Smoking Cessation for Cervical Cancer Survivors (Project SUCCESS)

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SPECIFIC AIMS

Strikingly high rates of tobacco smoking have been documented among cervical cancer survivors. Recent national data indicate that between 44% and 48% of cervical cancer survivors are current smokers.[1-3] The prevalence of smoking among cervical cancer survivors is over five times as high as that among lymphoma and prostate cancer survivors, and over 2.5 to 3 times as high as that among survivors of all types of cancer combined.[3,4] Furthermore, while overall smoking rates have declined substantially among cancer survivors and among the general population of smokers, the prevalence of smoking among gynecologic cancer survivors – particularly cervical cancer survivors – has remained extraordinarily high.[1,5] This is a critically important survivorship and public health issue given that smoking is a significant risk factor for cervical cancer [6] and continuing to smoke after a cancer diagnosis is associated with an increased risk of cancer recurrence, second primary cancers,[7] and the development and progression of other smoking-related morbidities such as cardiovascular and respiratory diseases.[8-11] Compared to survivors of other types of cancer, cervical cancer survivors have a significantly higher risk of developing any subsequent malignancy.[12-14] Thus, it has been recommended that cervical cancer survivors be provided with a survivorship care plan that addresses the dangers of continued tobacco use and the risk of subsequent malignancy that persists throughout the survivor's lifetime.[12] A crucial part of this survivorship plan should involve the delivery of smoking cessation treatment designed to address the specific needs of these women.[15] The vast majority of cancer survivors report a desire to quit smoking, and most are interested in cessation treatment programs.[16,17] Unfortunately, cessation counseling is rarely delivered by healthcare providers. Only two-thirds of patients smoking at the time of a cancer diagnosis are advised to quit by healthcare providers,[17] and very little research has focused on the development and evaluation of smoking cessation interventions for cancer survivors. Thus, there is a critical need to evaluate the efficacy of smoking cessation treatments among survivors of cervical cancer. The proposed study will be the first to target and address the specific treatment needs of this vulnerable and underserved population.

This study will evaluate the efficacy and cost-effectiveness of a theoretically- and empirically-based "**M**otivation **A**nd **P**roblem-**S**olving" (MAPS) approach to promoting and facilitating smoking cessation among cervical cancer and high grade cervical dysplasia survivors. Participants (N=300) will be recruited through the Stephenson Cancer Center or OU Physicians at the University of Oklahoma Health Sciences Center, via the ClinicalTrials.gov website, by responding to recruitment flyers and internet advertisements (e.g., flyers in clinics, Facebook), and through referrals from healthcare providers. Participants will be randomly assigned to one of two treatment groups: 1) Standard Treatment [ST] or 2) "**M**otivation **A**nd **P**roblem-**S**olving" (MAPS) ST will consist of a mailed packet of materials including a letter referring smokers to the Oklahoma Tobacco Helpline, Florida Quitline or to the national quitline number (1-800-QUIT-NOW) for participants residing in other states, free nicotine replacement therapy when ready to quit, and standard self-help materials. ST will be mailed a total of 3 times to participants with completed assessments (Baseline, 6 and 12 months). MAPS will consist of ST plus up to 6 proactive telephone counseling sessions delivered over a 12-month period. Telephone assessments across all treatment conditions will be administered at baseline and 3, 6, 12 and 18 months after baseline. The primary outcome is abstinence from tobacco at 18 months and the secondary outcomes are abstinence at other assessments, as well as quit attempts, cigarettes per day, use of the quitline across all post-baseline assessments, and cost-effectiveness.

MAPS is a holistic, dynamic approach to facilitating behavior change that utilizes a combined motivational enhancement and social cognitive approach based on motivational interviewing (MI)[18,19] and social cognitive theory.[20-22] MAPS is designed for all individuals regardless of their readiness to change, and specifically targets motivation and intrinsic motives for change, social cognitive constructs (e.g., agency/self-efficacy), and other factors of key relevance to cervical cancer survivors (e.g., stressors, anxiety, depression, family conflicts, finances, fear of cancer recurrence). Because MAPS revolves around a Wellness Program that addresses numerous barriers and concerns that are prevalent among cervical cancer survivors, we believe it is particularly appropriate for treating this population. Furthermore, the delivery of this intervention via telephone offers a less resource intensive modality while also minimizing participant burden.

The specific aims are to:

1. Compare the efficacy of a MAPS approach to promoting and facilitating smoking cessation to ST among cervical cancer survivors.
2. Assess the effects of MAPS on hypothesized treatment mechanisms (motivation, agency, and stress/negative affect) and the role of those mechanisms in mediating MAPS effects on abstinence.
3. Compare the cost-effectiveness of MAPS and ST.

