Study Protocol

Study Title: Blood Pressure Control in Hypertensive Smokers

NCT: NCT00113074

Approval Date: 09/20/2021

I. Project Introduction

I.1 ***Project to be reviewed by:***
IRB-03 VA Only

I.2 ***Project Title:***
Blood Pressure Control in Hypertensive Smokers

I.3 ***Short Title (optional):***

I.4 ***Provide a short summary of the purpose and procedures of the study proposed in this IRB application.***

- ***DO NOT include information on studies not proposed in this application.***
- ***Use LAY terminology only. This must be easily understandable by IRB community members and nonscientists.***
- ***DO NOT cut and paste technical abstracts from funding applications that may not be understood by a general audience.***

Cigarette smoking and hypertension both significantly increase the risk of cardiovascular morbidity and mortality, acting synergistically to produce an even greater risk than their combined independent effects. Quitting smoking, therefore, is especially important for patients with high blood pressure. Unfortunately, smoking cessation often produces a nontrivial weight gain averaging 5 kg, which may exacerbate hypertension in those with the disorder. Indeed, several studies have documented significant elevations in BP following smoking cessation, as well as increases in the prevalence of hypertension after quitting smoking. In this study, we will investigate the effectiveness of three interventions following smoking cessation: (a) a behavioral weight control program; (b) lifestyle modification to improve blood pressure control; or (c) self-help materials targeting weight management and blood pressure control. In addition, participants will be instructed to continue any ongoing care for their elevated blood pressure with their primary care provider.

- The Iowa City VA Health Care System is serving as the coordinating center for this project. Participants were enrolled at the University of Iowa, where they also received the study intervention. All data were also collected at and are now stored at the University of Iowa. All intervention and data collection activities for the project have been completed. All that remains is data analysis and manuscript preparation. The university portion of the project is now under the oversight of IRB-01 201703765. As the PI, who will be overseeing all remaining study activities, is a VA employee located at the Iowa City VA Health Care System, the current project (IRB-03 200611724) represents the coordinating activities between the two institutions and protocols.

This study has two phases:

In phase I, a total of 500 smokers with hypertension or pre-hypertension (based on the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7] criteria) will be provided with a brief, validated, combined behavioral and pharmacologic smoking cessation intervention.

During phase II, participants who are abstinent from smoking following the

phase I intervention or those who quit smoking on their own and enroll in the study will be randomized to: (a) a validated combined weight gain prevention and blood pressure control program; (b) a validated weight control program; or (c) self-help materials for managing body weight and blood pressure. These interventions are designed to supplement rather than to replace ongoing care participants are receiving for their elevated blood pressure. Therefore, they will also be instructed to continue to have their blood pressure managed by their primary care provider. The primary endpoints will be changes in blood pressure and body weight among abstinent smokers at one year follow-up.

I.5 ***Specify your research question(s), study aims or hypotheses (do not indicate "see protocol")***

Aim 1: To recruit 500 smokers with Stage I hypertension or pre-hypertension (based on JNC 7 criteria).

Aim 2: To provide those participants still smoking with a brief, validated, combined behavioral and pharmacologic smoking cessation intervention or behavioral intervention alone.

Aim 3: To randomize participants who are abstinent from smoking at the completion of a cessation intervention to: (a) a validated combined weight gain prevention and blood pressure control program; (b) a validated weight control program; or (c) self-help materials for managing body weight and blood pressure. Primary endpoints will be changes in blood pressure and body weight among abstinent smokers at one year follow-up

I.6 ***Background and significance and/or Preliminary studies related to this project. (do not indicate "see protocol")***

A. Background and Significance

A.1. Risks Associated with Elevated Blood Pressure and Cigarette Smoking

Hypertension is among the most prevalent and potent risk factors for cardiovascular disease, the leading cause of death in the United States (Fiebach et al., 1989; Kannel, 1996). An estimated 35% to 40% of all cardiovascular morbidity and mortality can be attributed to hypertension (Kannel, 1987). Atherosclerosis and coronary artery disease are the most common sequela of high BP (Kannel, 1990; Kannel, 1987), resulting in a significantly elevated risk for stroke, myocardial infarction (MI), and peripheral vascular disease (Fiebach et al., 1989; Goldstein et al., 2001; Grundy et al., 1998; Kannel, 1996; Thrift et al., 1998). Hypertension also is an important risk factor for renal disease and CHF, as well as mortality from both cardiovascular and non-cardiovascular causes (He & Whelton, 1997; Stamler et al., 1993). Although the prevalence of hypertension has declined considerably over the past 30 years (Burt et al., 1995a), about 25% of adults, and 50 million people total, in this country meet the criteria for hypertension (AHA, 2003; Burt et al., 1995b; Wolf-Maier et al., 2003).

The health consequences and medical costs associated with cigarette smoking are staggering as well. Cigarette smoking is linked to increased morbidity and mortality from cardiovascular diseases, various forms of cancer, and chronic obstructive lung diseases (US DHHS, 1990). The leading causes of death in the United States are heart disease, malignant neoplasms, and stroke. Cigarette smoking is a proven major risk factor for all three sets of disorders (Heckler, 1985). Although there was a decreasing trend in smoking rates during the 1980's (33.2% in 1980 vs. 25.5% in 1990), the overall percentage of adult smokers has not markedly decreased in recent years (25.0% in 1993 vs. 23.3% in 2000; CDC, 2002b; Giovino et al., 1994). Thus, cigarette smoking and hypertension both are

significant and highly prevalent risk factors.

The co-occurrence of smoking and hypertension results in an extremely adverse risk profile for cardiovascular disease. Independently, smoking and hypertension each carry at least a two- to threefold increase in risk for coronary heart disease (Kannel, 1996; Kannel & Higgins, 1990; Neaton & Wentworth, 1992). When they occur together, however, smoking and hypertension act synergistically to produce a level of risk that is significantly greater than additive (Rigotti & Pasternak, 1996). Relative to nonsmoking normotensives, cigarette smokers and hypertensives in the Nurses Health Study had a five and eightfold increase in risk, respectively, for fatal coronary heart disease and nonfatal myocardial infarction (Willet et al., 1987). When they occurred together, however, these two factors were associated with a relative risk of 27.4. Similar findings of heightened cardiovascular risk in hypertensive smokers have been reported in other studies, as well (Neaton & Wentworth, 1992; US DHHS, 1989).

Unfortunately, smoking and hypertension as concurrent risk factors are highly common. Despite the significant risk associated with smoking for those with high BP, the prevalence of smoking among hypertensives is similar to that of normotensives (Nothwehr et al., 1994). Findings from NHANES III indicate that 21% of participants with hypertension smoke cigarettes (Nothwehr & Perkins, 2002). Similarly, data from the CDC's 1997 Behavioral Risk Factor Surveillance System that were analyzed for this proposal revealed that the prevalence of smoking among those with high BP was 20%. The prevalence appears to be even higher among clinical samples (Bühler et al., 1988; Medical Research Council, 1985; MRFIT Research Group, 1982).

A.2. Weight Gain Following Smoking Cessation

Although smoking cessation should be a top priority for those with hypertension, quitting smoking leads to a nontrivial weight gain, potentially exacerbating their already high blood pressure. Considering that body weight is the strongest single predictor of BP (McCarron & Reusser, 1996) and that even small weight gains (e.g., 5 kg) are associated with an increased risk of developing hypertension (Field et al., 1999; Huang et al., 1998; Vasan et al., 2001), it is not surprising that postcessation weight gain may have an adverse impact on BP. Indeed, several prospective observational studies have demonstrated a significant increase in BP following smoking cessation (Jenner et al., 1988; Lee et al., 2001; Seltzer, 1974). Furthermore, smoking cessation has been associated with an increase in the prevalence of hypertension in some studies (Gerace et al., 1991; Lee et al., 2001). These increases in BP following smoking cessation appear to be largely, although not totally, the result of postcessation weight gain (Gerace et al., 1991). Together, this body of literature suggests that, although smoking cessation is associated with numerous health benefits for smokers with elevated BP, the weight gain associated with quitting may lead to increases in BP, which may carry additional cardiovascular risk.

A.3. Preventing Postcessation Weight Gain

Minimizing postcessation weight gain in those with elevated BP, therefore, is very important to prevent exacerbation of high BP, and to help motivate patients to remain abstinent. The literature on preventing postcessation weight

gain, however, is mixed. Several pharmacologic agents (e.g., nicotine replacement therapy [NRT], phenylpropanolamine [PPA], fluoxetine, Zyban) have been found to suppress postcessation weight gain while patients are taking the drug (Abelin et al., 1989; Borrelli et al., 1999; Hurt et al., 1997; Klesges et al., 1995). Once the drugs are terminated, however, one typically observes a "weight rebound" in drug-treated participants whereby weight gain at long-term follow-up is similar to those not receiving medication (Ward et al., 2001). Conflicting results also have been observed following lifestyle interventions to reduce postcessation weight gain. Although most early studies met with limited success (e.g., Hall et al., 1992; Pirie et al., 1992), more recent trials have demonstrated that long-term reductions in postcessation weight gain, at least in weight conscious smokers, can be sustained and smoking cessation can be enhanced (Danielsson et al., 1999; Marcus et al., 1999).

In one recent study, Spring et al. (2004) randomized women to a 16-week smoking cessation intervention combined with one of three weight management programs (Early Weight Plan, Late Weight Plan, Control Plan). Both active interventions included behavioral weight management counseling and a high-carbohydrate, low-fat prepackaged meal plan combined with moderate exercise, but differed in terms of when the intervention was delivered. In the Early Plan, participants received the intervention during the first eight weeks of the smoking cessation program, while the intervention was delivered to those in the Late Plan during the last eight weeks. Cessation rates did not differ by treatment group. Weight gain, however, was suppressed among those in the Late group relative to controls at the six-month follow-up. Thus, sequencing the interventions so that the weight management component was introduced after the smoking cessation program was completed was a particularly effective intervention strategy. These findings demonstrate that it is possible to successfully reduce postcessation weight gain without adversely affecting quit rates, and also demonstrates why sequencing the interventions is important.

Although there are emerging model programs suggesting that long-term weight suppression and cessation rates might be enhanced, some argue (with supporting data) that weight control efforts during the cessation process might not aid and, in some cases, may detract from smoking cessation efforts (Hall et al., 1992). It is further argued that the average weight gain (4.5 - 6.8 kg) following smoking cessation, while unacceptable to most smokers from a cosmetic standpoint, rarely places a person at increased medical risk (Perkins, 1994). Thus, it is argued that clinicians should focus on convincing smokers to accept the weight gain (Hall et al., 1992), and programs designed to reduce postcessation weight gain should be limited to those where the weight gain might place an individual at increased medical risk (Perkins, 1994). Examples of populations that might be at increased risk include hypertensives, diabetics, the already obese, or those at risk for high levels of postcessation weight gain (e.g., African Americans). To date, however, no studies have investigated the efficacy of a combined smoking cessation/weight control program in any of these medically at-risk populations.

A.4. Dietary Factors and Blood Pressure

In addition to weight control, specific dietary factors play an important role in the development and treatment of high BP. Sodium intake, in particular, has

been identified as having a strong relationship to BP (Chobanian & Hill, 2000). Numerous epidemiological studies have found that sodium intake is positively associated with BP (Elliott et al., 1996; Stamler, 1997). Intervention studies also have demonstrated that sodium restriction can be a beneficial strategy for lowering BP, particularly among those who are hypertensive (Cutler et al., 1997; Graudel et al., 1998; He & MacGregor, 2002). Thus, not only are smoking cessation programs among hypertensives needed, but conducting efficacy studies testing smoking cessation programs combined with dietary approaches to BP control should be a high priority.

A.5. Lifestyle Changes in Hypertensives

It is clear that those with high BP are motivated to make behavioral changes to improve their hypertension status. The majority of smokers being treated for hypertension (an estimated 58% of women and 65% of men) indicate that they are willing to quit (Kastarinen et al., 2002). Furthermore, among individuals with hypertension who participated in NHANES III, nearly half reported making an attempt to lose weight in the previous year, and 29% changed what they ate because of their health (Nothwehr & Perkins, 2002). Among former smokers, 27% quit smoking as a result of a health problem. Previous experience during the TONE trial (Whelton et al., 1998) also has shown that hypertensives can make long-term changes in their body weight and sodium intake to reduce their risk of hypertension. Interestingly, the weight loss observed in TONE (3.5 – 4.5 kg) is very similar to the weight gain that typically is experienced following smoking cessation.

Thus, the purpose of the current investigation is to evaluate whether we can maintain, or even lower BP in hypertensives who quit smoking by making lifestyle modifications to reduce sodium intake and prevent weight gain using the previously validated TONE protocol (Whelton et al., 1998). We anticipate that both the BP Control and Weight Gain Prevention interventions will prevent any negative changes in BP associated with smoking cessation, and will have a relatively more positive impact on body weight, dietary intake, and physical activity. If efficacious results are obtained, other medically at-risk populations (e.g., diabetics) also could be tested with this model. Thus, the potential for dissemination is high. Given that hypertension and smoking are two of the most significant risk factors for premature mortality and morbidity (JNC VI, 1997; CDC, 2002a), both are highly prevalent in the adult population, and both can be treated/controlled, the potential clinical significance of these preventive efforts is extremely high.

