EFFECT OF 2-WEEK NIGHTLY MODERATE HYPOXIA ON GLUCOSE TOLERANCE IN INDIVIDUALS WITH TYPE 2 DIABETES (SLEEPDIABETES)

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EFFECT OF 2-WEEK NIGHTLY MODERATE HYPOXIA ON GLUCOSE TOLERANCE IN INDIVIDUALS WITH TYPE 2 DIABETES (SLEEPDIABETES)

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BACKGROUND AND SIGNIFICANCE

Hypoxia in obese adipose tissue (AT) plays an important role in the development of whole-body insulin resistance by inducing local inflammation and the release of pro-inflammatory cytokines (reviewed in [1]). Detrimental effects of hypoxia are also evident in the altered glucose metabolism induced by sleep apnea, a condition characterized by intermittent and short hypoxic episodes [2, 3]. However, there are conflicting reports about the effects of altitude hypoxia on insulin action and glucose uptake [4].

Short-duration (4 hours) of exposure to moderate hypoxia has been shown to improve transient insulin sensitivity in type-2 diabetics [5], and more prolonged exposure was shown to increase whole-body glucose turnover and utilization in healthy subjects [6]. Exposure to hypoxic environments has also been shown to increase both whole-body glucose fluxes in healthy males and glucose uptake in human and murine skeletal muscle [7]. Controlled studies at altitude following acute exposure to hypoxia during exercise have reported improved carbohydrate metabolism, including increased glucose oxidation, reduced fasting insulin and glucose, and higher fluxes of glucose [8]. In addition, Cartee at al. reported enhanced insulin-independent translocation of glucose transporters by hypoxia during exercise [9]. Living at altitude in hypoxic conditions is associated with a lower prevalence of impaired fasting glucose and type 2 diabetes, as compared to low altitude [10].

Exposure to hypoxia has also been advocated as a possible therapeutic aid against obesity [11], hypoxia being known to reduce energy intake and to affect protein synthesis [12]. A highly publicized study showed reduced rates of obesity at high altitude [13]. Moreover, hypoxia has been shown to be beneficial as a complement to exercise in healthy non-obese [14], obese [15, 16] and athletes [17-19] to improve skeletal muscle function.

We have provided the first evidence that intermittent, nightly exposure to moderate hypoxia was beneficial in improving insulin sensitivity in healthy obese patients and, therefore, lowers the risk of developing type 2 diabetes [20]. Benefits included reduced fasting glucose levels and improved whole-body (skeletal muscle) and hepatic insulin sensitivity. *Whether such intermittent hypoxia improves glucose metabolism in people with type 2 diabetes is unknown.*

Reasons for the Protocol Modification and its Safety Implications:

The safety aspects and history of this protocol deserve further comment. It is important to the concept of using a hypoxia tent to treat diabetes to use as a home treatment. Although the degree of hypoxia generated by the tent was not a safety concern to the FDA, there was concern that safety would be compromised if the hypoxia of sleep apnea was added to the hypoxia of the tent. The initial approach to eliminating this safety concern in the study was to

ensure that the participants did not have sleep apnea. Although this is one way to eliminate the threat of sleep apnea-associated hypoxia, it has been very hard to identify these individuals.

Another way to eliminate sleep apnea-associated hypoxia is to treat the sleep apnea with C-PAP, the standard way in which sleep apnea is treated. C-PAP is a continuous pressure administered by mask and adjusted to be sufficient to keep the airway open during sleep. The C-PAP essentially draws air from the surrounding environment and creates the pressure to keep the airway open using a fan. Therefore, the C-PAP machine could be put in the hypoxia tent with a cord extending to a wall socket outside the tent to power the machine. In this way the C-PAP would draw in hypoxic air from the tent, but would also insure that additional hypoxia would not occur due to the C-PAP eliminating the sleep apnea.

Since it has been shown by Foster GD et al. [24] that 86% of overweight and obese diabetic subjects have sleep apnea, we feel that, in addition to including subjects without sleep apnea, we should include patients with sleep apnea controlled on C-PAP. Both of these groups of patients will be protected from any additional hypoxia associated with sleep apnea that would add to the safe hypoxia generated by the tent, but including the group with sleep apnea controlled on C-PAP will allow us to enroll and complete the study which has only enrolled one patient in over a year when limiting those studied to those without sleep apnea.

HYPOTHESIS AND AIMS

Aim: To determine the effect of 2-week overnight sleep in moderate hypoxia on glucose tolerance in participants with type 2 diabetes.

