Study Title: Smoking Treatment and Exercise Program for Underserved Populations (STEP UP)

Clinical Trials Identifier: NCT02873754

Protocol and Statistical Analysis Plan, 4/3/2017

**Title:** Mobile Health Intervention to Help Low-Income Smokers Quit Smoking and Increase Physical Activity
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**Background**

Cigarette smoking and physical inactivity are the two greatest behavioral health risks leading to chronic disease and premature death in the U.S. (Department of Health and Human Services, 2004). Smoking alone accounts for 1 in 5 deaths, and physical inactivity, coupled with poor diet, accounts for 1 in 6 (Mokdad, Marks, Stroup, & Gerberding, 2004). Both smoking and physical inactivity are more prevalent in low-income populations (Hisock, Bauld, Amos, Fidler, & Munato, 2012; Powell, Slater, Chaloupka, & Harper, 2006). Moreover, both frequently co-occur (Kaczynski, Manske, Mannel, & Grewal, 2008), thereby compounding their deleterious effects (Strine, Balluz, & Ford, 2007; Ferrucci et al., 1999). In light of this co-occurrence, a number of researchers have tested combined smoking and exercise interventions and found that they convey better outcomes than stand-alone smoking-cessation efforts (Weinstock, Barry, & Petry, 2008; Ussher, Taylor, West, & McEwen, 2000).

Contingency management (CM) is an intensive behavioral therapy that provides positive reinforcers (e.g., vouchers, money) to individuals contingent upon utilization of an intervention or demonstration of an outcome, often abstinence in the case of substance users. CM is a particularly powerful tool for generating behavioral change in low-income populations due to the greater inherent value of monetary incentives (Lynagh, Sanson-Fisher, & Bonevski, 2013). CM has demonstrated strong short-term efficacy in the treatment of substance use, with effect sizes eclipsing those of other behavioral treatments (Dutra et al., 2008). Incentive-based exercise interventions may be similarly effective for increasing exercise, with one study (Kurti & Dallery, 2013) demonstrating that rewarding participants with as little as $1.00 a day for meeting daily step goals increased the odds of meeting exercise objectives by a factor of 6.42.

Unfortunately, traditional applications of CM for smoking and other substance misuse have been hampered by the need for clinic-based verification of abstinence, which represents a major barrier to treatment for low-income populations (Gornick et al., 1996). As a result, these approaches have largely been relegated to inpatient and day-treatment programs. Our laboratory, however, has developed a smartphone application (app) which allows participants to video themselves multiple times daily while using a small carbon monoxide (CO) monitor and to transmit the data to a secure server. This innovation has made the use of CM for outpatient smoking cessation portable and feasible as well as highly efficacious in treating smoking in vulnerable populations (Hertzberg et al., 2013; Carpenter et al., 2015).

Financial incentives have similarly been applied to exercise interventions with positive short-term effects. The majority of such trials have tested the effect of directly incentivizing weight loss via varying combinations of diet and exercise (Volpp et al., 2008; Abrahms & Allen, 1974; Harris & Bruner, 1971; Jeffery et al., 1993; Jeffery et al., 1984). According to a recent meta-analysis of financial-incentive trials (Mantzari et al., 2015), the mean 6-month odds ratio (OR) for diet/exercise interventions was 1.66 (95% CI=1.28-2.15). Incentives to participate in physical activity have also been applied with slightly smaller effects (Charness & Gneezy, 2009; Jeffery, Wing, Thorson, & Burton, 1998; Pope & Harvey-Berino, 2013). However, a major drawback of these interventions is that they require extensive face-to-face contact between participants and

study personnel. Furthermore, despite immediate short-term gains, significant long-term effects on weight loss or engagement in physical activity were observed in none of these studies (Mantzari, 2015). Still, incentives may be particularly effective at promoting short-term increases in physical activity, which are expected to be beneficial during a smoking quit attempt. Note that the purpose of the physical-activity target in this project is to enhance smoking-cessation outcomes (and other secondary outcomes such as increased steps and improved mood) rather than weight control expressly.

In light of recent advances in the development of mobile interventions for exercise (Fanning, Mullen, & McAuley, 2012) and evidence that treating physical inactivity concurrently with smoking may increase short-term abstinence above and beyond typical smoking interventions (Spring et al., 2009), we have designed a Smoking Treatment and Exercise Program for Underserved Populations (STEP UP) that uses mobile CM (mCM) to simultaneously promote smoking cessation and physical activity.

The purpose of this pilot project is to evaluate the feasibility, acceptability, and efficacy of STEP UP. Given the heightened prevalence of smoking and physical inactivity among low-income populations, in addition to structural barriers to treatment, we propose to target low-income smokers with this intervention.

**Methods**

*Participants*

Participants will be adult men and women who smoke cigarettes. We plan to enroll 15 participants in order to reach a goal of 10 study completers.

