

Feasibility and acceptability of testing a menstrual-cycle timed smoking cessation intervention for women of reproductive age (*Project Phase*): Protocol of a pilot randomized controlled trial

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ABSTRACT

Background: Compared to men, women have unique barriers to smoking cessation and are less likely to utilize quitline services. While current clinical recommendations have called for sex/gender-specific smoking cessation protocols, quitlines have not been expanded protocols to address the unique needs of women. Menstrual cycles (and/or ovarian hormones) influence quit outcomes in women. This paper presents the study design and protocol for a randomized control trial (*Project Phase*) 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 and naturally-occurring menstrual cycles. Eligible participants are randomized to either the mid-Follicular Phase (FP) or Standard Care (SC-control) group. Counseling includes six weekly telephone sessions with four weeks 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). In addition to providing education on menstrual cycle and quitting, quit day for FP participants is set 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. Dried blood spots will be used to bioverify menstrual cycle phase and smoking status.

Discussion: If feasible and acceptable, our behavioral counseling intervention that times the quit day to the mid-follicular phase of the menstrual may increase quit outcomes among women of reproductive age and has potential for dissemination across quitlines nationally.

1. 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 Refs. [5–8]). Additionally,

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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 mid-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 mid-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 mid-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.

2. Methods

2.1. Study design overview

Participants will be randomized (1:1 ratio) to: (1) mid-follicular phase (FP) intervention, in which participants start a six-week telephone-based behavioral counseling program that includes education on the role of the menstrual cycle on quitting smoking with a goal of setting a quit date 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 (no education on menstrual cycle and smoking behavior change provided) without regard to menstrual timing. In addition to counseling, both groups will receive four weeks of the NRT patch with use starting on the quit day (Week 3 in counseling). 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.

2.2. 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 ≥ 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 some-

one 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 will be referred to the state quitline.

2.3. 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) (Fig. 1). For the direct referrals, trained quitline staff will initially assess callers for eligibility. Those who are potentially eligible will be 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 will be securely transmitted to the study's REDCap database [16]. Similarly, for self-referrals, an initial eligibility screen will be completed online via REDCap. Those who meet initial eligibility, will complete a full eligibility assessment via a telephone interview with study staff.

2.4. Enrollment and randomization

Upon completion of the telephone interview, potential participants will be 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 will be 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 will complete a 10-min welcome call to receive an orientation of the study (e.g., counseling sessions, assessment timelines/procedures, incentive structure). The SC group will initiate 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 will be instructed to notify study staff via phone call, text message, or email at the onset of menses.

2.5. Participant materials and mailings

After the welcome call, participants will 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 if treatment is delayed, the FP group will receive the same material in multiple mailings at a fre-

