Official Title: Vascular Impairment in Type II Diabetes Mellitus with Co-Morbid Obstructive Sleep Apnea
ClinicalTrials.gov ID (NCT number): NCT01629862
Protocol Date: 4/28/2017

PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

Jessie Bakker, PhD

PROTOCOL TITLE

Vascular impairment in type II diabetes mellitus with co-morbid obstructive sleep apnea

FUNDING

National Institutes of Health (NIH) R01-HL110350; American Heart Association (AHA) 14SDG20160000.

VERSION DATE

Version 27; 28 April 2017

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Although both diabetes mellitus (DM) and obstructive sleep apnea (OSA) have adverse effects on endothelial function, it is not clear whether these two conditions diverge regarding their action on the vascular smooth muscle cell and various inflammatory pathways. We will investigate the interaction between diabetes mellitus (DM) and obstructive sleep apnea (OSA) on vascular functioning by performing a two-part study.

Aim 1: To compare the vascular physiology of matched controls, patients with DM alone, patients with OSA alone, and patients with DM+OSA. We hypothesize that OSA and DM will demonstrate a synergistic effect on cardiovascular risk, demonstrated by patients with DM+OSA displaying impaired vascular reactivity compared with patients with DM or OSA alone.

Aim 2: In a 3-month, double blinded randomized controlled trial, to compare the vascular physiology of patients with both DM and OSA, receiving either active continuous positive airway pressure (CPAP) or sham-CPAP. We hypothesize that patients treated with active CPAP will show significant improvements in vascular reactivity compared with those assigned sham-CPAP.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

The obesity pandemic has led to the increased prevalence of major complications including DM and OSA. Various studies have shown important improvements in the vascular complications of DM, however refinements in glycemic control have not always led to improvements in the macrovascular complications of DM. Thus, some have suggested that alternative therapeutic pathways need to be targeted to lower vascular complication rates further.

One such potential target is OSA. OSA is highly prevalent (up to 86%) in obese people with DM, and yet only a fraction of these patients are currently being diagnosed, and even fewer are currently receiving therapy for OSA. OSA has been established as a significant cardiovascular risk factor independent from co-morbidities including DM. However, there is a possibility that there may be interactions between DM and OSA, such that vascular risk may be increased by both conditions, or that the overall risk may be limited by ceiling effects of the two diseases.

Previous research conducted by the PI and co-investigators has established that OSA subjects have impaired macrovascular functioning compared to both lean and obese controls, but similar to lean and obese patients with DM. In contrast, microvascular functioning in the OSA subjects was shown to be similar to the lean and obese controls and higher than the lean and obese DM patients. Various inflammatory cytokines were also shown to be expressed to a greater degree in OSA patients compared with both controls and DM patients. Hence, although both OSA and DM affect endothelial function, the conditions may diverge regarding their action on the vascular smooth muscle cell and inflammatory pathways.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

As mentioned under 'Specific Aims' above, the study consists of a cross-sectional study followed by a 3-month, double-blinded randomized controlled trial. All subjects will be enrolled by Partners researchers; there are therefore no local site restrictions.

For Aim 1 (cross-sectional study), we plan to enroll four groups of 40 subjects each: healthy controls, patients with OSA alone, patients with DM alone, and patients with DM+OSA. All four groups will be matched for age, gender, and body mass index (BMI), as well as duration of DM where appropriate.

For Aim 2 (randomized controlled trial), we plan to enroll 55 patients with DM+OSA. Data for all of these patients will be included in Aim 1, with additional data to be collected for Aim 2.

Inclusion Criteria

All patients: ≤70 years of age, weight ≤450 pounds (the maximum supported by the cardiac magnetic resonance (CMR) imaging table).
OSA patients: Respiratory disturbance index (RDI) ≥10 and <100 events/hour determined during two consecutive home sleep studies; no evidence of non-OSA sleep disorders, Epworth Sleepiness Scale (ESS) score ≤18 (/24) indicating normal/moderate daytime sleepiness levels, no history of motor vehicle accident/s or near-miss accident/s related to sleepiness within the previous two years; not a commercial driver; naïve to CPAP treatment; not currently receiving treatment of any kind for OSA.