B. Progress Report / Preliminary Studies

Collectively, our research team has a strong background in conducting smoking cessation research. Dr. Vander Weg has considerable experience in the development, delivery, and evaluation of tobacco use interventions. He is currently serving as co-investigator for an NCI-funded study investigating the extent to which elective surgery may serve as a teachable moment for quitting smoking (CA126371) and for a study funded by NIDA to examine the efficacy of gabapentin for helping tobacco users quit smoking (DA021583). He recently served as co-PI on an NCI-funded study of prolonged smoking cessation using prescription stepped-care (CA10666) and co-investigator for an NCI-funded

study assessing the efficacy of St. John's Wort for smoking cessation (CA119814). He also served as co-investigator for several additional NIH-funded studies including a clinical trial investigating the effectiveness of a tailored behavioral intervention at reducing tobacco use in a population of over 36,000 military recruits (HL53478), a school-based smoking cessation program for adolescents (DA12532), a study investigating the effectiveness of physical activity as an adjunctive treatment for smoking cessation (HL68569), an international study to build capacity for tobacco control work in the Eastern Mediterranean region (TW05962), and a study investigating the efficacy of the nicotine lozenge for ST cessation (Fraternal Order of Eagles). Dr. Vander Weg also developed a smoking cessation intervention for a prospective study of changes in energy balance following smoking cessation (HL46352) and was co-author of a school-based smoking prevention program for 9th grade students. Additionally, Dr. Vander Weg developed a behavioral smoking cessation intervention for participants in a prospective study of changes in energy balance following smoking cessation (HL 46352), was co-author of a school-based smoking prevention program for 9th grade students (Reynolds et al., 2000), and co-authored a smoking cessation program for low-income pregnant women enrolled in a home visitation program. Finally, he previously served as co-principal investigator for an LHS-funded prospective observational study of smoking relapse among low-income pregnant women.

Dr. Vander Weg also has experience conducting research on issues related to smoking and body weight. For example, he has conducted a laboratory study investigating the metabolic effects of smoking (Vander Weg, Klesges, & Ward, 2000). We also completed a study investigating short-term changes in energy balance following two weeks of smoking cessation (Vander Weg et al., 2001). Despite the relatively short follow-up period, smoking cessation was associated with a significant increase in body weight. Smoking cessation also was associated with an increase in energy intake, while no changes in energy expenditure (resting energy expenditure [REE], physical activity) were observed. Predictors of weight gain included higher baseline carbon monoxide (CO) level, lower baseline REE, and changes in energy intake. Thus, the only energy balance variable to change over the course of smoking cessation was energy intake. This is consistent with other studies (e.g., Stamford et al., 1986) that suggest that change in energy intake is most responsible for weight gain following smoking cessation.

C. Evolution of the Study over Time

C.1. Transfer of Grant

Notification of impending funding for the grant that is supporting the current investigation was originally received while the Principal Investigator was at the University of Memphis (the institution of record on the original application), but after he had accepted an offer to join the faculty at the Mayo Clinic in Rochester, MN. The grant was subsequently relinquished by the University of Memphis and transferred to the Mayo Clinic, where initial funding was received in September of 2004. Dr. Vander Weg relocated to the University of Iowa in September of 2006. An agreement was made with the Mayo Clinic and the National Heart, Lung, and Blood Institute (NHLBI) to transfer the grant to the University of Iowa. Recruitment continued at Mayo Clinic through December of 2006, and

arrangements have been made to continue following the participants recruited at the Rochester site through the end of their involvement in the study. The official application for transfer of the grant will be submitted to NHLBI following IRB approval of the study at the University of Iowa. Program staff at NHLBI have, however, already granted conceptual approval of the grant transfer.

A colleague of the Principal Investigator, Dr. Robert Klesges, who collaborated with him at both the University of Memphis and the Mayo Clinic, also received a grant from the NHLBI to address postcessation weight gain in hypertensive smokers, on which Dr. Vander Weg was the Co-Principal Investigator. Dr. Klesges modified the study design and procedures to match those of the current grant, and the protocols were functionally "joined" while both were still at the Mayo Clinic. Originally, the studies utilized separate two-group randomized designs. Upon merging the protocols, it was revised to a single three-group randomized design. This was done with the enthusiastic support and approval of NHLBI.

Dr. Klesges has since relocated to the University of Tennessee Health Sciences Center in Memphis, Tennessee. Consequently, the study has evolved into a multi-site clinical trial with sites in Memphis, Tennessee; Rochester, Minnesota; and (soon) Iowa City, Iowa. Cross-site training has occurred and conference calls are conducted between key staff and investigators from all three sites on a weekly basis. Bi-weekly conference calls among investigators also occur on an ongoing basis to support standardization and consistency across sites.

As noted above, when the application for the current study was originally submitted, it was intended to be conducted at the University of Memphis. At that time, the study called for recruiting a majority of African American participants. Given the demographic composition of both Rochester, MN and Iowa City, IA, however, this was no longer feasible. Consequently, the recruitment goals for the study were modified accordingly and with the approval of NHLBI. The subsequent relocation of Dr. Klesges to the University of Tennessee Health Sciences Center in Memphis, TN, which is a more demographically diverse area, has increased opportunities for minority recruitment for the multi-site trial. Dr. Klesges has a long history of successful recruitment of minority participants for clinical trials during the 20 years that he was on faculty at the University of Memphis. The Memphis, TN site will therefore assist with efforts to recruit African American participants into the trial.

C.2. Changes in Exclusion Criteria

The current protocol involves some changes to the exclusion criteria since the grant application was initially submitted to NHLBI. These changes were due in part to the recommendations of a Protocol Review Committee that was created upon the advice of NHLBI for the purpose of reviewing the plans and methodology for combining the protocols for the two grants. Several modifications were made primarily in an effort to reduce the restrictiveness of the inclusion criteria, and to allow enrollment for additional participants who might benefit from a program designed to help them quit smoking and control their blood pressure and/or weight. Other changes were made after consulting with physician colleagues and physician co-investigators at Mayo who were enlisted to provide medical oversight of the study when the grant was

transferred to that location.

As noted above, several of the original exclusion criteria were subsequently removed following consultation with our physician investigators as well as the Protocol Review Committee. In the current protocol, a known contraindication or sensitivity to nicotine replacement therapy (NRT) is no longer an absolute exclusionary factor. Instead, individuals who are not able or willing to use NRT will be given the option of receiving the behavioral portion of the smoking cessation program without NRT. Similarly, we consulted a dermatologist at Mayo who informed us that it was not necessary to exclude patients with a history of atopic or eczematous dermatitis or dermatosis from participation in the study or from receiving transdermal nicotine. In the event that these individual are unable to tolerate the nicotine patch, they will still be given the option of receiving only the behavioral portion of the smoking cessation intervention. Insulin-dependent diabetes mellitus, fasting blood sugar of ≥ 160 mg/dl, anemia (as measured by hemoglobin < 11g/dl), and history of a serious illness that might limit longevity also are no longer exclusionary, as it was felt that individuals meeting these criteria would not be placed at significantly increased risk by participating in the study, and might receive potentially important benefits. Exclusion criteria related to a body mass index (BMI) of ≤ 21 kg/m2 and unexplained weight loss of more than 10 pounds in the past year also were determined unnecessary by the physician investigators. Finally, the original protocol included an exclusion criterion related to the inability to collect 24-hour urine measures with a volume of ≥ 500 ml. However, because 24-hour urine samples are no longer being collected (they have been replaced by overnight measures of urinary chloride excretion), this exclusion criterion is no longer necessary.

Several other exclusion criteria were modified for the current protocol. For example, a serum creatinine level of ≥ 2 mg/dl was originally an exclusion criterion. However, this was replaced in the revised protocol by “history of severe kidney or liver failure.” In addition, exclusion criteria related to having a history of myocardial infarction, stroke, unstable angina, coronary artery bypass grafting or angioplasty/stenting were changed from the past six months to the past three months, as it was determined by our physician investigators that this would be a sufficient interval to determine medical stability. Exclusionary criteria related to arrhythmia were also changed from “uncontrolled arrhythmia” to “cardiac dysrhythmia (except atrial fibrillation) treated with anti-arrhythmia medications.” Additionally, use of current steroid treatment was removed as an exclusionary criterion, while “current use of a medication that may interfere with primary study endpoints or that may increase the risk of side effects from study medication that can not be discontinued” was added.

Several additional exclusion criteria were added to the revised protocol. These included the presence of untreated pheochromocytoma (due to potential risks associated with nicotine and nicotine replacement on the adrenal medulla). Additionally, participants who have valvular heart disease or pulmonary hypertension causing shortness of breath with walking, cycling at a moderate speed, or light housework will be excluded due to concerns regarding an increased risk of a cardiac event from exercise and an inability to modify their physical activity as recommended in portions of the interventions.

In order to increase our potential pool of eligible participants, we also modified the protocol to allow entry of individuals who had quit smoking on their own within the past two to six weeks. Consequently, participants do not need to be smoking upon entry into the study. These individuals can be eligible for random assignment to treatment conditions provided they meet other eligibility criteria including at least two weeks of prolonged abstinence from cigarette smoking.

Finally, the original protocol called for all participants to undergo exercise tolerance testing prior to being enrolled in the study. This was originally proposed as a method to screen for undiagnosed coronary artery disease. However, after consulting with our physician colleagues, as well as the Chair of General Internal Medicine at Mayo Clinic Rochester, it was determined that this procedure would not be necessary given that the physical activity recommended in the interventions does not include vigorous intensity activity. Furthermore, there was concern that the exercise tolerance testing procedure itself might present unnecessary risk. Instead, activity recommendations will be limited to light to moderate levels of intensity. Furthermore, additional safety screening procedures were implemented including the administration of the Physical Activity Readiness Questionnaire (PAR-Q) and the Rose Angina Questionnaire to assess for exercise-induced symptoms. Additionally, participants who successfully quit smoking and meet other criteria for randomization undergo an electrocardiogram to screen for occult CHD.

D. Collaborating Sites

This study is a multi-site clinical trial also being conducted at the University of Tennessee Health Sciences Center in Memphis, TN, and at the Mayo Clinic in Rochester, Minnesota. All three sites are utilizing the same protocol. The Memphis, TN site is being funded by a separate grant from the National Heart, Lung, and Blood Institute. The Rochester site is being funded by the same grant that is funding the Iowa City, IA site (NHLBI grant number HL72782, Mark Vander Weg, PI). Mayo Clinic Rochester was the PI's (M. Vander Weg) institution prior to relocating to Iowa City. During the remainder of the study in Rochester, Jon Ebbert, M.D. will serve as the site-PI for the study at the Mayo Clinic. He will also serve as a co-investigator for the overall parent study.

I.7 ***Literature cited / references (if attaching a grant or protocol enter N/A).***
See Attached.

II. Research Team

II.1 ***Principal Investigator***

Name	E-mail	College
Mark Vander Weg	mark-vanderweg@uiowa.edu	College of Public Health

II.2 ***Team Members***

VAMC Team Members

Name	E-mail	College	Contact	Key Prsn	UI COI	VAMC COI	Consent Process Involvement	Deactivated
Mark Vander Weg, PHD		College of Public Health	Yes			No	Yes	No

George Bailey, BS	Carver College of Medicine	No	No	No	No
Cassie Cunningham, MPH	Carver College of Medicine	Yes	No	Yes	No
David Katz, MD, MSc, MD	Carver College of Medicine	No	No	Yes	No
Kelly Miell, BA, MA, PHD	Carver College of Medicine	No	No	No	No
Monica Paez, BA	Carver College of Medicine	No	No	No	No

Non-VAMC Team Members

Name	Institution	Location	FWA	Role	DHHS	Contact	Key Prsn	UI COI	VAMC COI	Consent Process Involvement	Email

Nothing found to display.

II.3 ***The Principal Investigator of this study is:***
Faculty

II.5 ***Select research team member who is the primary contact for study participants.***
Cassie Cunningham

III. Funding/Other Support

III.1 ***Funding Sources***

Source Entered as Text	DSP Link	Type	Source Grant Title	Name of PI on Grant
Source is entered as text no		No Funding		

* new source name

III.4 ***Does any member of the research team have a personal significant financial interest in the project according to the VA Conflict of Interest Policy? If yes, please indicate which members below.***

Name	Has Conflict of Interest
Mark Vander Weg, PHD	No
George Bailey, BS	No
Cassie Cunningham, MPH	No
David Katz, MD, MSc, MD	No
Kelly Miell, BA, MA, PHD	No
Monica Paez, BA	No

IV. Project Type

IV.1 ***Do you want the IRB to give this project***
Regular (expedited or full board) review

IV.2 ***Enter the date you will be ready to begin screening subjects/collecting data for this project. (If you do not have a specified date, add "upon IRB approval")***
December 1, 2007

IV.3 ***Are you requesting a waiver of informed consent/authorization (subjects will not be given any oral or written information about the study)?***
No

V. Other Committee Review

V.1 ***Does this project involve any substance ingested, injected, or applied to the body?***

- ***Do not answer yes, if the involvement includes a device, wire, or instrument***

- Yes

V.1.a ***What is/are the substance(s):***
Nicotine replacement therapy (transdermal nicotine patch)

V.1.b ***Are any of these substances defined as a Schedule I - V Controlled Substance?***
No

V.2 ***Are any contrast agents used for any purpose in this study?***
No

V.4 ***Are all drugs or substances in this study being used within the FDA approved population (i.e., children, adults)?***
Yes

V.5 ***Are all drugs or substances in this study being used within the FDA approved indication (i.e., disease, condition)?***
Yes

V.6 ***Are all drugs or substances in this study being used within the FDA approved dose?***
Yes

V.7 ***Are all drugs or substances in this study being used within the FDA approved route of administration?***
Yes

V.9 ***Will any subject be asked to undergo a diagnostic radiation procedure (including radiographic, nuclear medicine, DEXA)?***
No

V.14 ***Will any subject be asked to undergo a radiation therapy procedure (including external beam therapy, brachytherapy, or nuclear medicine therapy)?***
No

V.20 ***Does this project involve the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into one or more human research participant?***
No

VI. Subjects

VI.1 ***How many adult subjects do you expect to consent or enroll for this project?***
912

VI.2 ***What is the age of the youngest adult subject?***
18.0

VI.3 ***What is the age of the oldest adult subject?***
75.0

VI.4 ***What is the percentage of adult male subjects?***
50

VI.5 ***What is the percentage of adult female subjects?***
50

VI.6 ***How many minor subjects do you expect to consent or enroll for this project?***
0

VI.13 ***Describe EACH of your subject populations***

- ***Include description of any control group(s)***
- ***Specify the Inclusion/Exclusion criteria for EACH group***

Participants will be cigarette smokers with elevated Blood Pressure (BP) who smoke at least five cigarettes per day. Patients will be eligible if their BP is in the Prehypertensive (120-139/80-89 mm Hg) or Stage I hypertensive (140-159/90-99 mm Hg) range based on JNC 7 criteria (Chobanian et al., 2003). However, we will exclude patients who are Stage II hypertensive (> 160/100 mm Hg). We will include patients who are using antihypertensive medications, provided their BP is not out of control (i.e., > 160/100 mm Hg), but will record medication, dose, and frequency so that these can potentially be adjusted for in the analyses.