Participants will be eligible for inclusion in the study if they meet the following criteria:

- current household income less than twice the federal poverty guidelines (Finer & Henshaw, 2006; for instance, someone from a family of 4 must have a household income less than $48,500 to be eligible)
- currently smoke >10 cigarettes a day
- smoking for at least the past year
- can speak and write fluent conversational English
- are 18-70 years of age
- are willing to make an attempt to quit smoking and increase physical activity

Participants will be excluded from the study for the following:

- inability to walk
- expected to have unstable medication regimen during the study
- currently receiving non-study behavioral treatment for smoking
- myocardial infarction in the past 6 months
- contraindication to nicotine replacement therapy (NRT) or bupropion with no medical clearance
- exclusive use of other forms of nicotine such as cigars, pipes, e-cigarettes, or chewing tobacco
- current pregnancy

- current imprisonment or psychiatric hospitalization

*Recruitment*

Participants will be recruited from outpatient clinics at Duke University Medical Center (DUMC). Flyers and brochures will be placed in DUMC clinic areas, and may also be placed in community settings such as local restaurants and grocery stores. We will also advertise in local newspapers and online classified services such as www.craigslist.com. We will contact administrators and/or clinicians at local area community health centers, including Lincoln Community Health Center, to get permission to provide recruitment materials at those sites. Upon approval by the Durham Veterans Affairs (VA) Medical Center IRB, we will post flyers and brochures at that facility and its community-based outpatient clinics. Any flyer posted at the VA-owned facilities will include the following statement: "This is not VA research, will not be conducted by VA, has not been reviewed by VA's Institutional Review Board, and is not endorsed by VA. VA is not responsible for any costs incurred by a Veteran if the Veteran enters the study as a research subject. The announcement is being provided for information only."

Any participant who contacts by telephone the study coordinator or other study staff regarding the study will be provided more information, and will be interviewed using an IRB-approved telephone screening. We will retain the deidentified telephone screening information for all callers so that we can analyze data regarding telephone screen-outs in order to determine recruitment and inclusion/exclusion feasibility.

*Study Procedures*

Table 1 provides a summary of study procedures, including the timing and location of each session and payments associated with them.

**Table 1. Study Procedures**

| Session # | Location of Visit | Procedures | Payment |
|---|---|---|---|
| **1** | Lab | Consent; questionnaires; urine drug screen and pregnancy test; carbon monoxide readings; equipment training; counseling session 1 of 5 | $100 |
| **1-3 weeks** | | | |
| **2** | Phone | Brief phone check-in for participants using bupropion; begin bupropion if eligible | n/a |
| **1 week** | | | |
| **3** | Phone | Counseling session 2 of 5; begin practice mCM monitoring | n/a |
| **1 week** | | | |
| **4** | Phone | QUIT DATE; counseling session 3 of 5; begin 4 weeks active mCM monitoring; begin nicotine replacement therapy (NRT) | n/a |

| | | | |
|---|---|---|---|
| **1 week** | | | |
| **5** | Phone | Counseling session 4 of 5; continue active mCM monitoring | n/a |
| **1 week** | | | |
| **6** | Phone | Counseling session 5 of 5; continue active mCM monitoring | n/a |
| **2 weeks** | | | |
| **7** | Phone or Text Message | Begin 1 week mCM wash-out period | Up to $798 mCM compensation |
| **2 weeks post-mCM treatment follow-up** | | | |
| **8** | Phone | Questionnaires; equipment return; treatment adherence measures | $50 for equipment return |
| **3 months after Session 1** | | | |
| **9** | Phone/Lab | Questionnaires; return to lab and provide a saliva sample if abstinence reported | $25 for assessment; $50 for saliva sample |
| **6 months after Session 1** | | | |
| **10** | Phone/Lab | Questionnaires; return to lab and provide a saliva sample if abstinence reported | $25 for assessment; $50 for saliva sample |
| | | **TOTAL COMPENSATION POSSIBLE** | **$1098** |

Once a participant reports to the laboratory to begin the study, the study staff member obtaining consent will explain the study in detail, provide the participant with an IRB-approved written consent form explaining the procedures and risks, and answer any questions. The initial consent process and documentation takes place in a quiet, private office at DUMC (Hock Plaza space), and participants are given the chance to thoroughly read the consent prior to participation. Participants are given a copy of the signed informed consent form, and are given phone numbers to call if they have additional questions about the consent form or the research, if they have any problems during the study, or if they have questions about participating in research studies in general. No study procedures will begin until informed consent has been obtained.

After providing informed consent, potential participants will provide a breath sample to assess CO level, and will complete measures (see Measures section herein) regarding mood, exercise and smoking history, and sociodemographic data. Urine samples will also be used to screen for illicit drug use (to document use). Because the study drugs are each Category C drugs, urine pregnancy tests will also be completed for women of childbearing potential. We have developed a short interview for female participants; this interview will help us determine which female participants must have a urine pregnancy test, and when the test should be done. Female participants of childbearing potential who are not pregnant must agree to use appropriate

contraception during the course of the study, and to notify study staff if they become pregnant during the study.

All enrolled participants will receive a tele-health intervention that combines evidence-based telephone cognitive behavioral therapy (CBT) for smoking cessation, access to nicotine replacement therapy (NRT) and bupropion, and intensive CM therapy administered via a smart-phone based application (mCM). The treatment components are separately described below. After randomization, participants will be given study equipment, including a smartphone (with the condition-appropriate app already installed), CO monitor, Jawbone UP2 fitness tracker, and a high-accuracy digital bathroom scale. Participants will receive training in use of all equipment at the screening visit. Participants will also complete session 1 of the CBT in person in order to enhance therapeutic rapport-building.

Study Devices. Smart phones to be used in this study are the DROID MAXX 2. The phone has an octa-core 1.7 Ghz processor, 2 GB RAM, and 5.5" full HD display. The operating system (OS) being utilized for the smart phones is Android 5.1.1 Lollipop, see FIPS 140-2 certificate 1998. The STEP UP mobile phone app is an adaptation of smoking-cessation mCM mobile phone apps that have been used in several IRB-approved studies (PRO0031703, PRO0050835, PRO0048990, PRO0061683, PRO0062101) with expert input from Dr. Miriam Morey. Dr. Morey is a Professor in the Duke University Department of Medicine and the Associate Director of Research at the Durham VA Geriatric Research, Education, and Clinical Centers. Dr. Morey is an exercise physiologist and her specialization is in the design and execution of behavioral clinical trials of physical activity.