Hypothesis: Exposure to moderate hypoxia (2400 m altitude) for 14 consecutive nights in obese, type 2 diabetic subjects will improve glucose tolerance

Primary endpoint: Results from the 75 g oral glucose tolerance test (OGTT) assessed by different statistical approaches including:

- Traditional area under the curve (glucose and insulin)
- Repeated measures mixed effect model
- Matsuda Index
- Kahn's calculation of indices of insulin sensitivity and insulin secretion

Exploratory endpoints: Fasting plasma fructosamine and hemoglobin A1-C as well as daily body weight

SUBJECTS

We plan to have n = 10 completers.

Inclusion criteria:

- Aged 20-65 yrs
- Have a BMI < 55 kg/m^2
- Body weight 450 lbs or less

- Have *either* been diagnosed with type 2 diabetes, or 125 mg/dl < Fasting Blood Sugar < 200 mg/dl, or hemoglobin A1-C ≥ 6.5%
- Non-smokers
- Weight stable over the previous 3 months (< 3 kg fluctuation)
- Known diagnosis of sleep apnea and ownership of a continuous positive airway pressure (C-PAP) device that must be worn throughout the nights spent in the tent
- If no known presence of sleep apnea, be willing to spend one night in a sleep laboratory (Louisiana Sleep Foundation) to assess presence of sleep apnea

Exclusion criteria:

- Diagnosed with T2DM ≥ 15 years ago
- Pregnant Women
- Current insulin treatment
- Treatment with sulfonylureas or glitinides
- Treatment with a GLP-1 agonist
- Any other diabetes medication other than an oral agent is exclusionary unless otherwise cleared by medical investigator.
- Chronic Obstructive Pulmonary Disease (COPD)
- Congestive heart failure
- Prior severe cardiovascular events such as stroke or myocardial infarction
- If treated for T2DM with other oral agent, no change in the treatment for 1 month before the study and the duration of the study
- Previously known diagnosis of sleep apnea without ownership of a continuous positive airway pressure (C-PAP) device or agreement to use owned CPAP device during the nights spent in the tent
- Presence of sleep apnea following a positive home sleep test (HST), or have unsafe oxyhemoglobin saturation levels (less than 78%) during a one night sleep monitoring assessment conducted at the Louisiana Sleep Foundation without ownership of a continuous positive airway pressure (C-PAP) device or agreement to use owned C-PAP device during the nights spent in the tent
- History of high altitude sickness
- History of altitude sickness
- Does not have access to a bed or sleeping surface equivalent to or smaller than a Queen size mattress.

RECRUITMENT

Potential participants will be recruited through the PBRC website, e-mails, flyer distribution, and word-of-mouth. Individuals will call or e-mail the Recruitment Core at PBRC and will undergo a phone screen to answer a series of yes or no questions regarding their age, gender, body weight and height, changes in body weight during the last month, presence of disease, and smoking status. Eligible individuals will be scheduled for their screening visit at the PBRC Outpatient Clinic.

SCREENING

Participants will report to the PBRC clinic after a >10-h overnight fast. The screening visit includes an explanation of the purpose of the study, a description of the procedures and the reading and signing of informed consent. Volunteers will then complete a brief personal and family medical history. Height, weight, waist and hip circumference, vital signs (blood pressure, pulse, oral temperature) will be measured. Volunteers will then have an EKG. Subjects with a previous sleep apnea diagnosis must possess a C-PAP device and must agree to use the CPAP device during the nights spent in the tent; if no C-PAP device is available for usage, the subject will not be eligible to participate in the study. If subjects are considered to be eligible up to this point, blood will be drawn for a complete blood count, blood chemistry (Chem15), and a hemoglobin A1-C as part of the draw. Subjects who do not meet the eligibility criteria will be immediately informed in person or by phone. An interview with a trained psychologist will identify potential barriers to enrollment into the SLEEPDIABETES study and also barriers to have the hypoxia tent system setup at the participant's home. Only subjects without a previous sleep apnea diagnosis and who meet all eligibility criteria will next undergo a two-step process to: (1) confirm the absence of sleep apnea (home sleep test, or HST), as well as (2) confirm these subjects without a sleep apnea diagnosis exhibit safe oxygen saturation levels (monitored sleeping study at the Louisiana Sleep Foundation, a certified sleep laboratory) while sleeping under the mild hypoxic conditions denoted by the study. Subjects previously diagnosed with sleep apnea and who possess a C-PAP device will not undergo testing at the Louisiana Sleep Foundation.

