Title: Feasibility and Acceptability of Timing a Quit Attempt to the Menstrual Phase in a Telephone-Based Smoking Cessation Intervention: Protocol of a Pilot Randomized Controlled Trial

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Abstract

Background: Compared to men, women smoke for different reasons, have unique barriers to cessation, and are less likely to utilize quitline services. While current clinical recommendations have called for sex/gender-specific smoking cessation protocols, quitline protocols have not been expanded to address the unique needs of women. Menstrual cycles (and/or ovarian hormones) influence quit outcomes in women. This paper presents the rationale, study design, and protocol for a preliminary randomized control trial designed to test the feasibility and acceptability of utilizing menstrual cycle timing to improve quit outcomes in women of reproductive age.

Methods/Design: Participants include treatment seeking women (n=116), between the ages of 18-40 with regular menstrual cycles. Eligible participants are randomized to either the Follicular Phase (FP) or Standard Care (SC) control group. Counseling included six weekly telephone sessions with four week of nicotine replacement therapy. The timing and frequency of sessions is identical to both conditions, with the exception of the quit day (week 3 of counseling). Quit day for FP participants is scheduled within 6-8 days post onset of menses; the SC group quit day is set for Week 3 of counseling regardless of their menstrual cycle phase.

Discussion: If feasible and acceptable, our behavioral counseling intervention that times the quit day to the follicular phase of the menstrual may increase quit outcomes among women. Moreover, our telephone based approach that is similar to quitline protocols also allows for wide dissemination across quitlines nationally.

Keywords:
Smoking Cessation, Women, Menstrual Cycle, Telephone-based interventions

Introduction

Cigarette smoking continues to be the leading preventable cause of death and disease.[1] Quitlines are broad-reaching, and cost-effective interventions for smoking cessation.[2] Typical services include a series of proactive telephone counseling sessions based on evidence-based strategies combined with provision of nicotine replacement therapy (NRT).[2] While considered a standard of care approach for smoking cessation, little research has examined strategies on how best to tailor services for specific high-risk populations, such as women.

Compared to men, women who smoke have greater difficulty quitting smoking and are at increased risk for relapse.[3] Indeed, we recently observed that while women are more likely to call a quitline, compared to men, women were less likely to engage in quitline services and more likely to relapse at follow-up.[4] These data suggest tailoring services to women may enhance the use of quitline services and response to treatment. Prior research has shown that women face unique barriers to cessation including negative affect, lack of social support, weight concerns, and less effectiveness of some smoking cessation pharmacotherapies (for reviews see [5–8]). Additionally, increasing evidence points to the role of the menstrual phase and/or ovarian hormones (e.g., progesterone and/or estradiol) in smoking behavior change. [9] While the mechanisms of action responsible for menstrual phase effects on smoking behavior is not entirely clear, one hypothesis is that the ovarian hormones illicit differences in the neurobiological drug reward response in response to nicotine.[10] Evidence for this hypothesis comes from prior research that observed more favorable smoking cessation outcomes when aided by the nicotine replacement therapy (NRT) patch in women who quit during the follicular phase (6-8 days post onset of the menses) [11,12] and with an increasing progesterone-to-estradiol ratio (which occurs during the late follicular phase). [13] Interestingly, cessation attempts *without* the use of the NRT patch yielded more favorable outcomes during the luteal phase (week prior to onset of the period). [14,15] Furthermore, withdrawal symptoms and, perhaps, craving are significantly greater during the luteal phase.[9] Taken together, these data suggest targeting the follicular phase in women of reproductive age who are pursuing NRT-aided smoking cessation via the quitline has potential benefit.

The primary goal of this pilot randomized controlled trial ("*Project Phase"*) is to determine the acceptability and feasibility of assigning quit day during the follicular phase (defined here as six to eight days post onset of menses) in a quitline setting (i.e., a standardized telephone-based cessation intervention) as compared to a standard-of-care condition. A second aim is to examine preliminary efficacy of a menstrual phase-timed intervention on smoking cessation outcomes during NRT-aided cessation attempts. Our third aim is to explore theoretically-relevant factors to the counseling intervention that are known to be associated with smoking cessation by menstrual phase.