We have modified the app to include physical-activity monitoring components and feedback. Step-tracking will be implemented via a Fitbit Flex 2 fitness tracker. The Fitbit Flex 2is a light-weight wristband capable of tracking physical activity, including steps. Data are transmitted from the Fitbit Flex 2to the smart phone via Bluetooth technology and the Fitbit Flex 2 App. Our STEP UP mobile app will pull the data from Fitbit's servers and integrate the data with smoking cessation data so that participants and study staff can monitor progress towards step goals. Within the STEP UP app, progress toward daily step goals will be conveyed twice daily at semi-random intervals and will also be available on-demand. The mCM manual includes the participant instructions, payment schedules, and app screenshots.

The CO breath monitor to be loaned to participants is the Bedfont/coVita iCO™ Smokerlyzer®. The device is a battery operated instrument that measures CO in ppm (http://www.bedfont.com/shop/smokerlyzer/ico_smokerlyzer). The Bedfont/coVita iCO™ Smokerlyzer® plugs into a smart phone by means of the headphone jack, and communicates with the smart phone app developed by our team. Participants are able to see the CO reading within the app, and the app collects the CO data directly. Data are stored in the same manner as the videorecordings that participants upload (see below and in "Protection From Risks: Data Security" herein).

With regards to FDA device issues, Bedfont/coVita will not be seeking 510k Clearance on the iCO™ Smokerlyzer® because it does not meet the standard/criteria of a medical device. Device manufacturers are required to follow FDA guidance to inform them of when a device necessitates 510k application. Per Jason Aversano at Bedfont/coVita, their regulatory team has determined that this is not necessary primarily because they do not make a medical claim about

the device, as it is not designed to diagnose a disease or illness. Simply measuring CO is not diagnosing a disease or illness and Bedfont/coVita makes no medical claim that the iCO™ Smokerlyer® can be used to screen for CO poisoning.

Text Messaging Within the App. Our group has developed a text-messaging support library for smoking cessation in collaboration with the Department of Veterans Affairs (VA) Public Health Group and NCI (US Department of Veterans Affairs & National Cancer Institute, 2013). This library is in use by the VA and was launched nationwide May 2013. As of June 1, 2015, 2,867 smokers had enrolled in the SmokeFreeVET smoking-cessation program that utilizes this support library. We will also use a physical-activity text-message library developed by Drs. Beckham and Morey that is currently being used by the GetFitVET program, an 8-week exercise intervention for veterans. Pilot data was collected from 10 lower-income individuals ranging from 23 to 65 years old who were interviewed regarding the content and wording of the individual messages and keywords in the library. All reported using a cell phone, with the majority using text-message communication daily. Qualitative data from these participants were used to modify the messages and keyword categories (e.g., framing messages from a positive stance, shorten messages). We recently completed a second pilot study with 15 participants, 5 earning under $30,000 annually. According to this study, messages providing encouragement were endorsed over those detailing the benefits of exercise and those pertaining to goal-setting.

Mobile CM Procedures. Participants will use the smart phone app, CO monitor, and Fitbit Flex 2 wristband step-tracker to participate in the contingency management portion of the study. The STEP UP intervention includes (1) a 1-week training period in which participants are compensated simply for uploading videos and wearing the wristband step-tracker, (2) a 4-week period of active mCM in which they are compensated based on their own CO readings and physical-activity levels (i.e., meeting step goals), and (3) a 1-week fading period in which participants are compensated for uploading videos, regardless of their CO readings, and for wearing the wristband step-tracker, regardless of steps taken. Reinforcement amounts are detailed in the mCM manual provided to participants. Participants will be eligible to earn up to $798 across the 6-week intervention and monitoring period.

After the one-week training period, participants will be compensated for CO readings suggesting abstinence and wearing the step-tracker, and will be rewarded a bonus for abstinent CO readings + reaching step goals established by the counselor. Because reinforcers are most effective when delivered immediately after the target behavior is performed (Lattal, 2010), the phone app is designed to allow therapists to provide quick feedback on abstinence status, financial amount earned, and how the amount was calculated.

In order to verify smoking abstinence, participants will use the smart phone app to provide video recordings of him/herself taking CO readings. For each video recording, participants will be asked to 1) begin a recording using the smartphone device; 2) breathe in and hold his/her breath for the duration of the countdown shown on the screen; 3) when prompted, expel all air from lungs into the CO monitor while being video-recorded; 4) hit submit to upload the encrypted video recording using encrypted network connections to the secure server.

Through the smart-phone app, participants log-in to a secure website to upload their video recordings and see personalized information regarding their reinforcement information. Study coordinators can monitor validity and compliance on a daily basis and offer feedback to ongoing

participants regarding compensation so they are well-practiced at the procedures by the time contingent reinforcement is initiated. During the practice week, participants will be compensated $1 (twice per day) for a valid smoking reading. After the practice week, monetary reinforcement becomes contingent on abstinence, operationally defined as CO readings that are < 6 ppm (after the first week). In the first week of abstinence, smoking cessation compensation will be based not on CO < 6ppm, but on a proportion of participant's baseline CO as defined by Lamb (Lamb, Morral, Kirby, Iguchi, & Galbicka, 2004). Because an escalating, versus a fixed reinforcement schedule has produced higher abstinence rates (Heil et al., 2008; Stoops et al., 2009), an escalating schedule will be used in this protocol.

