I have read this consent form. All my questions about the study and my part in it have been answered. By entering my initials in the box below, I freely consent to be in this research study.

By agreeing to participate in this study, I have not given up any of my legal rights.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **Page number:** 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **Page number:** 2
	2b	All items from the World Health Organization Trial Registration Data Set **Page number:** N/A
Protocol version	3	Date and version identifier **Page number:** 2
Funding	4	Sources and types of financial, material, and other support **Page number:** 2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Page number:** 2
	5b	Name and contact information for the trial sponsor **Page number:** 2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **Page number:** 2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **Page number:** 2
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Page number:** 5-10
	6b	Explanation for choice of comparators **Page number:** 5-10

Objectives	7	Specific objectives or hypotheses **Page number:** 8-9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Page number:** 9
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Page number:** 9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Page number:** Phase I: 11; Phase II: 15
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Page number:** Phase I:11-13; Phase II: 15
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **Page number:** Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Page number:** Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **Page number:** Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Page number:** Phase I: 13-14; Phase II: 15-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **Page number:** Phase I: 18; Phase II: 18-19
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Page number:** Phase I: 14; Phase II: 16-18

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **Page number:** 9, 13
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Page number:** Phase I: 11; Phase II: 15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Page number:** Phase I: 11; Phase II: 15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Page number:** Phase I: 11; Phase II: 15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **Page number:** Phase I: 11; Phase II: 15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **Page number:** Not applicable
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Page number:** Phase I: 13-14; Phase II: 15-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **Page number:** Phase I: Not applicable, automatic data collection only; Phase II: 15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **Page number:** 18

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Page number:** Phase I: 14; Phase II: 17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **Page number:** Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **Page number:** Phase I: Not applicable, automatic data collection only; Phase II: 17
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **Page number:** 18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **Page number:** 18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **Page number:** 18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Page number:** 18
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Page number:** 19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **Page number:** 19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **Page number:** 19-20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **Page number:** Not applicable

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **Page number:** 20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **Page number:** 20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **Page number:** 20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **Page number:** Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **Page number:** 20-21
	31b	Authorship eligibility guidelines and any intended use of professional writers **Page number:** 20-21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **Page number:** 21
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **Page number:** Appendix A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **Page number:** Not applicable.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.