We also will enroll former smokers who recently quit smoking on their own. Former smokers will be eligible if they have quit smoking in the past two to six weeks. Participants who enroll in the study who are already abstinent will not take part in the smoking cessation portion of the intervention (described below).

- Exclusionary criteria will include: (1) an inability to understand consent procedures; (2) history of unstable cardiovascular disease including myocardial infarction, stroke, and unstable angina in the past three months; (3) coronary artery bypass grafting or angioplasty/stent in the past three months; (4) cardiac dysrhythmia treated with anti-arrhythmia medication, except stable atrial fibrillation; (5) untreated hyperthyroidism or pheochromocytoma; (6) history of CHF (NYHA Class III or IV); (7) ECG evidence of 2nd or 3rd degree AV block; (8) uncontrolled or Stage II Hypertension as defined as BP consistently > 160/100 mm Hg; (9) history of severe liver or renal failure; (10) current substance abuse (includes alcohol use in excess of 21 drinks a week); (11) presence of an unstable psychiatric condition; (12) severe COPD; (13) symptomatic PVD; (14) pulmonary hypertension with shortness of breath; (15) congenital or valvular heart disease with shortness of breath; and (16) current use of a medication that may interfere with primary study endpoints or that may increase the risk of side effects from study medication that cannot be discontinued. Additionally, we will exclude women who are pregnant or plan to become pregnant within the next year [due to weight gain in pregnancy and potential confounds with results, and because nicotine replacement therapy (NRT) is not yet FDA-approved for use in pregnant women]. Individuals planning to move out of the area or travel extensively during the intervention also will be excluded. Dieters and individuals on a special diet will not be excluded from the study. However, individuals with a medical condition that would preclude any additional changes in their diet will not be allowed to participate. Similarly, we will not exclude participants who regularly engage in physical activity. Those who are unable to further

modify their physical activity, or who cannot engage in moderate intensity exercise (e.g., walking), however, will not be eligible to participate. Finally, because some of the intervention will be delivered over the phone, those who do not have access to a telephone will not be eligible for the study. Considering that the vast majority of residences have telephones, and because this has not been a major exclusionary factor in our other studies, we do not anticipate excluding many potential participants for this reason.

VI.13.a ***Does this study propose to enroll any subjects who are not Veterans?***
No

VI.14 ***Provide an estimate of the total number of subjects that would be eligible for inclusion in each of your study populations (include your control population if applicable)***
We plan to screen approximately 912 participants in order to have 500 eligible participants.

VI.15 ***Describe how you will have access to each of your study populations in sufficient number to meet your recruitment goals.***
There are many smokers and individuals with elevated blood pressure in the area and surrounding communities that will be available to participate in this study. Nationwide, the prevalence of cigarette smoking among adults is 21%. Rates are similar for Iowa and the surrounding areas. The proportion of the adult population aged 18 and older with an eligible blood pressure level (i.e., in the prehypertensive or hypertensive stage as defined by JNC-7 criteria) is approximately 60%. Therefore, the pool of potentially eligible participants from which to recruit is substantial. Furthermore, we are aware of no other clinical trials targeting smoking cessation that are currently enrolling participants in the greater Iowa City community. Therefore, through our recruitment plans, which include news paper and radio advertising, mass mailing, flyers, website advertising, brochures, and referrals from health care providers, we are confident we will be able to reach the target audience of adult smokers with elevated blood pressure.

VI.16 ***Do you <u>plan</u> to recruit/enroll non-English speaking people?***
No

VI.18 ***Do you propose to enroll any of the following in this study as subjects?***

- ***Employee of the PI or employee of a research team member***
- ***Individual supervised by PI or supervised by member of research team***
- ***Individual subordinate to the PI or subordinate to any member of the research team***
- ***Student or trainee under the direction of the PI or under the direction of a member of the research team***

- No

VI.20 ***Will subjects provide any information about their relatives?***
No

VI.23 ***Will anyone (other than the subject) provide you with information about the subject (e.g. proxy interviews)?***
No

VI.26 ***Is this project <u>about</u> pregnant women?***
No

VI.27 ***Will this project involve fetuses?***
No

VI.28 ***Does this project involve adult subjects who may be incompetent or have limited decision-making capacity on initial enrollment into the study?***
No

VI.32 ***Does this project involve subjects whose capacity to consent may change over the course of the study?***
No

VI.37 ***Does this project involve prisoners as subjects?***
No

VI.46 ***Do you propose to enroll any subjects diagnosed with Posttraumatic stress disorder (PTSD)?***
No

VII.A. Project Description (A)

VII.A.1 ***Where will project procedures take place (check all that apply)?***

- VAMC - Iowa City VAMC (no subjects seen here, just admin work)

VII.A.2 ***Is this project also being conducted by other researchers at their own sites (e.g. a multi-site collaborative project)?***
Yes

VII.A.3 ***What is the VA site's role(s) for this project (check all that apply)?***

- Coordinating Center

VII.A.4 ***Provide specific and detailed information describing how the VA investigator will coordinate all aspects of the study, such as:***

- ***Name, location, and IRB of record for each site,***
- ***Verification of IRB approval and continuing review for all sites***
- ***Managing variation in requirements from the IRBs or institutional policies of the different sites.***
- ***Outline all activities that will occur at each participating site***

- All data for the project have been collected. Recruitment and follow-up data collection have been completed. All that remains to be completed is data analysis and manuscript preparation. Hard copies of the data are stored at the University of Iowa and are maintained on University of Iowa servers under the oversight of IRB 201703765. The PI for this IRB is also the PI for the other IRB related to this project (201703765).

VII.A.5 ***Describe in detail the procedures that will be used to identify and report unanticipated problems from participating sites to the lead institution.***
As no more recruitment, intervention, or data collection will be conducted for this project, no unanticipated problems will need to be reported to the coordinating center.

VII.A.6 ***Describe in detail the procedures that will be used to identify and report unanticipated problems from the lead institution to participating sites.***
As noted above, all data collection activities have been completed. As such, no unanticipated problems will need to be reported by the coordinating center to the other participating sites.

VII.A.7 ***Describe in detail the procedures that will be used to communicate protocol modifications from the lead institution to the participating sites.***

As all data have been collected, no protocol modifications will be necessary.

VII.A.8 ***Describe in detail the procedures that will be used to communicate interim results from the lead institution to the participating sites.***
The principal investigator for the current protocol is also the principal investigator for the other project/IRB. As such, no need for communicating to another site will be necessary.

VII.A.9 ***Describe in detail the procedures that will be used to communicate other new information which may impact a subject's willingness to participate, or continue participating from the lead institution to the participating sites.***
Because all enrollment and data collection have been completed and no participants are currently enrolled in the project, no new information will be collected that may potentially impact participants' willingness to take part in or continue participating in the study.

VII.A.10 ***What are collaborating site roles for this project?***

- Clinical/participating site - 2
- Coordinating Center - Iowa City VA Health Care System

VII.B. Project Description (B)

VII.B.1. ***Does this project involve any of the following (Check all that apply):***

- ☑ **Interventional** – Includes **Clinical (or Treatment) trial**, **Physiology intervention/study**, **Behavioral intervention/study**, **Diagnostic Trial**.
- ☐ **Clinical (or Treatment) trial** – A prospective biomedical or behavioral research study of new treatments, new drug or combinations of drugs, new devices, or new approaches to surgery or radiation therapy. (NIH and ClinicalTrials.gov & FDA)
- ☑ **Physiology intervention/study** – A pharmacologic or measurement study aimed at understanding basic mechanisms of disease and/or of normal human physiology, often without any therapeutic intent (though a clinical trial could include such components, often labeled as “translational” or “basic science” aims.) Measurements in such studies could include, but are not limited to, a blood draw, EKG, EEG, MRI, auditory or sensory testing, checking vital signs, DEXA scans, eye tracking, specimen collection, exercise, fasting, special diets, etc.
- ☑ **Behavioral intervention/study** – May be used to refer to studies of individual or group behavior. This option does not include drugs, biologics, or devices but could include psychotherapy, lifestyle counseling, behavior modification, etc.
- ☐ **Diagnostic trial** – Protocol designed to evaluate one or more interventions aimed at identifying a disease or health condition (ClinicalTrials.gov & FDA)

- ☐ **Observational**
- ☐ **Expanded Access** – A process regulated by the Food and Drug Administration (FDA) that allows manufacturers to provide investigational new drugs to patients with serious diseases or conditions who cannot participate in a clinical trial. Examples of expanded access include non-protocol access to experimental treatments, including protocol exception, single-patient IND, treatment IND, compassionate use, emergency use, continued access to investigational drug, and parallel track (ClinicalTrials.gov & FDA).
- ☐ **Registry** – The collection and maintenance of data (not including biologic samples) in which: (1) the individuals in the registry have a common or related condition(s), and/or (2) the individuals in the registry are interested in being contacted for future studies by investigators other than those listed in Section II of this project.(UI Guide)
- ☐ **Repository** – The collection, storage, and distribution of human biologic samples and/or data materials for research purposes. Repository activities involve three components: (i) the collection of data and/or specimens such as blood, tissue, saliva, etc.; (ii) the storage of data or specimens, and data management function; and (iii) the sharing of data/specimens with recipient investigators other than the original investigators. (paraphrased from OHRP)
- ☐ **Other**

VII.B.2 ***Does this project involve a drug washout (asking subject to stop taking any drugs s/he is currently taking)?***
No

VII.B.11 ***Is there a separate, written protocol that will be submitted in addition to this IRB New Project form? (Note: a grant application is not considered to be a protocol)***
No

VII.B.18 ***Does this project involve testing the safety and/or efficacy of a medical device?***
No

VII.C. Project Description (C)

VII.C.1 ***Does this project involve any research on genes or genetic testing/research?***
No

VII.D. Project Description (D)

VII.D.1 ***Check all materials/methods that will be used in recruiting subjects (you will need to attach copies of all materials at the end of the application):***

- Other - No recruitment is ongoing for the project. Further, all prior recruitment was conducted at the University of Iowa, and is now under the oversight of IRB-01 201703765.

VII.D.8 ***Will a member of the research team discuss the study with the subject in person prior to the subject agreeing to participate?***

Yes

VII.D.9 ***Describe the physical location where the consent process will take place:***
The Preventive Intervention Center (PIC). Alternatively the consent process may be completed on site, such as local employers or organization that invite us to present information about the study.

VII.D.10 ***Will a member of the research team discuss the study with the subject by phone prior to the subject agreeing to participate?***
Yes

VII.D.11 ***Describe:***
A phone screen is approved. If an interested person calls in to the PIC, a member of the study team will answer questions the person might have, and also conduct the phone screen if the person is interested in participating in the study.

VII.D.12 ***Who will be involved in the consent process (including review of consent document, answering subjects' questions)?***

Name	Consent Process Involvement
Mark Vander Weg, PHD	Yes
George Bailey, BS	No
Cassie Cunningham, MPH	Yes
David Katz, MD, MSc, MD	Yes
Kelly Miell, BA, MA, PHD	No
Monica Paez, BA	No

VII.D.14 ***The PI has formally delegated the responsibility of conducting the consent process and obtaining consent to the individuals listed above. The individuals delegated this responsibility have received appropriate training to perform these activities.***
Yes

VII.D.15 ***Check all materials that will be used to obtain/document informed consent:***

- Other - A Power Point presentation will be used to provide information to potential participants before they sign consent. After the presentation, the participant will meet one-on-one with a study team member to review the consent, ask questions, and sign the consent if they are interested in participating.
- Consent Document

VII.D.16 ***Are you requesting a waiver of documentation of consent (either no subject signature or no written document)?***
No

VII.D.19 ***Before the subject gives consent to participate are there any screening questions that you need to directly ask the potential subject to determine eligibility for the study?***
Yes

VII.D.20 ***List any screening questions you will directly ask the potential subject to determine eligibility.***
1. What is your current age?
2. During the past 2 months, on average, how many cigarettes have you smoked per day?
3. Are you currently using any type of nicotine containing medication such as nicotine patches, nicotine nasal spray, nicotine inhaler, nicotine lozenge or

nicotine gum or receiving any other formal treatment for tobacco cessation?
4. Do you plan on staying in this area for the next 12 months?
5. Have you been diagnosed with high blood pressure, or are you aware if your blood pressure readings tend to be over 120/80mm Hg?
6. Have you been diagnosed with high blood pressure with your blood pressure readings being consistently > 160/100mm Hg?
7. Are you currently taking any high blood pressure medications? If so, Has your blood pressure typically been < 160/100 mm Hg?
8. Is there anyone in your household already enrolled and participating in this study?

VII.D.21 ***Will you keep a screening log or other record that would include information on people who do not enroll in the study?***
Yes

VII.D.22 ***Describe the information being collected and the purpose for keeping this information.***
Information from the initial phonescreen will be utilized so that those who enroll in the study can be compared to those who do not enroll for purposes of evaluating the overall representativeness of the sample. This information will include gender, race, ethnicity, age, smoking rate, and smoking history.

VII.D.23 ***Will this information be shared with anyone outside the VA research team members?***
No

VII.D.25 ***<u>After</u> the subject agrees to participate (signs consent), are there any screening procedures, tests, or studies that need to be done to determine if the subject is eligible to continue participating?***
Yes

VII.D.26 ***List and describe screening***
After the participant signs the consent, they will be asked questions (that can be found on the Visit 1 Screening Tool) to determine if they are eligible to continue participating in the study. The questions ask about the participant's health to determine if they meet the inclusion/exclusion criteria for the study. If the participant is found eligible for the study, they will be scheduled for a baseline visit. At the baseline visit, besides the data collection activities, the participant will also be asked to describe his/her medical history and complete two questionnaires about activity-induced symptoms such as angina which may be indicative of cardiac disease (Rose Angina, Par-Q). If a medical problem fitting the exclusion criteria becomes apparent at the baseline visit, the subject will not be allowed to continue further in the study.

