Sleep Quality and Mechanisms of Cardiovascular Risk in Adults with Hypertension

Document Date: 11/29/2023

NCT04009447

Purpose of the Study

The objective of the study is to elucidate the potential mechanisms responsible for the increased risk of CVD among patients with hypertension and comorbid insomnia. To address this issue, we propose to utilize a behavioral intervention to manipulate sleep quality in 150 adults with hypertension and comorbid insomnia, who will receive a 6-week Cognitive Behavioral Therapy for Insomnia (CBT-I) intervention, which has been shown to markedly improve sleep quality and promote consolidated sleep in approximately 60% of those treated. Blunted nighttime blood pressure dipping is one of several proposed mechanisms to be examined.

Background & Significance

There is a growing body of evidence that insomnia is a CVD risk factor. In a meta-analysis of 17 observational cohort studies, with a combined sample size of 311,260 participants free of CVD at baseline, Li and colleagues found that insomnia was associated with a 41% increased risk of myocardial infarction (MI), coronary heart disease (CHD), stroke, or CVD mortality over a 1-year follow-up period. Similarly, in an analysis of 13 prospective cohort studies of adults with insomnia (N=122,501), but absent of documented CVD, Sofi and colleagues found a 45% increased risk of developing or dying from CVD over a follow-up period of 3 years or more. As the latter authors, concluded, "Insomnia is associated with an increased risk of developing and/or dying from cardiovascular disease. The evidence that low-quality sleepers are at higher risk of myocardial infarction and other cardiovascular disease is extremely important for primary and secondary prevention." Even in the absence of an insomnia disorder diagnosis, poor sleep quality has been linked to CVD risk. In a meta-analysis of 20,432 adults, aged 20-65 years without history of CVD followed for 10-15 years, Hoevenaar-Blom et al.26 reported that poor sleep quality was associated with a 22% higher risk of developing CVD and a 34% higher risk of CHD incidence than those with good sleep quality. Lo and colleagues18 also recently reported a meta-analysis of studies including over 45,000 participants, spanning over 5 continents, showing that poor subjective sleep quality was associated with increased likelihood of hypertension. Similarly, in a review of 17 observational cohorts studies, which included a total sample of 58,924 participants with at least 1 year of follow-up data, Meng et al. found that insomnia was associated with an increased incidence of hypertension.

Although the link between insomnia and hypertension has gained wide acceptance, recent reviews note that this evidence is based upon clinic BP. However, clinic BP is markedly inferior to BP measured over 24-hours using wearable ABPM technology. In healthy adults, the normal circadian BP profile reveals that BP dips during the nighttime sleep period; importantly, a blunted nighttime BP dip (<10% dip in BP due to elevated nighttime BP) is the strongest BP predictor of CVD morbidity and mortality. Blunted nighttime BP dipping is characteristic of 30-40% of patients with hypertension, and there has been growing interest in strategies to target and lower nighttime BP in the management of hypertension. In patients with hypertension whose BP is managed using antihypertensive medications, there is compelling evidence that nighttime dosing of antihypertensive medications augments nighttime BP dipping. Moreover, this pharmacological chronotherapy has been shown to reduce the risk of adverse CVD events, underscoring that blunted nighttime BP dipping is an important mechanism contributing to

heightened CVD risk. However, for patients with insomnia and hypertension, it is possible that behavioral treatment of their insomnia may be a non-pharmacologic approach that could also benefit their BP as well as overall CVD risk. For example, current guidelines recommend consideration of non-pharmacologic interventions that include weight loss for overweight or obese patients, together with a heart-healthy diet comprising reduced sodium, lower saturated fat and limited alcohol consumption, which may lower systolic blood pressure (SBP) by approximately 11 mm Hg. Nonetheless, despite its association with hypertension and CVD risk, whether insomnia is a reversible CVD risk factor remains unknown.

A.2. Mechanisms Underlying the Link between Insomnia and CVD risk

Recent reviews and meta-analyses have emphasized that two critical kinds of studies are required in order to understand the link between insomnia, hypertension and increased CVD risk. First, there is a need for studies focusing on the possible mechanisms by which insomnia and poor sleep quality may contribute to CVD risk. Second, studies should determine if these mechanistic pathophysiological pathways can be modified if sleep quality is improved and/or insomnia successfully treated. As others also have noted, and as we have emphasized in a recently published commentary, the most conspicuous candidate mechanism by which poor sleep and insomnia are likely to contribute to CVD risk is by disrupting the normal circadian variation in BP, by blunting the extent to which BP falls during the nighttime sleep period. In the study proposed in this application, by evaluating whether nighttime BP dipping is modified when sleep quality is manipulated, we will help establish whether BP dipping is a mechanism by which insomnia contributes to CVD risk. In this way, we also propose to evaluate other putative bio-behavioral mechanisms. Our own work has documented that blunted nighttime BP dipping is related to nighttime SNS hyperactivity in men and women with hypertension. The SNS has long been implicated in the pathogenesis of hypertension, and more recently in various manifestations of CVD, and is a potential mechanism related to insomnia. In their systematic review of 32 studies, Aziz and colleagues reported that poor subjective sleep quality was associated with vascular abnormalities related to hypertension and CVD risk, including endothelial dysfunction and arterial stiffness. Both of these potential sleep-related mechanisms have also been related to blunted nighttime BP dipping, with elevated nighttime SNS activity speculatively involved. Recent evidence that blunted nighttime BP dipping is due to elevated nighttime systemic vasoconstriction is also consistent with the possibility that these vascular mechanisms contribute to CVD risk associated with insomnia. Indeed, vascular endothelial dysfunction is associated with blunted nighttime BP dipping in hypertension. Carroll and colleagues found that improved sleep quality in men and women with insomnia resulted in an improved lipid profile, an additional mechanistic pathway that would exacerbate the progression of vascular disease and increase CVD risk. Our conceptual model (Figure 1) illustrates how these candidate mechanisms may contribute to hypertension and CVD risk through their association with poor quality sleep and insomnia. As illustrated by this conceptualization, the putative mechanisms by which insomnia is hypothesized to convey increased CVD risk are interrelated pathways, with elements of a cascading pathophysiology. Improving sleep quality in those with hypertension and comorbid insomnia is therefore expected to result in favorable changes in these mechanistic pathways. Because these CVD mechanisms are also related to hypertension, it is possible that improved sleep quality may have a broader antihypertensive effect. Importantly, improvements in sleep quality that result from CBT-I are not transitory; a recent report documented that the improved sleep benefits are maintained for up to

10 years after completion of treatment. Sleep quality improvement following the CBT-I intervention may affect some mechanisms (e.g., augmented nighttime BP dipping) immediately, while other mechanisms (e.g., improved lipid profile) may emerge over several weeks, but could be sustained long term. Thus, our study design includes complete 6-month follow-up assessments in order to examine the possibility of progressive improvements in CVD risk mechanisms, and overall CVD risk.

In summary, the objective of this application is to further our understanding of the association between insomnia, hypertension, and CVD risk by focusing on the potential mechanisms involved. We aim to ascertain whether these mechanisms are affected favorably when sleep quality is improved by a behavioral intervention in those with insomnia, thereby also importantly determining whether poor sleep quality is a modifiable CVD risk factor. Exploratory aspects of this research study will include a focus on individual difference characteristics, with a particular interest in race, in view of extensive evidence that both poor sleep quality and nighttime BP non-dipping are especially common amongst African-American adults. Importantly, the study objectives are consistent with the call to consider nighttime BP a therapeutic target, and should help determine if interventions to improve sleep quality can favorably modify this characteristic of the circadian BP profile that appears to be a pathway leading to heightened CVD risk.

RESEARCH STRATEGY: B. INNOVATION

Insomnia and CVD Risk Mechanisms - To our knowledge, this is the first study that includes a sleep manipulation intervention as an approach to identifying the mechanisms that link insomnia to CVD risk. Several recent reviews and meta-analyses of this field have emphasized the need for studies designed to help identify these mechanisms. Previous studies have been limited by their cross-sectional designs, whereas the study proposed in this application should yield evidence of several mechanisms whereby insomnia conveys increased CVD risk.