SIGNIFICANCE

Despite public health efforts that have had a dramatic influence on reducing the prevalence of smoking, smoking remains the leading cause of preventable morbidity and mortality in the United States.[23] In addition to causing chronic bronchitis, emphysema, heart disease and cerebrovascular diseases, smoking is linked with increased risk of at least 15 different cancers and, in the presence of HPV, is a primary risk factor for cervical cancer.[6,24-27] Since the Pap test became widely integrated into clinical practice in the 1950s and 1960s, cervical cancer has been preventable, and incidence rates have dramatically declined.[28] Despite this decline, in the United States, approximately 250,000 women are survivors of cervical cancer, over 12,000 new cases of invasive cervical cancer are diagnosed each year, and approximately 4,200 women die from the disease each year.[28,29] Cervical cancer predominantly affects younger women with a median age at diagnosis of 49 years.[29] Furthermore, there are profound racial/ethnic and socioeconomic disparities in the incidence and mortality of the disease.[30] Compared to white women, the incidence of cervical cancer is 39% higher among African American women[31] and 80% higher among Latina women.[32] In addition, African American and Latina women are significantly more likely to die from cervical cancer.[31,32] Smoking prevalence is lower among African American (15.5%) and Latina (8.6%) women compared to non-Latina White women (18.8%).[33] However, women that are members of these racial/ethnic minority groups as well as women with low socioeconomic status are known to suffer disproportionately from the health consequences of smoking,[34-36] and existing evidence suggests that these individuals may have greater difficulty quitting smoking.[37 38 39] Moreover, disparities in tobacco use by SES have increased over the last several decades despite widespread availability of free, effective cessation treatment. Taken together, women with low socioeconomic status and women who are members of racial/ethnic minority groups suffer tremendous disparities with regard to cervical cancer related morbidity and mortality and the health consequences of smoking. Therefore, women who are current smokers and have a history of cervical cancer represent a particularly vulnerable subgroup at substantially elevated risk.

Recent national data indicate that a strikingly high proportion of cervical cancer survivors – between 44% and 48% – are current smokers.[1-3] This prevalence rate is extraordinarily high compared to the prevalence of smoking among other groups of cancer survivors. Specifically, it is over five times as high as that among lymphoma and prostate cancer survivors, and over 2.5 to 3 times as high as that among survivors of all types of cancer combined.[3,4] Continuing to smoke after a cancer diagnosis is associated with an increased risk of cancer recurrence, second primary cancers, and the development and progression of other smoking-related morbidities such as cardiovascular and respiratory diseases.[9] Furthermore, cervical cancer survivors have an increased risk for other subsequent tobacco-related cancers when compared with individuals who have never been diagnosed with cancer and survivors of other cancer types of cancer.[15] Therefore, there is a crucial need to provide these women with evidence-based smoking cessation treatment that has been designed to facilitate long-term cessation and prevent relapse while addressing survivorship issues related to cervical cancer.

Smoking Cessation Interventions among Cancer Survivors. The vast majority of cancer survivors who smoke report a desire to quit, and most are interested in cessation treatment.[16,17,40] Unfortunately, counseling about cessation is rarely delivered by healthcare providers. Only two-thirds of patients smoking at the time of a cancer diagnosis are advised to quit by healthcare providers,[17] and very little research has focused on the development and evaluation of smoking cessation interventions for individuals diagnosed with cancer. To date, fewer than 15 randomized clinical smoking cessation trials have been conducted with cancer patients.[41] With only a few exceptions, these studies have had small sample sizes (<30), measured only short-term smoking status, and most importantly, found no significant treatment effects.[42-47] Larger studies have also generally failed to find significant treatment effects.[48-51] Typically, interventions have focused on advice to quit, nicotine replacement therapy, written materials, and short intervention periods. Even fewer trials have addressed cessation among cancer survivors following the acute treatment phase, and no studies that we know of have specifically targeted women who have been diagnosed with cervical cancer.[52] Thus, there is a critical need to evaluate the efficacy of cessation treatments to promote long term abstinence and prevent relapse within this population.

Cervical Cancer Survivorship. The incidence and mortality of cervical cancer has declined substantially

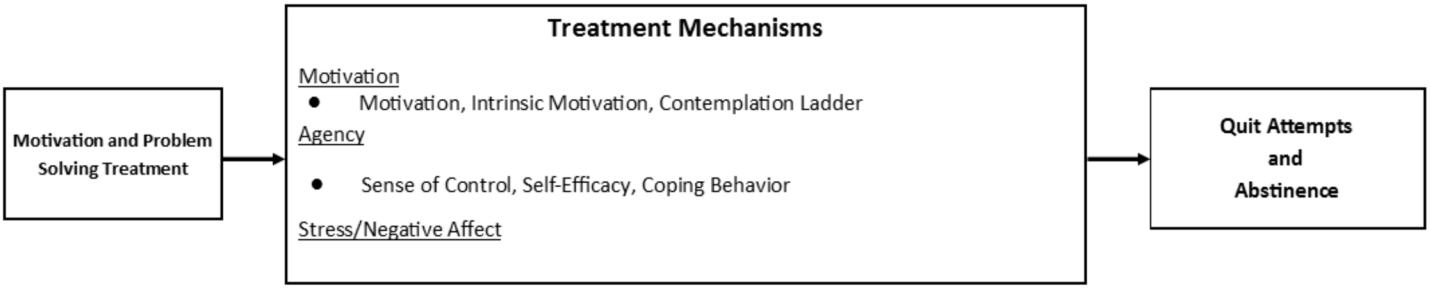
in the United States over the last four to five decades, and these declines are largely attributable to improvements in screening, early detection, and treatment.[28] Because cervical cancer generally affects younger women, women who are successfully treated can expect to live 25 to 30 years after treatment.[29] Therefore, post-diagnosis health behaviors of cancer survivors have begun to receive significant research attention. Such attention has been largely directed toward targets for tertiary prevention including smoking, alcohol use, physical activity, diet, and cancer screening as each of these behaviors may contribute substantially to poor outcomes related to cancer treatment sequelae.[5] As described above, no previous studies that we know of have specifically targeted survivors of cervical cancer. Multiple studies have documented that cervical cancer survivors suffer generally moderate to poor health related quality of life.[53] Longstanding psychosocial sequelae associated with the disease including anxiety, depression, stress related to family responsibilities, relationship issues, and difficulty with sexual functioning have also been well documented.[53-57] Moreover, cervical cancer survivors with lower socioeconomic status and limited social support are at even greater risk for poor outcomes.[53,58,59] Because MAPS is built around a Wellness Program, addresses life events, stressors, and other concerns of each individual (e.g., anxiety, depression, stress, fear of cancer recurrence, family conflicts, financial concerns, relationship and sexual issues) it is especially well-suited to address concerns of particular relevance to cervical cancer survivors. Furthermore, the delivery of the MAPS intervention and the collection of theoretical mechanisms data via telephone will offer a more cost effective and less burdensome approach.

