Title: Mobile Contingency Management for Smoking Cessation Among Socioeconomically Disadvantaged Adults

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RESEARCH PROTOCOL

Title of Project: Mobile Contingency Management for Smoking Cessation among Socioeconomically Disadvantaged Adults

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Abstract
Although smoking prevalence has declined to 13.7% among U.S. adults, smoking rates are much higher among socioeconomically disadvantaged adults. Lung cancer, primarily caused by smoking, is the leading cause of cancer death in the U.S. Lung cancer mortality is far greater among those of lower socioeconomic status (SES) than their higher SES counterparts. Contingency management (CM), the tangible reinforcement of abstinence and other desired outcomes, is an effective approach to promoting smoking cessation. The work of the investigators has indicated that offering small escalating financial incentives for abstinence dramatically increases cessation rates among low SES adults when incentives are included as an adjunct to clinic-based treatment. However, innovative approaches are needed for those who cannot attend office visits. Smartphones offer a means of reaching and increasing treatment access. The purpose of this project is to evaluate an automated mobile phone-based CM approach that will allow low SES adults to remotely benefit from financial incentives for smoking cessation. This CM approach will be evaluated in a randomized controlled trial that includes 532 socioeconomically disadvantaged males and females seeking smoking cessation treatment. Participants will be randomly assigned to either telephone counseling and nicotine replacement therapy (standard care [SC]) or SC plus mobile incentives (CM) for abstinence. Biochemically-verified abstinence at 26 weeks post-quit is the primary outcome variable. Cost-effectiveness will be evaluated, and potential mobile CM treatment mechanisms will be explored. If effective, this approach represents a critical step towards the widespread dissemination of CM treatment, with the goal of reducing tobacco-related disparities.

A. Specific Aims

The primary purpose of the proposed project is to evaluate an automated smartphone-based CM approach that will allow socioeconomically disadvantaged adults to earn financial incentives for smoking cessation without requiring in-person attendance for abstinence verification.

Aim 1 (Primary). To evaluate the impact of an *automated*, mobile phone-based CM approach relative to SC on smoking cessation among socioeconomically disadvantaged adults.

Hypothesis: Individuals randomly assigned to the mobile CM intervention will achieve significantly higher rates of biochemically-verified abstinence at the 26-week post-quit follow-up than those assigned to SC.

Aim 2. To compare the cost-effectiveness of two smoking cessation interventions (CM vs. SC).

Hypothesis: Mobile CM will be cost-effective relative to SC.

Aim 3. To identify mobile CM treatment mechanisms.

Hypothesis: Individuals randomly assigned to mobile CM will have greater motivation to quit, higher self-efficacy for quitting, and will be more engaged in treatment relative to SC, and these factors will mediate the relation between treatment group and cessation.

The proposed study will evaluate an intervention approach that increases the reach of a potentially effective and cost-effective smoking cessation intervention for socioeconomically disadvantaged smokers. After efficacy is established, the focus will turn to dissemination with the goal of reducing tobacco-related health disparities.

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B. Background and Significance

Although smoking prevalence has declined to 13.7% among U.S. adults overall, smoking rates are much higher among socioeconomically disadvantaged adults.[1] For example, 23.9% of those with Medicaid health insurance and 21.3% of those earning an annual household income of less than $35,000 continue to smoke cigarettes.[1] Lung cancer, primarily caused by cigarette smoking, is the leading cause of cancer death in the U.S. with a five-year survival rate of only 19%.[2,3] Lung cancer mortality is far higher among those of lower socioeconomic status (SES) than their higher SES counterparts.[2,3] Thus, smoking cessation is key to reducing lung cancer deaths. Although socioeconomically disadvantaged individuals are just as likely to initiate quit attempts as their more advantaged counterparts, they are less likely to succeed.[4] The work of the investigators has indicated that offering small escalating financial incentives for smoking abstinence (i.e., contingency management [CM]) dramatically increases cessation rates among socioeconomically disadvantaged adults when incentives are included as an adjunct to clinic-based smoking cessation treatment.[5-7] Nevertheless, innovative approaches to smoking cessation are needed for socioeconomically disadvantaged adults who may experience barriers to attending office visits.

Smartphone ownership is growing rapidly. In 2019, 81% of U.S. adults overall and 71% of adults earning less than $30,000 annually reported that they owned a smartphone.[8] Thus, smartphone interventions offer a means of increasing treatment access among socioeconomically disadvantaged adults. Internet[9-11] and mobile phone-based[12-14] CM approaches have been developed to reduce or eliminate the need for in-person visits. With these approaches, participants are asked to video record themselves while providing a breath sample, and then upload the recordings for review. Staff then review the uploaded video recordings and initiate payments when the participant has provided evidence of abstinence. This process requires the provision of expensive carbon monoxide monitoring equipment to participants, and staff are needed to evaluate carbon monoxide values, verify participant identity, and initiate the delivery of incentives. This investigative team has developed an ***automated*** approach to mobile CM[15] which has the potential to simplify financial incentives interventions for smoking cessation, reduce staff effort, and make CM interventions more accessible to individuals who are unable or unwilling to attend in-person abstinence confirmation visits. If effective, the development of this automated approach represents a critical step towards the widespread dissemination of CM treatment for smoking via state quit lines, hospital systems, and other practical venues.