The evidence that insomnia is a CVD risk factor has arisen from multiple observational studies, but whether it is a reversible risk factor is unknown - The proposed study will help establish whether those who respond to CBT-I with reduced insomnia symptoms and improved sleep quality are also likely to be characterized by ameliorated CVD risk.

Interventions that can achieve sustained improvements in sleep quality have the potential to abate the putative mechanisms that link insomnia to increased CVD risk – Because the improvement in sleep quality in response to CBT-I has been shown to persist for at least 10 years, the mechanisms conveying CVD risk are also likely to remain favorably modified. The proposed study includes a 6-month follow-up assessment to evaluate this possibility.

The mechanisms of insomnia-related CVD risk will be studied in the context of adults with hypertension – The proposed study will focus on adults with hypertension (and comorbid insomnia) because the presence of these two CVD risk factors has been shown to be interrelated, with their associated mechanisms of CVD risk also potentially shared. This patient population therefore affords the potential to show marked improvements in the mechanisms of CVD risk. The study outcomes should pave the

way for future research using CBT-I to target sleep in other medical conditions where insomnia is a common comorbidity.

Design & Procedures

The study design reflects our objective of identifying the mechanisms responsible for the increased risk of CVD among patients with hypertension and insomnia, and to determine if these mechanisms can be favorably altered by improving sleep quality. We propose to utilize a behavioral intervention to manipulate sleep quality in 150 adults with hypertension and comorbid insomnia. This mechanistic clinical trial design will assign all 150 participants to a 6-week CBT-I intervention, which has been shown to markedly improve sleep quality and promote consolidated sleep in approximately 60% of those treated; whereas approximately 40% do not respond to CBT-I.30 While CBT-I is generally effective, the anticipated wide-ranging treatment response will provide the prerequisite variability in sleep quality changes that will afford us the opportunity to help identify the mechanisms by which insomnia conveys CVD risk and by which improved sleep may lower CVD risk. Our design (see Figure 5 below) will include a 6-week run-in period, without treatment, to document the stability of sleep quality, ABP, and CVD risk mechanisms, which will serve as a basis of comparison following CBT-I treatment. Assessments will be performed at baseline, after the 6-week run-in period, after the subsequent 6-week CBT-I intervention, and at 6-month follow-up. Importantly, the study design will also establish whether these insomnia-driven CVD risk mechanisms are modifiable by CBT-I for participants who show improved sleep following treatment.

Screening Assessments. Initial telephone screening will be used to ascertain whether potential participants are likely to meet the study eligibility criteria, with a focus on previously observed clinic BPs and the presence of insomnia symptoms. For those who are likely eligible, the first of two screening sessions will be scheduled, at which informed consent will be first obtained. A medical history will be taken for eligible participants. For women, menopausal status will be documented by self-reported menstrual bleeding, using the criteria described by Tom and colleagues. Status categories are postmenopausal (natural or surgical), perimenopausal, and premenopausal. Menopausal status will be considered as a potential covariate in analytic models.

ReScreening - If a participant fails to meet all eligibility criteria, but remains interested in participating in the study, they will have the option to be rescreened at a future date. If the rescreening occurs within 3 months, only the eligibility criterion which made them ineligible initially will be reassessed in order to ascertain their eligibility at rescreening; if rescreening occurs after more than 3 months, then the full screening protocol will be repeated. The participant will be re-consented at the time of rescreening.

Office BP Screening Assessment. At the first lab screening session, BP will be determined by unattended automated office blood pressure (AOBP) measurement using the Omron HEM-907 Professional Intellisense BP Monitor. AOBP measurement minimizes the “white coat” effect and correlates more closely with ambulatory BP than do standard office measurement techniques. After seating the individual in a quiet room, a cuff of appropriate size will be wrapped around the individual’s non-dominant upper-arm and the Omron HEM-907 will be operated in automated mode: After starting the

monitor, the Research Assistant will leave the room, and after a lapsed time of 5 minutes, the monitor will take a total of three BP measurements, each 2 minutes apart; the average of these three readings will be used to define office BP at that visit. If BP meets the studies inclusion/exclusion criteria, a second screening session will be scheduled, and if BP continues to meet criteria, the individual will be enrolled as a study participant (assuming all other inclusion/exclusion criteria are also met). This method for office BP assessment also will be completed subsequently at all four laboratory assessment sessions.

Sleep Apnea Screening and Exclusion Assessments. A previous diagnosis of obstructive sleep apnea (OSA) is an exclusion criterion. The Snoring, Tiredness, Observed apnea, high BP, BMI, Age, Neck circumference and male Gender (STOP-BANG) questionnaire will be used to screen potential study participants for OSA.88 Potential participants scoring >3 on this scale, who otherwise meet all study eligibility criteria, will be required to complete a further screening assessment by the WatchPat device (Itamar Medical, Caesarea, Israel). The WatchPat device is a convenient tool that is worn in the comfort of potential participants' own bedroom and is found to be a sensitive and specific assessment for identifying the presence of OSA. Participants are given the option of using a Duke owned iPhone or their own smart phone that works with the WatchPat device. Potential participants showing an apnea-hypopnea index (AHI) > 15 will be notified that they are no longer eligible to continue, and will be encouraged to seek additional evaluation and treatment through their physician. If someone has completed a polysomnography sleep test in the last 3 months, these results can be used instead of the Watchpat device.

C.3. SLEEP MANIPULATION INTERVENTION

Cognitive Behavior Therapy for Insomnia (CBT-I). CBT-I is a well-established behavioral treatment for insomnia that successfully reduces insomnia symptoms and improves both subjective and objective measures of sleep quality. The approach to CBT-I for the proposed study is based on CBT-I programs that have been practiced and studied by research team members.94,95 CBT-I is manualized in a session-by-session guide. Our proposed study co-investigator, Dr. Christie Ulmer serves as a consultant and trainer on the nationwide dissemination of CBT-I (see biosketch). Dr. Ulmer will train study therapists to deliver CBT-I in accordance with the training approach adopted by the CBT-I dissemination effort. Further, our sleep consultant, Dr. Jack Edinger, will assist in the interventionist training and will oversee the fidelity measures and methods. CBT-I treatment will be delivered by Dr. Ulmer and one additional study therapist over 6 one-hour individual sessions.

Intervention Training and Fidelity. A second study therapist will be trained by Dr. Ulmer, according to consensus guidelines. Initial didactic training (covering session-by-session procedures, core components of CBT-I) will last three days and be followed by training cases. The therapists will be allowed to provide the intervention once they have demonstrated 100% competence and adherence with all required treatment elements. The therapist will meet weekly for supervision throughout the trial. All therapy sessions will be recorded. A random selection of twenty percent will be rated for fidelity. In order to protect against drift, the frequency of fidelity checks will occur equally across the beginning, middle, and end of the intervention period. Dr. Edinger will rate therapist treatment fidelity/adherence for recorded sessions using the adapted version of the Yale Adherence and Competence Scale. Recordings will be rated on the presence/absence of CBT-I elements. In addition, recordings will be rated on the

presence/absence of nonspecific treatment elements (e.g., therapeutic alliance, patient expectancies). Feedback from fidelity checks will be provided by Drs. Edinger and Ulmer.

CBT-I Intervention Protocol Summary. The CBT-I intervention will be delivered individually and in person by one of the therapists, over six one-hour weekly sessions. In circumstances where in-person visits prevent participation, the CBT-I intervention can be delivered via telephone. The CBT-I protocol is summarized below:

Session 1: Sleep Education and Introductions to CBT-I and Sleep Diaries. Participants will receive an overview of CBT-I treatment concepts and approach, in addition to education about sleep regulation processes and the cognitive and behavioral processes involved in the development of insomnia. At the end of the session, they will be instructed in establishing realistic treatment goals and the process for keeping weekly sleep diaries.

Session 2: Introduction to Sleep Restriction Therapy and Stimulus Control. The therapist will introduce Stimulus Control and Sleep Restriction Therapy guidelines and rationale. Sleep Restriction Therapy (SRT) is designed to strengthen the homeostatic sleep drive by restricting time in bed to actual sleep time as determined by sleep diary. The sleep "prescription", or allowable sleep window, is gradually increased over the course of treatment to extend sleep duration. Stimulus Control is a set of instructions designed to strengthen the association between the bed/bedroom and sleep, and to establish a consistent sleep–wake schedule. Participants will receive education and intervention based on treatment targets identified in Session 1 in addition to the sleep pattern information gleaned from the sleep diary review. Sleep hygiene education will be provided for topics that are relevant to the participant (e.g., the effects of alcohol on sleep). An initial "sleep prescription" will be established and participants will be asked to follow this sleep schedule during the upcoming week. Cognitive therapy will be used, as needed, to address dysfunctional beliefs about sleep and to enhance adherence.