Methods

Study Design Overview

Participants are randomized (1:1 ratio) to: (1) follicular phase (FP) intervention, in which participants start a six-week telephone-based behavioral counseling program such that their quit date will occur six to eight days post onset of menses, or (2) standard-of-care (SC) intervention in which participants start the six-week behavioral counseling program without regard to menstrual timing. In addition to counseling, both groups also receive four weeks of the NRT patch. Participants are followed for three months after their assigned quit date. After enrollment, participants complete weekly surveys and counseling phone calls during treatment. Assessments occur at Week 4 post-quit date (end of treatment) and Month 3 post-quit date (end of follow-up) via self-administered surveys. Self-collected dried blood spots (DBS) will be collected for accurate identification of the menstrual cycle (Week -1, Week 0, and Week 1) and to biochemically verify self-reported smoking abstinence (Week 4 and Month 3). This study received ethical approval by the University of Arizona's Human Subjects Protection Program in July 2018.

Participants

Women (n=116) who are between the ages of 18-40 years of age will be recruited. The eligibility criteria are self-reported smoking $\geq$ 5 cigarettes daily, intending to quit within the next 90 days, willingness to use the NRT patch, self-reporting regular menstrual cycles (24-36 days in length), and willing/able to comply with the protocol. Exclusion criteria include recent use (<3 months) of exogenous hormones (including hormonal contraceptives), recent (<3 months) pregnancy, recent (<3 months) lactation, plan to become pregnant in the next 3 months, contraindications to NRT, cohabitation with someone who been enrolled in this study, or have called the Arizona state quitline more than once in the past 12 months. Potential participants reporting contradictions to using the NRT may participate if they obtain their physician's approval in writing prior to participation in the study. Participants ineligible at the time of screening are referred to the state quitline.

Recruitment

Recruitment occurs via two routes: (1) direct referrals made through the state quitline, and (2) self-referrals via community-based recruitment (advertising on social media or flyers posted in the community) (Figure 1). For the direct referrals, trained quitline staff initially assess quitline callers for eligibility. Those who are potentially eligible are provided a brief description of the study and, if they are interested, referred to the study staff for a full eligibility assessment. Specifically, upon receiving verbal consent, the participant's data are securely transmitted to the study's REDCap database.[16] Similarly, for self-referrals, an initial eligibility

screen is completed online via REDCap. Those who meet initial eligibility, then complete a full eligibility assessment via a telephone interview with study staff.

Enrollment and Randomization

Upon completion of the telephone interview, potential participants are emailed a link to a REDCap database containing informed consent and baseline surveys. Participants may become ineligible during the baseline surveys if they report uncommon medical conditions or variables known to influence hormones or menstrual cycle (e.g., endometriosis, polycystic ovarian syndrome).[17]

Once final eligibility is confirmed by a study staff member and one principal investigator, participants are enrolled and stratified by recruitment source (direct referral versus self-referral) and randomized (1:1 ratio) in REDCap. Prior to the launch of the study, a randomization list was created by the study biostatistician who has no contact with study participants or counselors using the ralloc procedure in the statistical software Stata (Statacorp, College Station, TX). In addition to stratification, random block sizes were used to ensure balance across the conditions.

After randomization, participants in both groups complete a 10-minute welcome call to receive an orientation of the study (e.g., counseling sessions, assessment timelines/procedures, incentive structure). During this call, participants are informed of when they will commence the six-week intervention. Specifically, the SC group initiates the intervention within five business days (similar to typical quitline protocols). In contrast, the FP group initiates the intervention one week prior to the expected onset of menses. This allows the quit date (which occurs during the third week of the counseling protocol) to be set six to eight days post onset menses. Consequently, based menstrual cycle timing, the initiation of the behavioral counseling in the FP group may be delayed by up to three weeks. The FP group is also instructed to notify study staff via phone call, text message, or email at the onset of menses.