C. Preliminary Studies/Progress Report

The PI has developed a low-cost approach to incentivizing low SES adults for smoking cessation, which she has evaluated in several studies.[5-7,15] In the first of these studies (PREVAIL), participants were randomly assigned to SC (counseling and pharmacotherapy) with abstinent-contingent FI or SC alone. At 12 weeks post-quit, participants who received SC + FI achieved abstinence rates of **33% vs. 14%** (p<.01) for SC alone.[7] Participants completed 83% of smartphone-based assessments from 1-week pre-quit through 1-week post-quit (1 daily diary and 4 daily random assessments), and these data have provided a wealth of information about influences on smoking cessation among low SES adults.[16-22] This incentive schedule was also used successfully with adults experiencing homelessness.[5]

Based on these initial findings, the PI was awarded funding (PREVAIL II; R01CA197314) to evaluate the longer-term effectiveness of providing low-cost FI for biochemically-verified abstinence among low-SES adults as an adjunct to SC in the TTRP. Among the first 228 participants to complete the study (65% White, 25% Black, 7% American Indian, 65% female), those assigned to the SC + FI group had higher rates of biochemically-verified abstinence than SC at all visits after the quit date. At 12 weeks post-quit, **35% vs. 14%** achieved abstinence in SC + FI relative to SC. At 26 weeks post-quit - *14 weeks after incentives and cNRT ended* - biochemically-verified smoking cessation rates for SC + FI and SC were **17% vs. 11%**. Notably, participants have completed 82% of smartphone-based EMAs from 1-week pre-quit through 4-weeks post-quit (1 daily diary, 4 daily random assessments).

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Center (SCC) mHealth Shared Resource,[23] the PI's team has developed and evaluated the feasibility of an *automated*, mobile approach to assessing smoking abstinence, verifying identity, and incentivizing smoking cessation.[15] Technologies were combined including: 1) low-cost portable breath CO monitors that connect with mobile phones for remote biochemical verification of abstinence,[24] 2) mobile phone-based facial recognition software[25] to verify identity while a breath sample is provided, and 3) automatically-delivered incentives to a credit card.[26] These features are integrated into the *existing* INSIGHT mHealth platform, and will be employed to carry out the proposed study.

D. Research Design and Methods (What, When, How, Where)

Study Overview. Socioeconomically disadvantaged adults interested in tobacco cessation treatment (*N*=532) will be enrolled and randomized to: 1) Standard Care (SC), including 5 weeks of telephone counseling and 12 weeks of combination nicotine replacement therapy (patches + gum or lozenges), or 2) SC + automated, mobile phone-based CM through 12 weeks post-quit (CM). All participants will be followed from 1-week pre-quit through 26 weeks post-quit via web-based and smartphone-based (or other device-based) assessments. Global positioning system (GPS) coordinates will be collected during smartphone assessments. Biochemically-verified abstinence will be assessed throughout the study and during all follow-up assessments via the iCO monitor. Biochemically-verified 7-day point prevalence abstinence at 26 weeks post-quit will serve as the primary outcome variable.

Randomization Plan. Randomization will be stratified by sex (male vs. female), race/ethnicity (White vs. non-White), and cigarettes smoked per day (≤10 vs. >10).

Intervention. Standard Care (SC). Participants will be provided with all recommended components of an intensive tobacco treatment intervention[27] through the TTRP. Patients will complete a telephone or videoconferencing counseling session to create a quit plan (baseline/enrollment visit), and 5 additional weekly counseling sessions with a certified tobacco treatment specialist. Note, the baseline/enrollment visits may be completed remotely or in-person to aid in setting up the study phone and collecting electronic data. All participants will receive 12 weeks of combination nicotine replacement therapy (nicotine patches + gum or lozenges). To assess daily smoking status, participants will be asked to initiate a smoking status assessment and CO breath sample submission using a smartphone-based portable iCO breath carbon monoxide monitor twice per day, at least 8 hours apart. Participants will be compensated $1 per submitted breath sample submission (up to $2 per day). Participants assigned to SC will not receive incentives contingent on abstinence. However, each SC participant will be paired with a randomly selected CM participant who is farther along in the study (i.e., yoking). SC participants will receive the same incentive amounts earned by their paired CM counterpart, regardless of their abstinence status. Incentives will be paid out once per week. *This approach is taken to equate breath sample submission rates and earnings between groups, thus isolating the impact of abstinence-contingent incentives on cessation outcomes*.