Session 3: Introduction to Relaxation Therapy. Participants will be introduced to Relaxation Therapy. The therapist will review the sleep diary with the participant and modify the sleep prescription, as needed, in accordance with SRT99 principles. Participants will be reinforced for adherence and progress. Barriers to adherence will be discussed and addressed using education, motivational enhancement, and cognitive therapy. Participants will be asked to practice relaxation strategies, follow their sleep prescription, and continue to track their sleep on diary during the upcoming week.

Sessions 4 and 5: Sleep Prescription Titration. The therapist will review the sleep diary with the participant and modify the sleep prescription, as needed, in accordance with SRT principles. Barriers to adherence will be discussed and addressed using education, motivational enhancement, and cognitive therapy. Participants will be asked to continue using relaxation strategies, follow their sleep prescription, and track their sleep on diary during the upcoming week.

Session 6: Relapse Prevention. The therapist will review the sleep diary with the participant and provide instruction on adjusting their sleep schedule after treatment, as needed. Treatment gains will be reviewed, and the therapist and participant will jointly develop a plan for ensuring that treatment gains are maintained.

C.4. ASSESSMENTS OF INSOMNIA AND SLEEP

The following laboratory-based and ambulatory assessments will be completed at baseline and repeated following the 6-week run-in control period, following the 6-week CBT-I intervention, and at 6-month follow up.

Insomnia and Sleep Assessments. Sleep will be assessed by both subjective and objective measures. Subjective measures will include sleep diaries, self-report measures of sleep quality, insomnia severity, and perceived daytime sleepiness. However, the primary measures of sleep quality and their anticipated changes following CBT-I will be actigraphy-based objective measures.

Interview-Based Assessment of Sleep. The Duke Structured Interview for Sleep Disorders (DSISD) follows DSM-V and the International Classification of Sleep Disorders criteria, and will be administered to identify those with insomnia disorder at screening. The DSISD was developed by the proposed study consultant, Dr. Edinger, and has been shown to have good reliability and validity.

Actigraphy Sleep Assessments. Sleep and daily physical activity will be recorded using an accelerometer (Actigraph GT9X Link, Actigraph, Pensacola, Florida), unobtrusively worn on the wrist of the non-dominant arm. The Actigraph GT9X monitor is a small, lightweight device that utilizes a 3-axis MEMS accelerometer, with motion sampled at a frequency of 30-100 Hz, and has been utilized and validated in both healthy and patient populations.102,103 Participants will wear the Actigraph 24 hours/day for 7 consecutive days, at baseline, upon completion of the 6-week run-in period, upon completion of the CBT-I intervention, and at 6-month followup. The actigraphy data will be processed using ActiLife and ActiLife+Sleep software (Actigraph, Pensacola, Florida), which was developed in collaboration with the US and international sleep and activity research community; scoring of actigraphy data will proceed in accordance with the guidelines of the Society of Behavioral Sleep Medicine. Recorded sleep log times, confirmed by an event marker, will be used to establish “lights out” and “out of bed” times. ActiLife+Sleep software will be used to derive our primary outcome measure of sleep quality, sleep efficiency (SE). Other sleep parameters of interest will be Time in Bed (TIB), total sleep time (TST), wake after sleep onset (WASO), and sleep fragmentation index (SFI). Sleep duration will be defined as TST (calculated by subtracting all periods of wakefulness from the time spent in bed). WASO is calculated by summing wakefulness periods after initial sleep onset and before final awakening. Sleep efficiency is defined as the ratio of total sleep time divided by TIB ((TST/TIB)*100). Sleep fragmentation is defined as the sum of percent mobile and percent immobile bouts less than 1-minute duration to the number of immobile bouts for a given interval. Actigraphy also provides reliable measurements of daily life physical activity and has been extensively validated against self-report, observational measures, and oxygen consumption estimates of physical activity. Therefore, the ActiLife software will also be utilized to derive daily cumulative step count and daily energy expenditure (kcal/d). All physical activity and sleep parameters derived using actigraphy will be based on the 8-consecutive-days monitoring protocol and represented as average daily activity/sleep values at each assessment phase (baseline, upon completion of the 6-week run-in period, upon completion of the CBT-I intervention, and at 6-month follow-up).

Subjective Assessments of Sleep. Subjective insomnia severity will be evaluated utilizing the Insomnia Severity Index (ISI). The ISI provides a global measure of perceived insomnia severity. Total scores range from 0-28, with higher scores indicating higher severity. The ISI has excellent internal consistency (Cronbach alpha = 0.74) and temporal stability (r = 0.80). The ISI has been validated with sleep diaries and polysomnography (PSG). In clinical samples, a cut-off score of 11 was shown to have the greatest sensitivity and specificity for correctly identifying study participants meeting criteria for insomnia diagnosis. We also propose to use the Pittsburgh Sleep Quality Index (PSQI), a 19-item measure of sleep quality and disturbances over the past month, which has been shown to have internal consistency and validity. These subjective measures also will be used to document the extent to which the CBT-I intervention was effective at improving sleep quality in study participants, and are expected to show a strong association with changes in the objective actigraphy-based measures. Morningness Evenningness Questionniare will assess circadian rhythms.

Daily Sleep Diaries. Subjective sleep estimates will be obtained concurrent with actigraphy. Participants will record their sleep using the recently developed consensus sleep diary to assure comparability across insomnia research studies. The sleep diary is considered the gold standard of self-reported sleep.

C.5. ASSESSMENT OF MECHANISMS OF CARDIOVASCULAR RISK

The following laboratory-based and ambulatory assessments will be completed at baseline and repeated following the 6-week run-in control period, following the 6-week CBT-I intervention, and at 6-month follow up. Assessors will be blinded to the study phase at which data are collected.

Office BP Assessment. Automated office BP (AOBP) will be obtained using the Omron HEM-907

Professional Intellisense BP Monitor. The office BP assessment protocol is described under “Office BP Screening Assessment” described earlier in this application.

24-hour Ambulatory Blood Pressure (ABP) Monitoring. We will use the Oscar 2 ABP monitor (Suntech Medical Inc., Raleigh, NC), which has been validated previously according to US and International standards. Study participants will be instrumented with the ABP monitor between 6:00-10:00 am on a typical weekday (Mon-Fri), and the monitor will be programmed to take BP measurements every 20 minutes throughout the waking hours and every 30 minutes during the nighttime sleep period. We have used this procedure with excellent participant acceptability and compliance in numerous previous studies. A successful 24-hour study will require at least 80% of the total readings to be valid, with no more than two consecutive hours lacking a valid reading, and at least one valid measurement per hour during the nighttime sleep period.119 Unsuccessful ABP studies will be repeated. Because a single 24-hour ABPM record has been shown to be of greater prognostic value than multiple clinic BP readings, it has become an accepted gold standard for evaluating intervention effects on BP. In addition to mean 24-hour ABP, mean waking and mean nighttime BP will be computed, with the nighttime sleep period defined by selfreported sleep logs, in accordance with the Society for Behavioral Sleep Medicine (SBSM) guidelines. Nighttime BP dipping will be defined as the percentage of the decline in nighttime SBP ((mean daytime SBP - mean nighttime SBP/mean daytime SBP) × 100); SBP dipping defined in this way is a continuous variable that will be a primary outcome measure of sleep-related CVD risk mechanisms in

the proposed study. In addition, for descriptive purposes, a SBP dip ≥ 10% will be classified as normal "dipper", while <10% will be classified as "non-dipper", with secondary analyses evaluating intervention effects on dipping status. As noted earlier in this application, the causes and consequences of blunted nighttime BP dipping has been a focus of our prior research. Importantly, our recent work shows that ABPM does not disturb sleep, and a single successful 24-hour ABP study provides adequate representation of the diurnal ABP profile in patients with hypertension.17,51 24-hour ABP assessments will be obtained.