VII.D.27 ***Discuss how much time a potential subject will have to agree to consider participation and whether or not they will be able to discuss the study with family/friends before deciding on participation.***
The participant will be given ample time to decide whether or not to participate. They will be allowed to go home and discuss the study will family/friends and return at any time to continue participation in the study.

VII.D.28 ***How long after the subject agrees to participate do study procedures begin?***
When a participant agrees to participate and signs consent, they may begin screening procedures the same day if they feel ready.

VII.D.29 ***Provide a description of the enrollment and consent process for adult subjects***

- ***Describe each study population separately including control population***
- ***Include when recruitment and consent materials are used***
- ***Use 3rd person active voice "The Principal Investigator will identify subjects. For example, the principal investigator will identify potential subjects, the study coordinator will discuss the study with subjects over the telephone and schedule the first study visit, etc..."***
- ***Describe the steps that will be taken by the research team to minimize the possibility of coercion or undue influence during the consent process***

Several recruitment efforts, as described earlier, will be utilized (newspaper ads, mailings, etc). Recruitment methods are listed in section VII.D.1. Some other forms of recruitment plans are: As needed, we intend to purchase commercially available mailing lists from AccuData for purposes of conducting mass mailings to people who live in the area. We plan to use the UI email lists to send mass emails. We will also provide a "mass email" to the human resources department of area businesses and organizations for them to distribute to their employees. Such organizations will include Rockwell Collins, the VA Medical Center, and other large employers with the permission of the employer. We also plan to send a postcard about the study through the University of Iowa campus mail service to all faculty and staff.

Interested persons may call the Preventive Intervention Center (PIC) and will be asked several pre-screening questions. If qualified, they will be asked to visit the PIC for further explanation of the study. At their first visit to the PIC, a member of the study team will present a PowerPoint presentation to the interested person, which describes the study in greater detail. This presentation may be done in a group format if more than one interested persons come in to the PIC at the same time. If the person is still interested in participating after hearing the presentation, they will meet with a study coordinator, nurse, physician, or investigator to review the informed consent document in a one-to-one meeting. The research staff member will answer any questions the participant may have. If the participant agrees to participate in the study, they may sign the consent document at that time. A copy will be given to the participant. If the participant would like more time to consider participation, they will be given a blank copy of the consent and told to call the PIC with any questions. Once a participant has signed the consent, they will be considered enrolled in the study and screening procedures may begin if the participant is ready to enroll. This process of receiving the study explanation, PowerPoint presentation, review of informed consent, and question and answer session may also be performed at other locations, such as companies or organizations in the community who have invited us to their location. Reviewing and obtaining consent and the question/answer session will be done in private on a one-on-one basis to minimize any possibiltiy of coercion.

VII.D.37 ***Does the study include any form of deception (e.g., providing participants with false information, misleading information, or withholding information about certain study procedures)?***

Examples:

- ***Procedure includes a cover story that provides a plausible but inaccurate account of the purposes of the research.***
- ***Participants will be provided with false information regarding the particular behaviors of interest in the research.***

- ***Procedures include a confederate pretending to be another participant in the study.***
- ***Participants will be told that the research includes completion of a particular task, when in fact, that task will not be administered.***
- ***Study is designed to introduce a new procedure (or task) that participants are not initially told about.***
- ***If yes, a waiver of informed consent must be requested under question IV.3.***

- No

VII.E. Project Description (E)

VII.E.1 ***Will subjects be randomized?***

Yes

VII.E.2 ***Describe randomization scheme/assignment including ratio such as 1:1, 2:1 etc.***

Subjects who are able to quit smoking will be randomized to one of three lifestyle interventions according to a 1:1:1 ratio. The random allocation to conditions was conducted by a biostatistician, who placed each assignment in sequentially numbered and sealed envelopes. For each eligible participant who successfully quits smoking, randomization is done by opening the next available envelope, which has a 1 in 3 chance of getting assigned to each of the three interventions: Weight Gain Prevention, Blood Pressure Control, and Usual Care. The randomization assignment will be recorded on the randomization log.

VII.E.3 ***Will any questionnaires, surveys, or written assessments be used to obtain data directly from subjects in this study?***

Yes

VII.E.4 ***List all questionnaires, surveys, written assessments and ATTACH each one to the application. (NOTE: You are NOT prohibited from attaching copyrighted materials to this application)***

Participant contact form
Participant demographics
History of tobacco use
Fagerstrom Test for Nicotine Dependence and Stage of Change
Physical Activity Readiness Questionnaire
Rose Angina Questionnaire
Quick food scan – Fruits & Vegetables
Quick food scan – Dietary fat
Urinary chloride collection and monitoring forms
International Physical Activity Questionnaire (IPAQ)
Smoking Self-Efficacy
Smoking Decisional Balance
Weight Efficacy Lifestyle Questionnaire
Weight Decisional Balance
Weight Concerns Scale
Exercise Confidence Survey
Exercise Decisional Balance
Treatment Evaluation I
Treatment Evaluation II
Health and Lifestyle Questionnaire – 6 Months
Health and Lifestyle Questionnaire – 12 Months

VII.E.5 ***Does this project involve creating any audiotapes, videotapes, or photographs?***
Yes

VII.E.6 ***Provide a detailed description in sequential order of the study procedures following the consent process - DO NOT cut and paste from the Consent Document.***

Describe study populations separately if they will be participating in different procedures - include CONTROL population if applicable.

DESCRIBE:

- ***What subjects will be asked to do/what happens in the study (in sequential order)***
- ***The time period over which procedures will occur***
- ***The time commitment for the subject for individual visits/procedures***
- ***Long-term followup and how it occurs***

Below is a description of the study procedures. Please also see the attached Study Timeline and Flowchart.

Participants will be 500 cigarette smokers with elevated Blood Pressure (BP) who smoke at least five cigarettes per day. Patients will be eligible if their BP is in the Prehypertensive (120-139/80-89 mm Hg) or Stage I hypertensive (140-159/90-99 mm Hg) range based on JNC 7 criteria (Chobanian et al., 2003). However, we will exclude patients who are Stage II hypertensive (> 160/100 mm Hg). We will include patients who are using antihypertensive medications, provided their BP is not out of control (i.e., > 160/100 mm Hg), but will record medication, dose, and frequency so that these can potentially be adjusted for in the analyses. Participants will be instructed to continue to have their blood pressure managed under the care of their primary care provider. Participants must give the study team permission to access their medical records. This information will be used to help the study team determine whether the study is appropriate for the participant, and/or to monitor the participants medical status as needed during the course of the study.

- We also will enroll former smokers who recently quit smoking on their own. Former smokers will be eligible if they have quit smoking in the past two to six weeks. Participants who enroll in the study who are already abstinent will not take part in the smoking cessation portion of the intervention (described below).

Exclusionary criteria will include: (1) an inability to understand consent procedures; (2) history of unstable cardiovascular disease including myocardial infarction, stroke, and unstable angina in the past three months; (3) coronary artery bypass grafting or angioplasty/stent in the past three months; (4) cardiac dysrhythmia treated with anti-arrhythmia medication, except stable atrial fibrillation; (5) untreated hyperthyroidism or pheochromocytoma; (6) history of CHF (NYHA Class III or IV); (7) ECG evidence of 2nd or 3rd degree AV block; (8) uncontrolled or Stage II Hypertension as defined as BP consistently > 160/100 mm Hg; (9) history of severe liver or renal failure; (10) current substance abuse (includes alcohol use in excess of 21 drinks a week); (11) presence of an unstable psychiatric condition; (12) severe COPD; (13) symptomatic PVD; (14) pulmonary hypertension with shortness of breath; (15) congenital or valvular heart disease with shortness of breath; and (16) current use of a medication that may interfere with primary study endpoints or that may increase the risk of side effects from study medication that cannot be discontinued. Additionally, we will exclude women

who are pregnant or plan to become pregnant within the next year [due to weight gain in pregnancy and potential confounds with results, and because nicotine replacement therapy (NRT) is not yet FDA-approved for use in pregnant women]. Individuals planning to move out of the area or travel extensively during the intervention also will be excluded. Dieters and individuals on a special diet will not be excluded from the study. However, individuals with a medical condition that would preclude any additional changes in their diet will not be allowed to participate. Similarly, we will not exclude participants who regularly engage in physical activity. Those who are unable to further modify their physical activity, or who cannot engage in moderate intensity exercise (e.g., walking), however, will not be eligible to participate. Finally, because some of the intervention will be delivered over the phone, those who do not have access to a telephone will not be eligible for the study. Considering that the vast majority of residences have telephones, and because this has not been a major exclusionary factor in our other studies, we do not anticipate excluding many potential participants for this reason.

Participants will be recruited through community advertising and via referral from their primary care provider. Participants who respond to advertisements or study referrals will be given information about the potential risks and benefits of study participation. Informed consent will be obtained at that time. They also will be questioned for eligibility at this time. Participants who are interested and who meet initial eligibility criteria will be scheduled for a Baseline Visit. The entire length of the study for each participant will be approximately 14 months. Due to the length of the study and number of visits, the participants will be given "Take Home Logs" that will help them keep track of the visit schedule. It is also a place that they can write any adverse events and concomitant medication use, which will help them remember to report the events or medications at the next study visit.

Baseline (Please note that in order to improve clarity, this visit is referred to as the Screening Visit in the Participant Consent Form)
Baseline Visits will be conducted at the Preventive Intervention Center. Participants also will be asked for demographic information and to complete a medical history form. All of the inclusion/exclusion criteria will be reviewed. A brief physical exam will be performed for participants who have not seen his/her regular primary care provider in the past 3 years or who do not have a regular primary care physician. In addition, vitals will be taken (height, weight, pulse, and blood pressure). Waist circumference will also be measured. Percentage of body fat will be measured using a bioelectrical impedance analysis, which involves briefly stepping on a scale-like device. Adverse events and concomitant medications will be recorded. Because NRT is not FDA-approved for use during pregnancy, any female participant who has the potential to be pregnant will be given a urine pregnancy test.

Participants will be questioned about any recent symptoms provoked by moderate intensity physical activity (e.g., walking, cycling at a moderate speed, general housework). Specifically, we will use the Physical Activity Readiness Questionnaire (PAR-Q) and the Rose Angina Questionnaire to assess major signs and symptoms of cardiovascular disease (e.g., angina) in order to ensure that the intervention does not place participants at increased risk for a cardiac event.

The participant will be asked their tobacco use history and to report their current tobacco use. Self reported tobacco use will be followed by an expired-air Carbon Monoxide (CO) assessment. Carbon monoxide is a by-product of incomplete

combustion of tobacco products, and is commonly used to assess both smoke exposure and as a validation of smoking cessation. This procedure involves having the subject hold his/her breath for approximately 10-15 seconds and then exhale into a disposable tube attached to a small machine that indicates carbon monoxide levels in parts-per-million. This is a safe, non-invasive procedure.

The participant will be asked to complete some questionnaires to assess self-efficacy and outcome expectations related to smoking cessation, as well as level of motivation to quit smoking. Self-efficacy for smoking cessation will be assessed using the Smoking Self-Efficacy Questionnaire. Outcome expectations regarding smoking cessation will be assessed using a measure of decisional balance. Motivation to quit smoking will be assessed using the Readiness to Quit Smoking ladder. The participants will be asked to complete the Forgiving Personality scale to assess the participant's level of forgiveness.

The baseline visit is estimated to take approximately 2-3 hours to complete. It can be spread out over days if the participant does not have time to complete all screening procedures or needs more time to review the consent.

Smoking Cessation
All participants who meet screening criteria at the baseline visit will come back and meet for a total of four sessions with a health educator to address smoking cessation. The study team will try to schedule the sessions as described here, but flexibility will be allowed for life circumstances, holidays, weather, etc. Sessions may be conducted over the phone or in person. In Session 1, about 1 week after the baseline visit but before the participant's "quit" date, the focus will be on preparing to quit and surviving the first days as a nonsmoker. Establishing quitting rituals, building support, and using the "Five A's" (Anticipate, Avoid, Alter, Alternatives, and Active) will be emphasized. Session 2, scheduled within 24 hours of the quit attempt, addresses maintaining motivation and coping with negative emotions and nicotine withdrawal. Session 3 will occur approximately one week postcessation. As in all sessions, problem solving and support building will be emphasized. In addition, dealing with negative cognitions will be addressed. In the final session, conducted three weeks postcessation, preventing relapse will be the emphasis. In a mailing prior to this session, participants are asked to do homework before the session that will facilitate making an individualized relapse prevention plan. Participants are asked to identify high-risk situations and difficulties encountered in previous cessation attempts and are walked through a series of suggestions in the event of a slip.

At each session the participant will be asked to report their current smoking status, followed by an expired air carbon monoxide (CO) assessment. On the forth cessation visit if the participant fails the CO test (i.e., CO > 10 ppm), yet still claims to be abstinent from smoking, a salivary cotinine test will be given to provide a confirming/disconfirming assessment. Cotinine is a specific major metabolite of nicotine that can be detected in saliva for 45 to 80 hours. The procedure involves having the subject place a small cotton dental roll on his/her tongue for three minutes. At the end of this time, the subject expels the roll into a small vial. For those participants who fail the CO test but report using a nicotine replacement therapy (which would alter the results of the salivary cotinine test) will instead be tested for thiocyanate via blood draw. The amount of thiocyanate in a person's blood provides information about their level of exposure to cigarette smoke. Adverse events and concomitant medications will be reviewed at each session. Each of the 4 sessions will take approximately 1 hour to complete. If the session is completed over the phone, the physical assessments will not

be taken.

Next, there will be 4 follow-up phone calls. These calls are used to identify early relapse, encourage participants, and provide support. They also are used to review materials and information provided during the sessions with the health educator. The calls are made in the first few months of the intervention. Calls will take approximately 10-15 minutes each to complete.