Contingency Management (CM). CM participants will receive counseling and nicotine replacement therapy (as described above) in addition to small financial incentives in exchange for biochemically-verified abstinence. Financial incentives will be provided through 12 weeks post-quit. The proposed incentive amounts are similar to the schedule used in the PI's ongoing PREVAIL II trial (R01CA197314; see preliminary studies) and past work[5,7,15] with $205 in possible earnings by 4 weeks post-quit, and an additional $70 in "booster" incentives during each of weeks 8 and 12 weeks post-quit to promote continued abstinence or to help individuals return to abstinence after a lapse. Participants will be asked to initiate a smoking status assessment and CO breath sample submission using a smartphone-based portable iCO breath carbon monoxide monitor twice per day, at least 8 hours apart. Participants will be compensated $1 per submitted breath sample submission (up to $2 per day). Daily abstinence is defined as: 1) a self-report of abstinence combined with 2) a breath CO sample of ≤6 ppm (consistent with biochemical verification guidelines[28]) and 3) identity verification (facial recognition is described below). Participants who demonstrate abstinence during both daily assessments on the quit day will receive a $10 credit to strongly reinforce the initiation of the quit attempt and to maintain consistency

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with the reinforcement schedule we have successfully used in our preliminary research.[5-7,15] Thereafter, credits may be earned starting at $4 per day and increasing by $0.25 per day until $10 per day is reached during the 4th week post-quit. Participants who are non-abstinent (or who do not provide a sample) will not earn incentives that day, though they may begin earning incentives for abstinence again the next day. However, the amount will reset to the starting level of $4 per abstinent day. Participants may earn $10 per abstinent day during post-quit weeks 8 and 12 (see **Table 1**).

Table 1. Abstinence-Contingent Incentive Schedule (CM Group).

Time	ABSTINENCE-CONTINGENT INCENTIVES Day							WEEKLY TOTAL $
	1	**2**	**3**	**4**	**5**	**6**	**7**	
Quit Day	$10	-	-	-	-	-	-	**$10**
Week 1	-	$4	$4.25	$4.50	$4.75	$5	$5.25	**$27.75**
Week 2	$5.50	$5.75	$6	$6.25	$6.50	$6.75	$7	**$43.75**
Week 3	$7.25	$7.50	$7.75	$8	$8.25	$8.50	$8.75	**$56**
Week 4	$9	$9.25	$9.50	$9.75	$10	$10	$10	**$67.50**
Week 8	$10	$10	$10	$10	$10	$10	$10	**$70**
Week 12	$10	$10	$10	$10	$10	$10	$10	**$70**
							TOTAL POSSIBLE $:	**$345**

Facial Recognition/Verification. Microsoft Face API was previously integrated into the INSIGHT platform for the feasibility study.[15] At baseline (pre-quit), participants in both study groups will take a photo of themselves or upload a photo which will be stored as a reference photograph for identity verification. Participants will be instructed to keep their appearance consistent with the baseline photo (e.g., glasses, hats, pony tail). Two photographs will be taken at random times during the exhalation phase of the iCO breath sample submission to verify identity. Participants cannot tell when the photographs are taken, and they do not receive immediate feedback about whether there is an identity match. Photographs are encrypted and stored on the study server for later viewing by study staff as needed. When there is a facial recognition mismatch, the abstinence-contingent incentive schedule (CM group only) is automatically paused and flagged to prompt staff to review the stored photos. The staff may click “thumbs up” for an identity match, and then the incentive schedule will resume and catch up to the present. If the staff clicks “thumbs down” for a non-match, the payment will not be delivered and the payment schedule will reset. As a check on facial recognition validity, five percent of all completed smoking status assessments will be randomly selected for review across sex, and race/ethnicity categories. Two staff members will separately review all selected facial recognition assessments for accuracy, and agreement between reviewers will be assessed (44,688 possible facial recognition assessments [i.e., 532 participants x 84 possible per person] x 80% compliance = 35,750 x 5% = 1788 manual checks per staff member].

Mobile Health Platform. The mHealth Technology Shared Resource at the NCI-designated SCC has developed the INSIGHT™ mHealth Platform which empowers researchers to build, test, and launch technology-based assessment and intervention tools. Applications are developed using state-of-the-art cross-platform design tools. Businelle (Co-I) is the Scientific Director of the Shared Resource. The investigators have worked with the programmers to guide the development of the automated CM approach, which will be used in the proposed study (see preliminary studies).

Intervention Hardware. Participants will use their own smartphones or they will be provided a smartphone and cellular service. Participants who use their own phones will be compensated $40 per month to defray the costs of phone service. All participants will be provided with a Bedfont iCO Smokerlyzer portable breath CO monitor for verification of abstinence. Replacement monitors will be

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provided as needed. The iCO monitor was previously integrated into the INSIGHT platform for the PrevailGO feasibility study.[15]

Measurement of Abstinence. Smoking abstinence will be measured via self-report and expired CO twice per day from the scheduled quit date through four weeks post-quit. Twice daily smoking status assessments will also occur during weeks 8 and 12 post-quit. To earn the maximum gift card payment, participants must report continued abstinence from the quit date and provide CO breath samples of ≤ 6 ppm twice per day during all assessment weeks. The primary outcome measure will be self-reported abstinence and expired CO assessed remotely via smartphone-based assessment and iCO at 26 weeks post-quit.