(1) Home Sleep Test (HST): Subjects without a sleep apnea diagnosis will first undergo a home sleep test conducted by the Louisiana Sleep Foundation under the direction of Dr. John K. Schwab, MD, DABSM, the chief medical director of the Foundation. Subjects will obtain the home sleep test from Dr. Schwab and will be given instructions on how to wear the device during a single night of sleep. The device will record breathing rates and oxygen saturation levels throughout the single night of sleep. After the single night sleep, subjects will be instructed to return the device to the Louisiana Sleep Foundation where Dr. Schwab will review the sleep data and identify the potential presence of sleep apnea. If the presence of sleep apnea is detected, subjects will be immediately informed of their ineligibility to participate in the study. If a negative test for sleep apnea is concluded, subjects will next undergo a monitored sleep study.

(2) Monitored Sleep Study: Subjects who have a negative test for sleep apnea following a HST will next undergo a monitored night of sleep under hypoxic conditions at the Louisiana Sleep Foundation. Subjects will arrive at the Louisiana Sleep Foundation on the evening of their monitored sleep study. A sleep technician will closely monitor the subject's oxyhemoglobin saturation throughout a single night of sleep under hypoxic conditions (2400 m altitude). Hypoxic conditions will be achieved via a hypoxic tent, as previously described and conducted at Pennington Biomedical Research Center [20]. Following the technician-monitored night of sleep, Dr. Schwab will review the sleep data and provide insight as to the subject's ability to participate in the study given expected oxyhemoglobin saturation levels at 2400 m. Subjects

who exhibit <78% oxyhemoglobin saturations, or who display sleep data of safety concern to Dr. Schwab, will be informed of their ineligibility to participate in the study.

If the HST and sleep center monitoring are within safe ranges for study participation following evaluation by Dr. Schwab, the participant will officially be accepted into the study and will begin baseline testing (Day 0) within weeks and in agreement with schedules. All subjects who have a known sleep apnea diagnosis, possess a C-PAP device, and are agreeable to using the C-PAP device during the nights spent in the tent will be accepted into the study as well.

EXPERIMENTAL DESIGN

This study includes outpatient and in-home visits and will consist of three periods:

1) **Baseline** measures of glucose tolerance (OGTT) and body composition (DXA)
2) **Intervention** involving 14 night stays in simulated altitude (hypoxic tent in home)
3) **Post-treatment** (after 14 nights in hypoxia) measures of glucose tolerance

After screening, subjects will be asked to maintain their usual diet and physical activity levels.

Baseline:
A 75-g OGTT will be performed. Body composition will be measured by DXA. Fasting plasma fructosamine will also be collected via blood draw. A urine pregnancy test will be performed on all females of child-bearing potential prior to the DXA.

Intervention: Nightly exposure to hypoxia
Over the following 14 nights, participants will sleep under a tent simulating an altitude of 2400m (~7500 ft) for 7-12 hrs each night depending on their usual sleep pattern in their bedroom. Each participant will be informed that their partner or household member, or any other individuals, are prohibited from entering or sleeping in the tent.

Post treatment measurements:
After the 7th night of hypoxic sleep, participants will come to the Pennington Biomedical clinic to provide a fasting blood sample to measure glucose and insulin. We will also collect information of the quality of their sleep under the hypoxic tent.
The morning of the 14th exposure to hypoxia, participants will come to the Pennington Biomedical clinic facilities in a fasting state to perform a post intervention assessment. Approximately 15 min after arrival, a 75-g OGTT will be performed. Fasting plasma fructosamine and hemoglobin A1-C will also be collected via blood draw.

Table 1. Schedule of Procedures

	Screening	Sleep Screening (HST & Sleep Study)	Baseline (Day 0)	Mid-Intervention (Day 7)	Post-Intervention (Day 14)
Health questionnaire	X				
Body weight	X		X	X	X
Vital signs*	X				
Electrocardiogram	X				
Blood draw	X		X	X	X
Oral glucose tolerance test			X		X
Body composition by DXA			X		
Urinalysis	X				
Urine Pregnancy Test			X		
Oxyhemoglobin saturation**		X			

* blood pressure, pulse, oral temperature

** Only performed on subjects without previous sleep apnea diagnosis. Time between screening and sleep screening, as well as sleep screening and baseline testing (Day 0), will vary depending on scheduling at Pennington Biomedical and the Louisiana Sleep Foundation.

METHODS AND PROCEDURES

Urine and blood.