Participant Materials and Mailings

After the welcome call, participants receive materials via mailings. Materials include: (1) additional study information such as payment schedule and counselor contact information, (2) self-help material including a booklet (the booklet for the FP group includes content about the menstrual cycle such as cycle-related weight gain and mood changes) and quit day behavioral contract signed by counselors, (3) training and supplies for dried blood spot collection, and (4) engagement materials such as water bottles, bracelets, and lip balm. The SC group receives a single mailing of all materials. In contrast, to maintain program engagement during their delay, the FP group receives the same material in multiple mailings at a frequency of approximately one mailing per week until commencement of the behavioral counseling protocol.

Further, after intervention initiation, all participants receive a quit day card. Study staff mail the card with an encouraging note to reinforce the quit day set during counseling. Participants receive two additional mailings between end of treatment (Week 4) and follow-up (Month 3). These mailings remind participants of the upcoming primary assessments, as well as provide an opportunity to update any contact information that may have changed during their time in the study.

Dried Blood Spot (DBS) Training and Collection

One week prior to the study assigned quit date, all participants complete standardized training to self-collect the dried blood spots. During this 30-minute phone call, participants review the study-supplied written and video training materials, and collection materials (e.g., microlancets, collection cards).[18] The participant then practices collecting DBS and sends a picture of the completed DBS sample via text message or email to the study staff to receive feedback on their sample. Staff troubleshoot problems as necessary.

Participants then complete five DBS samples. The samples collected at Week -1, Week 0 (quit date), and Week 1 will be analyzed for progesterone. The samples collected at Week 4 (end of treatment and one week after the discontinuation of NRT treatment) and Month 3 will be analyzed for cotinine.

Self-Administered Surveys

Upon initiation of the study intervention, participants complete weekly self-administered survey via REDCap. Participants receive a link to the surveys via email or text (per their preference) on the day of their counseling session. If surveys are not completed by the time of their counseling session, counselors remind them to complete the surveys. Participants are able to complete surveys within two days of each counseling session. Counselors monitor for completion during this timeframe. For the end of treatment (Week 4) and follow-up (Month 3) the window was expanded to within two weeks and within four weeks of the time point. The surveys included at each time point are displayed in Table 1.

Smoking Cessation Intervention

The behavioral counseling for *Project Phase* is modeled after standard state quitline protocols.[19,20] Based on best practices to quit smoking, the intervention includes six weekly counseling sessions using evidence-based cessation interventions combined with a four-week supply of the nicotine patch. The dose for the patches is prescribed based on their current smoking history. The six-week counseling protocol is identical to each condition. Session timing and frequency is guided by best practices and includes multi-session proactive and reactive calls.[21] Specifically, the first three weeks on counseling focuses on identifying triggers to smoke, preparation to quit, setting a quit day (week three in counseling), education on the use of NRT for quitting

smoking. The final three weeks focus on maintenance of smoking cessation and relapse prevention. During each week, participants are also directed to specific pages in their self-help quit booklet to complement the session content covered by the counselors. Each session lasts approximately for 25-30 minutes. Key counseling content includes: increasing motivation for smoking behavior change with collaborative, individualized treatment plans, support with goal setting, improving skills (e.g., self-monitoring) to identify smoking "triggers" and manage urges, improving smoking cessation self-efficacy, and addressing addiction with education for using NRT. One week prior to the set quit day, participants are mailed a two-week supply of the patch (with usage of the patch starting on the set quit day), with an additional two-weeks mailed after completion of the quit day counseling. At the end of each session, the counselor texts participants key content covered during the session along with a reminder for the next scheduled session.