Measures. Measures of sociodemographic characteristics, tobacco use, health, mental health, substance use, and several hypothesized treatment mediators and moderators are detailed in the REDcap appendix. Questionnaires will follow a similar paid schedule as our previous studies, with weekly assessments from 1 week-pre-quit through 4 weeks post-quit, and additional assessments at 8, 12, and 26 weeks post-quit. Participants will be compensated $50 for completing a baseline REDCap assessment. Participant will be paid $20 for briefer assessments on the quit day, and post-quit weeks 1, 2, 3, 4, 8, and 12. Participants will be paid $50 for completion of a final follow-up assessment and breath sample submission. Participants will be compensated via Greenphire reloadable study credit card.

Ecological Momentary Assessment. Participants will complete paid smartphone-based EMAs from 1-week pre-quit through 4 weeks post-quit, with follow-up assessment weeks at 8 and 12 weeks post quit. Those who complete 50%-74% of prompted assessments will receive a $10 credit, those who complete 75%-89% of assessments will receive a $15 credit, and those who complete 90% or more of their assessments will receive a $25 credit each assessment week. EMA items were selected to capture hypothesized mediators (i.e., motivation, self-efficacy, treatment adherence/engagement). Participants will be prompted to complete *daily diaries* each morning 30 minutes after the usual wake time to assess smoking status, cigarettes smoked (if lapsed) and medication adherence (e.g., application of the nicotine patch, amount and frequency of gum/lozenges use) for the previous day. Participants will be prompted to complete *random assessments* twice per day during waking hours to assess motivation to quit and self-efficacy. See the INSIGHT app appendix for the details of these assessments. The smartphone application will record participants' location via global positioning systems (GPS) each time they answer questions in the app to provide contextual information about cravings, smoking, and other treatment relevant variables.

Smart Phone Training. Participants will receive hands-on training with the study phone and iCO and they will find information about app features and instructions for submitting breath samples via the app main menu.

Data Loss Prevention. Phones will be programmed to connect to our secure server 4 times daily to upload encrypted data, to overcome the potential loss of data if participants lose or change phones, which has rarely occurred in our previous research. This strategy will also allow the staff to monitor participant EMA completion rates and call participants when this rate is low. Importantly, EMA data are password protected and encrypted within the Insight app. Thus, study data are only accessible by the research team. Data will be remotely deleted from lost phones and one replacement phone will be provided.

Disclosure of Results to Participants. Study results will not be disclosed to participants.

Future Use of Data. Identifiers might be removed and the de-identified information may be used for future research without additional informed consent from the subject.

E. Chart Review

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This protocol does not involve a chart review. However, please note that many participants are referred to the TTRP (see protocol #6951) via electronic health record referral. Thus, participant's address, phone number, sex, race, ethnicity, date of birth, referring clinic and referral date will be received and stored in a RedCAP database.

F. Biospecimens

No biospecimens will be collected as part of this protocol.

G. Banking/Repository/Database

Questionnaire, anthropometric, expired carbon monoxide, GPS, and intervention cost data will be collected and stored via RedCAP and the INSIGHT mobile health platform. No biospecimens will be stored.

H. Inclusion / Exclusion Criteria

Interested participants may be included in the study if they: 1) report an annual household income of <200% of the federal poverty threshold (i.e., low-income), 2) provide a copy/photo of driver's license or other documentation as proof of identity and U.S. residence, 3) earn a score ≥4 on the REALM[29] indicating >6th grade English literacy level (i.e., a 7th grade reading level is necessary to complete assessments), 4) are willing to quit smoking 1-2 weeks after enrollment, 5) are ≥ 18 years of age, 6) currently smoke ≥5 cigarettes per day, 7) have a CO level of >6 ppm, 8) are willing to abstain from smoking cannabis and other combustible tobacco products while participating in the study (they raise CO levels and mask cigarette abstinence), and 9) have no contraindications for NRT. Participants will be excluded if they do not meet these inclusion criteria. Participants will not be terminated from the study.