With regards to reinforcement for physical activity, participants are reinforced $1 each day he/she wears the step-tracker. In addition, participants will be assigned daily step goals derived based on baseline practice-week activity level. Participants recording under 5,000 steps per day at baseline will be given an initial goal of increasing their daily steps by 500 steps during the first week (Tudor-Locke & Bassett, 2004; Tudor-Locke, Craig, Thyfault, & Spence, 2013). Participants recording 5,000 steps or more per day will be given an initial goal of increasing their daily steps by 1,000 steps. Daily step goals will increase accordingly each week (i.e., by 500 steps per day if under 5,000 or by 1,000 steps per day if 5,000 or over; Tudor-Locke & Bassett, 2004; Tudor-Locke, Craig, Thyfault, & Spence, 2013). If participants fail to reach daily step goals 4 of 7 days of a given week, their daily step goals will not be increased the following week. Participants who meet their step goal on a given day will receive a bonus if they have also remained abstinent from smoking. Failure to meet the daily step goal will result in the normal abstinence-contingent payment without the bonus. No reward will be provided for participants who meet their daily step goal but fail to demonstrate abstinence, as the primary goal of the intervention is to increase exercise in the service of promoting smoking cessation.

Participants will be asked to return the smart phone and fitness tracker at the end of the treatment period. Participants will be allowed to keep the CO monitor since it has a limited number of uses. To ensure that participants return the phone and fitness tracker, we are providing postage paid return mailers and adding a $50 incentive for equipment return.

Cognitive Behavioral Therapy for Smoking Cessation. Both the STEP UP and comparison condition will receive a participant manual and 5 sessions of cognitive-behavioral telephone counseling focused on smoking-cessation and increasing physical activity. The smoking-cessation content is consistent with the Public Health Service Clinical Practice Guide, and is the same used in our published pilot studies and currently funded mCM trials (R01CA037220; 1I01HX001109; 1I01RX001301). The physical-activity portion of the manual and participant workbook are based on telephone-counseling content used in clinical trials exercise interventions run by Dr. Morey at Duke University Medical Center and the Durham VA Medical Center.

Pharmacotherapy for Smoking Cessation. Treatment will include standard pharmacotherapy for smoking cessation. This consists of bupropion, nicotine patch, and an 8-week course of $\leq$ 2 rescue methods (i.e., nicotine gum or lozenge) in participants who are medically eligible to take them. Participants will begin bupropion use two weeks prior to the scheduled quit date, and will be asked to continue using the medication until the 6-month follow-up. Participants will be screened for suitability for NRT and bupropion. If any participant reports a contraindication to NRT or bupropion and reports having a primary care physician, the study coordinator and/or study physician, Scott Moore, MD, PhD, will attempt to contact the physician for medical

clearance. If no contact from the primary healthcare physician can be made, the participants' health information will be evaluated by the study physician, Scott Moore, M.D., Ph.D., who will provide medical clearance (or not) to participate in the trial and to use smoking-cessation pharmacotherapy. Study medications will be provided via mail.

Text-Messaging Support. Text-messaging support has been shown to provide a small effect on decreasing smoking and increasing physical activity. Both arms will receive text messages *via* the app (i.e., not *via* a SMS paid plan). Specifically, participants will receive one smoking-cessation and one physical-activity message (randomly selected from a general library that includes 178 messages) per day during the intervention period. Text messages will be delivered as part of the smart phone app. Participants will also receive content-specific messages upon entering key phrases (i.e., “no time”, “bad weather”, “pain”, “cravings”, “smoked”, “stress”) associated with 83 additional messages.

Post-Treatment Session and 3-Month and 6-Month Follow-Up. To eliminate the burden of travelling to study appointments for assessments, telephone surveys will be conducted at the end of the mCM/mobile assessment phase. At that phone visit, participants will complete measures (read aloud by study coordinator) about treatment acceptability, smoking, medication adherence, self-efficacy to quit/remain quit, and physical activity.

Participants will be contacted by phone at 3- and 6-months post-screening visit. During the phone visit, participants will complete measures (read aloud by study coordinator) about smoking, medication adherence, self-efficacy to quit/remain quit, and physical activity. If participants report smoking abstinence at the 3 and 6-month follow-ups, they will be asked to come to the laboratory to provide a saliva sample and CO reading to bioverify smoking abstinence. If any participant is unable to come to the laboratory, he/she will be asked to provide a saliva sample by mail. When saliva is collected by mail, participants are sent instructions, saliva vials, a brief tobacco use assessment (that includes use of nicotine replacement therapies in the prior week), and a postage-paid padded envelope for returning the sample to the study coordinator. At each time point, any participant who provides a saliva sample will be paid $50. All sample identification will be with an assigned study number rather than patient identifiers. Saliva samples will be mailed to Salimetrics, LLC for cotinine assay (see “Smoking-Cessation Outcome Measures and Biochemical Verification” herein).

Participant Reimbursement. Participants who drop out will receive partial reimbursement for the time and effort they devote to the study. Because monetary reinforcement is an essential part of the intervention we are studying, participants will receive payments as reinforcers during treatment in addition to payments they receive to compensate for their time and effort on the study. Participants are paid: 1) $100 for completion of the screening visit and mCM training; 2) up to $798 for mCM; 3) $50 for equipment return at the end of treatment; 4) $25 each for the assessments at 3- and 6-month follow-up; and 5) $50 (each) for provision of saliva samples at 3- and 6-month follow-up. Participants could be paid up to $1098 for their complete participation.