While the structure and frequency of the telephone sessions are the same between randomization groups, counseling content and materials differ in a few ways: (a) participants receive information on the role of the menstrual cycle on influencing smoking behavior change, (b) every session has menstrual-cycle-based content (e.g., bloating, premenstrual cramps) and how it may influence smoking behaviors, and (c) counseling specifically focuses on menstrual cycle symptoms as triggers to smoke or conditioned stimuli (e.g., negative affect, bloating, weight gain) with participants encouraged to develop stimulus and urge management strategies specific to identified triggers. Given the importance of scheduling a quit date 6-8 days post onset of menses, participants in the FP condition are sent reminders. Once participants have completed counseling session 1, they are sent automated surveys through REDCap that ask if they have started menses. These are sent every other day. Participants also receive materials in their welcome kit that remind them to notify study staff of the first day of their period, as well as reminders at the end of the welcome call and the first two counseling sessions. Once the survey is complete, or the participant notifies study staff, the quit day and third counseling session are set.

Counselor Trainings and Treatment Fidelity

Trained masters-level behavioral counselors, who are matched to study participants per schedule availability, deliver both interventions. Training consists of role-playing, didactic sessions, and readings on nicotine dependence and treatment, including the unique barriers in smoking cessation among women and the role of the menstrual cycle. Counselors are trained on evidence-based cognitive behavioral counseling and motivational interviewing strategies to facilitate smoking cessation. Other skills include increasing motivation to quit, preparing for setting a quit date, how to identify the correct menstrual timing of the quit date for FP participants, how to provide social support and positive reinforcement, facilitating problem solving to overcome barriers, and education on usage of the nicotine patch including dosage, side-effects monitoring,

and safe disposal. All counselors are required to pass competency ratings prior to initiation of counseling. Competency criteria include (a) tobacco dependence and knowledge, (b) women and smoking, (c) counseling skills, (d) preparation for the quit day, (e) pharmacotherapy for smoking cessation, and (f) relapse prevention. Counselors are rated as being '*aware', 'knowledgeable', or 'proficient'* in each category; counselors have to attain a rating of '*knowledgeable to proficient*' to be competent in each criterion. Counselors will engage in weekly supervision meetings with the PIs to problem solve participant issues.

Behavioral counseling intervention processes will be assessed in both conditions throughout the counseling period. Process data will include number of sessions, average time per counseling session, and counselor ratings of participant engagement (e.g., interest in session topics, distraction, and responsiveness to session materials). Counselors will maintain session-specific checklists. All calls will be recorded, and sessions will be reviewed against checklists with the expectation being to maintain $\geq$90% fidelity.

Participant Compensation

Participants earn up to $160 in Amazon e-gift cards for their participation based off the completion of study tasks such as counseling sessions, surveys, and dried blood spot samples. Payments are sent via email research staff on a weekly basis and are tied to completion of the survey assessments and DBS collection to encourage compliance and retention.

Study Outcomes

The primary, secondary, and exploratory outcomes are displayed in Table 1. Our first aim, which focused on feasibility and acceptability, includes the following outcomes: (a) recruitment rate (i.e., average number of participants enrolled per month), (b) retention rate (i.e., total number of participants who completed to Week 4 and Month 3 out of the total number of participants enrolled), (c) ability to correctly identify menstrual phase (i.e., total proportion of FP participants who have a DBS progesterone level of <2 ng/ml on quit date[22]), and (d) participant overall study satisfaction at Week 4 and Month 3. Our second aim, which focused on preliminary efficacy, includes outcomes of self-report 24-hour and seven-day point prevalance abstinence. These outcomes will be assessed using timeline follwback (TLFB) methods at Week 1 (one-week post quit day), Week 4 (end of treatment) and Month 3.[23] Abstinence will be biochemically verified at Week 4 (after NRT treatment has ended) by measuring cotinine in the self-collected DBS.[24]