Finally, participants receive six mailings over the course of the study. The first mailing, sent one week postcessation, provides information and a worksheet to facilitate relapse prevention. The next mailing, sent four weeks postcessation, focuses on coming off the patch. Nine weeks into the study, participants receive a mailing about stress management. The remaining three mailings are sent during months 7, 9, and 11. The topics covered include secondhand smoke, helping friends/family members to quit smoking, and a general review of some of cessation program items.

During the smoking cessation portion of the study, participants will be given nicotine replacement therapy (NRT) in the form of a nicotine patch to help them quit smoking. Nicotine levels obtained from the patch generally are lower than those obtained from regular smoking. Because participants will enter the study smoking differing amounts of cigarettes, we will titrate initial patch dose according to self-reported cigarette consumption. The dosing schedules will be based off of the participants cigarette use, but can be slighly altered based on actual number of days between study visits if needed. Participants who report smoking > 20 cigarettes per day initially will be placed on the 21 mg patch, participants who report smoking 10-19 cigarettes each day will initially be placed on the 14 mg patch, and participants who report smoking 5-9 cigarettes will initially be placed on the 7 mg patch. Participants initially placed on the 21 mg patch will use the following dosing schedule: 21 mg for two weeks, 14 mg for two weeks, 7 mg for two weeks, and then off. Participants initially placed on the 14 mg patch will use the following dosing schedule: 14 mg for two weeks, 7 mg for four weeks, and then off. If a participant is initially placed on the 7 mg patch, we will use the following dosing schedule: 7 mg for six weeks and then off. Patch use will commence the day of the participants' quit date.

This dosing schedule will have a maximum of six weeks of exposure to the patch for any participant. Each participant will have the side effects of the medication discussed with him or her and receive detailed instructions regarding proper use of the patch. We will monitor concomitant smoking and nicotine patch use by using self-report and exhaled CO. As a safety measure, participants who clearly demonstrate repeated concomitant smoking while wearing the patch will have their nicotine replacement therapy stopped. Participants are instructed to take off the patch if they are going to smoke a cigarette. We also will monitor participants' use of over-the-counter nicotine replacement products (lozenge, gum or patches), as well as any prescriptions for NRT (inhaler or nasal spray) and/or sustained release bupropion (Zyban) or varenicline (Chantix).

The cessation portion of the study including 4 cessation visits and 4 follow up calls will take approximately 5 hours to complete.

If a participant fails to quit smoking, they will not be allowed to proceed on to randomization. The particpant will be allowed to go through the smoking cessation program a second time if desired. During this second round, they will be provided with 6 weeks of the nicotine patch at no cost to them. Participants that recycle through the

smoking cessation program are still considered part of the evaluable study population. If a participant fails to quit smoking after the second round, they will not be able to go through the smoking cessation program a third time. Participants that do not quit smoking will be contacted six and 12 months later and asked to complete a brief questionnaire by phone asking about their health and current lifestyle patterns (described later). They will not be asked to take part in any other follow-up assessments.

If a participant is able to quit smoking and is scheduled for randomization, the participant will also be able to receive nicotine gum to assist with relapse prevention. Participant will be instructed on proper use of the gum and given a hand out about the gum. Participant with dentures, conditions such as TMJ (TemporoMandibular Joint) Disorder, or active Peptic Ulcer disease will not be given the gum since it is contraindicated. All other participants who wish to have the gum will be given 1 box (approx 110 pieces of 2mg gum) at the randomization visit. The participant can request up to two more boxes, for a maximum of 3 boxes per participant.

In another effort to increase abstinence rates, participants will also be given the Forever Free™ handouts. These copyrighted handouts are produced by the Moffitt Cancer Center. Forever Free™ is a series of eight booklets developed to help individuals who have recently quit smoking. Forever Free™ was designed to help prevent relapse. These handouts will be given to participants after the randomization visit, to read on their own.

Randomization

Following the smoking cessation sessions, all participants who are abstinent from smoking based on two-week prolonged abstinence criteria will come in for a randomization visit (Please note that in order to improve clarity, this visit is referred to as the Group Assignment Visit in the Participant Consent Form). The participant will be asked to report their current smoking status, followed by an expired air carbon monoxide (CO) assessment. For those who fail the CO test (i.e., CO > 10 ppm), yet still claim to be abstinent from smoking, a salivary cotinine test will be given to provide a confirming/disconfirming assessment. For those who fail the CO test but report using a nicotine replacement therapy (which would alter the results of the salivary cotinine test) will instead be tested for thiocyanate via blood draw. Participants who do not successfully quit smoking will be given a chance to recycle through the smoking cessation intervention a second time.

At this visit the study staff will perform an interval medical history with the participant, to ensure nothing critical has changed from the screening visit. Vitals will also be taken again (weight, pulse and blood pressure). Waist circumference will also be measured. Percentage of body fat will be measured using a bioelectrical impedance analysis. Inclusion/exclusion criteria will be reviewed again. Adverse events and concomitant medications will be reviewed. The participant will have an electrocardiogram (ECG) performed by study staff and reviewed by a physician for evidence of 2nd or 3rd degree AV block and to assess for previous silent myocardial infarction. If the ECG results are inconclusive, the participant will be advised to consult his/her primary care provider and will not be able to participate in the study. If the participant is still interested in participating in the study, he/she should contact his/her primary care provider in order to perform an exercise stress test. The test would be conducted under the supervision of the primary care provider. If the results of the exercise stress test indicate that it is safe for the individual to enroll in the study, and the primary care provider and the

study physician clear them for participation, then they will be allowed to enroll provided they meet other eligibility criteria.

In addition, potential participants will be questioned about any recent symptoms provoked by moderate intensity physical activity (e.g., walking, cycling at a moderate speed, general housework). Specifically, we will use the Physical Activity Readiness Questionnaire (PAR-Q; Thomas, Reading, & Shephard, 1992) and the Rose Angina Questionnaire (Rose, 1962) to assess major signs and symptoms of cardiovascular disease (e.g., angina) in order to ensure that the intervention does not place participants at increased risk for a cardiac event.

Current physical activity level will be assessed using the long version of the International Physical Activity Questionnaire (IPAQ). The IPAQ is a 27-item, self-administered survey designed to assess physical activity patterns over the past seven days. Respondents are asked to provide detailed information about moderate and vigorous physical activity they engaged in during the past week across several domains. The participant will also be asked to report on their dietary intake by completing two commonly-used dietary screeners. Percent of energy intake from fat will be assessed using the National Cancer Institute (NCI) Fat Screener. The Fat Screener is a brief survey that assesses respondents' consumption of 15 different food groups that were determined to be most predictive of overall dietary fat intake. Use of regular versus reduced fat margarine also is assessed. Fruit and vegetable intake will be assessed using the All Day version of the NCI Fruit and Vegetable Screener. The Fruit and Vegetable Screener assesses the frequency of consumption and portion size for 10 types of fruits and vegetables.

The participant will be asked to complete some questionnaires to assess self-efficacy and outcome expectations related to smoking cessation, weight control, and physical activity. Self-efficacy for smoking cessation will be assessed using the Smoking Self-Efficacy Questionnaire. Self-efficacy for physical activity will be measured with the Exercise Confidence Survey, and self-efficacy for weight control will be assessed with the Weight Efficacy Lifestyle Questionnaire. Outcome expectations regarding smoking cessation, physical activity, and weight control will be assessed using measures of decisional balance. In addition, worries about weight gain after quitting smoking will be assessed with a Weight Concerns Scale.

Participants will be asked to complete a brief (7-item) questionnaire to assess the extent to which they learned and retained key information provided in the smoking cessation intervention, and to provide their impression of the helpfulness of various parts of the intervention.

Any female participant who has the potential to be pregnant will be given a urine pregnancy test. Those participants that are abstinent from smoking and meet all other criteria will be randomized to one of three treatment conditions.

Lastly, participants will be instructed to test five overnight urine samples at home using chloride titrator sticks in order to measure baseline dietary sodium intake. Urinary chloride provides a good option for estimating dietary sodium intake, and is less participant burden then collecting 24 hour samples. Participants will be instructed to collect overnight urine samples (2200 to 0600) each morning in containers provided by the study laboratory. Participants will then place a chloride titrator stick into the urine sample for a period of 20 minutes. Each test strip has a capillary column containing

silver dichromate that forms silver chloride when reacting with chloride ions. After the column becomes saturated, a moisture sensitive signal appears at the top. A line appears on the column providing a value ranging from 0.0 to 10.0. The participant will mark the titrator stick reading on a chart provided by the study staff. Participants will be instructed to measure overnight urinary chloride levels for five days, as this is the number of samples recommended to ensure an accurate estimate of mean sodium intake. After five overnight samples the participant will mail or fax the chart back to the study staff.

The randomization visit will take approximately 2 hours to complete, plus the participant's at-home time collecting overnight urine samples.

Interventions

The participants are randomly assigned to one of three conditions consisting of: 1) a Weight Gain Prevention intervention; 2) a Blood Pressure Control Program focusing on lifestyle modification; or 3) a Usual Lifestyle condition. In addition to the lifestyle interventions being evaluated in the present study, participants will be instructed to continue to have their blood pressure managed by their primary care provider.

1. Weight Gain Prevention Intervention

There have been several successful behavioral trials that targeted weight control and/or nutritional modification for the control of Blood Pressure including the multi-center clinical trial TONE; Trials of Nonpharmacologic Interventions in the Elderly. The Weight Gain Prevention intervention used in this study was derived from the Weight Loss Only program developed for TONE. The focus of the intervention will be on preventing weight gain following smoking cessation. Because participants will enter the study at a wide range of body weights, the emphasis will be on preventing the weight gain that accompanies quitting smoking rather than weight loss per se. Each participant will be provided with a copy of The CalorieKing Calorie, Fat & Carbohydrate Counter 2007 Edition, published by Dietclub.

Participants will be advised to engage in 30 minutes or more of moderate intensity activity on most, and preferably all, days of the week. Moderate intensity activities include those that range from 3.0 to 6.0 METS, or 4 to 7 kcal x minute-1. Examples include brisk walking, cycling at moderate speed, and general household cleaning. Participants will be given flexibility in both the specific types of moderate activity they choose to engage in, as well as the method in which they choose to accumulate their activity over the course of the day (e.g., several short bouts of activity vs. a single 30-minute period of exercise).

The Weight Gain Prevention intervention will consist of five individual and 12 group sessions lasting 30-60 minutes conducted over a 12-week period. Sessions will be held in person, but can be made up over the phone if the participant is unable to attend a session. As noted above, the intervention is modeled after the TONE Weight Loss Only protocol. The group sessions, which are largely didactic in format but also include group discussion, address a variety of proven weight management strategies including nutrition education, behavioral skills training, problem solving, "relapse" prevention, and moderate increases in physical activity. Participants also will be instructed to self-monitor their dietary intake and physical activity as a means of gaining additional insight into their behavior patterns, as well as to evaluate success in meeting behavioral goals.

Each of the individual sessions will focus on reviewing participants' success with meeting dietary, physical activity, and weight goals, and problem solving strategies for increasing adherence and success. Consequently, these sessions will provide more specific, individualized instruction tailored to the needs of each individual participant.

At each session a small snack will be provided to the participants, prepared by the bionutrition department of the General Clinical Research Center (GCRC). The snacks will be designed to be low calorie, nutrient dense, and will illustrate the principles of what is being discussed at the intervention.

At all sessions, tobacco use status, serious adverse event information, and weight will be recorded. At the individual sessions, the participant will be asked about concomitant medications (smoking cessation, weight management, and blood pressure medications only), followed by an expired air carbon monoxide (CO) assessment, and a blood pressure reading. The weight gain prevention intervention portion of the study including 12 group sessions and 5 individual sessions will take approximately 17 hours to complete.

2. Blood Pressure Control Intervention

The intervention for those assigned to the Blood Pressure Control condition is patterned after the TONE Weight Loss + Sodium Restriction program. The rationale for addressing weight gain prevention in the Blood Pressure Control intervention is based on the well-documented relationships between smoking, dietary intake, body weight, and blood pressure. Smoking cessation typically leads to weight gain (Vander Weg et al., 2001; Ward, Klesges, & Vander Weg, 2001). Increases in body weight, consequently, are associated with an elevation in BP (Huang et al., 1998; Juhaeri et al., 2002). Thus, the goal of the intervention is to limit cessation-induced weight gain in order to improve BP control. Each participant will be provided with a copy of The CalorieKing Calorie, Fat & Carbohydrate Counter 2007 Edition, published by Dietclub.

Results from past studies indicate that the weight gain that occurs following smoking cessation is due primarily to increases in energy intake, although the removal of the acute thermic effect of nicotine also may play a role (Stamford et al., 1986; Vander Weg et al., 2000; 2001). Therefore, the intervention is aimed at reducing the positive energy balance that occurs following smoking cessation by limiting postcessation increases in energy intake, and promoting increased energy expenditure through physical activity.

In addition to promoting weight control, the Blood Pressure Control intervention will target a variety of nutritional recommendations designed to lower blood pressure, including sodium restriction. Numerous epidemiological studies have demonstrated an inverse association between dietary sodium and BP (Elliott et al., 1996; Stamler, 1997). Further, clinical trials have shown sodium restriction to be associated with a reduction in BP, particularly among those with hypertension (He & MacGregor, 2002; Sacks et al. 2001). In accordance with the TONE combined Weight Loss + Sodium Restriction intervention, the goal for sodium intake will be <= 1500 mg/day. Although this level is significantly less than that typically consumed in the American diet, it is considerably higher than what is required to meet the body's nutritional needs (Mahan & Escott-Stump, 1996). This level of sodium restriction was associated with a significant decrease in BP in TONE, both when used as a solitary intervention and when combined with weight loss (Appel et al., 2001; Whelton et al., 1998).

In addition to sodium restriction, the BP Control intervention will incorporate the

nutritional recommendations that are included in the DASH (Dietary Approaches to Stopping Hypertension) diet plan (Vogt et al., 1999). DASH was a multicenter randomized feeding study that compared the impact of three diet plans on blood pressure. The combination diet that was developed for DASH is rich in fruits, vegetables, and low-fat dairy products, and includes whole grains, poultry, fish, and nuts. It also emphasizes reduced consumption of red meat, sweets, and sweetened beverages. Nutritionally, the plan produces a diet that is considerably higher in potassium, magnesium, calcium, fiber, and protein than is typically consumed in the U.S. and lower in dietary fat and cholesterol (Vogt et al., 1999). The combination diet was associated with the most favorable blood pressure outcomes in the original DASH trial (Appel et al., 1997), and has been recommended by the National High Blood Pressure Education Program for preventing and managing hypertension (Windhauser et al., 1999).