**Study Measures**

Table 2 outlines measures to be given at each time point in the study.

**Table 2. Study Measures and Schedule of Administration**

| | Baseline | Weekly | PT* | 3 Months | 6 Months |
|---|---|---|---|---|---|
| Background Variables | | | | | |
| Demographics | X | | | | |
| Fagerström Test of Nicotine Dependence | X | | X | X | X |
| Minnesota Nicotine Withdrawal Scale | | | X | X | X |
| General Smoking History Questionnaire | X | | | | |
| NRT & Bupropion Contraindications | X | | | | |
| Stanford 7-Day Physical Activity Recall | X | | X | X | X |
| Intrapersonal Variable | | | | | |
| Short Form 36 Health Survey | X | | X | X | X |
| Global Self-Efficacy for Quitting Smoking | X | | X | X | X |
| Readiness-to-Change Questionnaire | X | | X | X | X |
| NRT & Bupropion Self-Efficacy | X | | X | X | X |
| Physical Activity Self-Efficacy | X | | X | X | X |
| Social Support | X | | X | X | X |
| Positive and Negative Affect | X | X | X | | |
| Physical Vigor | X | X | X | | |
| Process Measures | | | | | |
| Treatment-Acceptability Survey | | | X | | |
| Use of Smoking-Cessation Aids | | X | X | X | X |
| Morisky Adherence Questionnaire | | X | X | X | X |
| Outcome Measures | | | | | |
| Prolonged Abstinence: 7-day | | X | X | X | X |
| Prolonged Abstinence: 30-day | | | | X | X |
| Quit Attempts | | | X | X | X |
| Timeline Follow-Back-Quit Attempts | | | X | X | X |
| Steps (Assessed by Step-Tracker) | X | X | X | | |

***Post Treatment**

Demographic Measures. Age, race, gender, marital status, education, employment status, travel time, cell and smartphone use will be collected from each participant at baseline.

Physical Activity-Related Measures. The Stanford 7-day Physical Activity Recall (PAR) Scale (Sallis et al., 1985) will be used to quantify total engagement in physical activity at baseline, post-quit, 3-month follow-up, and 6-month follow-up. During the mobile monitoring period (baseline, treatment, and 1-week post-treatment) mean daily steps will be collected remotely and tabulated each week.

Smoking-Related Measures. The Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), Minnesota Nicotine Withdrawal Scale (Hughes &

Hatsukami, 1986), and a general smoking history questionnaire (e.g., number of cigarettes smoked/day, age of first smoking, number of previous quit attempts, living with a smoker) will be used to measure smoking behaviors. Participants will be asked to respond to several questions to determine if he/she has contraindications to receive smoking-cessation medications.

Quality of Life. Physical- and mental-health quality of life will be measured at baseline, post-treatment, and at 3- and 6-month follow-ups using the Short Form 36 Health Survey (Ware & Sherbourne, 1992).

Self-Efficacy, Readiness to Change, and Social Support. A single item ("How confident are you that you will be able to quit smoking?" 1 = "Not at all confident" to 4 = "Very confident"; Shiffman et al., 2000) will be used to measure global self-efficacy for quitting smoking at baseline, post-treatment, 3-month follow-up, and 6-month follow-up. The use of a global measure of SE is supported by previous studies in which multiple-item SE questionnaires formed a unifactorial construct (Baer, Holt, & Lichtenstein, 1986). The Readiness-to-Change Questionnaire (RCQ; Rollnick, Heather, Gold & Hall, 1992), which is designed to assess attitudes toward quitting smoking (Heather, Rollnick, & Bell, 1993), will also be administered at those time points. Self-efficacy for taking NRT and bupropion as prescribed will be assessed on a 10-point Likert scale. Self-efficacy for increasing physical activity will be similarly assessed on a 10-point Likert scale. Social support will be assessed using a single item used in the NIH PROMISE study (Williams et al., 1992): "Do you have someone you feel close to, someone you can trust and confide in?"

Affect and Physical Vigor. Positive and negative affect and physical vigor will be quantified at baseline, each week during the 6-week intervention and monitoring period, and at post-treatment. Positive and negative affect will be measured using 2 Likert-scale items: "During the past week, to what extent have you felt positive (e.g., happy, proud, excited)/negative (e.g., angry, irritable, upset)?" Responses range from 1 ("Very slightly or not at all") to 5 ("Extremely"). Physical vigor will be measured using 5 items from the Shirom-Melamed Vigor Measure (Shirom, 2003). Participants will be prompted to indicate how often they have felt each of the following during the past week: "I feel full of pep," "I feel I have physical strength," "Feeling vigorous," "I feel energetic," and "Feelings of vitality", with responses ranging from 1 ("Never or almost never") to 7 ("Always or almost always").

Measures of Treatment Acceptability. Participants' satisfaction with the intervention will be assessed via an in-depth interview, including 17 Likert-scale survey items, at the end of treatment. These items will assess: 1) reactions to the topics discussed and skills reviewed; 2) comfort with the counselor; 3) opinions of the materials used in session and homework (e.g., participant workbook); 4) overall satisfaction with the intervention at that point in time; and 5) comfort with the mHealth applications (mCM for smoking cessation and physical activity and supportive messaging).