Echocardiogram

Patients with insomnia are at increased risk of heart failure and of cardiovascular events. A focused echocardiogram (2-D images of the heart in the parasternal long axis and apical 4-chmaber views, pulsed wave Doppler of mitral inflow, and tissue Doppler imaging of the mitral annulus) will be performed to examine echocardiographic predictors of cardiovascular morbidity and mortality. Left ventricular mass, left ventricular global longitudinal strain (an index of systolic function), and measures of diastolic function of the left ventricle will be examined to determine if these parameters are modified by improved sleep quality. This will be performed pre-CBTI and at the 6 month follow-up. Dr. Hinderliter will read all the echocardiograms and will be sent these images using DukeBox. The images will only include the date, therefore a transfer of a limited dataset of PHI has been established.

24-hour Urinary Catecholamines and Electrolytes. Patients will be asked to collect urine over a 24-hour period. Urine samples will be kept cold by storage in a portable cooler throughout each 24-hour sample period. Urine will be collected in two containers provided to each participant in a portable cooler, with careful instructions to collect daytime/awake urine in containers labeled accordingly, including the last collection before bedtime; any nighttime/sleep period urine collection will be collected in the container labelled "nighttime", and participants will be instructed to void using that collection container as soon as they get up in the morning. Samples will be assayed for norepinephrine, epinephrine, and creatinine. Catecholamine levels will be expressed as urine concentration (g/ml) per urine concentration of creatinine (mg/ml), yielding norepinephrine and epinephrine values of g per mg creatinine for each sample. This provides catecholamine excretion indices that are corrected for individual differences in body size and urine volume. We will also assay for sodium and potassium as dietary habit changes may be contributory mechanisms of BP change, worthy of exploration. In prior studies of circadian changes in sympathetic activity, urinary catecholamine data have proven informative, with low subject burden and excellent compliance. The 24-hour urine collection will be done twice, before and after CBT-I.

Vascular Endothelial Function - Flow Mediated Dilation (FMD). Our approach for assessing endothelial function conforms to the recently published guidelines for assessment of flow-mediated arterial vasodilatation.

Longitudinal B-mode ultrasound images of the brachial artery, 4-6 cm proximal to the antecubital crease, will be obtained at end-diastole (ECG R-wave gated digital image capture) using a dedicated Acuson Sequoia ultrasound platform. All images will be acquired with participants supine, utilizing an 11 MHz linear array probe with stereotactic holder in our temperature-controlled clinical research

laboratory, by Michael Ellis, RDMS, RVT, who has over 20 years of experience performing the standardized image acquisition protocols for our ultrasound FMD assessments. In an unpublished evaluation of 20 healthy men and women who underwent our FMD assessment protocol on two consecutive days, repeat FMD values showed a correlation of r=0.81, p<.001, and a mean absolute difference of 0.64%. Images will be obtained and stored digitally at resting baseline, as well as during and following inflation to 220 mm Hg of an occlusion cuff placed around the forearm, 2 cm below the elbow. All arterial diameter measurements will be performed by the same experienced member of the research team, blinded to participant identity and the study phase at which the assessment was made, using edge detection software (Brachial Analyzer, MIA-LLC, Coralville, IA). FMD response will be assessed from 10-120 seconds post-deflation of the forearm cuff, with peak arterial diameter quantified using polynomial curve fitting, and FMD thereby defined as the maximum percent change in arterial diameter relative to pre-inflation resting baseline. As others have reported, using this rigorous standardization of FMD methodology, our FMD assessments will be obtained with optimal reproducibility, reflected in a coefficient of variation of approximately 10% or less. Peak hyperemic flow and shear stress will be derived by standard formulae based upon Doppler velocity measurements during the first 10 seconds following deflation of the occlusion cuff.

Arterial Stiffness. Aortic pulse wave velocity (PWV), measured using the Complior system (Artech Medical, Pantin, France), will be our validated index of central arterial stiffness. Pulse pressure waveforms will be recorded from the right carotid and right femoral arteries, and PWV through the descending aorta, measured in meter/sec, is calculated from measurements of pulse transit time and the distance travelled by the pulse, derived from the distance between the two recording sites. The PWV assessment will be performed by Michael Ellis, RDMS, RVT, who has over 10 years of experience with this procedure. This will be performed pre-CBTI and at the 6 month follow-up.

Blood Assays. Blood will be drawn and processed by our research phlebotomist between 8:00 am and 10:00 am, after 12 hours of overnight fasting, on each of the four laboratory assessment visits, in order to measure: total cholesterol, HDL- and LDL-cholesterol, VLDL-cholesterol, and triglycerides; inflammatory activity measured by high sensitivity C-Reactive Protein (hsCRP); At baseline assessment only, thyroid stimulating hormone (TSH) will be assayed to ascertain if hypertension is due to hyper- or hypothyroidism.

Atherosclerotic Cardiovascular Disease (ASCVD) Risk. Although we are interested primarily in whether improved sleep quality will lower the mechanisms of insomnia-related CVD risk, we will also explore computed ASCVD risk (for participants aged ≥ 40 years) from the Pooled Cohort Equations recently validated and recommended by the clinical practice guideline expert panel of the American College of Cardiology/American Heart Association. These equations estimate the 10-year risk of a primary ASCVD event (including myocardial infarction and stroke) among patients without pre-existing CVD. Patients are considered to be at "elevated" risk if the Pooled Cohort Equations predicted risk is ≥ 7.5%. For example, a 50-year old white male smoker with a systolic BP of 130 mm Hg, no diabetes, and total cholesterol of 200 mg/dL with HDL cholesterol 30 mg/dL would have a 10-year ASCVD risk of 13.2%. Lowering systolic BP to 120 mm Hg and raising HDL to 50 mg/dL, with total cholesterol remaining at 200 mg/dL, would almost half his risk, reducing it to 6.9%. Indeed, we also have recently shown that both pharmacological and behavioral interventions to treat depression can lower the calculated 10-year risk of an ASCVD

event. Because several large population studies have shown that insomnia and short sleep duration are linked to hyperlipidemia,136 the CBT-I intervention holds promise for both lowering BP and improving lipid profiles, thereby reducing 10-year ASCVD risk.

C.6. QUALITY OF LIFE (QOL) ASSESSMENTS

CBT-I has been shown to result in marked improvements in QoL in medical patient populations where insomnia is commonly comorbid. In the present proposal, we will explore QoL changes that may accompany improved sleep quality following the CBT-I intervention. We will also explore QoL and psychosocial distress as potential moderators of the changes in CVD risk mechanisms accompanying sleep quality changes. A demographic information will be complete once and will be used to assess ethnicity, smoking, and alcohol use and menopausal status where applicable. The following assessments will be made at baseline, post-6-week run-in, post-CBT-I intervention, and at 6-month follow-up.

Health-Related Quality of Life will be measured using the Short Form-36 Health Survey (SF-36), which provides a physical health and mental health QoL summary score.

Depressive Symptoms. The Beck Depression Inventory II (BDI-II)139-141 will be used to assess depressive symptoms. It is a widely used self-report measure of depressive symptoms, consisting of 21 items, each corresponding to a specific category of symptoms and attitudes. The inventory has been studied extensively since it was first developed in 1961. It has been shown to be both a reliable and valid measure of the severity of depressive symptoms. In cardiac populations, depressive symptoms assessed using the BDI and the revised BDI-II, as well as changes in BDI over time, have been related to clinical outcomes. It should be emphasized that the BDI-II is not a diagnostic instrument, but rather a method for determining the presence and severity of depressive symptoms.

Anxiety Symptoms. Anxiety will be measured using the state and trait anxiety versions of the State-Trait Anxiety Inventory (STAI). The STAI consists of two separate 20-item self-report inventories, one measuring state anxiety and the other trait anxiety. The STAI has been shown to be associated prospectively with increased CVD risk and all-cause mortality.

Perceived Stress will be measured by the Perceived Stress Scale (PSS). The PSS152 consists of 10 items that are evaluated on a 5-point Likert scale.

Daytime Sleepiness will be assessed by the Epworth Sleepiness Scale (ESS), an 8-item measure of perceived daytime sleepiness.

Socioeconomic Status (SES). SES will be measured by interview assessment of annual household income, occupation, and years of education. In addition, subjective SES will be assessed with the MacArthur Scale of Subjective Social Status.