DM patients: A clinical diagnosis of type 2 DM; glycated hemoglobin (HbA1c) <8.0% indicating stable glycemic control.

Healthy controls: Normal fasting plasma glucose (<100 mg/dl); RDI<10 events/hour determined during two consecutive home sleep studies; no evidence of any other sleep disorder/s.

Exclusion Criteria

All patients: Hematocrit <32, metallic implants or other contraindication of CMR; pregnancy; collagen vascular disease; hepatic or renal disease; cardiopulmonary disease; use of medications that could affect sleep/breathing, or that could interact with nitroglycerin, non-English speakers.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

The study procedure for Aim 1 (visits 1-2) will be the same for all four subject groups (healthy controls, OSA patients, DM patients, OSA+DM patients). Patients enrolling in Aim 2 will first complete Aim 1 (visits 1-2) followed by Aim 2 (visits 3-6).

Study procedures will take place at different locations within Longwood Medical Area. In the case of inclement weather or if the subject does not wish to walk, a taxi or shuttle bus will be arranged to transport subjects. Subjects will be accompanied between sites at all times until the final procedure of each visit, apart from times when the subject will be in a hospital/clinic waiting room.

- *Visit 1: Screening Visit*

Location: BWH Ambulatory Clinical Center or *BWH Clinical Trial Center*
Time Required: Approximately 2.0 hours
Staff Responsible: Licensed physician, co-investigator, ACC/CTC nursing staff

All subjects will attend the BWH ACC or BWH CTC for a screening visit. Only patients who have indicated that they do not take medication/s for type 2 diabetes will be required to attend fasting. Eligibility criteria will be re-assessed verbally, and informed consent sought by a co-investigator who is not directly involved in the subject's clinical care. A licensed physician will conduct a physical examination (blood pressure, height and weight, neck, waist and hip circumference), and a thorough endocrine examination. The battery of questionnaires will then be completed. A urine sample will be obtained from females of menstrual age so that a pregnancy test can be performed; a positive result is grounds for exclusion from the study. A screening blood sample of approximately 30mL will be taken by the ACC/CTC nursing staff in order to assess exclusion criteria (plasma glucose, glycated hemoglobin, hematocrit, and eGFR). All subjects will be shown how to fill in the sleep diary, which they will complete during the seven days immediately preceding the two home sleep studies. Subjects will be given a list of foods containing a high amount of nitrates, and requested to avoid these foods during the three days immediately preceding visit 2 (and visit 6, if completing the randomized controlled trial).

Lastly, all subjects will be given a home sleep study device and shown how to operate it. They will take this home, and when final results of screening blood samples are available, a co-investigator will contact them via telephone. Those meeting entry criteria for the study will be asked to begin the 1-week sleep diary followed by two consecutive home-based sleep studies. Visit 2 will be scheduled, and subjects will bring the sleep study device to this appointment. Those who do not meet entry criteria will be asked to return the device to the investigators (at investigators' expense).

List of questionnaires:

- Clinical Sleep Questionnaire including Epworth Sleepiness Scale;
- Short-Form 36 Health Survey;
- Pittsburgh Sleep Quality Index;

- Functional Outcomes of Sleep Questionnaire;
- Rapid Eating Assessment for Patients;
- Typical Week Physical Activity Survey;
- BIDMC Cardiac MR Center Questionnaire.

- *Visit 2: Vascular Testing, Cardiac MRI and Exercise Study*

Locations: BWH Ambulatory Clinical Center or *BWH Clinical Trial Center (early morning), BIDMC Microcirculation Laboratory (mid-morning), BIDMC MRI Laboratory (late morning), BWH Shapiro Cardiovascular Center (early afternoon)*
Time Required: Approximately 5 hours
Staff Responsible: Licensed physician, ACC/CTC nursing staff, MRI technician, co-investigator

Subjects will arrive at the ACC/CTC in the morning, in a fasting state. Fasting will continue until the completion of vascular testing. DM subjects will not take their short-acting insulin and/or oral hypoglycemic agents during the fasting.