Measures of Treatment Feasibility and Adherence. Feasibility of participant retention will be assessed by detailed tracking of attendance at each treatment session. Measures will include number of counseling sessions completed, the number of missed or cancelled appointments, and the proportion of participants who withdraw/drop out or are lost to follow-up. Participants who withdraw from treatment will be contacted to elicit feedback on their reasons for dropping

out. Feasibility of the use of the mHealth applications will be assessed by tracking: 1) the proportion of required videos uploaded using the mCM app; 2) participants use of the text-messaging keywords; 3) information regarding lost or stolen cell phones; and 4) participants' use of and comfort with the mHealth apps at the beginning and end of the intervention. We will also assess the number of participants who have a) mobile smart phones and b) current subscription to and size of mobile data plans (which will inform budgeting for a larger trial).

Medication adherence to NRT and bupropion will be assessed. Individuals who are optimally adherent have been found to be more than twice as likely (52%) to be abstinent at 6 months than were those with lower adherence (25%; Catz et al., 2011). Optimal adherence will be defined as using > 80% of their NRT and bupropion. The primary self-report measure of adherence will be the number of days NRT (and bupropion if prescribed) are used during the study period. Participants will also complete the Morisky Adherence Questionnaire (Morisky, Green, & Levine, 1986). This 8-item questionnaire is a general adherence measure that produces unintentional and purposeful non-adherence subscales. The questionnaire has been validated with smokers as an adherence screening measure (Toll, McKee, Martin, Jatlow, & O'Malley, 2007) and as a post-treatment measure of adherence (Catz et al., 2011). Days of medication use will be recorded at each telephone session and follow-up during treatment, post-treatment and 3- and 6-month follow-ups (for bupropion).

Smoking-Cessation Outcome Measures and Biochemical Verification. Our choice of primary and secondary smoking endpoints follows recommendations by the Society of Research on Nicotine and Tobacco (SRNT; Hughes et al., 2003). Self-reported and bio-verified prolonged abstinence at the 3- and 6-month follow-ups will be the primary endpoints. Prolonged abstinence will exclude tobacco use in the first 2 weeks following the quit date (Hughes et al., 2003). Self-reported prolonged abstinence will be verified by cotinine assay. CO and saliva samples will be collected from participants who report prolonged abstinence at each follow-up. Saliva samples will be sent to the Duke University Nicotine Research Program to be analyzed for the presence of cotinine using a standard cut point of 10 ng/ml to determine abstinence. A blind sample of 5% will be rerun to assure test accuracy of saliva samples. Secondary smoking outcomes will include 7- and 30-day point prevalence abstinence at each assessment, where abstinence is defined as no tobacco use in the prior 7 or 30 days respectively. Additionally, participants will be asked if they have made one or more quit attempts in each follow-up period using a time-line follow back method (Lewis-Esquerre et al., 2005). We have recent experience using this method to assess daily smoking behavior (Carpenter et al., 2015).

**Potential Risks**

There is a risk of discomfort or distress in answering questions on the study measures. However, distress and discomfort related to questionnaire completion is usually temporary and well-tolerated. Risks also include discomfort related to quitting smoking. Quitting smoking may cause difficulty concentrating, poor sleep, increased appetite, anxious or depressed mood, and craving for cigarettes. Participants will be offered NRT, and there are risks associated with the use of NRT. Minimal risks associated with wearing a nicotine patch include skin irritation, dizziness, lightheadedness, increased heart rate or blood pressure, nausea or vomiting. If a participant indicates a contraindication to NRT (e.g. uncontrolled hypertension), medical clearance for NRT will be sought from the participant's primary care physician and/or the study physician. If a participant with a seizure disorder, history of or current hepatitis and/or cirrhosis, renal

impairment, and/or uncontrolled diabetes wishes to enroll in the study, he/she will not receive contraindicated medications.

Participants who are medically eligible will also be prescribed bupropion SR. Risks of bupropion use include dry mouth, insomnia, nausea, constipation, headache, shakiness or jitteriness, skin rash, sweating, allergic reaction, change in appetite, weight loss, dizziness, tremor, thinking abnormally, hot flashes, worsening depression or suicidal thoughts and behavior, and ringing in the ears. At the highest dosage of bupropion to be used in this study, seizures occurred in 1 out of every 1000 (0.1%) who took this drug. Participants are informed that they are not required to take bupropion, and will be allowed to participate in the study if they refuse to do so.

The risk of doing moderate exercise is low, and may be associated with risk of injury, falls, fainting, dizziness, or muscle soreness. There is even the risk of sudden death or stroke. To minimize these risks during exercise, participants will be instructed to exercise at a comfortable level and to never push themselves to a point beyond where they feel safe. Participants will also be monitored and instructed to report symptoms such as unusual shortness of breath, dizziness, tightness or pain in the chest or arms, skipping heart beats, numbness, loss of balance, nausea, or blurred vision.

There is a potential risk associated with the loss of confidentiality of study data. Specifically, collection and transfer of videotaped carbon-monoxide monitoring have risks with regards to privacy and confidentiality. Please see “Protection Against Risk and Data Security Measures” for details on reduction of risk with regards to the proposed videotaping.

**Protection Against Risk and Data Security Measures**

While participants may benefit from quitting smoking and increasing physical activity, there are no guaranteed benefits to the individual participant and no immediate benefits of the proposed research to others. There are potential benefits to others from the information generated that potentially will be helpful in developing new combined treatments for smoking and physical activity. In our opinion, the anticipated benefits of this study outweigh the potential risks.