MAPS Overview and Rationale. MAPS is a holistic, dynamic framework for behavior change that integrates treatment elements from both motivational interviewing (MI)[18,19,60] and social cognitive theory.[20,21,61] MAPS is structured around a Wellness Program that addresses a wide array of concerns and barriers to change, similar to patient navigation programs.[62] The overarching theoretical rationale for MAPS is the social cognitive model of behavior change.[21,63,64] Social cognitive theory posits that "High levels of both motivation and self-efficacy are important ingredients … an individual may fail to engage in a specific behavior despite high levels of self-efficacy if the motivation for performance is low or absent."[65] Similarly, Miller et al.[66] note that "the key element for lasting change is a motivational shift that instigates a decision and commitment to change. In the absence of such a shift, skill training is premature." That is, theory posits that effective smoking cessation treatments require both enhancing the motivation to achieve and maintain change, as well as developing the self-efficacy and skills necessary to do so. Nevertheless, current interventions often focus largely on either motivation or problem-solving/skills training despite the strong theoretical and empirical bases for focusing on both. When motivation is addressed, the focus is typically on motivating individuals to initiate a quit attempt, with little to no focus on the motivation to maintain change.[20,67]

In contrast to previous approaches, MAPS utilizes an innovative combination of motivational enhancement and social cognitive treatment techniques, is designed for all individuals regardless of their readiness to change, and specifically targets motivation, agency/self-efficacy, and stress/negative affect. Although stage-based conceptualizations of behavior change also emphasize both motivation and skills training, motivational shifts are conceptualized as relatively stable changes in "stage."[68] In contrast, MAPS is unique in that it conceptualizes motivation as a fluid construct that can fluctuate on a moment-to-moment basis depending on context. Counselors carefully assess and attend to changes in motivation so that treatment strategies are appropriately matched to motivation in the moment. MAPS is built around a Wellness Program that in addition to focusing on smoking cessation and relapse prevention, also addresses life events, stressors, and other concerns of each individual (e.g., anxiety, depression, stress, fear of cancer recurrence, family conflicts, financial concerns, relationship and sexual issues, etc.). By addressing the larger context in which smoking cessation occurs, not only are many of the barriers to success addressed, but we believe that adherence is increased because individuals perceive that the counselors care about them as whole people, and are not solely interested in their smoking behavior. Most importantly, our previous research has supported the efficacy of MAPS for motivating quit attempts, increasing cessation, and preventing relapse.[69-71]

Major Hypothesized Mechanisms. Both research and theory identify motivation, agency, and stress/negative affect as critical mechanisms underlying behavior change.[72-75] As such, MAPS specifically targets these mechanisms and they are hypothesized to underlie MAPS effects on behavior change.

Figure 1. Proposed Treatment Mechanisms



Motivation. Motivation prospectively predicts both the decision to make a quit attempt and the likelihood of cessation.[68,76] Further, motivation can change rapidly,[77-80] consistent with a recent model positing that motivation is dynamic and characterized by frequent fluctuations.[80] Motivation for the maintenance of change has received much less attention, although the extant empirical data indicate that motivational deficits are important in determining the maintenance of abstinence - 24% of all relapse episodes are characterized by a distinct lack of motivation to maintain abstinence[81] and a decline in motivation over time prospectively predicts relapse.[82] In addition, the specific motives underlying cessation are important.[83] Intrinsic motives predict abstinence whereas extrinsic motives do not, and only intrinsic motives are associated with long-term abstinence.[84,85] In sum, the data indicate that: motivation influences the initiation of a quit attempt, cessation, and the maintenance of abstinence; type of motives influence long-term success; and, motivation can fluctuate rapidly. Therefore, MAPS utilizes an approach with a specific emphasis on motivation and on appropriate therapeutic responses to common rapid fluctuations in motivation that occur throughout the change process.

Agency. Agency reflects the ability to intentionally affect one's behavior or life situation.[86] Self-efficacy is a form of agency that is context and behavior dependent (i.e., varies based on the behavior and situational demands). Self-efficacy has predicted cessation outcomes in numerous studies.[87-89] Therefore, based on both data and social cognitive theory,[21] MAPS targets agency as a key mechanism with particular relevance to cervical cancer survivors. MAPS is hypothesized to influence agency via the removal of barriers to quitting and maintaining abstinence, standard problem-solving and coping skills training, and increased motivation.[21,90-92]

Stress/Negative Affect. Stress and negative affect, measured in many different ways, predict cessation outcomes. Affective predictors include affective responses to smoking-related acute events, individual differences in affective vulnerability, depressive symptoms, and the magnitude and trajectory of stress/negative affect over time. [19,81,87,93-97] In addition to the stress/negative affect engendered by cessation, life stressors such as those experienced by cervical cancer survivors, have been shown to have adverse effects over time on motivation, self-efficacy, and abstinence. [98,99] Further, social cognitive theory posits that weak motivation for abstinence can increase stress/negative affect, particularly during high-risk situations.[21] Thus, MAPS is hypothesized to reduce stress/negative affect via its impact on decreasing ambivalence and increasing motivation, through the application of coping skills training and problem-solving, and through utilization of a holistic approach in which other life concerns and stressors are addressed.