Analysis Plan

Feasibility and acceptability (primary outcomes), including recruitment, retention, satisfaction and correct identification of menstrual phase, will be described using frequencies and percentages, and 95% confidence

intervals. Baseline characteristics of dropouts and non-compliers will be compared with completers and compliers using t-tests and regression methods. Demographics will be described with means, standard deviations, ranges and frequencies/ proportions and will be explored as correlates for successful cessation and feasibility outcomes using logistic regression. Barriers to and satisfaction with the intervention will be summarized with descriptive statistics. We will investigate potential efficacy (secondary outcome) by comparing smoking cessation rates between arms at Week 1, Week 4 and at Month 3 follow-up, estimated from generalized linear mixed models with a logit link. Fixed effects of time, group, and their interaction will be included to allow for different patterns of change over time. A random effect of subject will be included. Mixed models account for the correlated data due to repeated measures on participants and yield valid results when data are missing completely at random and at random.[25] If the missing outcome data rate is higher than 10% we will perform sensitivity analyses using multiple imputation.[25]Finally, we will address our third aim by modeling factors associated with smoking cessation (e.g., social support, weight concerns, urge coping) by menstrual phase using multiple logistic and linear regression models.

Power Analysis

A sample of 116 yields precision (half-width of a 95% confidence interval [CI]) to estimate our primary outcomes of feasibility (e.g., recruitment, retention) to within ±5%, conservatively assuming a base rate of 50% (which maximizes the standard error) and the formula for a 95%CI for a binary proportion. This sample size also yields 80% power to detect a difference of 20% in the difference between recruitment strategies (ASHLine vs. Facebook). Assuming a dropout rate of 20%, the sample size yields more than 85% power to detect a difference of 15% in adherence. As this is a pilot study, it is not properly powered to definitively test efficacy for important differences between groups. However, potential efficacy can be determined: this sample size yields 90% power assuming no dropout to detect a difference of 20% in cessation rates, 83% assuming 20% dropout, and 77% assuming 30% dropout. Furthermore, it provides 80% power to detect a standardized effect size for continuous outcomes (urge coping) of 0.53 (medium sized) for n = 116 (assuming no dropout); 0.60 assuming 20% dropout, and 0.64 assuming 30% dropout. This sample size is large enough to reasonably estimate, in conjunction with sensitivity analysis, relevant variance components, recruitment, and dropout rates for use in a future definitive trial. [26,27]

Discussion

Although the current clinical guidelines for smoking cessation call for specific interventions designed to address the women-specific challenges,[28] these are currently lacking. Women have a higher risk for smoking-related morbidity and mortality, they are more likely to relapse, and more likely to expose infants and children

to secondhand smoke than men.[8] This study addresses current gaps in the field and extends findings of women and smoking by testing a novel intervention of timing quit-dates to the follicular phase to improve smoking cessation outcomes. Utilizing menstrual phase effects on smoking-related behavior could double the odds of successful smoking cessation attempts in women at little to no cost.[9,11–15]

Project Phase is the first to examine the role of the menstrual cycle in a quitline-based intervention. The use of this novel intervention element (coordinating the timing of the quit date to the menstrual cycle) within the standard quitline setting may provide women with easier access to smoking cessation help, as well as services that are more effective. Due to the nature of the quitline setting, this intervention is low-cost. Study outcomes will provide preliminary data for a larger scale randomized controlled trial to examine the efficacy of this novel intervention on smoking outcomes. If effective, our study can be adopted by quitlines (now a standard care for smoking cessation) and can be a unique opportunity to enhance quit rates in women.

Contemporary associative learning theory and principles of cognitive behavioral therapy have guided the framework of the counseling component with a specific focus on the menstrual cycle for the active intervention (i.e., the follicular phase group) in Project Phase. Specifically, while counseling focuses on stimulus and urge management strategies in response to triggers in both conditions, participants in the intervention condition specifically receive additional guidance on associations between menstrual-cycle-related symptoms (e.g., bloating, negative affect, weight concerns, reactivity to environmental cues) as conditioned stimuli to smoke and learn adaptive compensatory urge management strategies specific to these triggers. Our intervention model is the first to extend current evidence-based cessation counseling to the menstrual phase specific symptoms within a quitline setting.