Inclusion of Pregnant Women. The findings of a recent Cochrane review suggests that NRT may be an effective smoking cessation treatment for pregnant women.[30] There has been no evidence of serious adverse events associated with NRT among pregnant women,[30] and NRT does not appear to impact birth outcomes.[31] In contrast, continued smoking during pregnancy is associated with adverse outcomes including preterm delivery, small size for gestational age, and childhood overweight.[32] The American College of Obstetricians and Gynecologists (ACOG) advises that NRT may be used with supervision, after a discussion with the patient about the risks of continued smoking and the possible risks of NRT.[33] Although we do not expect many individuals who are pregnant to participate in the study, they will not be excluded from participation. Following completion of informed consent and study enrollment, the following safeguards will be employed for pregnant women: 1) approval will be sought from the participant's obstetrician/physician to offer NRT, 2) the participant's personal physician will be notified when the patient has been provided with NRT, and 3) NRT side effects will be tracked via smartphone-based daily diary assessments. The staff physician will be automatically notified in real-time via encrypted email when moderate/severe side effects are endorsed, and the physician will then follow-up with the participant to obtain additional information and to provide guidance. At the discretion of the staff physician, the participant's personal physician may also be notified of the side effects/symptoms. This process will allow the participant's physician to offer guidance and follow-up to their patient regarding their use of NRT during the pregnancy at regular prenatal visits, and potential side effects/adverse events will also be tracked and addressed as part of the study. Non-pregnant participants will be advised to refrain from becoming pregnant while participating in the study, and pregnancy status will be assessed during screening and again at 4 and 8 weeks post-quit date. Physician approval for NRT will be sought in cases where a participant becomes pregnant.

I. Gender/Minority/Pediatric Inclusion for Research

The study has no inclusion/exclusion criteria based on gender or race/ethnicity. The current study focuses only on adults who are 18 years of age and older (no maximum age). Children <18 years of age will be connected with the Oklahoma Tobacco helpline through our online portal. Separate smoking

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cessation interventions designed for children are warranted and preferable as the smoking characteristics and cessation-related needs of children and adults are likely to be very different.

J. Recruitment and Enrollment

Recruitment. Adults will be recruited nationwide. The PI (Kendzor) is the PI/Director of the TTRP, which will serve as a recruitment site. The TTRP offers free tobacco cessation treatment to adults from campus and the community. Tobacco cessation referrals from the OUHSC and SCC clinics are received through the electronic medical record, and also by telephone, social media, email, fax, internet, or walk-in. External referrals will also be generated through print and radio advertising, and on-site recruiting at partnering organizations that serve socioeconomically disadvantaged adults (e.g., regional food bank, health alliance for the uninsured). See TTRP protocol #6951 for approved advertising materials.

Informed Consent. Potential participants will be scheduled for a telephone or videoconferencing appointment to receive detailed information about the study. Research staff will provide an oral overview of the consent form, and individuals will have the opportunity to have their questions answered. Participants will be advised that participation is voluntary, and made aware that standard TTRP treatment, connection with the Oklahoma or other state tobacco helplines, and other treatment options are available to them if they do not wish to participate. Participants will review the consent form via REDCap and sign electronically. Participants will be mailed or emailed a copy.

K. Risks and Benefits

Potential Risks. Study data will not be de-identified, given that information such as names, study assessment dates, and contact information will be required for participant contact and data analysis. Participation in this study poses minimal risk to participants. However, one potential, although unlikely, risk to participants is loss of confidentiality. The severity of harm in the case of loss of confidentially may range from mild to severe depending upon the individual and the specific circumstances. Side effects from NRT (nicotine patches, gum, lozenges) are possible, though adverse experiences are usually mild in nature. Potential risks arising from use of nicotine patch therapy include nausea, erythema, and other dermatologic reactions.

Protections against Risk.

General Protections. Each participant will be assigned an identification number that will be utilized in place of names in all electronic and print data files. The file containing the links between participant names and identifiers will be kept in a separate password-protected file, which will be destroyed 12 months after the completion of the study. All print information will be stored in a locked filing cabinet in the TTRP. Electronic data will be maintained on the investigators/staff computers, and all computers will be password protected. CO and anthropometric measures will be collected in a private room. Participant REDCap data are not stored on participant's devices, and may only be accessed with a password through the web-based RedCAP program. Project staff will complete extensive training focused on each of the following topics: 1) project rationale and objectives, 2) the informed consent process, 3) general data collection procedures (e.g., computer data collection, privacy), and 4) measurement of CO and anthropometric data.

EMA Protections. Participant responses to study questions will be encrypted and stored on the study smartphone. The following features are designed to address smartphone/EMA data security issues: 1) the data stored on the smart phone device are in a SQLite database in a sandbox environment, where read/write operations are only available through the programming application (i.e., no file or output is readable to end users); 2) a 10 character password (only known to researchers) is required to authenticate the current user before data can be manually accessed or manually downloaded from the smart phone to the server; 3) the web browser application linking the investigator's computer to the database is on HTTPS protocol (SSL certificate with encryption) which will guarantee the data transfer from web browser to the backend database is well protected; and, 4) the backend databases are

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hosted by Microsoft Azure and the OUHSC. These steps will ensure the security of EMA data. Software will be downloaded onto each study phone so that phones can be remotely wiped if lost.

Nicotine Replacement Therapy. Adverse experiences associated with the nicotine replacement therapy are almost always mild in nature. Potential risks arising from use of nicotine patch therapy are mostly limited to nausea, erythema, and other dermatologic reactions. The incidence of side effects with the patch is small and can be locally treated or reversed with discontinuation of the patch. The risk of nicotine toxicity is extremely low. Appropriate warnings about not smoking while using the patch will be issued each time patches are dispensed. Management of AE's are done in accordance with standards of clinical practice and almost always are relieved by a reduction in dose, or although rarely necessary, discontinuation of NRT.