APPROACH

Project Design and Procedures. Participants will be women with a diagnosis of cervical cancer or high grade cervical dysplasia who report smoking any cigarettes within the past 30 days, recruited through the Stephenson Cancer Center or OU Physicians at the University of Oklahoma Health Sciences Center, via the ClinicalTrials.gov website, by responding to recruitment flyers and internet advertisements (e.g., flyers in clinics, Facebook), and through referrals from healthcare providers. Participants will be followed for a period of 18 months, and randomly assigned to one of two groups: 1) Standard Treatment [ST], or 2) Motivation and Problem Solving [MAPS]. ST will consist of a mailed packet of materials including a letter referring smokers to the Oklahoma Tobacco Helpline, Florida Quitline or to the national quitline number (1-800-QUIT-NOW) for participants residing in other states, free nicotine replacement therapy when they are ready to quit, and standard self-help materials. ST will be mailed a total of 3 times to participants with completed assessments (at Baseline, 6 and 12 months). MAPS will consist of ST plus up to 6 proactive phone counseling sessions delivered over a 12-month period. The timing of counseling sessions in MAPS is flexible and determined jointly by the participant and the counselor.

Assessment calls will occur at Baseline and at 3, 6, 12, and 18 months after Baseline. The primary outcomes are abstinence from tobacco at the 18-month follow-up and abstinence across all follow-ups. Secondary outcomes are smoking quit attempts, cigarettes per day, use of the quitline, and cost-effectiveness. Participants will be scheduled to complete a baseline assessment call within one week. Following the baseline assessment, participants will be randomly assigned to ST or MAPS. Participants will schedule their first counseling call at that time (see Table 1).

Recruitment. Participants will be women with a diagnosis of cervical cancer or high grade cervical dysplasia who report smoking any cigarettes within the past 30 days, recruited through the Stephenson Cancer Center or OU Physicians at the University of Oklahoma Health Sciences Center, via the ClinicalTrials.gov website, by responding to recruitment flyers and internet advertisements (e.g., flyers in clinics, Facebook), and through referrals from healthcare providers.

Participant Eligibility. Inclusion criteria: ≥ 18; current smoker with a history of at least 100 lifetime cigarettes and a self-report of smoking within the last 30 days; history of cervical cancer or high grade cervical dysplasia (we have defined survivorship as beginning at the time of cancer diagnosis, consistent with the NCI definition); has a working cell phone; valid home address; speaks English, Spanish or both languages. Exclusion criteria: current use of tobacco cessation medications; self-report of being pregnant or lactating; or, another household member enrolled in the study; or contraindication of nicotine patch use unless under the supervision of a physician as advised by project staff.

Table 1. Schedule of Study Procedures and Assessments	**Screening**	**Baseline**	**Month 3**	**Month 6**	**Month 12**	**Month 18**
Inclusion/Exclusion Criteria	X	X				
Compensation		$60	$60	$60	$60	$60
TREATMENT PROCEDURES						
Standard Treatment (ST)	Delivered at Baseline, and Months 6 and 12					
Motivation And Problem Solving (MAPS)	ST plus up to 6 MAPS Counseling Calls delivered over 12 months					
DEMOGRAPHICS, MENTAL HEALTH						
Demographics and Smoking History		X				
Cancer stage at diagnosis, time since diagnosis, current stage, treatment status	X					
Subjective Social Status		X	X	X	X	X
Fear of Cancer Recurrence Inventory (FCRI)	X	X	X	X	X	X
MOTIVATION						
Contemplation Ladder		X	X	X	X	X
Reasons for Quitting (Intrinsic and Extrinsic Motivation)		X	X	X	X	X
Motivation		X	X	X	X	X
AGENCY: SENSE OF CONTROL, SELF-EFFICACY, COPING BEHAVIOR						
Sense of Control		X	X	X	X	X
Self-Efficacy Scale		X	X	X	X	X
Coping Inventory		X	X	X	X	X
STRESS, NEGATIVE AFFECT						
Perceived Stress Scale (PSS)		X	X	X	X	X
Positive and Negative Affect Scale (PANAS)		X	X	X	X	X
Depression (CES-D)		X	X	X	X	X
SMOKING-RELATED MEASURES						
Heaviness of Smoking Index (HSI)		X	X	X	X	X
Wisconsin Smoking Withdrawal Scale (WSWS)		X	X	X	X	X
Wisconsin Inventory of Smoking Dependence Motives (WISDM-37)		X	X	X	X	X
SMOKING STATUS, BIOCHEMICAL VERIFICATION, QUITLINE USE						
Smoking Status (SRNT)	X	X	X	X	X	X
Use of the Quitline Cessation Services (including Pharmacotherapy)		X	X	X	X	X
Cotinine (only among participants reporting abstinence)			X	X	X	X
PATIENT REPORTED OUTCOMES						

Functional Assessment of Cancer Therapy – Cervix Cancer (FACT-Cx)	X	X	X	X	X	X
EQ-5D (for health utilities)		X	X	X	X	X

Screening and Informed Consent Procedures. After being screened in-clinic or completing a secure online screener via REDCap, potential participants will be contacted by research staff at Moffitt Cancer Center or Stephenson Cancer Center. All eligible individuals will be invited to participate. A detailed description of the study will be provided and informed consent will be obtained. For those who agree to enroll in the study, research staff will obtain informed consent either in-person or over the phone. When participants are consented over the phone, research staff will read the informed consent document to participants and will document in our database that verbal informed consent has been obtained. A copy of the informed consent document and project materials will be provided to participants either in-person or by mail. All informed consent materials will be available in both English and Spanish. Women who decline or are ineligible will be given self-help materials and a referral to other cessation programs if they so desire.