Data will be downloaded from the home sleep study device using custom software. The respiratory disturbance index (RDI) will be calculated; subjects with a RDI<10 will continue the study in either the DM only group or the healthy control group, and subjects with a RDI≥10 will continue the study in either the OSA only group or the DM+OSA group.

A blood sample (approximately 90mL) will be obtained by the ACC/CTC staff. 3-lead ECG will be recorded for ten minutes while seated. A non-invasive pulse wave analysis reading will be taken, which uses a small sensor placed on the wrist.

A co-investigator will accompany each subject to the BIDMC Microcirculation Laboratory where vascular testing will take place. Macrocirculation testing involves taking an ultrasound video of the brachial artery before and after a cuff is placed on the upper arm at supra-systolic pressure for five minutes, and before and after the administration of nitroglycerin. Microcirculation testing involves monitoring the blood flow of the forearm before and after the administration of acetylcholine and sodium nitroprusside. A licensed physician will then take two skin punch biopsies (used to evaluate potential changes in cellular proteins such as eNOS, P-eNOS, A20 or TNF-alpha, which may be up- or down-regulated with OSA and/or DM). Finally, DM patients will undergo a brief neuropathy evaluation.

All subjects will be provided with lunch, then accompanied to the BIDMC MRI Laboratory for a cardiac MRI scan.

Following the MRI, subjects will be accompanied to the BWH Shapiro Cardiovascular Center for optional exercise testing. Subjects will be asked to cycle for up to 30 minutes on an exercise machine until peak exercise, as determined by the patient, is reached. Heart rate and blood pressure will be monitored throughout. The exercise testing will add approximately 1 hour to Visit 2, when applicable.

Subjects enrolled in Aim 1 only (i.e. healthy controls, those with DM only, and those with OSA only), will finish the study at this point. The following visits are for subjects with DM+OSA who have consented to the 3-month randomized controlled trial.

- *Visit 3: Beginning of Run-In Phase*

Location: BWH Ambulatory Clinical Center or *BWH Clinical Trial Center*
Time Required: Approximately 30 minutes
Staff Responsible: Co-investigator

Subjects will be fitted with a mask and shown how to wear and clean it appropriately. If the subject finds the mask comfortable during this time, they will take it home and attempt to wear it while awake and/or asleep at home.

- *Visit 4: Randomization & Device Allocation*

Location: BWH Ambulatory Clinical Center or *BWH Clinical Trial Center*
Time Required: Approximately 1 hour
Staff Responsible: Co-investigator

Subjects who did not tolerate wearing the mask during the run-in phase will be excluded at this point.

Eligible subjects will be randomized to the treatment arm (active CPAP) or placebo arm (sham CPAP) of the trial. All subjects will be given a device which can be set to sham CPAP, active CPAP, or auto-PAP. The devices are identical, and subjects will not be aware of the settings in their allocated device.

Those assigned to the active CPAP group will need to undergo a one-week titration procedure using auto-PAP in order to determine a therapeutic pressure for ongoing CPAP use; the device will be set to auto-PAP mode. Those assigned to the sham CPAP group will not need to undergo a titration; the device will be set to sham CPAP mode.

Time will be available for questions and troubleshooting, with emphasis placed on strategies to maximize adherence.

- *Visit 5: Beginning of Randomized Controlled Trial*

Location: BWH Ambulatory Clinical Center or *BWH Clinical Trial Center*
Time Required: Approximately 30 minutes
Staff Responsible: Co-investigator

All subjects will return after one week, when adherence data will be downloaded from each device.