Although the DASH dietary plan involves a wide range of dietary goals targeting several food and nutrient groups, it was specifically designed to be practical, palatable, and feasible for implementation in the general population (Vogt et al., 1999). Findings from the original DASH study suggested that adherence to the diet plan was exceptionally high (> 90%) based on both subjective and objective measures (Windhauser et al., 1999). Thus, we are confident that the DASH combination diet can be successfully adopted by participants in this trial.

As with the Weight Gain Prevention the primary rationale for incorporating increases in physical activity is for the weight controlling effects (Blair, 1993; Grilo et al., 1993). However, studies also have demonstrated hypotensive benefits from physical activity that are independent of weight loss (Arroll & Beaglehole, 1992; Whelton et al., 2002). Thus, physical activity appears to provide multiple benefits in terms of BP control, and will comprise an important component of the intervention. Because several studies have shown strength training to be effective at reducing BP (see Kelly & Kelly, 2000 for review), participants also will be encouraged to engage in resistance training as well as aerobic activities. Participants will be given flexibility both in the specific types of moderate activity they choose to engage in, as well as the method in which they choose to accumulate their activity over the course of the day (e.g., several short bouts of activity vs. a single 30-minute period of exercise).

The BP Control Intervention will consist of five individual and 12 group sessions lasting 30-60 minutes conducted over a 12-week period. Sessions will be held in person, but can be made up over the phone if the participant is unable to attend a session. As noted above, the intervention will be modeled after the TONE Weight Loss + Sodium Restriction protocol. Individual sessions will focus on reviewing participants' success with meeting treatment goals and problem solving strategies for increasing adherence and success. Consequently, these sessions will provide specific, individualized instruction tailored to the needs of each participant. The group sessions will address a variety of proven educational and behavioral strategies for modifying diet and physical activity. Several of the intervention components involve strategies similar to those included in the smoking cessation intervention (e.g., self-monitoring, problem solving, relapse prevention). Attempts will be made to emphasize these similarities and to build on previous mastery experiences as a means of promoting continuity across intervention components and enhancing self-efficacy.

At each session a small snack will be provided to the participants, prepared by the bionutrition department of the General Clinical Research Center (GCRC). The snacks will be designed to be low calorie, nutrient dense, and will illustrate the principles of what is

being discussed at the intervention.

At all sessions, tobacco use status, serious adverse event information, and weight will be recorded. At the individual sessions, the participant will be asked about concomitant medication (smoking cessation, weight management, and blood pressure medications only), followed by an expired air carbon monoxide (CO) assessment, and a blood pressure reading. The Blood Pressure Control intervention portion of the study including 12 group sessions and 5 individual sessions will take approximately 17 hours to complete.

Although the two proposed lifestyle interventions may seem fairly intensive (four session smoking cessation intervention plus a four-month BP Control or Weight Gain Prevention program), brief interventions are not likely to be successful at modifying multiple complex behaviors such as smoking, diet, and physical activity. Additionally, participants are likely to be highly motivated to make these lifestyle changes given their high-risk status (Kastarinen et al., 2002; Nothwehr & Perkins, 2002). Furthermore, the length of the intervention is comparable to that used by Spring et al. (2004), one of the few studies to date to demonstrate a significant reduction in postcessation weight gain following lifestyle modification. In addition, the BP Control and Weight Gain Prevention interventions, which are by far the most intensive components of the intervention, were previously shown to be acceptable and successful at reducing weight and BP among patients with hypertension (Whelton et al., 1998). Attendance at the intervention sessions during the first nine months, the most intensive phase of the intervention, averaged 88% (Chao et al., 2000). Attendance at follow-up data collection visits conducted out to 30 months averaged over 85% (Whelton et al., 1998). To date, attendance at the group and individual sessions in the present study at another site has averaged 91% (when make up sessions are taken into consideration). To reinforce attendance, small, low-cost items will be given out at some of the intervention group sessions (for both the Blood Pressure Control group and the Weight Gain Prevention group). The items, for example, may advertise the study logo, or may reinforce healthy behaviors.

3. Usual Lifestyle Condition

To determine the relative effectiveness of the Blood Pressure Control and Weight Gain Prevention interventions, results will be compared to participants assigned to a Usual Lifestyle condition. Participants in this group will receive self-help materials designed to help them manage their body weight and blood pressure. These will consist of two books published by Mayo Clinic Health Information: Mayo Clinic Healthy Weight for Everybody and Mayo Clinic on High Blood Pressure: Taking Control of Your Hypertension. However, they will not receive any additional instructions for making lifestyle changes other than they would normally receive from their primary care provider.

Follow-up Visits

Two follow-up visits will be conducted at six- and 12-months post cessation. Participants will be asked to return to the Preventive Intervention Center for these visits. The procedures performed at these visits will be largely the same. The participant will be asked to report their current smoking status, followed by an expired air carbon monoxide (CO) assessment. For those who fail the CO test (i.e., CO > 10 ppm), yet still claim to be a nonsmoker, a salivary cotinine test will be given to provide a confirming/disconfirming assessment. For those who fail the CO test but report using a nicotine replacement therapy (which would alter the results of the salivary cotinine

test) will instead be tested for thiocyanate via blood draw.

Vitals will also be taken (weight, pulse, blood pressure and waist circumference). Percentage of body fat will be measured using a bioelectrical impedance analysis. Serious adverse event information, and concomitant medication (smoking cessation, weight management, and blood pressure medications only) will be recorded. Current physical activity level will be assessed using the long version of the International Physical Activity Questionnaire (IPAQ). The participant will also be asked to report on their dietary intake by completing two commonly-used dietary screeners. Percent of energy intake from fat will be assessed using the National Cancer Institute (NCI) Fat Screener. Fruit and vegetable intake will be assessed using the All Day version of the NCI Fruit and Vegetable Screener.

The participant will be asked to complete some questionnaires to assess self-efficacy and outcome expectations related to smoking cessation, weight control, and physical activity. Self-efficacy for smoking cessation will be assessed using the Smoking Self-Efficacy Questionnaire. Self-efficacy for physical activity will be measured with the Self Efficacy for Exercise Behaviors Survey, and self-efficacy for weight control will be assessed with the Weight Efficacy Lifestyle Questionnaire. Outcome expectations regarding smoking cessation, physical activity, and weight control will be assessed using measures of decisional balance. In addition, worries about weight gain after quitting smoking will be assessed with a Weight Concerns Scale. Participants will also be asked to complete a 25-item health and lifestyle questionnaire that assesses the following domains: self-perceived health, health related quality of life, changes in blood pressure and blood pressure medication, smoking status and quit attempts, physical activity, body weight and weight control behaviors, dietary intake, and lifestyle changes made in an effort to control blood pressure. Participants who did not quit smoking and who were not randomized to treatment conditions will also be asked to complete this questionnaire by phone.
Lastly, participants will be instructed to test five overnight urine samples at home using chloride titrator sticks in order to measure baseline dietary sodium intake. Participants will be instructed to collect overnight urine samples (2200 to 0600) each morning in containers provided by the study laboratory. Participants will then place a chloride titrator stick into the urine sample for a period of 20 minutes. After the column becomes saturated, a moisture sensitive signal appears at the top. A line appears on the column providing a value ranging from 0.0 to 10.0. The participant will mark the titrator stick reading on a chart provided by the study staff. After five overnight samples the participant will mail the chart back to the study staff.

Participants assigned to either the Weight Gain Prevention or Blood Pressure Control intervention will be asked to complete a brief (9-item) questionnaire at the six-month follow-up to assess their impressions of the helpfulness and effectiveness of various parts of the lifestyle intervention.

The six and 12 month follow-up visits will take approximately 2 hours to complete each, plus the participant's at-home time collecting overnight urine samples. For participants who attend the 12 month visit, we will provide them with a certificate of appreciation to thank them for their participation in the study. If they are still smoke free, we will also give them the certificate of achievement to recognize their hard work.

VII.E.7 ***Will you attempt to recontact subjects who are lost to follow-up?***
No - those lost to followup will not be recontacted

VII.E.9 ***Will subjects be provided any compensation for participating in this study?***

Yes

VII.E.10 ***Cash/check***
Yes

VII.E.16 ***Other***
No

VII.E.19 ***Describe the compensation plan including***

- ***Compensation amount and type per visit***
- ***Total compensation***
- ***Pro-rating for early withdrawal from study***

A participant can receive up to $100 for participation in the study. This money is for the time spent in this study. If the participant starts the study but stops before finishing the study, he/she will receive part of this money based on which visits have been completed. Partial payment will be made as follows:
Completion of Screening Visit = $25
Completion of Screening and Group Assignment Visit = $25, ($50 total)
Completion of Screening, Group Assignment, and 6 Month Follow Up Visits = $25 ($75 total)
Completion of Screening, Group Assignment, 6 Month, and 12 Month Follow Up Visits = $25 ($100 total)

- Please note: Participants who do not quit smoking during the smoking cessation portion of the study are not eligible to continue in the study (to the group assignment visit, interventions, or follow up visits). However, we ask that they complete a short phone interview at the 6 and 12 month time points. For those phone visits they will be compensated $10 (compared to $25 for the in-clinic follow up visit).

Participants that enter the study who have already quit smoking on their own, have the screening and group assignment visit combined. Those such participants would receive $50 for completing that joint screening/group assignment visit. After that, the payment for the rest of the study is the same as above, with the total compensation for completing all visits equaling $100.

VIII. Risks

VIII.1 ***What are the risks to subjects including***
- emotional or psychological
- financial
- legal or social
- physical?

Potential risks and adverse effects of nicotine replacement and study procedures will be explained to each participant when informed consent is obtained. Each participant will be instructed to keep a record and notify the Preventive Intervention Center (PIC) of any potential adverse effects, illnesses, or hospitalizations. Potential risks to study participants may include:

I. Randomization
Although all participants will receive a free smoking cessation intervention, only those who quit smoking and are randomly assigned to either the Blood Pressure Control or Weight Gain Prevention condition will receive the free lifestyle modification intervention designed to help them minimize postcessation weight gain and improve control of their blood pressure. Thus, some participants will not receive an intervention

that may be found helpful for improving blood pressure or weight control.

II. Nicotine Withdrawal
Smoking cessation is associated with a variety of nicotine withdrawal symptoms including depressed mood, difficulty sleeping, irritability, anxiety, difficulty concentrating, restlessness, and increased appetite or weight gain. These symptoms typically are not severe and dissipate within a few weeks of cessation, with the exception of weight gain, which may persist for up to one year.

III. Teratogenicity
Epidemiological studies have not revealed an increased teratogenic risk in women smokers exposed to nicotine through cigarette smoke. Although studies on the teratogenic effect in humans of the nicotine patch have not been conducted, it has not been shown to be teratogenic in animals. However, we have elected to exclude pregnant women from this study, as the safety profile for the study medication is unknown in this group.

IV. Nicotine Replacement Use
Although most persons do not experience any major adverse effects from the nicotine patch or nicotine gum, it is possible that a participant could experience any of the following side effects. All participants will be questioned or evaluated for side effects at each follow-up visit:
a. Skin erythema, pruritus, edema, burning, and rash at the application site of the patch
b. Headache, Dizziness, dry mouth
c. Arthralgia, myalgia, back pain
d. Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, vomiting, heartburn, hiccups
e. Impaired concentration, depression, headache, insomnia, abnormal dreams, nervousness
f. Cough, sinusitis
g. Allergy to nicotine
h. Cardiovascular side effects (cardiac arrhythmia, tachycardia, vasospasm, elevated blood pressure)
i. Jaw or mouth soreness from chewing the gum

Although these adverse events have been reported in those who use nicotine replacement therapy, they have been infrequent and are less likely to be observed in persons who are regular cigarette smokers. In addition, many of these same symptoms are reported by persons who quit smoking without nicotine replacement therapy and have been attributed to nicotine withdrawal from smoking cessation.

V. Physical Activity
Increasing one's physical activity slightly increases the risk of a cardiac event such as angina or a myocardial infarction. Steps will be taken, as described above, to minimize this risk among participants in the study.

VI. Venipuncture
There is a risk of minor bruising and infection at the site of the blood draw.

VIII.2 ***What have you done to minimize the risks?***

- ***If applicable to this study ALSO include:***

- ***How you (members of your research team at Iowa) will monitor the safety of individual subjects.***
- ***Include a description of the availability of medical or psychological resources that subjects might require as a consequence of participating in this research and how referral will occur if necessary (e.g. availability of emergency medical care, psychological counseling, etc.)***

Several procedures will be in place to minimize participants' risks:

I. Data Safety and Monitoring Board
An external Data Safety and Monitoring Committee will be asked to periodically review study data for the occurrence of outcomes of interest and adverse events. The committee will be asked to address the risk benefit profile for the study and may make recommendations for early stoppage of any component of the trial based on regular review of all pertinent study data. The committee will meet a minimum of twice each year.

II. Voluntary Participation
It will be made clear to all participants that participation is voluntary and that they can withdraw from the study if their initial or on-going experience makes it oppressive, burdensome, or otherwise uncomfortable. It also will be made clear that they are free not to participate in any portion of the program without prejudice.

III. Confidentiality
Information collected during the project will be kept confidential within the limits allowed by law, and scientific publications will present data in such a way that it is not possible to determine the identity of individual participants. All computerized data will be password protected, with only the Principal Investigators, Project Coordinator, and Data Manager having access to the security system. All new research assistants and project staff will be trained in confidentiality procedures.