Baseline Assessment and Randomization. Eligible women who choose to participate will complete telephone-administered questionnaires where data are entered directly into a database. The system includes online error checking and is used in all of our ongoing research projects. After completing the assessment, participants will be randomly assigned to ST or MAPS using a form of adaptive randomization called minimization.[100,101] Compared to techniques such as stratification, minimization results in better group balance with respect to participant characteristics. Minimization also provides for balanced treatment groups throughout the randomization process. Thus, for trials like this one that have extended accrual periods, the treatment groups remain balanced with respect to participant characteristics that may be related to time of accrual. In this study, we will randomize based on race/ethnicity, age, education, cigarettes/day, cervical cancer or dysplasia stage, cervical cancer or dysplasia treatment status, and time since diagnosis. After completing the assessment and randomization procedures, the 3-month follow-up assessment will be scheduled, and MAPS participants will schedule their first counseling call.

Financial Compensation and Retention Procedures. Participants will receive financial remuneration after completing each assessment call to compensate for the time and inconvenience associated with participation ($60 for each of the 5 assessment calls and up to a total of $300). The inclusion of compensation makes study participation more feasible and acceptable, which increases the representativeness of the sample and generalizability of the results. Compensation also increases follow-up rates, which reduces biases, and we have consistently achieved follow-up rates of approximately 80% even among very low-SES and racially/ethnically diverse smokers.[69,102] Other procedures to reduce attrition include: 1) mailing postcard reminders and calling to remind participants of upcoming assessment calls; 2) maintaining communication with participants throughout the study period via mailing birthday cards, holiday cards, etc. (each mailing includes a stamped address update postcard with the study return address); 3) Having a staff member available at all times during business hours as well as evenings and weekends to conduct assessment calls; 4) requiring that in addition to a functional phone number (necessary for counseling calls), participants must have a home address so that they can be contacted by mail if necessary; and 5) obtaining names, addresses, and phone numbers of up to three collaterals (i.e., relatives/friends) who can provide information on participants' whereabouts during the study (permission to contact the collaterals will be obtained from participants).
In addition to being compensated for the time associated with completing assessments, all participants will be compensated up to a total of $150 for completing the assessments, up to a total of $150 for costs incurred as a result for the use of study-related cell phone minutes, and up to a total of $120 for returning the cotinine tests. Compensation for completing assessments will be provided at baseline, 3, 6, 12, and 18 months from baseline (5 times points x $30 = $150). Compensation for study-related cell phone use will be provided at baseline, 3, 6, 12, and 18 months from baseline (5 time points x $30 = $150). Compensation for returning the cotinine tests will be provided at 3, 6, 12, and 18 months (4 time points x $30 = $120).

TREATMENT PLAN

Nicotine Replacement. All participants are eligible to receive a 12-week supply of nicotine patches and

lozenges. Participants will receive educational materials describing potential side effects; proper use of the patch and an illustration demonstrating the proper placement of the patch on the body. The nicotine patch and lozenge regimen will be based on the participant's self-reported smoking rate and will not be validated once assigned. At the time of enrollment, a research staff member will determine the proper dose. Participants who smoke >10 cigarettes/day will receive 8 weeks of 21 mg. patches, 2 weeks of 14 mg. patches, 2 weeks of 7 mg. patches, and 12 weeks of 2 mg. lozenges. Those who smoke <10 cigarettes/day will receive 8 weeks of 14 mg. patches, 4 weeks of 7 mg patches, and 12 weeks of 2 mg. lozenges.

Standard Treatment (ST). ST will consist of 1) a mailed packet of materials including a letter referring smokers to the quitline, 2) free nicotine replacement therapy when they are ready to quit, and 3) standard self-help materials. ST will be delivered a total of 3 times to participants with completed assessments (at Baseline, 6 and 12 months).

MAPS. MAPS will consist of ST plus up to 6 proactive telephone counseling sessions over a 12-month period. Each call will last approximately 30 minutes. Calls are scheduled based on participants' needs in negotiation with the counselor. For example, call timing can be negotiated to be clustered around the timing of a specific quit attempt. This is consistent with many interventions that load treatment during the period when relapse risk is highest.[103] Similarly, a woman not motivated to quit might negotiate the next call to occur many months later, or to occur sooner if specific barriers are noted that the individual wishes to address (e.g., stress, social support, family problems). Similarly, individuals struggling with maintaining abstinence may have several calls in a shorter period of time to get them through the problematic period, while others need less frequent help.