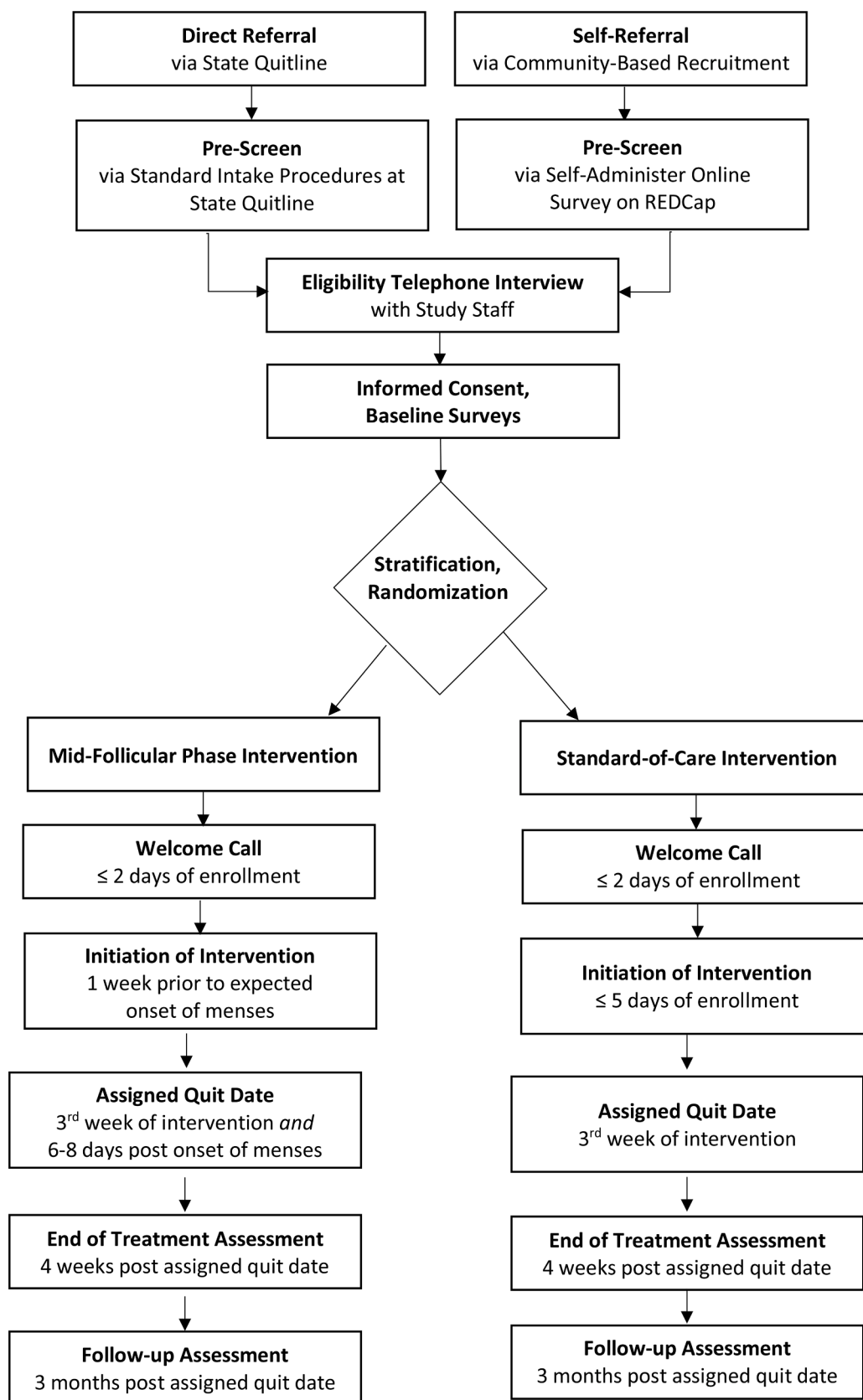


Fig. 1. Study flow overview.

quency of approximately one mailing per week until commencement of the behavioral counseling protocol. If there is no delay, materials will be sent similar to the SC group.

Further, after intervention initiation, all participants will receive a quit day card to reinforce the quit day set during counseling. Participants will also receive retention mailings between end of treatment (Week 4) and follow-up (Month 3) to remind participants of the upcoming primary assessments, as well as to provide an opportunity to update any contact information, if needed.

2.6. Dried blood spot (DBS) training and collection

One week prior to the assigned quit date, all participants will complete standardized training to self-collect the dried blood spots. During this 30-min phone call, participants will 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 will troubleshoot problems as necessary.

Participants will complete five DBS samples. The samples collected at Week -1, Week 0 (quit date), and Week 1 will be analyzed for progesterone to confirm menstrual phase following current recommendations (ref) [19,20]. 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 to confirm self-reported smoking abstinence following current recommendations (refs) [21–23].

2.7. Self-administered surveys

After initiation of counseling, participants will complete weekly self-administered survey via REDCap. On the day of the scheduled counseling session, participants will receive a link to the surveys via email or text. If surveys are not completed by the time of their coun-

seling session, counselors will remind them to complete the surveys. Participants will be able to complete surveys within two days of each counseling session. For the end of treatment (Week 4) and follow-up (Month 3) the window will be 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.

2.8. Smoking cessation intervention

The behavioral counseling for *Project Phase* is modeled after standard state quitline protocols [24,25]. Based on best practices for smoking cessation, 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 [26]. 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 will be directed to specific pages in their self-help quit booklet to complement the session content covered by the counselors. Each session is expected to last approximately for 25–30 min. Key counseling content will include: 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 will be 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 will text participants key content covered during the session along with a reminder for the next scheduled session.

Table 1
Overview of study outcomes.

Outcome	Domain (Aim)	Name	Source	Time Point											
				SC	BL	W -2	W -1	W0 ^a	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 [27]	Screening Interview, Counselor Call, Survey	X	X	X	X	X	X	X	X	X	X	X	X
Secondary	Smoking (2)	Nicotine Inventory	Survey	X				X					X	X	
Secondary	Smoking (2)	Cotinine [22]	DBS										X	X	
Secondary	Menstrual (2)	Menses Onset	Screening Interview	X	X										
Secondary	Menstrual (2)	Menstrual Cycle Monitoring Form [33,34]	Survey	X	X	X	X	X	X	X	X	X	X	X	
Secondary	Menstrual (2)	Progesterone, Estradiol	DBS				X	X	X						
Exploratory	Counseling (3)	Intrapersonal Support Evaluation [35]	Survey	X											
Exploratory	Counseling (3)	Weight Control Scale [36]	Survey	X											
Exploratory	Counseling (3)	Patient Health Questionnaire 2	Survey	X											
Exploratory	Counseling (3)	Center for Epidemiologic Study – Depression 10 ^{37,38}	Survey	X									X	X	
Exploratory	Counseling (3)	Minnesota Tobacco Withdrawal Scale [39]	Survey				X	X	X						
Exploratory	Counseling (3)	Anxiety Sensitivity Index [40]	Survey	X									X	X	
Exploratory	Counseling (3)	Revised Adverse Childhood Events [41]	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	X	

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

While the structure and frequency of the telephone sessions are the same between randomization groups, counseling content and materials in the FP condition 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. Education on the role of the menstrual cycle increases participant's knowledge of sex hormones as they relate to smoking behavior change and provides a rationale for quitting post onset of their period. Given the importance of scheduling a quit date 6–8 days post onset of menses, participants in the FP condition will be sent reminders. At the end of counseling session 1, they will be sent automated surveys every other day that ask if they have started menses. 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 if the participant notifies study staff, the quit day and third counseling session will be set.

2.9. Counselor trainings and treatment fidelity

Trained masters-level behavioral counselors, who are matched to study participants per schedule availability, will 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.

2.10. Participant compensation

Participants will 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 will be 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.

2.11. 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 [19]), 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-h and seven-day point prevalence abstinence. These outcomes will be assessed using timeline followback (TLFB) methods at Week 1 (one-week post quit day), Week 4 (end of treatment) and Month 3 [27]. Abstinence will be biochemically verified at Week 4 (after NRT treatment has ended) by measuring cotinine in the self-collected DBS [22].

2.12. 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 [28]. If the missing outcome data rate is higher than 10% we will perform sensitivity analyses using multiple imputation.²⁸ 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.

2.13. 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 $\pm 5\%$, 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 [29,30].

3. Discussion

Although the current clinical guidelines for smoking cessation call for specific interventions designed to address the women-specific challenges [31], 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 mid-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 (education on the role of menstrual cycle on quitting and 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 and tailored services to quit. 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 of reproductive age.

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 mid-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 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 mid-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 [32]. 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. Re-

sults 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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