One potential critique is the possible delay for individuals quitting during their follicular phase can be problematic for those who feel that they want to quit right away. The potential three-week delay is a time when the motivation for smoking cessation may decline and participants may be discontinuing their participation. Alternately, this can be an opportune time for behavioral counselors to facilitate motivation and increase preparation around quitting that otherwise may not be possible in a quitline setting where a quit day is set within a week of program enrollment. We anticipate that our implemented retention strategies (use of weekly mailing during the waiting period, multiple retention mailings, participant incentives) will proactively address this potential issue. Finally, our study only uses the NRT patch as a form of pharmacotherapy. NRT is less effective in women whereas varenicline is most effective in women.[29] However, the use of varenicline in quitlines is extremely limited. Thus given our primary goal to enhance quit rates in women within quitline settings, we did not use varenicline in the current project.

Our evidence-driven, telephone-based intervention that uses a menstrual-cycle timed quit attempt approach could improve smoking cessation rates, and ultimately reduce morbidity and mortality among

women of reproductive age and their children. Project Phase integrates emerging evidence related to ovarian hormones and smoking outcomes with state-of-the-science quitline cessation programs. Results from this study will guide protocol development and generate hypothesis for larger randomized controlled trials while developing a portable intervention that could be implemented and disseminated nationally at very low-cost.

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Figure 1. Study Flow Overview