Counselor Qualifications and Training. We have adopted the therapist selection criteria employed in major clinical trials of MI-based approaches: 1) master's degree in counseling, psychology or social work, and 2) 2+ years of clinical experience.[66] This, along with our training and ongoing monitoring, will ensure that the delivered treatments are of the highest quality. Drs. Wetter and Vidrine are clinical psychologists with extensive experience in MAPS. Dr. Vidrine will conduct the counselor training and supervision. Counselors will receive 20 hours of MAPS training initially. Training will continue until the counselor reaches performance criteria for competence and adherence to the protocol. Counselors will also participate in 1-2 hour "booster" training sessions every 2 months. Dr. de Dios will supervise all Spanish language cases and bilingual therapists.

Treatment Fidelity and Monitoring of the Trial. To monitor deviation or drift from the protocol, all counseling calls will be digitally recorded and encrypted. A random sample of 10% of calls will be coded to ensure adequate competence and protocol adherence. A counselor who falls below performance criteria will receive additional training. The Motivational Interviewing Treatment Integrity Manual (MITI, 2nd edition)[104] has empirically validated reliability and validity and is used to code sessions and ensure treatment fidelity. The MITI works well for ensuring that counselors are following the protocol and utilizing the general MI spirit. In addition, the MITI is modified slightly to include coding of discussions around social cognitive/problem solving strategies and transitions between motivational enhancement and problem-solving. To monitor implementation, we will review weekly monitoring reports to track call completion and follow up rates. Dr. de Dios will be responsible for the fidelity monitoring of the Spanish language cases through the same process outlined above.

ASSESSMENTS

Assessments. Research Electronic Data Capture (REDCap) will be used to administer all questionnaires over the phone, in person, and/or via a web-based link when convenient for the participant. REDCap is a secure, web-based application designed to support data capture and utilizes a computer-administered self-interview format. This system is used in all of our current research and is designed to comply with all HIPAA regulations. Having research staff read the questionnaire items to participants will help overcome problems related to low literacy levels. Finally, we will attempt to reduce the inconvenience associated with completing assessments by providing financial compensation for participants' time. In sum, the battery of instruments comprehensively assesses our hypothesized mechanisms and associated variables of interest. A copy of each assessment instrument is included in the Appendix and all measures are listed in the Procedures Table (Table 1).

Smoking Abstinence. Abstinence assessments are based on recommendations from the Society for Research on Nicotine and Tobacco (SRNT).[105] We will report both prolonged and point-prevalence abstinence

at all follow-up assessment points. Prolonged abstinence refers to abstinence beginning with the initiation of treatment and including a grace period. The prolonged abstinence measure utilizes SRNT's recommendation for determining relapse (i.e., 7 consecutive days of smoking or smoking in each of 2 consecutive weeks). We will also evaluate two point-prevalence abstinence measures: 1) no smoking during the previous 7 days, and 2) no smoking during the previous 30 days. For all abstinence measures, we will analyze both completers only, and intent to treat in which smokers lost to follow-up are considered smoking. Abstinence at all follow-ups will be biochemically verified using a saliva cotinine level of <20 ng/ml.

Participants who self-report abstinence will be mailed a prepaid envelope, instructions for providing the cotinine sample, and a saliva cotinine kit. Research staff will contact participants by phone to ensure the arrival of packet, review the contents of the packet, and answer any questions participants may have about collecting a saliva specimen. Although cotinine cannot comprehensively validate the various abstinence definitions and timeframes, the most comprehensive review on biochemical validation concluded that misreporting is typically very low (~2%), and that adjustment for misreporting almost never influences analyses regarding relative treatment efficacy.[106] As such, our biochemical validation procedures are well justified both scientifically and practically.

PSYCHOLOGICAL DISTRESS ASSESSMENT AND MANAGEMENT PLAN

If a participant: 1) states that she is thinking about harming herself or others, or 2) uses actions or words to lead us to believe that she may be in eminent danger or in danger of harming another person, research staff will execute our standard crisis procedures. These procedures are described in detail in Appendix H. Once the plan is executed, a trained counselor will assess the participant using the "Crisis Assessment" (Appendix I). Participants will also be encouraged to follow ups with a mental health professional of their choice. Our team will have extensive interactions with participants throughout the course of the study. Therefore, our plan is appropriate for our target population.

STATISTICAL CONSIDERATIONS

Data Analysis Approach. The primary outcome is abstinence from smoking at the 18-month assessment. To test the treatment effect at 18 months, we will conduct logistic regression analysis with abstinence as the outcome variable, and treatment (a two-level categorical variable) as the predictor, adjusting for covariates, specifically, factors used in the minimization procedures (race/ethnicity, language, age, education, income, cigarettes/day, cervical cancer stage, and time since diagnosis). Interactions between treatment and specific covariates of interest may be included and tested for exploratory purposes.

Because the primary and secondary outcomes and mechanisms include repeated measurements that are correlated within subjects, our data analytic approach will also utilize generalized linear mixed model regression (GLMM)[107,108] to analyze the effects of MAPS across the 3, 6, 12, and 18 month timepoints. For abstinence, we will assume a logit link and binomial variance function for the GLMM, and parameterize them with blocking on individual nested within treatment conditions. Treatment and time will be included, as well as their interaction, with adjustment for relevant covariates. The effects of interactions between treatment and specific covariates will also be examined. Similarly analyses will also be conducted to assess the MAPS effects on quit attempt and use of the quitline (both binary). To assess MAPS effects on continuous measures such as cigarettes per day and mechanisms, the GLMM analysis will be replaced by linear mixed model (LMM) analysis (i.e., a special case of the GLMM). Similarly, the logistic regression analysis for the 18-month assessment will be replaced by multiple linear regression. Normalizing transformations for continuous measures (such as cigarettes per day) will be applied as appropriate. Alternatively, Poisson GLMM or Poisson regression could be used to analyze the effect of MAPS on cigarettes per day. In addition to examining the effects of treatment on primary and secondary outcomes and mechanisms, we will also assess the mediation (indirect) effects of treatment on abstinence through the mechanisms (motivation, agency, stress/negative affect) using single and/or multiple mediator models.[109] With the primary outcome being abstinence at the 18-month assessment, potential mediators will be mechanisms measured at the previous time points (i.e., 3, 6, and 12 months), one at a time. A recommended approach to estimating and/or testing for the indirect effects for a binary outcome variable is via coefficient standardization in the *b* path (e.g., logistic regression), as appropriate, and bootstrapping.[109-111] Appropriate covariates including mediators measured as baseline will be