IV. Nicotine Replacement Therapy
Nicotine replacement therapy (NRT) is one of the pharmacological agents approved by the FDA for use in smoking cessation. There currently are five types of NRT available (gum, patch, lozenge, nasal spray, and the inhaler). We propose to use the nicotine patch as the nicotine replacement product for this study because the patch is easier to use for most participants, delivers a predictable nicotine dose (as it does not rely as heavily on correct technique to use it), and may be more socially acceptable for most patients as it is easily concealed under clothing and does not require public use. Nicotine Gum will also be made available to participants to assist with relapse prevention after they have quit smoking. The nicotine patch we have chosen to utilize in this proposal is Novation. The Novation patch is a 24-hour patch that can be obtained as an over-the-counter product without a prescription. The Novation patch is manufactured in three different strengths: 21 mg, 14 mg, and 7 mg. Nicotine levels obtained from the patch generally are lower than those obtained from regular smoking. Recognizing that participants may enter the study smoking differing amounts of cigarettes, as a safety measure we will titrate initial patch dose by using self-reported cigarette consumption. After determining that it is appropriate to dispense study medication to a participant, the dosing regimen will be determined. Participants who report smoking  20 cigarettes each day will be initially placed on the 21 mg patch, participants who report smoking 10 - 19 cigarettes each day will be initially

placed on the 14 mg patch, participants who report smoking 5 - 9 cigarettes will be initially placed on the 7 mg patch. If a participant is initially placed on the 21 mg patch we will use the following dosing schedule: 21 mg patch for two weeks, 14 mg patch for two weeks, 7 mg patch for two weeks, and then off. If a participant is initially placed on the 14 mg patch, we will use the following dosing schedule: 14 mg patch for two weeks, 7 mg patch for four weeks, and then off. If a participant is initially placed on the 7 mg patch, we will use the following dosing schedule: 7 mg patch for six weeks, and then off. Participants will start the nicotine patch on their quit date. This should coincide with Session 2 of the behavioral smoking cessation intervention. The patch will be discontinued after six weeks of use. Nicotine gum is an over-the-counter product that will be given in 2mg pieces, with up to 3 boxes (approximately 6 weeks of regular use).

Participants will have the side effects of nicotine replacement discussed with them and receive detailed instructions regarding proper use of the patch and of the gum. We will monitor concomitant smoking and nicotine replacement use. As a safety measure, nicotine replacement use will be discontinued in a participant that clearly demonstrates repeated concomitant smoking and nicotine replacement therapy use. We also will monitor all participants for use of other pharmacological agents for smoking cessation (e.g., bupropion, varenicline, nicotine nasal spray, nicotine inhaler, nicotine lozenge).

Potential side effects of medication (NRT) will be monitored at each clinic visit while participants are using the patch. Additionally, participants will be given a pager/voice mail number that they can call in the event of adverse effects. Our experience with nicotine replacement is that there will be very few calls to report “adverse” effects. Most calls that we do get occur predictably within the first three days of cessation and are actually symptoms of smoking withdrawal that are being confused as side effects (e.g., craving for a cigarette). Most of the remaining adverse effects are the result of improper use of the product (e.g., failure to move the patch from one area to another). Remediation will be given as necessary. In the case of a true adverse effect, an RN or study physician will be on call to discuss the problem with the participant and, if necessary, to take him or her off of the product.

Participants will be given detailed instructions about nicotine patch use. These rules are: (1) Never smoke and use the patch at the same time; (2) each day, put on a new patch. Use only one patch each day; (3) the patch can cause your skin to become red and get irritated. Put each patch on a different site each day. Don’t use the same site for at least seven days; (4) after removing used patches, fold the adhesive areas together, place them in the pouch provided, and return them at your next visit; (5) keep this medicine out of reach of children and pets. It may be especially harmful if swallowed; (6) the patch should not be used if you are pregnant. If you think you might be pregnant, or have plans to become pregnant during the study, do not use the patch. They will also receive detailed instructions on the use of the nicotine gum: 1) Do not smoke or use other nicotine replacement products while using the gum; 2) Chew only 1 piece of gum at a time; 3) Never chew more than 24 pieces of gum in a day.

V. Physical Activity

Since two thirds of the participants will receive an intervention involving moderate levels of physical activity (3 to 6 METS), exclusionary criteria are needed to ensure that we do not increase the risk of a cardiac event. As such, a detailed medical history will be obtained. Participants who are recruited from the community rather than a primary care clinic (and who therefore may not have received a recent medical evaluation) will undergo a brief physical examination prior to entry into the study. In addition, all

participants who successfully quit smoking will have their current medical status reviewed and updated prior to randomization to treatment conditions. They will also receive an assessment of vital signs (BP, pulse, and respiratory rate) and an electrocardiogram (ECG). We included the ECG to assess for previous silent myocardial infarction but recognize the limitations of a static ECG for detecting active ischemia. In addition, potential participants will be questioned about any recent symptoms provoked by moderate intensity physical activity (e.g., walking, cycling at a moderate speed, general housework). Specifically, we will use the Physical Activity Readiness Questionnaire (PAR-Q; Thomas, Reading, & Shephard, 1992) and the Rose Angina Questionnaire (Rose, 1962) to assess major signs and symptoms of cardiovascular disease (e.g., angina) in order to ensure that the intervention does not place participants at increased risk for a cardiac event. Finally, participants will be instructed to take part in light to moderate intensity physical activities as part of the intervention, and will not be asked to engage in activities that are vigorous in intensity. It is important to note that individuals with a history of myocardial infarction, stroke, or unstable angina during the past three months, as well as those who underwent coronary bypass or angioplasty in the past three months will have been excluded during the screening process. Individuals with Stage II or uncontrolled hypertension, a history valvular heart disease, congestive heart failure, cardiac dysrhythmia (except atrial fibrillation) controlled by anti-arrhythmia medication, and ECG evidence of 2nd or 3rd degree AV block also will be excluded.

VI. Monitoring of Side Effects and Adverse Events

Participants will be appropriately monitored until the end of the study. For any adverse experience reported during the study, the nature, onset, duration, intensity, and remedial action taken will be recorded. Principle Investigator Mark Vander Weg and a study nurse or physician will monitor each participant for adverse events and side effects. At any point, Dr. Vander Weg may withdraw a participant from the study for health-related reasons. Trained study personnel will explain side effects to each participant as part of the informed consent process, and participants will be provided a copy of the informed consent document that will include a list of potential side effects. All participants will be encouraged to contact the study clinic if untoward symptoms, illnesses, or hospitalizations of any nature occur.

VII. Monitoring Adherence

Monitoring adherence is critical in a clinical trial, for safety considerations and as the interpretation of study results must take into account whether the intervention regimen was followed. Great emphasis will be placed on developing a sophisticated system for monitoring, scheduling, and tracking participants. Every detail of all of the study visits will be planned and staff roles clearly delineated. A detailed appointment reminder card and telephone follow-up system will be devised. All persons will be mailed visit reminders and receive phone calls on the day prior to scheduled visits. All missed appointments will be followed up within 24 hours by a call to the subject or to someone on the list of contacts the participant has provided. If the appointment has been missed, another appointment will be made promptly. If the participant cannot be reached, a search will be made immediately starting with a list of contacts, including family, friends, ministers, clubs, etc. Extreme effort will be maintained to achieve all appointment windows. Appointment windows and protocol adherence status are tracked constantly. Several steps can be taken to minimize adherence problems prior to enrollment. An important factor in preventing adherence problems before enrollment is selection of appropriate subjects. Ideally, only those persons likely to follow the study protocol should be enrolled. Also of importance is a truly informed participant.

Sufficient time will be spent with each potential participant to instruct him or her about the study and what will be expected of him or her. After enrollment, to increase adherence, clinic personnel will strive to maintain the participants' interest and enthusiasm. Clinic personnel will maintain close contact with participants, make clinic visits pleasant and convenient, and provide clear written and verbal instructions about the study.

A protocol for study medication discontinuation has been developed as part of the operations manual. For some problems that require temporary cessation of the study medication that are mild, the investigator and participant may agree to re-challenge the patient with study medications.

VIII. Operations Manual
An operations manual has been developed for the study and the procedures will be strictly followed. All clinical trials personnel will be trained in all study procedures in which they will be involved, or in which they could potentially be involved, including recruitment, informed consent, measurements, randomization, drug handling, specimen handling, participant follow-up, adverse events, side effects and outcome determination. Adherence to the procedures in the operations manual will be assured by periodic assessment and retraining.

VIII.3 ***Does this study have a plan to have an individual or committee review combined data from all subjects on a periodic basis (such as summary or aggregate safety and/or efficacy data)?***
Yes

VIII.4 ***Describe the plan to review combined data from all subjects, such as summary or aggregate safety and/or efficacy data. Include the following:***

- ***Describe what data will be summarized and reviewed***
- ***Describe how frequently data will be reviewed.***

An external Data Safety and Monitoring Committee will be asked to periodically review study data for the occurrence of outcomes of interest and adverse events. Baseline data, outcome data, safety data, and enrollment information will be summarized for the committee. The committee will be asked to address the risk benefit profile for the study and may make recommendations for early stoppage of any component of the trial based on regular review of all pertinent study data. The committee will meet a minimum of twice each year, both meetings will be by phone.

VIII.5 ***Will overall safety monitoring be performed by individual(s)/committee at The Iowa City VAMC. (NOTE: If this study involves more than minimal risk, in most cases these should be individuals who are not members of the study research team.)?***
No

VIII.7 ***Will overall safety monitoring be performed by individuals or committee not associated with The Iowa City VAMC (such as a study Data Safety Monitoring Board)?***
Yes

VIII.8 ***Describe the membership and note if members are affiliated with the sponsor, are researchers involved in the conduct of the study at any site, or if members are completely unaffiliated.***

The DSMB is comprised of the following four members: Geoff Williams, M.D. (Committee Chair) from the University of Rochester, Nancy Sherwood, Ph.D. from Health Partners Research Foundation, Frank Treiber, Ph.D., from the Medical College of Georgia, and Larry Weber, Ph.D. from Tulane University. Collectively, these individuals have considerable experience and expertise in the relevant fields of smoking cessation, body weight, blood pressure, and biostatistics.

experts in their respective fields; Smoking Cessation, Blood Pressure, Biostatistics, Body Weight, and others. They are independent persons at different institutions chosen for their expertise but not affiliated with the sponsor. The National Heart, Lung, and Blood Institute (NHLBI) approved the board members, but did not pick them.

IX. Benefits

IX.1 ***What are the direct benefits to the subject (do not include compensation or hypothesized results)?***

Participants will benefit by being involved in a no-cost behavioral program that may help them to quit smoking. They also will benefit by receiving free nicotine patches to help them quit. They may also benefit by receiving free nicotine gum to prevent relapse. Those assigned to the Blood Pressure Control or Weight Gain Prevention conditions also will receive a free behavioral program to help them prevent weight gain and control their blood pressure. Given the substantial potential benefits and the minimal risks for participants involved in this project, it is felt that the benefits significantly outweigh the possible risks.

IX.2 ***What are the potential benefits to society in terms of knowledge to be gained as a result of this project?***

Elevated blood pressure and cigarette smoking continue to be major preventable causes of death in the United States, and improvements in treatment options are needed. This project has the potential to substantially increase the effectiveness of existing smoking cessation and BP control interventions for hypertensive smokers, with minimal risks to subjects.

X. Privacy & Confidentiality

X.1 ***What are you doing to protect the privacy interests of the subjects?***

First, participants will not be identified by reviewing charts or other personal data. All recruiting will be done to a general audience, not to specific individuals. Next, we will not ask questions of a sensitive nature in the initial screening. We will wait until the participant has reviewed and signed the informed consent before administering the more personal screening questions. We will not ask questions that are not needed for eligibility purposes. In the consent process, the participant will be given the opportunity to ask questions, and to not participate if they so choose. During the study, the participant is given the option of skipping questions that they wish not to answer. Finally, when performing study procedures and collecting study data, the staff will ensure that the participant feels comfortable and is given the appropriate privacy for procedures.

X.2 ***Are you collecting the Social Security Number of any subjects for any purpose?***

Yes

X.3 ***Provide the intended usage of SSN:***

- To provide compensation to subjects

X.4 ***How will information/data be collected and stored for this study (check all that apply):***

- Electronic records (computer files, electronic databases, etc.) - All electronic data are maintained at the University of Iowa under IRB-01 201703765. The project uses a secure network to enter data. The computer system is password protected, along with the database. Only members of the study team are able to log into the data base. The study database containing study results only use the subject ID code, not the participants name or personally identifiable information. The server containing the study data is password protected and kept in a secure, locked office. The audio recordings of sessions will be destroyed after they have been review for quality purposes, or at completion of the study.
    - Name - Mike Mueller
    - Title - Database Administrator
    - University/VA Job Classification - staff
- Biologic samples (blood draws, check swabs, saliva samples, tissue samples, etc.) - All biologic samples were collected and stored at the University of Iowa under IRB-01 201703765. Biologic samples were labeled with the subjects ID number, then packaged and shipped in accordance with IATA requirements through the mail to the lab for testing. The sample will be logged into study records using the same study ID number. The log will be kept in a secured specimen room. Study team members handling and shipping biologic samples will demonstrate current IATA training.
    - Name - Mary Cherrico
    - Title - Head Nurse, Preventive Intervention Center
    - University/VA Job Classification - staff
- Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - Paper records are stored in a locked room at the University of Iowa Preventive Intervention Center and are currently under IRB-03 201703765. An ID code was assigned to each participant for data entry purposed. Only the Principle Investigator, Research Coordinator, and Data Managers have access to the ID coding system which is kept in a secure location so it can not be decoded.

X.5 ***Do the confidentiality protections indicated above allow only members of the research team to access the data/specimens?***

Yes

X.7 ***Does your study meet the NIH criteria for a Certificate of Confidentiality or will you be applying for Certificate of Confidentiality?***

No

XI. Data Analysis

XI.1 ***Describe the analysis methods you will use, including, if applicable, the variables you will analyze***

The main statistical analyses will be for the three-group randomized clinical trial with the primary analyses restricted to participants that do not relapse to smoking. Participants who discontinue study participation will be assumed to have relapsed to smoking. Therefore, analyses will be restricted to those with available data.