Subjects who are to continue with sham CPAP will have their device returned to them with no changes, although they will not be aware as to whether the mode of treatment has been changed. Subjects assigned to the active treatment group will also have pressure information downloaded from their device. A co-investigator will analyze these data and decide on a suitable fixed CPAP pressure. The mode of the device will be changed to active CPAP at this pressure, but again, the subjects will not know whether the settings of the device have been changed.

Time will be available for questions and troubleshooting, with emphasis placed on strategies to maximize adherence.

Subjects will use their sham / active CPAP devices for the next three months at home. During this time, subjects will attend face-to-face meetings with an unblinded co-investigator as required and/or requested by the subject. Subjects will perform regular blood sugar checks as needed. It may be necessary for some subjects to undergo an additional home-based sleep study while using active or sham CPAP; advice will be sought by a licensed physician.

- *Visit 6: End-Trial Vascular Testing & Cardiac MRI*

Locations: BWH Ambulatory Clinical Center or *BWH Clinical Trial Center (early morning), BIDMC Microcirculation Laboratory (mid-morning), BIDMC MRI Laboratory (late morning), BWH Shapiro Cardiovascular Center (early afternoon)*
Time Required: Approximately 5 hours
Staff Responsible: Licensed physician, ACC/CTC nursing staff, MRI technician, co-investigator

After three months of sham/active CPAP, subjects will return to the ACC or CTC in a fasting state. Adherence data will be downloaded from each device, followed by a repeat ECG measurement, questionnaires, pulse wave analysis, pregnancy testing and blood samples (approximately 90mL).

A co-investigator will accompany the subject to the BIDMC Microcirculation Laboratory for repeat vascular testing, skin biopsies, and a neuropathy evaluation.

All subjects will be provided with lunch, then accompanied to the BIDMC MRI Laboratory for a repeat cardiac MRI scan.

- *Post-Enrollment: CPAP Follow-Up*

Following Visit 6, a research assistant will access the medical record of each patient (either Beth Israel Deaconess Medical Center, or Brigham and Women's Hospital) to collect data regarding current CPAP use. If no data are found in the medical record, a research assistant will call each patient to gather this information over the phone.

The purpose of this follow-up is to investigate long-term engagement with sleep therapy following enrollment in a clinical trial. All patients who were recruited from sleep clinics were offered an appointment with their sleep specialist after study completion for ongoing sleep care. All patients who were recruited from other sources were offered a referral to a local sleep physician. We are interested in determining the rates of attendance at these clinical visits, and ascertaining whether there are differences in long-term CPAP usage by recruitment source.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Patients with DM will already have a clinical diagnosis and will be well-established on treatment. We therefore do not suspect that we will identify any patients with undiagnosed DM. However, if this occurs, the primary care physician will be informed of the diagnosis with permission from the patient.

Patients with a high likelihood of having OSA in the clinical setting would have a diagnostic sleep study performed (either at home or in the laboratory). A CPAP titration would then occur if OSA is demonstrated (with the titration either performed manually overnight, or using an auto-PAP device at home). Patients in Aims 1 and 2 of the research study will all undergo two consecutive home sleep studies, and many will be diagnosed with OSA at that point. Patients with a diagnosis of OSA who are either not eligible for Aim 2, or do not wish to participate in Aim 2, will discuss their diagnosis with Dr. Bakker who will advise the patient as to the best way of

obtaining treatment. The diagnostic report will be forwarded to the primary care physician with permission of the patient.