adjusted for in the *a* and *b*-path analyses. Mediators in the final mediator model will be selected using a backward selection approach.[112] We will also compute and compare proportions of mediated effects along with their standard errors across the single and multiple mediator models, as well as across time points where the mediators are measured.[113] A larger proportion of the mediated effect in general suggests a larger mediation effect. Additional mediation analysis for repeated measures abstinence analyses will be conducted using a similar approach with both *a* and *b* paths involving repeated measures analysis, as applicable.[113]

Missing Data and Dropouts. It is anticipated that some individuals will drop out or be lost to follow-up, as is typical in smoking cessation treatment studies. Our primary analysis for examining abstinence at 18 months will utilize an intent-to-treat approach by coding missing abstinence data as smoking. However, we will also conduct sensitivity analyses by examining alternative approaches for handling missing data, including multiple imputation (under a missing at random assumption),[114,115] and selection models (under an assumption of non-ignorable missingness, or missing not at random).[114,116-118] In the multiple imputation approach, we will conduct analyses to examine whether participants who drop out of the study differ from those who do not, and include those covariates in our multiple imputation models, to mitigate the potential impact of non-ignorable missingness. Regardless of the approach used to handle missing data, it is unlikely that serious biases in estimation or considerable loss of efficiency in inference will result when the proportion of missing data low (e.g., not more than 10%; even more so when the missing data proportions are similar in MAPS and ST).

Overall, robust results based on both the primary and sensitivity analyses will strengthen our study findings.

Power. Our power analysis is based primarily on the comparison of 18-month abstinence rates between MAPS and ST. Because an intent-to-treat approach will be used, power is calculated based on the full sample without attrition (N=300; 150 per group), given that individuals lost to follow-up will be treated as smoking). All power analyses assume a significance level of 0.05 and a two-sided test. Based on the *Guideline*,[20] we estimated that abstinence for ST would be approximately 10%. Using a chi-square test to examine the effect of treatment on abstinence at 18 months, a sample size of 300 (150 per group) will provide 80% power to detect an overall treatment effect that corresponds to abstinence rates of 10% and 21.9% in ST and MAPS respectively. Relative to examining abstinence over time, these calculations represent the worst case scenario. Table 2 presents detectable differences across a range of possible abstinence rates. Analyses conducted using GLMM will have greater power to detect the same average differences across time.

Table 2. Detectable differences in binary smoking outcomes with 80% power (abstinence, quit attempt)

ST (n=150)	MAPS (n=150)
5.0%	14.60%
10.0%	21.90%
20.0%	34.40%
30.0%	45.70%
40.0%	56.20%

Although the proposed mediation analyses for aim 2 are theoretically-grounded and hypothesis-driven (see Figure 1), they are quasi-exploratory in nature, and the sample size for this study was based on power to detect a significant difference for Aim 1. Nonetheless, power for the mediation analyses (Aim 2) has been calculated as follows. For the mechanism analyses (Aim 2), power is based on a conservative 25% attrition rate (N= 300; 112 per group). Because the mechanism variables are continuous, a sample size of 300 (112 per group at 18 months) will provide 80% power to detect an effect size of 0.376 standard deviation (SD) unit (difference in means between the ST and MAPS divided by common SD), using a two group t-test with a 0.05 two-sided significance level. Because we have excellent power to detect treatment effects on the primary outcome and mechanisms, as well as the effects of mechanisms on abstinence (with power generally greater using continuous predictors than binary predictors such as treatment group), we expect to have good power to detect mediation effects. We note, however, that the power calculated for analyses in Aim 2 should be considered in the context of inflated type 1 error due to multiple analyses and hypothesis tests (including the mediation analyses) being performed for this aim. We feel that this inflated type 1 error is acceptable given the quasi-exploratory nature of this aim. Nevertheless, future studies focusing on testing specified mediational models should be sufficiently powered using approaches of Fritz and MacKinnon[119] or Thoemmes et al.[120], as appropriate.

Cost Effectiveness

Methods overview. Cost-effectiveness analyses (CEA) will compare the two interventions: ST and MAPS. The conventional CEA summarizes study findings in terms of the incremental cost-effectiveness ratio (ICER).[121,122] The ICER, calculated as the difference in mean costs between the new and standard treatment divided by the difference in mean effectiveness between the new and standard treatment, estimates the additional resource consumption needed to achieve an increase in an additional unit of effectiveness. The ICER is then compared with a commonly cited or published threshold value associated with an intervention already found to be cost-effective to determine whether a new intervention is cost-effective.