The study is completely voluntary and participants are informed that they are free to refuse to answer any items on the questionnaires or questions from the interview that they do not wish to answer. They are also informed that they are free to decline participation in any procedure and can withdraw from the study at any time.

Potential risks will be minimized by carefully screening potential participants according to the inclusion/exclusion criteria, closely monitoring symptom levels, and following established laboratory procedures associated with participant safety.

We have included at the end of this full protocol a data flow diagram that describes data movement within the study. We will be providing the study phones to participants for the course of the monitoring period and will retrieve them at the conclusion of monitoring. Phones will be equipped with the STEP UP mobile app developed by our team, and with Fitbit Flex 2 App to allow data to be transferred to Fitbit’s servers. Their API states that they use OAuth 2.0 to authenticate API requests and that must be done over secured (SSL/TLS) connections.

Participant data that is updated to Fitbit's servers will be deidentified, and no actual participant information will be provided to Fitbit in order to set up the accounts.

On the smart phones, we will restrict access to the following applications: internet browsers, installation of apps, deletion of apps, and in-app purchases. We will prevent access to music, podcasts, movies, TV shows, apps, and other websites. We will prevent ability to change the following: accounts, cellular data use, background app updates, location services, contacts, calendars, reminders, photos, Bluetooth sharing, microphone, Twitter, Facebook, and advertising. We will have the ability to remotely wipe the phones if they are not returned. We will encourage participants via consent to only enter information on the phone that they are comfortable with sharing with the entities listed below.

Regarding mobile information security, we have taken care in previous projects using similar methods and technology to develop procedures to limit the risk of breach of confidentiality and privacy. For example, the smart phone is programmed such that a staff member will set up the telephone and enter the participant's code into the phone. When uploading a video, participants upload directly from the phone to an approved website that has been vetted by Duke's information security officers, and the phone programming ensures that the video is uploaded into the correct participant's area of the website. This ensures that study participants' data is stored in the correct place, and that study participants cannot view any other participants' data. Participants are asked to review their videos before posting, and they can choose not to upload any video that they do not wish to upload for any reason. In previous studies that have been run using this methodology, we have had no participant complaints regarding issues of privacy and confidentiality related to use of the smart phone videotaping procedures. In order to enhance participants' privacy, we will restrict access to several of the telephone's ancillary applications, and we have the ability to remotely delete data from any phones that are not returned to the study team.

For the study's website, we will use shared server space provided by InMotion Hosting, Inc (website www.Calhounlab.com). We will be using AES-256-CBC encryption with SHAI for message authentication and RSA as the key exchange mechanism. The video recordings will be collected on devices that are FIPS-140-2 compliant. The data at rest at InMotion Hosting is AES-256 encrypted at rest, and the data being transferred are encrypted at transfer (AES-256). Data will be unencrypted only by study staff members who have access to the secured server at InMotion Hosting; the encryption key is held only by our staff. This will ensure all video uploads and data that the participant sends over the internet via their phones will only be transferred over encrypted network connections, essentially nullifying the possibility of someone gaining access to the video before it reaches our server. InMotion also runs audits regularly of the websites hosted within their shared servers to prevent scriptside vulnerabilities, as well as having a 24/7 support team monitoring their servers. The web application written for this study has been checked for SQL injection, Code Injection, XSS, and RFI vulnerabilities and has passed. The site will only be accessible by the study participants and the study coordinators via 512-bit SHA-2 hashed passwords.

In previous studies using this methodology that have been run in the Traumatic Stress and Health Research Laboratory, we have had no participant complaints regarding issues of privacy and confidentiality related to use of the smart phone videotaping procedures. As security controls have not been validated for InMotion Hosting, we will include a statement in the

informed consent that the data/videos voluntarily submitted will be sent to InMotion and are no longer covered by Duke privacy protections.

Data that links participants to information collected in the course of a given study will be kept separately from identifying information in an electronic, password-protected MS Access database stored at duhsnas-pri\dusom_psych\private\Beckham Logs\STEP UP; the key connecting identifying information and data will be stored here as well. Hard copy paper records will be stored in a locked filing cabinet in the study coordinator's locked office, within Dr. Dennis' laboratory space at Hock Plaza. Information from the interview and/or questionnaires may be entered into a computerized database that will be stored on the DUMC server at duhsnas-pri\dusom_psych\private\ Beckham Logs\STEP UP in a password-protected database separate from the "logbook" of identifying information. This database is accessible only by Dr. Dennis and study staff. Any staff members who leave the study for any reason will have access to study resources, including data, removed immediately.

**Data and Safety Monitoring Plan**

Quitting smoking and increasing physical activity should enhance rather than jeopardize health status, and potential serious adverse events (SAEs) for participants in this project are not expected. Regardless, we will minimize potential risk by careful screening of potential participants (e.g., medical clearance by their primary care provider if there are contraindications to smoking cessation pharmacotherapy).

Dr. Dennis will serve as the primary safety monitor for the proposed study, and Scott Moore, M.D., Ph.D. will serve as the study physician and Medical Monitor. As Medical Monitor, Dr. Moore will provide additional safety monitoring with regards to medication use. Dr. Moore is a board-certified psychiatrist with years of experience in the provision of smoking cessation services. He has served as the medical director of the Durham VA Medical Center's smoking cessation clinic, and has served as a study physician on several smoking cessation studies run by our group. As study physician, Dr. Moore will ensure participants are medically cleared to participate in this trial and will review all reports of adverse events sent by the study coordinator and evaluate the patient as necessary to determine whether there is any corrective action needed. Dr. Moore will review all reports of adverse events sent by the study coordinator and determine whether there is any corrective action to be taken.