Potential Benefits. Potential benefits to patients include the provision of an evidenced-based treatment for tobacco cessation (counseling + NRT), and a new treatment with the potential to further increase the chances of successful smoking cessation. In addition, the knowledge gained from this study may be utilized to improve our understanding of tobacco cessation treatments. Such information may facilitate the development of more effective tobacco cessation interventions that may be utilized within cessation clinics and programs**.**

Risks in Relation to Benefits. The possible risks of participation in this study are minimal and reasonable in relation to benefits. The health benefits gained from participation in a tobacco cessation intervention far outweighs the risks of continued tobacco use.

L. Multiple Sites

Data collection will occur remotely via telephone, videoconferencing, and web- and smartphone-based surveys from the University of Oklahoma Health Sciences Center.

M. Statistical Methods

Sample Size Calculations/Power Analysis.

Aim 1 (primary). An intent-to-treat approach will be used, in which participants who do not demonstrate biochemical verification of abstinence will be classified as smoking. Our power calculation, which was based on comparing 7-day biochemically-verified point prevalence abstinence rates between the two treatment groups at the 26-week follow-up, will assume a sample size of 532 (266 per group). Based on 6-month cessation rates in our own preliminary research[6] and the results of other CM studies, we estimate smoking cessation rates of 21% for CM and 12% for SC. Given these assumptions, and using a two-sided significance level of 0.05, we will have 80% power to detect a 9% difference in abstinence rates between the CM and SC groups.

Aim 2. We did not conduct a separate sample size calculation for the cost-effectiveness analysis (CEA) because Gardiner et al.[34] demonstrated that for a trial to be sufficiently powered for CEA, the sample size would need to be many times greater than that based on effectiveness alone. Since cost-effectiveness analysis is often not the primary endpoint of trials, the sample size is rarely powered for CEA both due to budgetary and human subject protection concerns.

Aim 3. Mediation analyses will be conducted to identify variables (e.g., self-efficacy) that mediate the relation between treatment condition and smoking cessation at 12 and 26 weeks post-quit. Guidelines[35] indicate that with 532 participants, we will have 80% power to detect *small* effect sizes of Cohen's *d* ≥ 0.14 for both the effect of treatment condition on a mediator and for the effect of the mediator on smoking cessation outcomes. We will explore models where the mediator is measured at multiple time points, including at the secondary endpoints (7 measurements [not including week 26 because it coincides with the primary outcome]) and in the EMA assessments (3 EMAs/day X 6 post-quit weeks [not including week 26 because it coincides with the primary outcome] = 126 measurements). Given the effective sample size for these models ($N_{\text{eff}} = N(1-\rho)/(1+\rho)$) and assuming strong autocorrelation among the repeated measures (ρ=0.7), we will have >80% power to detect smaller effect sizes of *d* ≥

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0.14 for both the effect of treatment condition on a mediator and for the effect of the mediator on cessation.

Analysis Plan.

Aim 1. Evaluate the impact of an automated, mobile phone-based CM approach relative to SC on smoking cessation among socioeconomically disadvantaged adults.

Logistic regression. Logistic regression analyses will be conducted to evaluate the influence of CM vs. SC on biochemically-confirmed 7-day point prevalence smoking abstinence (binary) at 26 weeks post-quit. Continuous/prolonged abstinence and 30-day point prevalence will be examined as secondary endpoints. The impact of treatment group on cessation at earlier points (4, 8, 12 weeks post-quit) will also be evaluated. Covariates may include age, sex, race/ethnicity, nicotine dependence, insurance status, and education.

Generalized linear mixed models (GLMM). GLMM will be used to evaluate the influence of treatment group on smoking cessation as a repeated outcome measure while accounting for covariates (see logistic regression section above). GLMM is a flexible analytic approach with wide use in health sciences research. GLMM can handle fixed and random effect model parameters, nested designs, and repeated measures with various correlation structures. GLMM can also handle normal and non-normal outcomes such as dichotomous smoking status variables, different variance functions, as well as unbalanced designs where the number of repeated observations varies across individuals.

Missing Data and Dropouts. Although it is typical to classify participants lost to follow-up as smoking in CM studies, there are potential problems with this approach, especially when comparing interventions with differential dropout rates. Thus, we will conduct sensitivity analyses assuming different missing data mechanisms. For example, we will consider a multiple imputation approach, which uses smoking and demographic characteristics to account for potential missing-at-random mechanisms.

Aim 2. Compare the cost-effectiveness of two smoking cessation interventions (CM vs. SC).