Selection of Subjects

Inclusion Criteria. Systolic BP ≥ 130 mm Hg based upon two standardized BP screening assessments a current diagnosis of insomnia disorder as defined in the International Classification of Sleep Disorders (ICSD-3);84 or undiagnosed, but suspected, insomnia disorder that is confirmed at their screening lab visit; an age range of 30-60 years.

Exclusion Criteria. Uncontrolled hypertension (screening office BP > 160/100 mm Hg); antihypertensive medication use; cardiovascular medications; previously diagnosed moderate or severe obstructive sleep apnea; severe obesity defined by BMI>40 kg/m2; pacemakers; atrial fibrillation; acute coronary syndrome or coronary revascularization procedure within 6 months of enrollment; congestive heart failure; identifiable cause of hypertension (e.g., primary hyperaldosteronism, renal artery stenosis, untreated hyper- or hypothyroidism, chronic kidney disease, Cushing's disease, pheochromocytoma, coarctation of the aorta); severe uncorrected valvular heart disease; current pregnancy; active diagnosis of psychosis, bipolar disorder, current treatment of PTSD with exposure based therapy; severely impaired hearing or speech; participation in another interventional study to address insomnia; rotating shift workers; diabetes; prominent suicidal or homicidal ideation (as assessed through a clinical interview); psychiatric hospitalization within the past 12 months; unstable comorbid sleep disorder requiring assessment and/or treatment outside of the study protocol; medical or psychiatric conditions judged to be the primary cause of insomnia; alcohol or drug abuse within 12 months; dementia; inability to comply with the assessment procedures or inability to provide informed consent.

Identification. The study coordinator and research associate will identify patients using the electronic medical records (Maestro). A detailed description is below in Subject Recruitment. If a participant is interested and their electronic medical record (EMR) is not available, study staff can ask the participant the eligibility criteria that would have been collected in the EMR to collect the medical history necessary to determine eligibility.

Subject Recruitment and Compensation

A total of 150 men and women who meet systolic BP criteria for hypertension (SBP≥130 mm Hg) and have comorbid insomnia will comprise the study sample. Participants will be recruited by various general mechanisms. The primary approach will be through the new Recruitment and Engagement Policy at DUMC. All internal staff have received training and will adhere to the new policy. We will use DEDUCE within the PACE environment and screen potentially eligible patients in Maestro. Once patients are identified, we will submit them to the honest broker to export name, address, email address and phone number so we can send them a letter or email and a brochure introducing the study to them. Potential patients will be called about a week later after they receive to letter or email to determine interest. Per DOCR guidelines, no potential patients will not be contacted more than 3 times. No patient who has opted out of research will be contacted.

Another mechanism will be through the network of primary care clinics, led by co-investigator Dr. Anthony Viera, Chair of the Department of Family and Community Medicine, where we will enlist the

support of primary care physicians in the Duke Health System. Hypertension is one of the most common presentations in the primary care setting, with approximately 103 million American adults meeting the new ACC/AHA diagnostic criteria of 130/80 mm Hg,81 and approximately 40% of primary care patients reporting difficulty sleeping. There are a currently 27 Duke Primary Care Clinics, with a total of 77,016 patients diagnosed with hypertension, 29,951 with an insomnia diagnosis, and 16,980 patients with a diagnosis of both hypertension and insomnia. Patients who meet our BP criteria and who have (or are suspected to have) comorbid insomnia, and have elected not to receive antihypertensive pharmacotherapy, will be informed by their primary care physician (PCP) about our study. If interested, they will be given an information leaflet with our contact information.

Facebook/Instagram Ads – We would like to use Facebook and Instagram to recruit and have added possible text and pictures for these ads in recruitment tools. We would also like a Qualtrics survey for interested participants to enter their contact information. This Qualtrics survey will be delivered via our lab webpage, social media ads/posts, and QR codes on study fliers. Participants will fill in their name, phone number, email address, and best times to contact, and study coordinators will respond to requests. Identifying information for ineligible and uninterested participants will be destroyed.

Maestro Care screening: This study will use tools available in Maestro Care to help identify and recruit potential participants before consent is signed. Only key personnel who are delegated the task of patient identification/ recruitment will have access to information in Maestro Care. Once identified and screened further to ensure they are qualified, letters, phone calls and emails will be used to recruit these participants. Potential patients will be called about a week later after they receive to letter or email to determine interest. Per DOCR guidelines, no potential patients will not be contacted more than 3 times. No patient who has opted out of research will be contacted. Patients may be associated with a pre-consent status of “Declined” or “No Longer a Candidate” in Maestro Care prior to consent, if necessary. The association with the study cannot be removed from Maestro Care.

Maestro Care MyChart messaging: This study will use a MaestroCare MyChart recruitment invitation to help identify potential participants pre-consent. Potential subjects are identified via a report generated within Maestro Care by the DOCR Maestro Care Analyst team. A recruitment invitation will be sent by a DOCR analyst to potential subjects via MyChart. The patient will indicate if they are interested or not interested and the study coordinator will be sent an Inbasket message (Maestro Care internal message) indicating the response. Only key personnel who are delegated the task of patient identification/recruitment will have access to the Inbasket messages. Only patients who express interest will be contacted by key personnel, who will then follow the recruitment process approved by the IRB for this study. If a patient expresses interest and the study team determines the patient is not qualified for the study prior to contacting them, they will be sent an approved email letting them know. If a patient does not open their MyChart message, the Maestro or Epic Analyst can send up to two additional "tickler" notifications, at least a week apart, to let the patient know they have an unread message.

The final recruitment strategy will be advertising in local newspapers, posting flyers at area community centers (e.g., churches), and using hospital TV screens to display approved flyers. As for previous studies, we also will set up a BP and insomnia screening booth at area health fairs and community

events. These methods have proven very successful at recruiting large samples of men and women with the early stages of untreated hypertension in our previous studies.16,83 Initial phone screening will establish whether potential participants are likely to meet the study's eligibility criteria. If appropriate, the first screening session will be scheduled, which will include office blood pressure measurements, medical history, and physical examination. Because the study demands a series of four lab visits, plus screening visits, and a total of four 24-hour ABP monitoring assessments, we are proposing $300 reimbursement per participant, $200 post CBT-I and $100 at follow-up. Partial reimbursement will be available for participants who do not finish the study. Our previous studies of unmedicated patients with hypertension indicate that adequate subject reimbursement is ultimately cost-effective. A further and very significant incentive in the currently proposed study is that all eligible participants will receive a state-of-the-art intervention for their insomnia to improve their sleep quality.

UNC-Chapel Hill was added as a recruitment site and will use these recruitment mechanisms as well. The UNC IRB is relying on the Duke IRB and the IAA is attached.

Study Interventions

SLEEP MANIPULATION INTERVENTION

Cognitive Behavior Therapy for Insomnia (CBT-I). CBT-I is a well-established behavioral treatment for insomnia that successfully reduces insomnia symptoms and improves both subjective and objective measures of sleep quality. The approach to CBT-I for the proposed study is based on CBT-I programs that have been practiced and studied by research team members. CBT-I is manualized in a session-by-session guide. Our proposed study co-investigator, Dr. Christie Ulmer serves as a consultant and trainer on the nationwide dissemination of CBT-I (see biosketch). Dr. Ulmer will train study therapists to deliver CBT-I in accordance with the training approach adopted by the CBT-I dissemination effort. Further, our sleep consultant, Dr. Jack Edinger, will assist in the interventionist training and will oversee the fidelity measures and methods. CBT-I treatment will be delivered by Dr. Ulmer and one additional study therapist over 6 one-hour individual sessions.

Intervention Training and Fidelity. A second study therapist will be trained by Dr. Ulmer, according to consensus guidelines. Initial didactic training (covering session-by-session procedures, core components of CBT-I) will last three days and be followed by training cases. The therapists will be allowed to provide the intervention once they have demonstrated 100% competence and adherence with all required treatment elements. The therapist will meet weekly for supervision throughout the trial. All therapy sessions will be recorded. A random selection of twenty percent will be rated for fidelity. In order to protect against drift, the frequency of fidelity checks will occur equally across the beginning, middle, and end of the intervention period. Dr. Edinger will rate therapist treatment fidelity/adherence for recorded sessions using the adapted version of the Yale Adherence and Competence Scale.98 Recordngs will be rated on the presence/absence of CBT-I elements. In addition, recordings will be rated on the presence/absence of nonspecific treatment elements (e.g., therapeutic alliance, patient expectancies). Feedback from fidelity checks will be provided by Drs. Edinger and Ulmer.