Patients who continue to Aim 2 will be randomized to either active-CPAP or sham-CPAP. Patients who are well-established on active CPAP during the trial will continue their treatment once the study has finished, with the cost of their CPAP equipment to be met by their insurance provider. Patients in this group who do not tolerate active-CPAP will be referred to a sleep physician so that alternative treatments (such as oral devices, or surgery) can be arranged. The cost of this will be met by the patient and/or their insurance provider. Patients randomized to the sham CPAP arm will require a titration on active CPAP at the conclusion of the study. A referral will be organized for these patients. The cost of the titration and equipment will be met by the patient and/or their insurance provider.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Most of the techniques described in this protocol are associated with minimal discomfort. Blood draws and skin biopsies will be conducted under sterile conditions by experienced nursing staff, and a licensed physician respectively. Overnight sleep studies, BP measurements, ECG measurements, pulse wave analysis and all vascular testing procedures and CMR imaging are generally well-tolerated, and are carried out by trained staff members. All procedures outlined in this protocol have been used by the PI and co-investigators in previous studies without incident.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Subjects will not be entered into the study unless they are healthy, other than having DM and/or OSA. All procedures (blood drawing, skin biopsies, vascular testing, CMR imaging, exercise testing) are conducted by trained staff members, who will monitor patients at all times.

Skin biopsies will be performed by a licensed physician under sterile conditions. Lidocaine is injected intradermally to provide adequate anesthesia. After the skin biopsy is taken, adequate pressure will be applied to the wound until satisfactory hemostasis has been obtained. Steri-strips will be applied afterwards, and careful instructions on how to care for the wound and avoid infection will be provided. All subjects are given a licensed

physician's phone number and pager to reach 24 hours a day in case of emergency.

If any pain or discomfort is noted by the subject during inflation of the blood pressure cuff during FMD, testing will be aborted. Nitroglycerin is given to the subjects during NID by a licensed physician. Subjects will be monitored for a minimum of ten minutes after administration of nitroglycerin. A licensed physician is required to confirm that the subject has not experienced an adverse event related to nitroglycerin, before the subject leaves the premises.

Subjects agreeing to CMR imaging will be excluded if they have any MRI contraindications such as metallic implants (e.g. pacemaker). These studies will be performed in MRI suites that are properly staffed and equipped for clinical patient scanning at BWH. Subjects will be given earplugs to minimize noise that occurs during imaging. The operator and subject will communicate with each other while the images are captured to ensure the subject's comfort. CMR imaging for LV function and structure is non-invasive and does not use ionizing radiation. Before discharge, it will be stressed that all subjects will have the opportunity for restorative sleep in the hospital if they intend driving home. Taxi vouchers will be provided if necessary.

Researchers will be in regular contact with subjects over the 3-month sham / CPAP treatment period. Any subject in the sham-CPAP arm who experiences a sleepiness-related accident or near-miss during this time will be removed from the study. However, given that patients experiencing excessive daytime sleepiness at baseline will not meet study entry criteria, this is unlikely to occur.

Subjects will be accompanied between sites at all times until the final procedure of each visit, apart from times when the subject will be in a hospital/clinic waiting room.

All adverse events possibly related to study interventions will be reviewed in weekly meetings, and serious adverse events related to the study procedures will be promptly reported to Partners Human Research Committee (PHRC) and the hospital authorities. Guidelines of the PHRC regarding reporting of adverse events will be followed. The study will be stopped if any unexpected serious adverse events are found possibly related to study interventions that threaten general health and well-being of study subjects.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for