Incremental cost-effectiveness ratio (ICER). Conventional cost-effectiveness analysis (CEA) summarizes study findings in terms of the incremental cost-effectiveness ratio (ICER). The ICER, calculated as the difference in mean costs between the new (i.e., CM) and standard treatment (i.e., SC) divided by the difference in mean effectiveness between the two, estimates additional resources needed to achieve an increase of one unit of effectiveness. The ICER is then compared with a commonly published threshold value associated with an intervention established as cost-effective. To avoid the issue of zero denominators and to better address uncertainty, we will also employ the net benefit approach. This approach 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 results both in terms of the conventional ICER and the CE acceptability curve; 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. An additional benefit is that this approach has been incorporated into a regression framework to allow for covariate adjustments and the examination of interaction effects.[36] Shih et al. further extended this framework to a Bayesian regression framework to allow for more flexible inferences.[37] This is relevant to the proposed study as there may be moderating factors that impact efficacy or cost-effectiveness.

Measures of costs and collection of cost data. The cost model will include all necessary personnel, hardware, and material costs. If existing resources are used without charge (e.g., office space), we will estimate these costs given that they would be required for implementation. For SC, the costs will capture study personnel, supply of NRT (including postage and packaging charges), and telephone bills (for the delivery of telephone counseling sessions). For CM, costs will include the SC costs plus the costs associated with staff time to program mobile devices to collect CO breath sample and deliver financial incentives and train participants to properly use the app related to the intervention, as well as monitor the progress and make the financial transaction for participants meeting the abstinence target.

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Staff will keep logs of time spent on each of the tasks related to delivering the intervention, net of additional time spent to satisfy research components. From these task-specific time logs, we will identify tasks related to the automation of CM and estimated costs of automation by multiplying staff time (in minutes) spent on these tasks with their wage rates. This information will be useful for decision makers contemplating whether to automate their CM-based intervention. Hardware, software, and material costs will be tracked through invoices. All intervention-related costs will be expressed in local market terms for personnel, office space, furnishings, and equipment. We will not include the cost of smartphones because once the efficacy of mobile CM is established, implementation will capitalize on the wide availability of mobile devices. Although success in smoking cessation can lower healthcare costs in the long-run by lowering the risks of tobacco-related illnesses, research has shown that future cost savings associated with health improvement from smoking cessation were balanced out by future cost increases driven by greater longevity.[38] Therefore, we will not model costs of smoking later in life.

Measures of effectiveness. Two commonly used measures, number of quitters and years of life saved (YOLS), will be used to compare the ICER from this study with other studies. The number of quitters in each arm will be retrieved from the abstinence assessment at week 4 and subsequent follow-ups. We will extrapolate from abstinence to YOLS using a published algorithm that models YOLS per quitter.[39] The algorithm extrapolates YOLS from abstinence by first calculating annual mortality rate by ages for smokers and non-smokers, then applying the relative decline in excess mortality attributable to smoking cessation to the published life tables to estimate the increase in life expectancy due to cessation at each age. This algorithm was favored over other methods of extrapolation because it was built from a model with good face validity and has been adopted in many related CE studies. We will revise the algorithm using more current estimates of age-specific smoking-attributable deaths from tobacco control.[40] We have also included quality-adjusted life years (QALY), which will be calculated based on EQ-5D-5L, the latest version of EQ-5D.[41]

Analysis. We will assess the economic impact of the interventions within two time frames: short- and long-term. The short-term analysis will use "number of quitters" as the effectiveness measure and assess cost-effectiveness based on information collected at weeks 4, 8, 12 and 26. The long-term analysis will extrapolate the intervention effect to lifetime and utilize YOLS and QALY. A 3% discount rate will be applied to costs and outcomes accrued in the second year and forward. We will first perform deterministic analysis in which point estimates of ICERs or cost differences will be calculated. To obtain the 95% CIs, we will apply nonparametric bootstrapping methods to the person-level data. We will conduct one-way sensitivity analyses to examine the impact of alternative measures of cost and outcomes or key assumptions. We will then apply the Bayesian approach, using WinBUGS software, to construct the CE acceptability curve and conduct probabilistic sensitivity analysis (PSA). The PSA assigns distributions for each key parameter to characterize uncertainties (e.g., gamma distribution for costs and binomial for abstinence), propagates all parameter uncertainties through the model simultaneously using simulation methods, and generates an empirical distribution for either the ICER or the net benefit. We will apply the regression-based CEA. Individual-level net benefit will be regressed on covariates, plus a binary variable reflecting CM vs. SC. The regression coefficients associated with the binary treatment variable will provide information on the cost-effectiveness of CM vs. SC. 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.

Aim 3: Identify CM treatment mechanisms. The PROCESS macro for SPSS/SAS will be used to identify variables (e.g., self-efficacy, motivation) that mediate the relation between treatment condition and smoking cessation outcomes. This method uses an ordinary least squares path analytic framework to estimate direct and indirect effects in single and multiple mediation models, and bootstrapping methods are incorporated to generate confidence intervals. The macro can also be used to evaluate complex moderated mediation models (e.g., sex as a moderator) including those with dichotomous outcomes (e.g., abstinence vs. non-abstinence). Mplus software can be used to explore potential mediators of the effect of CM on smoking cessation outcomes while accounting for the correlation among repeated EMA

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measurements. Specifically, we will use a multilevel structural equation modeling framework, that produces a less biased indirect effect and unconflates the between and within components of the indirect effect.