CBT-I Intervention Protocol Summary. The CBT-I intervention will be delivered individually and in person by one of the therapists, over six one-hour weekly sessions, as summarized by the CBT-I protocol below: Session 1: Sleep Education and Introductions to CBT-I and Sleep Diaries. Participants will receive an overview of CBT-I treatment concepts and approach, in addition to education about sleep regulation processes and the cognitive and behavioral processes involved in the development of insomnia. At the end of the session, they will be instructed in establishing realistic treatment goals and the process for keeping weekly sleep diaries.

Session 2: Introduction to Sleep Restriction Therapy and Stimulus Control. The therapist will introduce Stimulus Control and Sleep Restriction Therapy guidelines and rationale. Sleep Restriction Therapy (SRT) is designed to strengthen the homeostatic sleep drive by restricting time in bed to actual sleep time as determined by sleep diary. The sleep "prescription", or allowable sleep window, is gradually increased over the course of treatment to extend sleep duration. Stimulus Control is a set of instructions designed to strengthen the association between the bed/bedroom and sleep, and to establish a consistent sleep–wake schedule. Participants will receive education and intervention based on treatment targets identified in Session 1 in addition to the sleep pattern information gleaned from the sleep diary review. Sleep hygiene education will be provided for topics that are relevant to the participant (e.g., the effects of alcohol on sleep). An initial "sleep prescription" will be established and participants will be asked to follow this sleep schedule during the upcoming week. Cognitive therapy will be used, as needed, to address dysfunctional beliefs about sleep and to enhance adherence.

Session 3: Introduction to Relaxation Therapy. Participants will be introduced to Relaxation Therapy. The therapist will review the sleep diary with the participant and modify the sleep prescription, as needed, in accordance with SRT principles. Participants will be reinforced for adherence and progress. Barriers to adherence will be discussed and addressed using education, motivational enhancement, and cognitive therapy. Participants will be asked to practice relaxation strategies, follow their sleep prescription, and continue to track their sleep on diary during the upcoming week.

Sessions 4 and 5: Sleep Prescription Titration. The therapist will review the sleep diary with the participant and modify the sleep prescription, as needed, in accordance with SRT principles. Barriers to adherence will be discussed and addressed using education, motivational enhancement, and cognitive therapy. Participants will be asked to continue using relaxation strategies, follow their sleep prescription, and track their sleep on diary during the upcoming week.

Session 6: Relapse Prevention. The therapist will review the sleep diary with the participant and provide instruction on adjusting their sleep schedule after treatment, as needed. Treatment gains will be reviewed, and the therapist and participant will jointly develop a plan for ensuring that treatment gains are maintained.

Risk/Benefit Assessment

The primary risks of this study are minimal and are primarily associated with confidentiality. There is some risk attendant to confidentiality of self-report data. In order to ensure confidentiality of data, all

records will be identified by the patient's identification number, not by name. All raw data will be kept in a locked file cabinet. Although several previous psychosocial interventions may be associated with increased risk, we believe that it is unlikely that this treatment will be harmful to patients. Nevertheless, we will carefully monitor symptoms and refer those patients with high levels of depression or distress for treatment. We also will include a Study Advisory Committee (SAC) to monitor study progress and adverse events.

With the blood draw, there is a risk of bruising at the site of the draw and rarely, fainting and/or infection. The Oscar 2 ABPM has built in safeguards to avoid over-inflation or prolonged inflation of the cuff, as well as a measurement abort key that can be activated by the participant. The participant could experience mild disomfort as the cuff inflates and rarely, mild skin irrataion and bruising. The FMD assessment will include blood pressure cuff inflation for 5 minutes, which has the risk of causing tingling and discomfort in the arm. The sublingual glyceryl trinitrate used during the FMD procedure can cause a headache or a sensation of flushing. Because of this, participants with a history of migraines will be allowed to do the FMD procedure without taking nitroglycerin. There are no known risks associated with use of the actigraphy.

The risk of serious injury due to study participation is negligible. All measurement techniques have been used extensively by the investigative team without a single adverse event. Procedures for protecting subjects against potential risks include screening procedures. Patients will be referred to their local physicians when needed. We also will take special precautions to ensure the safety of patients with clinically significant depression, i.e., patients with BDI-II scores >29 (moderate-severe depression) or who are actively suicidal. Although we are not pre-selecting patients with hypertension and comorbid insomnia based upon their level of distress or depressive symptoms, our assessments may determine the presence of significant clinical depression. In the unlikely event that patients are determined to be actively suicidal, they will be queried for suicidal plans, intent and past suicidal behaviors. Those with current active suicidal ideation, history of suicidal acts within the past 12 months, or bipolar disorder or psychosis will not be enrolled in the study and appropriate referral or admission procedures will be initiated. If a patient exhibits moderate-severe depression (e.g., BDI-II >29) at baseline, we will inform the participant and, with his or her permission, notify their primary care physician. Any participant who is determined to be actively suicidal over the course of the study will be referred for psychiatric evaluation and possible hospital admission. If they are found to be at immediate risk, emergency procedures will be followed including requesting an ambulance to take the patient to the emergency department (ED) for immediate evaluation and treatment. Patients who score >29 on the BDI-II and are not actively suicidal will be informed about the results of our assessment, and with their consent, we will inform their physicians for further evaluation and possible treatment. In this manner, we believe that risk will be minimized. Any enrolled patient who becomes actively suicidal (i.e., who scores >1 on item 9 of BDI-II) will be immediately evaluated by our study psychologist for suicidal plans and intent. If a patient is considered acutely suicidal, he or she will be dropped from further participation and will be referred for either urgent evaluation by a psychiatrist or prompt ED evaluation. Our medical director or PI will contact the patient within 24 hours after the referral to ensure that the patient has followed through with the referral. We also have referral sources in place to provide psychiatric treatment if necessary. This protocol has been used successfully in our previous work, including studies of patients with major depression.

If a patient scores >29 on the BDI-II at the time of the post-treatment assessment, he or she will be informed of the results and, with the patient's permission, we will notify their primary care physician so that further evaluation, referral or treatment can be initiated as appropriate.

Adequacy of Protection Against Risks

a. Informed Consent and Assent

Consecutive patients in Duke University Medical Center Primary Care Clinics, who meet the study eligibility criteria will be offered the opportunity to participate in the study. The recruitment process will involve an initial screening by the research study staff under an IRB-approved waiver of HIPAA Authorization (by conforming with the Duke IRB's federally mandated conditions for granting such a waiver - http://irb.duhs.duke.edu/). If a patient appears to qualify, a letter will be mailed to them introducing the study. For patients interested in participating in the study, full details of the procedures involved, risks and benefits will be provided in written and oral form. Enrollment in the study will require potential participants to read and sign a written informed consent form, approved by the Duke Medical Center IRB. It will be made clear to subjects that they may withdraw at any time without penalty, and that they may contact the IRB chairman (at a phone number provided) if for any reason they believe that their privacy or health have been compromised.

b. Protections Against Risk

As noted earlier, the primary risks for participants are those associated with confidentiality. To ensure that confidentiality is maintained, we will store our non-electronic patient records in locked cabinets within a locked area, with access limited to study staff. Electronic records will be maintained in a secure network setting, with access available only to selected study personnel. In addition to network security, individual workstations for data entry and analysis will be accessible only by password. Also as noted earlier, all electronic records will be identified only by a study identification number.

All project staff will have fulfilled Duke University mandatory HIPAA training requirements. All aspects of the study protocol will meet HIPAA requirements specified by the Human Studies Committee and the Privacy Office at Duke University.

The protocol will be approved by the Duke University Medical Center IRB before it is implemented. All investigators have completed the required education and certification in the protection of human research subjects.

In the unlikely event of an adverse medical event during assessment or any other on-site phase of study participation, the patient's attending physician and/or the emergency services at DUMC will be contacted immediately. In addition, the principal investigators and medical director of the study will be notified of all such events.