research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Blood pressure measurements are generally well-tolerated, although the cuffs can occasionally cause some discomfort. ECG monitoring is not painful, though the sensors can cause some skin irritation. Pulse wave analysis is generally well-tolerated, as the sensor is placed on the wrist and is therefore non-invasive. Blood drawing can cause some initial pain and minor bruising, with minor risk of infection and a theoretical possibility of anemia. Sleep studies can lead to poor sleep quality and therefore sleepiness the following day. Measurement of brachial artery flow-mediated dilation can be uncomfortable due to the ischemic stimulus to the upper arm, but this discomfort rarely requires the procedure to be stopped. Measurement of nitroglycerin-induced dilation can lead to headaches in some cases. Monitoring of skin blood flow with laser Doppler can occasionally cause redness to the heated area which disappears soon after the measurement is complete. Iontophoresis of acetylcholine / sodium nitroprusside can cause a slight tingling sensation. There are no known short- or long-term risks of CMR, and patients with pacemakers or other implants that are not MRI-compatible will not be studied. The CMR technique is noisy which can cause some discomfort to the subject; earplugs will be provided, and the subject can request that the scan be stopped at any time. Skin biopsies can be painful at the site although this is usually minor, and there is a risk of persistent bleeding and/or location infection. The neuropathy evaluations do not pose any substantial risk or discomfort. The monofilaments are plastic, and produce a very mild vibratory stimulus. Blood draws or skin biopsies can sometimes elicit a vasovagal response with some dizziness or lightheadedness, which will be closely monitored by a licensed physician who will be present. Risks of exercise testing include fatigue and muscle strain, and in extreme cases, abnormal blood pressure/heart rate responses. Due to the need for vascular testing to take place in a fasting state, there is a risk of hypoglycemia particularly amongst the DM patients. However, we are only studying patients with well-controlled DM, and subjects will be closely supervised by a licensed physician during testing. CPAP treatment has no major side effects although some patients may experience anxiety and/or local skin irritation caused by the mask interface. Sham CPAP is noisier than active CPAP which may lead to further daytime sleepiness or fatigue beyond that caused by untreated OSA. Individuals will be cautioned against drowsy driving.

Subjects with a high likelihood of OSA would likely undergo a diagnostic sleep study (at home or in-laboratory) and CPAP titration (either manual or using auto-PAP) as part of standard clinical care. All other procedures outlined here are solely for research purposes.

The PI and co-investigators are certified in the research ethics training program offered by the Collaborative Institutional Training Initiative (CITI). All staff members of the Sleep Laboratory are trained in the responsible conduct of research, confidentiality issues and optimal data storage/acquisition methods. The potential risk to the patients regarding privacy and confidentiality are minimal.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

There are no direct benefits to the patients or healthy controls enrolling in this study. Patients treated with active CPAP during Aim 2 are likely to experience a marked reduction in overnight symptoms of OSA, which will then likely to lead to improved long-term health.

Results of the study will likely benefit future patients suffering from both OSA and DM, highlighting OSA as a potential treatment target to improve vascular functioning. Currently, few patients with DM undergo investigation for co-morbid OSA despite the high prevalence of patients with both conditions. Treatment of OSA among these patients will almost certainly reduce ongoing cardiovascular morbidity and mortality.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

Both men and women will be recruited, although we expect that males will outnumber females in the OSA groups, due to the higher prevalence of OSA amongst males.

We expect the proportion of minorities to represent those in the New England area. All potentially eligible subjects will be considered for inclusion regardless of race, ethnicity, or nationality.

The risk factors for OSA are different between children and adults, and CPAP is not the first-line treatment for OSA in children. Individuals under 18 years of age will therefore be excluded. The difference in endothelial

function between OSA patients and controls is not obvious beyond the age of 50; we will ensure that a range of ages are recruited to investigate this further.

Finally, OSA can occur during pregnancy due to other risk factors occurring during this period, and there is also a paucity of safety data concerning the vascular measurements undertaken during pregnancy. We therefore plan to exclude pregnant women.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Subjects who do not speak English will be excluded, as the battery of questionnaires is in English. These have not been validated for use in other languages.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
http://healthcare.partners.org/phsirb/nonengco.htm

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Subjects will be recruited from the community, using advertisements on bulletin boards, local newspapers, newsletters, websites, and email broadcasts including the phone number of the co-investigator/s. Flyers will be placed at the Joslin Diabetes Center.

OSA and DM patients will be recruited from local clinics. Advertisements will be displayed in the clinic areas, alternatively potential patients may be approached by their sleep / DM physician. The physician will either give the phone number of a potential subject to the co-investigator/s, or provide the phone number of the co-investigator/s to the subject. Our research assistant will access medical records in order to determine which patients with upcoming appointments are eligible for the study, and communicate this information with the appropriate physician. Only information that is necessary to determine eligibility will be accessed (demographics, problem list, medication list, clinic notes and results if needed).