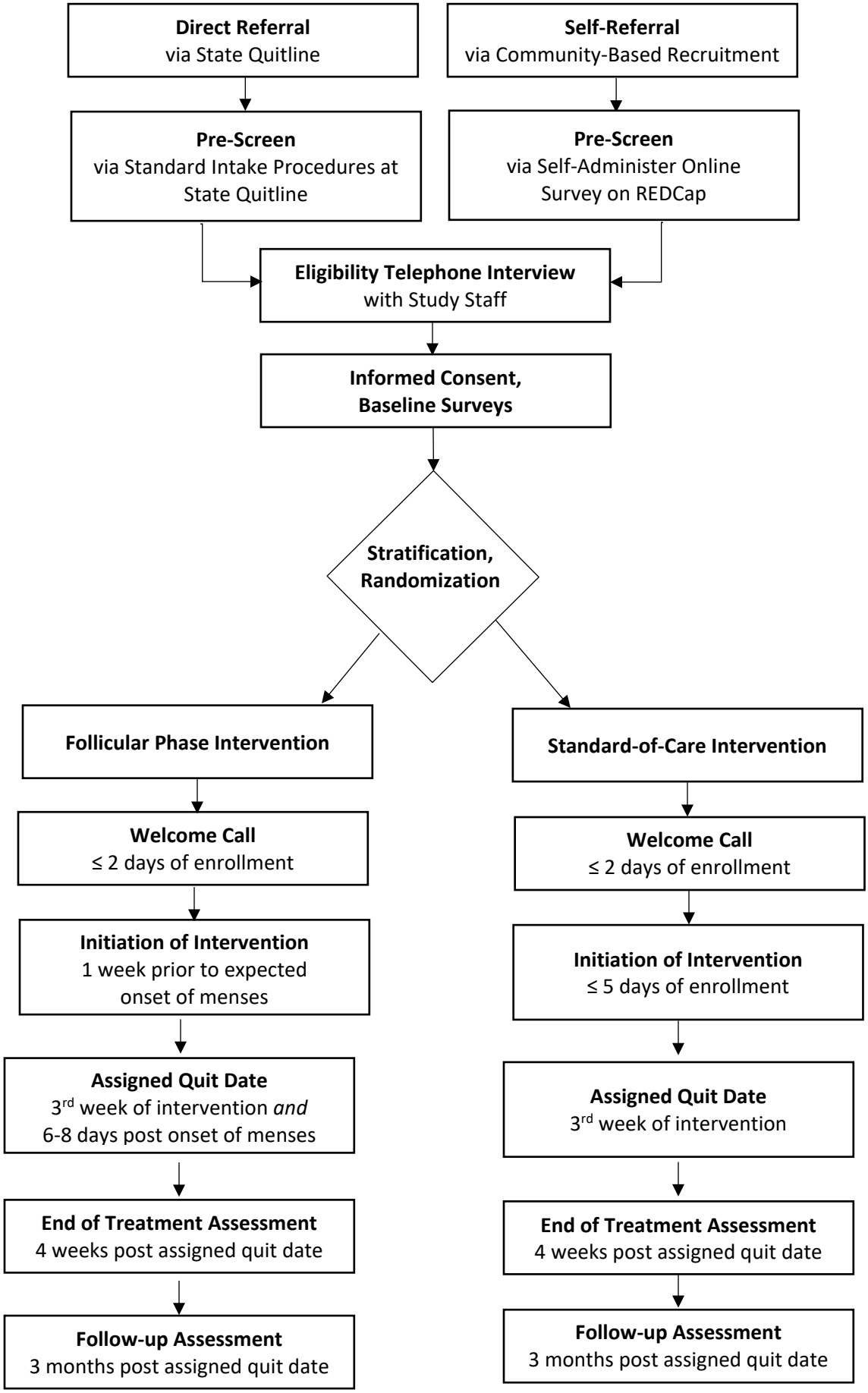

Table 1. Overview of Study Outcomes

Outcome	Domain (Aim)	Name	Source	Time Point									
				SC	BL	W -2	W -1	W0*	W1	W2	W3	W4	M3
Primary	Feasibility (1)	Recruitment Rate	Study Records	X									
Primary	Feasibility (1)	Retention Rate	Study Records									X	X
Primary	Feasibility (1)	Correct Phase Identification[17]	DBS					X					
Primary	Acceptability (1)	Participant Satisfaction	Survey									X	X
Secondary	Smoking (2)	Timeline FollowBack[23]	Screening Interview, Counselor Call, Survey	X	X	X	X	X	X	X	X	X	X
Secondary	Smoking (2)	Nicotine Inventory	Survey	X				X				X	X
Secondary	Smoking (2)	Cotinine[24]	DBS									X	X
Secondary	Menstrual (2)	Menses Onset	Screening Interview	X	X								
Secondary	Menstrual (2)	Menstrual Cycle Monitoring Form[30,31]	Survey		X	X	X	X	X	X	X	X	X
Secondary	Menstrual (2)	Progesterone, Estradiol	DBS				X	X	X				
Exploratory	Counseling (3)	Intrapersonal Support Evaluation[32]	Survey		X								
Exploratory	Counseling (3)	Weight Control Scale[33]	Survey		X								
Exploratory	Counseling (3)	Patient Health Questionnaire 2	Survey		X								
Exploratory	Counseling (3)	Center for Epidemiologic Study – Depression 10[34,35]	Survey		X							X	X
Exploratory	Counseling (3)	Minnesota Tobacco Withdrawal Scale[36]	Survey				X	X	X				
Exploratory	Counseling (3)	Anxiety Sensitivity Index[37]	Survey		X							X	X
Exploratory	Counseling (3)	Revised Adverse Childhood Events[38]	Survey		X								
-	Descriptive (3)	Demographics	Screening Interview, Survey	X									
-	Descriptive (3)	Smoking/Medical History	Screening Interview, Survey	X									
-	Descriptive (3)	NRT Compliance	Phone Interview					X	X	X	X		
-	Descriptive (3)	Health/Medication Changes	Survey			X	X	X	X	X	X	X	X

* W0 is quit week. **Key**: DBS: Dried Blood Spots. M: Month. NRT: Nicotine Replacement Therapy W: Week.