Further data safety and monitoring will be provided by the PI. There will be several ongoing mechanisms for monitoring and reporting of adverse events (AEs), including serious adverse events (SAEs): 1) ongoing participant contact via study personnel; 2) a telephone number provided to participants to report concerns related to study participation; 3) weekly meetings between Dr. Dennis and study personnel.

The PI will meet at least weekly with study personnel to discuss participants' reactions to the intervention, proper delivery of the intervention, and any adverse events or unanticipated problems. Regular meetings between investigators and the project manager will allow for ongoing progress reports, including the number of participants currently involved in the study groups, attrition rates, and scheduled data collection from participants, as well as notification and review of any AEs. Safety monitoring for AEs will be conducted in real time by the PI and/or project manager. The following information about adverse events will be collected: 1) the onset

and resolution of the AE, 2) an assessment of the severity or intensity (use existing grading scales whenever possible), 3) an assessment of the relationship of the event to the study (definitely, probably, possibly or not related), and 4) action taken (e.g., none, referral to physician, start or increase concomitant medication). The PI will determine the severity of the event, will assign attribution to the event, and will monitor the event until its resolution. Any adverse events will be reported to the IRB in accordance with the IRB guidelines.

In order to monitor possible adverse events, participants will be instructed to report any adverse effects of study participation as soon as possible to research staff; they will have contact information needed to report these problems to study personnel. Participants will also be questioned about any side effects of the study medications (i.e., nicotine replacement therapy and bupropion) to further monitor any adverse reactions.

**Outcome Measurement and Biochemical Verification**

Self-reported and bioverified prolonged abstinence from smoking at the 3 and 6-month follow-up will be the primary end-point. Prolonged abstinence will exclude tobacco use in the first two weeks following the quit date to give participants time to achieve initial abstinence (Hughes et al., 2003). Self-reported prolonged abstinence will be verified by cotinine assay, a metabolite of nicotine in the saliva. Saliva samples will be collected from participants who report prolonged abstinence at each follow-up. They will be mailed to Salimetrics LLC for saliva cotinine assays. Saliva samples will be analyzed for the presence of cotinine using a standard cut point of 10 ng/ml to determine abstinence. A blind sample of 5% will be run again to assure test accuracy of saliva samples. Secondary smoking outcomes will include 7- and 30-day point prevalence abstinence at each assessment, where abstinence is defined as no tobacco use in the prior 7 or 30 days, respectively.

**Data Analyses**

Descriptive statistics will be used to summarize all study variables, including smoking history and current use, nicotine-dependence level, self-efficacy, readiness to change, and social support. For continuous variables, means, standard deviations, ranges, and histograms will be generated. For categorical variables, frequencies and proportions will be generated. Individual and mean trajectory plots of the longitudinal outcome variables will be constructed to understand their general trends over time (i.e., post-treatment, 3- and 6-month follow-ups). We will examine all variables to determine if parametric distributional assumptions (e.g., normality for the continuous variables) are valid. Variables not meeting distributional assumptions will either be transformed or modeled using non-parametric or semi-parametric methods (e.g., quasi-likelihood methods; McCullagh & Nelder, 1989). In order to describe the compliance/completion of the sample in terms of smoking-cessation aids and intervention completion, these variables will be summarized. In terms of descriptors for outcome measures, we will record number of quit attempts, quality of life, and number of weekly steps, and utilize time-line follow-back data to identify when participants may have lapsed. Potential covariates (e.g., age, gender, minority status) will be evaluated for inclusion in models. If any of these variables have a significant bivariate effect on treatment outcomes, they will be entered first in statistical models.

Missing Data. Because the main predictors of interest, treatment group and demographics, are collected at baseline, we do not anticipate much missing data. We do, however, anticipate

missing values in the longitudinal outcomes owing to dropout, an inability to reach participants, or item non-response. Multilevel modeling (MLM), which employs maximum and pseudo-maximum likelihood estimation, is proposed to address this issue. MLM uses all available data; as such, it can accommodate data missing at random. Because individuals with the least missing data have the most influence on model results, analyses will be conducted to determine whether missingness is systematic (i.e., associated with individual differences in either baseline parameters or time-related changes in observed variables). If data are deemed not to be missing at random, additional approaches to deal with missingness in the response will also be explored, including imputing missing values by multiple-imputation procedures as described by Schafer (Schafer & Graham, 2002).

The feasibility and acceptability of STEP UP will be assessed. Content analysis of the cohort interviews will yield descriptive data regarding participants' perceptions of specific components of the treatment at each development phase. Participant feedback will be used to evaluate the user experience so that the phone app and counseling procedures can be enjoyable to the target population. We will describe participant recruitment (proportion of participants screened/enrolled), participant treatment retention (number of sessions completed, drop outs). Acceptability of STEP UP will be assessed via descriptive analyses of the ordinal-level outcomes on the treatment-acceptability survey completed at the conclusion of the RCT. Participants' responses to open-ended questions will be compiled for content analysis. In addition to evaluating participant satisfaction, we will describe use of mHealth applications (adherence with mCM videos, compliance with wearing the step-tracker, comfort with the app), medication adherence, participant smoking-cessation and physical-activity content knowledge before and after treatment, and treatment fidelity. All of these data will provide critical information prior to planning a larger RCT.

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**Data Flow Diagram for PRO00074576**