The primary efficacy endpoints are BP and body weight. Since the aim is to evaluate long-term efficacy, the primary analysis will evaluate treatment effects at 1-year. Analyses will also be conducted to assess changes in BP and body weight at six months. The primary analysis will be restricted to participants that have not relapsed to smoking and who provide follow-up data. Secondary analysis will performed using all

participants. The primary analysis will be performed using ANCOVA to assess for treatment effects adjusting for the baseline value of the dependent variable, study site, and any baseline variables found to differ significantly between groups. In all cases, each of the two experimental groups will be compared to the UL group. Since there are two pair-wise treatment comparisons of interest (BPC vs. UL; WGP vs. UL), we will utilize Fisher's least significant difference (LSD) approach to protect against inflation of the experiementwise error rate. An initial omnibus test will be used to test the null hypotheses that all group means are equal. Rejection of the null hypothesis will result in subsequent pair-wise comparisons between treatment groups. Conversely, if the null hypothesis associated with the omnibus test is not rejected, pair-wise comparisons will not be necessary.

Secondary endpoints will include servings of fruits and vegetables per day, dietary fat intake (% of total energy from fat), overnight urinary chloride excretion (mmol/day), and self-reported physical activity (kcal/kg/day). The analyses for the secondary endpoints will be similar to that for the primary endpoints, with groups compared using ANCOVA to assess for treatment effects adjusting for baseline values, study site, and baseline variables found to differ significantly between groups. In all cases, each of the two experimental groups will be compared to the UL group.

Relapse to tobacco use will be analyzed as an exploratory endpoint. At every contact following randomization subjects will be assessed for relapse to tobacco use, with relapse defined as using tobacco on seven consecutive days or using tobacco at least one day per week on two consecutive weeks. This definition is consistent with that proposed by the Society for Research on Nicotine and Tobacco (Hughes et al., 2003). For subjects that relapse, the date of relapse will be defined as the first day of tobacco use in the 7-day or 2-week period. Subjects that discontinue study participation prior to the 1-year follow-up visit, who have not already met relapse criteria, will be assumed to have relapsed to using tobacco. For these subjects, the date of relapse will be assigned as the day following their last study visit. Time to relapse will be analyzed using Cox proportional hazards regression (PROC PHREG) with time to relapse as the dependent variable and intervention group as the independent variable. For subjects that do not relapse to using tobacco, the time to relapse will be censored as of the date of their 1-year follow-up visit. Additional multivariable analyses assessing characteristics associated with relapse to tobacco use will be considered. However these analyses will be considered exploratory in nature since our ability to perform meaningful multivariable analyses will be dependent on the number of subjects that relapse to tobacco use.

A number of additional analyses will be performed to describe the study characteristics and assess comparability between study groups. Participant adherence will be assessed as percentage of contacts completed and compared between groups using the rank sum test. The percentage of subjects that use other products (or programs) for smoking cessation, blood pressure or weight control will be summarized separately and compared between intervention groups using Fisher's exact test. Changes in hypertension status will be noted and coded as: -1=decrease in status, 0=no change, +1=increase in status; and changes in hypertension medication status will be noted and coded as: -1=decrease in medication, 0=no change, +1=increase in medication. Using these coded variables, changes in hypertension status and medication status will be compared across treatment groups using the Kruskal-Wallis test.

Analyses for phase 1 (smoking cessation)

Although the primary analyses are for the randomized trial, the first phase of this investigation (open-label smoking cessation phase) will provide meaningful data regarding smoking cessation efforts for individuals. For this phase, the primary outcome will be prolonged tobacco abstinence at the final program session (session 4) defined as self-reported abstinence from all tobacco (not even a puff) for the last 14 days, confirmed by expired CO<10 ppm. The percentage of participants that discontinue the program prior to the 4th session will be summarized along with the reason for discontinuation. The overall abstinence rate at the end of the program will be summarized using a point estimate and 95% confidence interval, with subjects that discontinue study participation assumed to be smoking. In addition, logistic regression will be used to perform exploratory analyses to assess potential participant characteristics associated with abstinence at the end of treatment. Participant characteristics considered in this analysis will include: age (years), gender, smoking rate (cpd), and level of nicotine dependence (FTND).

XI.2 ***Provide the rationale or power analysis to support the number of subjects proposed to complete this study.***

This study is a multi-site, randomized clinical trial, with study sites in Iowa City, IA, Rochester, MN, and Memphis, TN. The sample size calculations provided below reflect the target number of participants for the entire trial, across each of the three sites. Only subjects that meet criteria for tobacco abstinence at the end of the 4-week smoking cessation phase will be eligible for randomization, and of these participants, only those that meet criteria for prolonged abstinence through 1-year follow-up will be included in the primary analysis. Because methodological factors such as abstinence criteria and length of follow-up can have a significant impact on the primary endpoints, we consulted the extant literature and chose only studies that were fairly similar to the proposed project to obtain estimates for sample-size planning. The majority of these studies present data as change from baseline. For this reason, sample-size calculations for the present investigation are based on an analysis of change scores. However, an alternative to analyzing change scores is to analyze follow-up data using an analysis of covariance model with the baseline value included as a covariate. In addition to adjusting each subject's follow-up score for his or her baseline score, the analysis of covariance approach has the advantage of being unaffected by baseline differences. This approach also typically has greater statistical power to detect a treatment effect than analyzing change scores (Vickers et al. 2001). Therefore, sample-size requirements based on an analysis of change scores will provide similar or greater statistical power for analyses that are performed using an ANCOVA approach.

Primary Endpoint: Blood Pressure

For this endpoint sample-size requirements were determined based on preliminary data from the TONE trial. In this trial the mean change from baseline for the combined Weight Loss plus Sodium Restriction intervention was observed to be -5.3 mmHg (SPB) and -3.4 mmHg (DBP). Effect sizes of similar magnitude have been observed in other studies evaluating lifestyle modification interventions for controlling blood pressure (e.g., Blumenthal et al., 2000; PREMIER Collaborative Research Group, 2003; Singh et al., 1995; Wassertheil-Smoller et al., 1992). From the TONE trial, the pooled estimate of the standard deviation of SBP change from baseline was approximately 14.5 mmHg for SPB and 9.4 mmHg for DPB. Based on these assumed standard deviations, Table 4 lists the sample-size required to provide statistical power of 80% to detect a range of differences between groups with respect to mean BP change from baseline using a two-tailed, alpha=0.025 level test. As can be seen from Table 4, an effective sample-size of 145 per group is required to provide statistical power of approximately 80% to detect

differences between groups consistent with the magnitude of effect observed for the Weight Loss plus Sodium Restriction intervention from the TONE trial.

Table 4. Sample-size for Detecting Difference in Blood Pressure Change from Baseline

Sample-size requirements for SBP			Sample-size requirements for DBP		
Difference Between Groups (mmHg)	Standard Deviation (mmHg)	Sample Size Required per group*	Difference Between Groups (mmHg)	Standard Deviation (mmHg)	Sample Size Required per group*
5.1	14.5	155	3.1	9.4	176
5.2	14.5	149	3.2	9.4	166
5.3†	14.5	144	3.3	9.4	156
5.4	14.5	139	3.4†	9.4	147
5.5	14.5	134	3.5	9.4	139

* Sample-size required to provide statistical power of 80% using a two-sided, alpha=0.025 level test.
† A difference of this magnitude is consistent with the effect observed for the Weight Loss plus Sodium Restriction intervention from the TONE trial.

Primary Endpoint: Body Weight
We identified 5 smoking cessation studies that had weight change data (mean±SD) presented for subjects that met continuous abstinence criteria at 1-year follow-up. For those that met criteria for continuous abstinence, the observed weight change from baseline to 1-year follow-up in these studies was 6.2±5.1 kg (N=20; Dale et al., 1998), 5.9±7.3 kg (N=17; Gritz et al. 1990), 4.5±2.9 kg (N=35; Hjalmarson et al. 1997), 5.9±3.8 kg (N=51; Klesges et al., 1997) and 4.8±3.9 kg (N=88; Pirie et al., 1992). From these 5 studies, the pooled estimate of the standard deviation of weight change from baseline to 1-year is 4.2 kg. In order to be conservative, for sample-size planning of the current investigation the standard deviation of weight change from baseline to 1-year is assumed to be 5.0 kg. Based on this assumption, Table 5 provides the sample-size required to provide statistical power of 80% to detect a range of differences between groups with respect to mean weight change from baseline to 1-year.

Table 5. Sample-size for Detecting Difference in Body Weight Change from Baseline

Difference between groups (kg)	Standard Deviation (kg)

Effect Size‡ Sample
Size
Required
per group*
2.50 5.0 0.50 78
2.25 5.0 0.45 95
2.00 5.0 0.40 120
1.75 5.0 0.35 157
* Sample-size required to provide statistical power of 80% using a two-sided, alpha=0.025 level test.
‡Difference between groups divided by the common standard deviation.

In order to be clinically meaningful, we believe that the mean difference between treatment groups should be 2.0 kg or larger. Thus for the body weight endpoint, an effective sample-size of N=120 subjects per groups is required to provide statistical power of 80% to detect a clinically relevant difference between groups. An effective sample-size of 145 subjects per group will provide statistical power of 87% (two-sided, alpha=0.025 level test) to detect a mean difference between groups of 2.0 kg.

Secondary Endpoints:
In general, for a continuous endpoint an effective sample-size of N=145 per group will provide statistical power of 80% to detect a difference between group means consistent with an effect size (i.e. difference between groups divided by the common standard deviation) of 0.37. For the secondary endpoints of total energy, dietary fat intake, urinary sodium excretion, and self-reported physical activity, Table 6 provides the minimum difference that can be detected between groups with statistical power of 80% (two-sided, alpha=0.025 level test) using an effective sample-size of N=145 per group. The standard deviation estimates provided in Table 6 are for the distribution of the given endpoint measured at a single time point. The analyses of the 6- and 12-month outcomes will be performed using ANCOVA with the baseline measurement included as a covariate. Since the power analysis presented in Table 6 does not account for the potential reduction in error variance achieved by adjusting for the baseline value, the minimal detectable difference indicated in the table should be considered a conservative estimate. Thus, an effective sample-size of N=145 per group will provide ample statistical power to evaluate these secondary endpoints.

Table 6. Minimum Detectable Difference for Secondary Endpoints

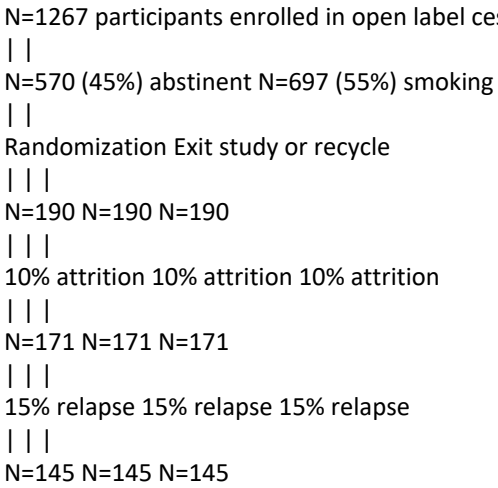
Endpoint Estimated
Standard Deviation Reference for SD Estimate Minimal Detectable Difference*
Total Energy, kcal/day 426.5 Eck et al. 1996 158 kcal/day
Dietary fat intake, g/day 18.8 Eck et al, 1996 7 g/day
Urinary chloride excretion, mmol/dayb 65 TOHP Research Group, 1992
Whelton et al., 1998 24 mmol/day
Physical activity, kcal/kg/day 1.5 Dunn et al., 1999 0.6 kcal/kg/day
aDifference between group means that can be detected with statistical power of 80% using a two-sided, alpha=0.025 level test with N=145 per group.
bEstimates based on data utilizing urinary sodium excretion.

As noted above, the sample size calculations reflect the total number of participants to

be enrolled across the three study sites. The specific enrollment goal for the Iowa City site is 500 participants. We anticipate that we will need to screen approximately 912 individuals in Iowa City to reach the target number of 500 participants enrolled.

Anticipated Attrition
As noted above, we will need a total of approximately 435 randomized subjects (N=145 per group) across all three study sites that meet criteria for prolonged abstinence through 1-year follow-up in order to have adequate statistical power to detect anticipated group differences in our primary and secondary endpoints. In order to achieve an effective sample-size of N=435 several levels of ineligibility and attrition must be considered. Overall we estimate that we will need to enroll approximately 1267 participants across all three sites into the study. Of the 1267 participants recruited, we anticipate that N=570 (45%) will be abstinent at the end of the open label cessation phase and eligible for randomization. Of those randomized we anticipate that 10% (N=57) will discontinue study participation prior to 1-year and an additional 15% (N=78) will relapse to smoking. Therefore, as outlined in Figure 2, we anticipate that a total of 1267 participants enrolled in the initial smoking cessation phase will result in an effective sample-size of approximately 435 (145 per group). Considerable effort will be made in an attempt to reduce the actual amount of attrition to less than that estimated. The Iowa site is responsible for attaining 500 of the 1267 participants. From statistics at the other recruiting sites, we estimate that the Iowa City site will have to screen approximately 912 participants in order to have 500 eligible for the cessation phase of the study.

Figure 2. Participant Flow and Attrition.



XII. Future Research

XII.1 ***Do you wish to keep any information about subjects involved with this research project so that members of the current research team may contact them in the future for your own research projects?***
No

XII.2 ***Do you wish to keep any information about subjects involved with this research project so that other researchers may contact them for future research?***
No

XII.4 ***Does this project involve storing any data, tissues or specimens for future research?***

No

XIII. Other Mod and/or Comments

XIII.1 ***Most modifications should be made in the appropriate section (see Index) of the project itself. If you need to describe other changes, or wish to add comments about something you changed, please do so here.***

XIII.2. ***Have you permanently stopped enrolling new subjects into this study?***
Yes

XIV. P&T / MRPC / RBC Mod Checklists

XIV.1 ***Are any new drugs being added?***
No

XIV.4 ***Is either dose or duration of therapy changing?***
No

XIV.7 ***Have new risks been identified (new adverse reaction, new interaction, new toxicity)?***
No

XIV.10 ***Have there been any changes to the Investigator's Brochure or package insert?***
No