At screening, 9.5ml of blood will be collected for CBC, Chem15 panel, and hemoglobin A1-C analysis. Urine will also be collected at screening for urinalysis. Approximately 39.5 mL of blood will be taken at baseline, and 41.5 mL of blood will be taken at post-intervention for the OGTT, fructosamine, and hemoglobin A1-C analysis. Archives (~10 mL; serum and plasma) will be collected at baseline, mid-intervention, and post-intervention for future analysis. Following the 7th night spent in the hypoxic tent, ~2 ml of blood will be drawn for plasma glucose and insulin concentrations. A total of approximately 122.5 mL (approx. 8.5 Tbl.) of blood will be taken.

Vital signs

Vital signs will be measured while the subject lying on a bed. Body temperature (sublingual) will be measured using an electronic thermometer (Sure Temp 679, Welch Allyn) and blood pressure using a manometer (Baumanometer. W.A. Baum Co., Inc. USA). Heart rate will be measured by radial arterial pulse for 60 seconds.

Overnight exposure to hypoxia (simulated altitude)

Pennington staff will visit the participant's home and setup the hypoxic tent system. This person will also instruct participants on how to use the equipment. Participants will spend 14 consecutive nights in the "altitude tent", with the simulated altitude being set at 2400m over sea-level. Hypoxia will be obtained by nitrogen dilution of the ambient air in an airtight tent (Hypoxico Inc., NY). Briefly, ambient air is filtered and a small part of the oxygen removed before the modified air is flushed in the airtight tent. Altitude is mimicked by lowering the oxygen content rather than reducing the atmospheric pressure. However the physiological stimulus is comparable and has been used in multiple studies involving different populations. This altitude corresponds approximately to the altitude of most mountain resorts and of Mexico City, one of

the largest metropolises in the world. It has been chosen because it is within the range of the altitudes eliciting a physiological response to hypoxia, and has been proven to be safe in obese patients during a 1-week exposure [11].

Oral glucose tolerance test

Glucose tolerance will be assessed using an oral 75 g oral glucose tolerance test (OGTT). Subjects will be studied after an overnight fast. An intravenous line will be placed and one baseline sample will be drawn at -5 minutes. The subjects will then consume a 75 g glucose beverage within 5 minutes. Blood samples will be collected at 30, 60, 90, and 120 to measure serum glucose, insulin, and free fatty acid concentrations. Whole body insulin sensitivity will be calculated using the Matsuda insulin sensitivity index (10,000/square root of [fasting glucose x fasting insulin] x [mean OGTT glucose x mean OGTT insulin]). We will also assess insulin secretion as described by Dr. SE Kahn. In brief, the early insulin response during the OGTT, also known as the insulinogenic index is calculated as the ratio of the change in insulin to the change in glucose concentrations from 0 to 30 minutes. The oral disposition index (DIo), a measure of b-cell function is calculated as [Δ insulin0-30min/Δ glucose0-30min] x 1/fasting insulin. Complementary to the glucose response, we would also monitor the changes in the blood FFAs as a measure of the adipose tissue capability to suppress lipolysis in response to insulin. So, it can be used as a marker of insulin sensitivity in terms of adipose tissue. We will calculate the insulin sensitivity index for blood FFAs by the formula: ISI (ffa) = 2/(INSp × FFAp) + 1), where INSp and FFAp indicate insulinemic and blood FFA areas, respectively, of the person under study recorded during the OGTT.

DXA scan

Dual X-Ray absorptiometry (DXA) scans will be performed using the GE iDXA whole-body scanner to assess body composition. The protocol requires that participants lie on a table wearing a hospital gown and no metal containing objects, while the scanner emits low energy X-rays and a detector passes along the body. The scan takes 10 minutes and the radiation dose is less than 1 mrem, equal to about 12 hours of background radiation. Fat mass is calculated from weight (kg) on a scale and % body fat and fat-free mass by subtracting fat mass from total body weight (kg).

Sample size. This is a pilot study to test the impact of mild hypoxia in participants with type 2 diabetes. We therefore did not perform a power analysis.

Data analysis

Data will be expressed as mean +/- SE. Values before and after exposure to hypoxia will be compared using the paired Student's t test or a Wilcoxon rank signed test. Despite the pilot nature of this study, the results may be published as a short communication depending on the potential changes in insulin sensitivity.