N. Data and Safety Monitoring Plan

The PI (Kendzor) will be responsible for all data monitoring and for compliance with all federal and OUHSC IRB policies and procedures for monitoring progress, safety, reporting of unanticipated problems or adverse events, and assuring actions resulting in suspension of the study are reported.

The study will be monitored for data validity and participant safety by the Data and Safety Monitoring Committee (DSMC)[42] of the Stephenson Cancer Center. The DSMC will be responsible for monitoring rates of enrollment and for reviewing patient safety, risks of participation, protocol adherence by the research team, safety and confidentiality of data collection, data entry, and statistical issues. The DSMC will decide upon their meeting frequency based on level of risk, size and complexity of the clinical trial. Relevant unanticipated problems, adverse events, or participant concerns will be reviewed at these meetings.

Unanticipated problems. For all protocols conducted at the OUHSC, the PI is required to submit to the IRB within five (5) university business days of discovering any unanticipated problems (both internal and external) involving risks to participants and others.

Serious adverse events. A serious adverse event is defined as follows: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or a medically significant event. Risks of participation will be continually monitored and appropriate measures implemented in cases of unforeseen adverse events. If a serious adverse event occurs, the study PI (Kendzor) will notify the IRB and the designated program person at the National Institutes of Health in writing. These events will be reported regardless of whether they appear to be related to study procedures. Given the non-invasive, minimal risk nature of the proposed research, we anticipate no serious adverse events related to the interventions or the study procedures.

Adverse Experiences Associated with Nicotine Replacement Therapy. Individuals who report a medical condition that precludes the use of nicotine replacement therapy (NRT; e.g., recent heart attack, uncontrolled hypertension) will be excluded from the study. The incidence of side effects with NRT is low and can be locally treated or reversed with discontinuation of the patch. The risk of nicotine toxicity is extremely low. Management of adverse events are done in accordance with standards of clinical practice and almost always are relieved by a reduction in dose, or although rarely necessary, discontinuation of NRT use.

Adverse Experiences Associated with Nicotine Abstinence/Withdrawal. Participants may also experience nicotine abstinence/withdrawal effects. These effects may include irritability, difficulty concentrating, insomnia, anxiety, dysphoria, and increased hunger. None of these effects results in serious adverse events.

Data Quality and Integrity. Because of the ongoing monitoring of the project, study investigators and staff will maintain quality assurance procedures for all data. The Insight™ platform, developed by the mHealth Shared Resource, will be used to deliver all automated messages for intervention and assessments. The Insight™ platform has two primary components: a web-based Content Management System (Insight-CMS) and an Insight-app (a shell in smartphones). Insight™ is a secure platform and is designed to comply with all HIPAA regulations. Data may also be collected via REDCap, which is a secure web database, and sent to OUHSC servers using the OUHSC secure file transfer system. The servers are password protected and backed up regularly. The data and referral information will only be accessible to the study investigators and staff.

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Several procedures will be used to maintain the integrity of the data. All participants' information or responses will be temporarily saved on password-protected, encrypted smartphones or tablets. When there is active connection, encrypted data will be automatically sent to our OUHSC mHealth Shared Resource secure servers multiple times per day. Access to all databases are limited to specific users at the discretion of the MPIs. Additional quality assurance procedures will include a data collection protocol documented in a protocol manual, and regular meetings among the investigators and project staff to review problems and solutions and discuss concerns.

O. Data Sharing

Data storage, or data transfer if there is a request, will follow all OUHSC's requirements for data security. In all components of the research project, participants will be assigned unique identification numbers, and this identification numbers will be used in all data transfer and data analysis. Dr. Shih (Co-Investigator) at the MD Anderson Cancer Center will require access to deidentified study data for cost-effectiveness analysis (aim 3). She will be given access to the Insight and RedCAP databases and provided with a username and password to login and download de-identified study data directly to her computer. De-identified data files may also be transferred on a password-protected and encrypted drive and will be maintained on institutional servers with appropriate antivirus software. Final de-identified data files will be maintained by the PI (Kendzor) at OUHSC. De-identified study data may be shared via publicly available data repositories in response to requests or requirements from funding agencies and scientific journals.

P. Confidentiality

The Insight™ platform, developed by the OUHSC/SCC mHealth Shared Resource (Director: Dr. Businelle, co-I), will be used to deliver intervention components and assessments. The Insight™ platform has two primary components: a web-based Content Management System (Insight-CMS) and the Insight-app (a shell in smartphones). Insight™ is a secure platform and is designed to comply with all HIPAA regulations. Data will also be collected via REDCap, which is a secure web database, and sent to OUHSC servers using the OUHSC secure file transfer system. The servers are password protected and backed up regularly. The data and referral information will only be accessible to the study investigators and staff.

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