Potential Benefits: This study has several potential benefits. First, patients receiving CBT-I are likely to benefit from marked reductions in their insomnia symptoms and improvement in their sleep quality;

these benefits have been documented to persist for many years after completion of the 6-week CBT-I intervention. Study participants will also receive state-of-the-art evaluation of their blood pressure observed over 24-hours on four occasions, thereby providing themselves and their primary care physicians the most appropriate and valuable information on which hypertension management can be based. Our comprehensive assessments of CVD risk mechanisms will also be made available to participants' physicians upon completion of the study, again helping optimize their medical management.

Potential Benefits of the Proposed Research to Research Participants and Others
While most participants should benefit from improved sleep and/or reduced insomnia complaints, as well as a comprehensive evaluation of their blood pressure and possible lowering thereof, there are no guaranteed benefits to the individual participant and no immediate benefits of the proposed research to others.

Information gathered from participants may help us to establish a link between sleep impairment and how insomnia has adverse effects on CVD risk. In our opinion, the anticipated benefits of this study outweigh the potential risks.

ANALYSIS PLAN

Data will be entered into a secure Microsoft Access database. Entry to the database is limited to key personnel and is password protected at the point of the workstation and the application. Standard double-entry and data checking approaches will be performed for all measures.

General Analytic Approach: Descriptive statistics will be performed on all study variables. In order to mitigate potential bias due to transient improvements in either sleep or BP dipping, we will utilize a 6-wk run-in phase after which participants will have their sleep efficiency and BP dipping markers re-assessed to ensure stability. Although we do not anticipate significant variation in either sleep or BP parameters during this pre-treatment phase, we will exclude participants who no longer meet inclusion criteria following the 6-wk run-in period. This practice has been shown to result in an increased magnitude of treatment improvements and therefore may improve the statistical power and potential precision of the proposed analyses.155-158 Markers of sleep efficiency and BP dipping collected after our run-in phase will therefore be used as our baseline assessment measures.

Regression-based analytic approaches will be used to examine associations between improved sleep efficiency, ABP indices, and mechanisms of CVD risk. In order to minimize potential confounding of treatment improvements due to either misdiagnosis or transient fluctuations in sleep, we will use assessments collected after the run-in period as our baseline time point. For our 6-week outcomes, improvements in sleep efficiency and ABP will be examined using simple regression analyses as detailed below. In contrast, our 6-month outcomes will be examined using repeated measures mixed models with an unstructured covariance matrix, using both 6-week and 6-month levels of the outcome modeled jointly. Incorporating both outcomes into a unified, mixed modeling approach will allow us to examine improvements in sleep as they associate with trajectories of BP dipping improvements and also allows for more robust handling of missing data.

For our primary aim examining improvements in sleep efficiency and ABP, we will focus on nighttime BP dipping as the outcome of interest with a prespecified significance level of P = .05. Because other ABP outcomes could plausibly be improved with CBT-I and will partially reflect improvements in nighttime dipping, we will conduct parallel analyses of nighttime average BP and 24-hour BP levels. Consistent with contemporary recommendations examining secondary outcome measures as supportive and/or explanatory, we will maintain a P = .05 for all for secondary outcome measures. Patterns of missing data will be characterized using Rubin'scriteria and managed accordingly using Harrell's multiple imputation (mult.impute) procedure in R. We will carefully examine all model assumptions and reparameterize as indicated. All analyses will be carried out using SAS (Cary, NC) or R (http://cran.r-project.org/) software.

AIM 1: Determine whether the circadian BP profile contributes CVD risk associated with poor sleep by evaluating whether it is modified by changes in sleep quality in men and women with hypertension and comorbid insomnia

Hypothesis 1: Improved sleep quality will be accompanied by: (i) enhanced nighttime BP dipping; (ii) lower average nighttime BP; (iii) lower average 24-hour BP.

Analysis Plan: General linear models will be used to examine the associations between improvements in sleep quality on improvements in BP dipping, controlling for age, gender, race, baseline sleep efficiency, baseline mean 24-hour BP, and pretreatment BP dipping, with post-treatment BP dipping as the criterion. Significance will a priori be set at P = .05. For follow-up analyses of 6-mo BP dipping, linear repeated measures mixed models will be examined in which 6-wk and 6-mo BP dipping both serve as outcome variables using the same covariates above. As an a priori explanatory analysis for our follow-up analyses, we will examine potential time X sleep efficiency interactions in order to examine the extent to which the association between sleep efficiency and BP dipping at six weeks differs from that at six-months. In addition, we will conduct an area under the curve analysis to examine overall associations that apply to both 6-wk and 6-mo in order to determine whether larger improvements in sleep are associated with larger improvements in BP outcomes in an overall sense.165-167 Because other ABP outcomes could plausibly be improved by CBT-I and also will reflect improved nighttime dipping, we will conduct parallel analyses of nighttime average BP and 24-hour BP levels.

AIM 2: Evaluate candidate mechanisms of CVD risk related to sleep quality in patients with hypertension and comorbid insomnia

Hypothesis 2: Improved sleep quality will be accompanied by: (i) reduced nighttime SNS activity; (ii) enhanced vascular endothelial function; (iii) reduced arterial stiffness, and; (iv) improved lipid profile.
Analysis Plan: General linear models will be used to examine the associations between improved sleep efficiency and improvements in mechanisms of CVD risk, controlling for age, gender, race, baseline sleep efficiency, and the pre-treatment (post run-in) level of the outcome. For our analyses of vascular endothelial function only, we also will adjust for baseline arterial diameter, consistent with our prior work. Follow-up analyses will follow the same approach as in Hypothesis 1, using linear repeated measures mixed models with 6-wk and 6-mo levels serving as the outcome variables.

Exploration of Mechanistic Relationships: For additional explanatory purposes in relation to our mechanistic conceptual model (Figure 1), we propose to conduct mediation analyses using the more commonly known Baron and Kenny approach as well as the newer MacArthur approach.170 By the MacArthur definition, the potential mediator must be during or post-treatment; therefore, changes in mechanisms of CVD risk occurring between baseline and 6-wk will be considered as potential mediators. The outcome then will be participants' post-treatment change in BP dipping, which will be assessed at 6-month follow-up. We will first fit a model to examine the relationship between changes in sleep efficiency and the mediator (C) (i.e., changes in mechanisms of CVD risk), as noted for Hypothesis 2. We will then fit a model examining the relationship between the mediator and post-treatment change in BP dipping. Finally, we will test for mediation using an extension of the Sobel first-order test, which examines the extent to which the associations between improved sleep efficiency and BP dipping are attributable to improvements in mechanisms of CVD risk. To fully understand these relationships, we will also investigate the MacArthur approach which is less restrictive in its assumptions, where improvements in BP dipping are attributable to improvements in mechanisms of CVD risk if there is evidence of a non-zero association between sleep efficiency and mechanisms of CVD risk, and either 1) mechanisms of CVD risk or 2) their interaction with changes in sleep efficiency also are non-zero.

Power and Sample Size Considerations: Our power estimates were derived from prior data assessing sleep efficiency and nighttime BP dipping among individuals with HTN using the following assumptions: an initial sample size of 150 individuals, attrition of 15%, an alpha of 0.05, and a correlation of r = 0.30 between sleep efficiency and BP dipping. Using these assumptions, we will have 80% power to detect correlations of r>=0.25 between improvements in sleep efficiency and BP outcomes, suggesting that we will have adequate power to test the proposed hypotheses. In a more conservative scenario for comparing the worst 1/3 of the sample in terms of sleep efficiency change to the best 1/3, and assuming 50 participants in each group, there is 0.85 power at the two-sided 0.05 significance level for the detectable effect size theta=0.6 via the following equation: (n per group) = 50 = 2*(((1.96 + 1.04) / 0.6)**2). In the present proposal, this corresponds to a difference of 2.2% in SBP dipping between high and low sleep efficiency groups.

Exploratory Analyses of Effect Modification: In addition to our formal analyses, we will conduct exploratory analyses of effect modification, which will be interpreted as hypothesis generating. Candidate markers for effect modification will include background and clinical characteristics, such as race, gender, baseline insomnia severity, baseline anxiety, and the presence of elevated depressive symptoms (BDI > 14). Specifically, we will examine the interaction terms between these candidate moderators, changes in sleep efficiency and mechanisms of CVD risk using the same general linear modeling approach noted for Hypothesis 2.