We will also use clinical and research lists from both Partners Healthcare ('RPDR') and Beth Israel Deaconess Medical Center ('Clinical Query') to send mail-outs to patients seen by physicians that we approach for their approval.

Potentially eligible subjects will first call a research assistant who will discuss the eligibility criteria, study procedures, risks, time commitments, and potential benefits as outlined in the consent form. Subjects will be encouraged to ask questions. If interested, a consent form will be sent in the mail to all eligible subjects, who will have at least 24 hours consideration time before attending the screening visit. A co-investigator will attend the screening visit in order to discuss the study procedures, risks and benefits face-to-face before obtaining consent.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Participants enrolling in Aim 1 will receive up to $200: $50 for completion of the sleep studies, $100 for completion of vascular testing, and $50 for completion of the MRI.

Participants enrolling in Aim 2 will receive an additional $400: $300 for completion of the 3-month trial and vascular testing, and $100 for completion of the 2nd MRI.

If a participant completes only the screening visit, they will receive $25.

In addition, taxis will be provided free of charge to all patients if necessary following the sleep study. Parking costs will also be reimbursed.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
http://healthcare.partners.org/phsirb/recruit.htm

Guidelines for Advertisements for Recruiting Subjects
http://healthcare.partners.org/phsirb/advert.htm

Remuneration for Research Subjects
http://healthcare.partners.org/phsirb/remun.htm

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

All potential subjects will have at least 24 hours to consider participation from receiving the consent form in the mail, to attendance at the screening visit. As mentioned above, a co-investigator will be present at the screening visit to outline the study procedure, risks/benefits and time commitments before obtaining written informed consent.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
http://healthcare.partners.org/phsirb/newapp.htm#Newapp

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects
http://healthcare.partners.org/phsirb/infcons.htm

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

We will have a weekly meeting, directed by Dr. Bakker, during which we will review and monitor all of the data. These meetings will include collaborators with expertise in DM (Dr. Aris Veves) and CMR (Dr. Raymond Kwong). Dr. Bakker will be responsible for this review and for determining any alteration or termination of the study. The study will be stopped if any unexpected adverse events are found that threaten general health and well-being of study subjects.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

Dr. Bakker will monitor and review adverse events in study subjects. All adverse events possibly related to study interventions will be reviewed in weekly meetings and any serious adverse event/s related to the study procedures will be promptly reported according to PHRC policy: (http://healthcare.partners.org/phsirb/adverse_events.htm).

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

Dr. Jessie Bakker will be present during the consent procedure, and all data collection periods. This will ensure that the study protocol is followed, and quality data are obtained. All data will be reviewed at a bi-annual meeting of the co-investigators.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
http://healthcare.partners.org/phsirb/datasafe.htm

Adverse Event Reporting Guidelines
http://healthcare.partners.org/phsirb/adverse_events.htm

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

All records are maintained confidential with only the investigators and technicians involved having access to the information. The subject's data will be coded by unique numbers so as to maintain both confidentiality, and blinding during data analysis. The study staff and investigators will be careful to preserve patient confidentiality under all circumstances.

With the permission of the subject, data collected that has direct clinical relevance (for example, sleep study data and blood work) will be compiled and forwarded to the relevant clinician.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

All procedures except circulation function testing and MRI will be conducted in Partners sites. The subject will be given a different medical record number at BIDMC and the same identifier number as being used at BWH will be used also for BIDMC testing.
De-identified skin biopsy slides will be sent to a pathology laboratory in Greece for analysis.
De-identified skin biopsy slides will be sent to a laboratory in Germany for analysis.
De-identified skin biopsy slides will be sent to a laboratory within BIDMC for analysis.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

The testing done at BIDMC will only be used for the purpose of this study, and will not be used for any other purpose not described in this protocol. Subjects will be allowed to withdraw their specimens or data at any time by contacting the study investigators.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

The data from testing conducted at BIDMC will be labeled with the same subject identifier as used in the tests done at BWH.