The net benefit approach, introduced more recently, [123,124], transforms the ICER into the net benefit, defined as $NB(\lambda) = \lambda \bullet \Delta E - \Delta C$, where λ represents a societal willingness-to-pay (WTP), ΔC represents the incremental costs; and ΔE represents the incremental effectiveness. We will report the CEA results both in terms of the conventional ICER and the CE acceptability curve,[123,125] the latter informs decision makers of the probability that the new intervention is more cost-effective than the standard treatment at various levels of societal WTP. The net benefit approach has been incorporated into a regression framework to allow for covariate adjustments and examination of interaction effects in CEA.[126] Shih and colleagues further extended this net benefit regression framework to a Bayesian regression framework to allow the inclusion of prior knowledge and more flexible inferences.[127,128] This regression-based approach is relevant to our study as there may be moderating factors such as individual characteristics that affect the cost-effectiveness of interventions.

Measures of costs and collection of cost data. For each of the two intervention arms, the costs associated with implementing the intervention will come from three sources: study personnel, production of materials, and materials to participants. Project staff will keep logs of time spent on each of the tasks related to implementing the intervention, net of additional time that may be spent to satisfy the research and evaluation components of the project. Costs of developing training materials and information systems will apply to each intervention arm, whereas costs associated with training counselors will apply only to MAPS. Any hardware costs necessary for implementing the intervention will be tracked through invoices. Material costs will be obtained from invoices maintained by project staff from vendors delivering intervention materials. All intervention-related costs will be expressed in local market terms for personnel, office space, furnishings, and equipment. The cost model will include all personnel, hardware, and material costs necessary to implement the interventions. Even if the research team uses existing resources at Moffitt Cancer Center, Stephenson Cancer Center, or the quitlines without charge (e.g., office space, phones, computers), we will estimate all of the expenses necessary for implementing MAPS since these expenses would be required for the implementation of population-based tobacco control programs. We will not include other health care costs. This decision was based on the existing evidence regarding the heath care cost consequences associated with smoking and cessation and the expectation of how this evidence impacts the difference in costs among different intervention arms. Although smokers incur greater health care costs than non-smokers,[129-133] it has been shown that cost savings related to improvement in health from cessation may be balanced out by future cost increases due to greater longevity.[134] In addition, former smokers incur greater short-term health care utilization and costs than continuing smokers.[132,135] That increase in cost however, is likely linked to a health event that precedes and motivates the successful quit attempt. That is, higher health care costs are concurrent with but not caused by smoking cessation.

Measures of Effectiveness. Two commonly used effectiveness measures in studies comparing the cost-effectiveness of cessation interventions are number of quitters and years of life saved (YOLS).[136] To facilitate comparing ICER estimated from our CEA with that from other published studies, we will include both measures. The number of quitters in each treatment arm will be retrieved from the primary abstinence endpoint at month 18. We will extrapolate from abstinence to YOLS using a published algorithm that models YOLS per quitter for persons in various age-specific subgroups.[137] In addition, to assist decision making in selecting among interventions targeted at different conditions that compete for limited budgets, we also included quality-adjusted life year (QALY) as an additional effectiveness measure, and calculate QALY from the health utilities obtained from the EQ-5D. This algorithm was favored over other published methods of extrapolation because it was built from a model with good face validity and has been adopted in many related CE studies.[136]

Analysis. We will compare the cost-effectiveness of the interventions in three time frames: short-term, mid-term and long-term. The short-term and mid-term CEA will use "number of quitters" as the effectiveness measure and assess cost-effectiveness based on information collected at Months 3 and 6 (short-term), Month 12 (mid-term), and month 18 (long-term), respectively. The long-term analysis will extrapolate the intervention effect to lifetime and use YOLS and QALY as the effectiveness measure. A 3% discount rate will be applied to costs and outcomes accrued in the second year and forward. First, we will work with the lead biostatistician of

this study (Dr. Li) to address the issue of missing data using analytical approaches such as multiple imputation or selection models (details see above) and obtain imputed values for individual with missing value in cost and/or effectiveness variable. Next, we will perform deterministic CEA based on ICER. We will then apply the Bayesian approach to construct the CE acceptability curve and conduct probabilistic sensitivity analysis (PSA).[138,139] The PSA assigns distributions for each of the key parameters to characterize uncertainties in each parameter, propagates all parameter uncertainties through the model simultaneously using simulation methods, and generates an empirical distribution for either the ICER or the net benefit;[140,141] it has been incorporated in more recent CEA *Guideline*s.[142] We will conduct the Bayesian analysis using WinBUGS, with costs modeled as a gamma or lognormal distribution and abstinence from tobacco or as a binomial distribution.

Finally, we will apply the regression-based cost-effectiveness analysis. Individual-level net benefit will be regressed on covariates, plus a binary variable indicating the ST vs. MAPS arm. Using the "ST" arm as the reference group, the regression coefficients associated with the treatment binary variable will provide information on the cost-effectiveness of the MAPS intervention compared to ST. The regression model will be analyzed in two ways: 1) GLMM to examine how cost-effectiveness varies over time, and 2) Bayesian regression to systematically update information gathered at each time point.

Table 3. Project Phases and Timeline	
Phase 1: 1 Year	Refinement of Treatment Manuals, Counselor Training, Data Management and Tracking Systems, Focus Groups, Pilot Testing
Phase 2: 3.5 Years	Enroll 300 participants, Implement Procedures (Recruitment, Screening, Randomization, Treatment Delivery, Assessment, etc.)
Phase 3: 0.5 Years	Complete Data Analysis and Prepare Manuscripts for Publication

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