D.2. METHODOLOGICAL ISSUES

For this mechanistic study, we considered several alternative designs, including a cross-sectional observational study and a two-group randomized design. A cross-sectional design was rejected because differences in CVD risk factors between patients with poor sleep quality and good sleep quality could be due to other factors besides their sleep. However, because the study objective was mechanistic, with the (favorable) manipulation of sleep quality of primary interest as the independent variable, and

because CBT-I has emerged as the gold standard for treating insomnia, we could not uphold the principle of equipoise in a design that randomized participants to an intervention that would likely be markedly less effective in treating their insomnia (e.g., sleep hygiene, no treatment, wait-list control). Moreover, the study objective is not to ascertain the efficacy of CBT-I, so a randomized design and comparison group is not required. Indeed, with the efficacy of CBT-I at approximately 60%,30 the more ethically defensible design was considered to be that all participants should receive the CBT-I intervention, with a time-equivalent run-in phase serving as a within-participant control phase to help establish that more marked alterations in sleep quality (60%) should be attributed to the CBT-I intervention, with an estimated 40% showing minimal to clinically insignificant changes.

A second aspect of our methodologic considerations was the selection of a primary measurement to serve as a manipulation check for sleep quality changes associated with the CBT-I intervention. We selected sleep efficiency, determined from actigraphy, because it is an objective and continuous measurement of sleep quality that: (i) has been shown to improve markedly following CBT-I; (ii) has been shown to be related to the development of hypertension, and; (iii) from our pilot studies, it is the index of sleep quality that was most clearly related to nighttime BP dipping and vascular endothelial function. Therefore, while sleep efficiency will serve as the primary index of sleep quality changes, we will also explore effects on other actigraphy-based sleep parameters, including total sleep time (TST), wake after sleep onset (WASO), and sleep fragmentation index (SFI). Insomnia aside, the evidence showing that poor sleep quality is a CVD risk factor has been based on large-scale meta-analytic studies of subjective measures of sleep quality and duration; this is because such data are widespread, and studies incorporating objective measures are relatively few. However, the available evidence shows that in smaller scale studies, objective measures of sleep quality show more robust associations with CVD risk. Nonetheless, we have included two important subjective measures of sleep, the ISI110 and the widely used PSQI, which we will use to provide supportive evidence of sleep quality changes and their association with changes in putative mechanisms relating sleep to CVD risk.

With respect to participant inclusion/exclusion criteria, we chose to focus on hypertension with comorbid insomnia because of the putative mechanisms of CVD risk, including blunted nighttime BP dipping, heightened sympathetic activity, arterial stiffness, and endothelial dysfunction being evident in this population, and therefore affording the opportunity for their improvement following CBT-I as a manifestation of sleep-related mechanisms of CVD risk. We also adopted the new ACC/AHA guidelines for defining hypertension at lower BP levels, with our selection of systolic BP≥130 mm Hg as the inclusion criterion. We also excluded antihypertensive medication use, as different classes of medications have different half-lives and may distort the patient's normal circadian BP profile. Many individuals with recently diagnosed hypertension refuse antihypertensive therapy in favor of attempting lifestyle changes first; for those with comorbid insomnia, enrolling in our proposed study will provide them an opportunity to help control their BP, as well as improve their sleep. We also elected to exclude sleep apnea because of its association with hypertension presenting a potential confounding of our observations. Interestingly, a recent review and meta-analysis failed to find conclusive evidence that continuous positive airway pressure (CPAP) reduced the risk of CVD events in sleep apnea patients. However, in addition to compliance with CPAP therapy being difficult to ascertain, sleep apnea is frequently comorbid with insomnia, and when sleep apnea is diagnosed, comorbid insomnia is rarely treated, further complicating our understanding of sleep apnea and its treatment effect on BP.

Data & Safety Monitoring

Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

Safety Monitoring

Although blood pressure will be monitored by research staff during the study, blood pressure management will continue to be up to participants' health care providers (HCPs). Patients who exhibit screening "office" averaged BP greater than 160/100 mm Hg across the two screening sessions will not be eligible to participate in the study and will be provided their screening BPs with the recommendation that they provide this information to their HCP within 72 hours. For participants already enrolled in the study, if "office" averaged BP values exceed 160/100 mm Hg, the participant will be provided those BP readings at that time, and will be encouraged to share the results with their HCP within 72 hours; with patient written consent, we also will provide the BP readings to their HCP. All eligible participants will have completed the CBT-I intervention within approximately 3 months from study enrollment. Both pre- and post-treatment ambulatory blood pressure records and study-assessed "office" blood pressures will be provided to participants at that time (i.e., after ~12 weeks), and with their consent (using a Redcap electronic medical authorization or paper authorization form), also will be provided to their HCP for follow-up as needed. In the event that participants do not have a HCP, a list of local family HCPs who are accepting new patients will be provided to them.

Participants will undergo follow-up assessments 6 months after the CBT-I intervention. Any intervening treatments including antihypertensive medications, will be documented. It should be emphasized that participants will not be prohibited from initiating pharmacologic treatment for high blood pressure at any time during the study. At all assessment phases, participants' medications will be documented. Upon completion of their participation in the study (approximately 9 months after initial screening assessments confirmed their eligibility), for participants who exhibit no improvement in their insomnia symptoms, we will refer them back to their HCP for consideration of alternative approaches to treating their insomnia.

Potential participants suspected by questionnaire and diagnostic sleep interview to have obstructive sleep apnea will also have an overnight sleep apnea screening assessment using the WatchPAT One (Itamar Medical) system. Moderate to severe sleep apnea is an exclusion criterion, as defined by an apnea-hypopnea index (AHI) >15. Potential participants excluded due to an elevated AHI will be provided a letter indicating their AHI and invited to share this information, indicating suspected sleep apnea, with their HCP.

Although we are not selecting, or excluding, hypertensive patients based upon their level of distress or depression, our assessments may determine the presence of severe depression. If patients are acutely

suicidal, they will be evaluated by our licensed study clinical psychologist (Dr. Blumenthal); appropriate referral or admission procedures will be initiated, and they will be dropped from further study. Specifically, should participants become acutely suicidal [if they endorse a response of 2 or 3 on item 9 (suicide item) on the BDI-II at the end of the 6-week run-in or after the 6-week CBT-I treatment program] they will be evaluated by our study psychologist within 24 hours and will be referred for treatment as needed.

Reporting Mechanisms of AEs/SAEs to the IRB, FDA, DSMB and/or NIH:

Any adverse events (AEs) will be reported to the DUMC IRB in accordance with the local Human Research Protection Program's Standards of Practice. These guidelines require immediate reporting of any serious adverse events (SAEs) that are potentially study-related. Any SAEs that are potentially study-related will be reported to the DSMB within 48 hours via Duke's secured email system. Consistent with NHLBI policy (NHLBI Adverse Events and Unanticipated Problems Reporting) , any SAEs and unanticipated problems (UPs) will be reported to NHLBI. All research projects conducted at DUMC are required to have annual IRB review. Reports of non-serious AEs or unanticipated problems that may increase risk for study participants or others are required as part of the annual progress reports. Additionally, any changes to the project between review periods must be approved by the IRB prior to implementation. Because there are no study medications involved in this project, we do not expect any reporting to the Food and Drug Administration (FDA). Additional reports will be made to the NIH in accordance with the institute's standards of practice.

Plans for Interim Analysis of Efficacy Data and Stopping Rules: At present, there are no planned interim analyses of outcome data.

Trial Stopping Rules: We do not anticipate that the proposed study will be stopped for any reason other than completion of study enrollment and procedures.

HIPAA Compliance: All project staff will have fulfilled the Duke University's mandatory HIPAA training requirements. All aspects of the study protocol will meet HIPAA requirements specified by the Human Studies Committee and the Privacy Office at Duke University.

IRB Review and Investigator Certification: The protocol will be approved by the Duke University Medical Center IRB before it is implemented. All investigators have completed the required education and certification in the protection of human research subjects.

ClinicalTrials.gov Requirements: The clinical trial is registered with ClinicalTrials.gov as recommended by NIH.