Data collection, storage and confidentiality

All results will be kept in locked file cabinets and restricted-access computers. All of these will be kept separate from records with names and other personal information. The only people who

will know that these patients are research participants are members of the research team. No information about them, or provided by them during the research, will be disclosed to others without their written permission, except if it is necessary to protect their rights or welfare (for example, in case of injury or emergency care), or if it is required by law. When the results of the research are published or discussed in conferences, no information will be included that would reveal the identity of these patients. Participants will be identified by codes when the data gathered in this procedure is presented or published. Authorized representatives of the National Institutes of Health may need to review records of individual participants. As a result, they may see their name; but they are bound by rules of confidentiality not to reveal the patients' identity to others.

RISK/BENEFIT ASSESSMENT

The known risks, inconveniences or side effects involved in this study are the following:

Procedure	Risk
EKG	There are no risks associated with this test. There is a small possibility there may be some redness or irritation if you happen to be allergic to the adhesive on the electrodes.
Body composition by DXA	The amount of radiation used for this procedure is very small. The radiation dose for this scan is equivalent to the radiation you are naturally exposed to in the environment in less than one day. **Scans will not be performed on any subject who is pregnant, and all females should inform the DXA technologist if there is any possibility that they are pregnant.**
Blood Draws	Bruising, bleeding, pain, infection. These will be minimized by using trained phlebotomists with sterile techniques.
Sleeping under hypoxia (simulated altitude ~ 2400m)	Some patients may feel a slight discomfort and feeling of claustrophobia while sleeping in an airtight tent. Participants will be free to exit the tent if they feel claustrophobic. There should not be any risk associated to sleeping at altitudes <2500m since: (1) those participants with diagnosed sleep apnea will wear a C-PAP device while sleeping under the tent to maintain airway pressure, and (2) those participants with suspected sleep apnea or participants that showcase unsafe oxygen saturation levels during the single night stay throughout testing at the Louisiana Sleep Foundation will be excluded. Recent reviews suggest an acclimatization process for higher altitudes [21, 22]. Acute altitude sickness may nonetheless be experienced by some volunteers, with symptoms as headache, anorexia, and nausea, which might however be transient [21]. High altitude pulmonary edema is very unlikely at such altitude, being known to occur at much higher altitudes and with exercise [23]. However, we will exclude participants with high altitude sickness and monitor for altitude sickness by asking participants about symptoms (which usually happen in the first 6-24 hours) such as headache, nausea, vomiting, dizziness, insomnia, loss of appetite and dyspnea. Adverse events will be monitored throughout the study, and participants with acute altitude sickness will be withdrawn from the study.

Risk Classification: The study risk can be classified as moderate since we have already used this same paradigm in 8 participants with obesity (see reference #20) and we will exclude all potential participants with congestive heart failure, prior cardiovascular events such as stroke or myocardial infarction and those with diagnosed sleep apnea and lack a C-PAP device to wear throughout the nights spent in the tent.

Minimizing Risks: All study procedures will be monitored by the investigators and/or the medical investigator of the study to minimize potential risks and discomforts to study subjects. Research participants will be immediately withdrawn from the study upon evidence of any serious adverse event.
Eligible subjects without a previous sleep apnea diagnosis will undergo an extensive two-step sleep evaluation, involving a home sleep test as well as a monitored sleep test at the Louisiana Sleep Foundation, to identify the presence of sleep apnea as well as closely monitor and evaluate oxyhemoglobin saturation levels during a single night sleep at 2400 m in the hypoxic tent, respectively. Sleep data will be thoroughly evaluated and assessed on a subject-by-subject basis by the chief medical director of the Louisiana Sleep Foundation to ensure the upmost safety precautions are taken. Only those subjects who exemplify safe oxyhemoglobin saturation levels during both sleep evaluation tests will be allowed to enroll in the study.
Eligible subjects with previous sleep apnea diagnosis who possess a C-PAP device will be required to use the C-PAP device throughout the nights spent in the tent.

Adverse Event Reporting: Adverse event monitoring will occur at mid-intervention (Day 7) and post-intervention (Day 14) visits, and participants will be instructed to call the study coordinator (Dr. Kara Marlatt) at the onset of any abnormal effects (headache, nausea, vomiting, dizziness) between visits.

Data Safety Monitoring Plan. Drs. Ravussin and Greenway will be responsible for monitoring the data, assuring protocol compliance, and conducting safety reviews after completion of the first participants and then every 6 weeks. During the entire study, Dr. Greenway will monitor adverse events and determine if they are attributed to the study procedures. If any of those adverse events are suspected to be related to study procedures, they will be immediately reported to the PI and the IRB.
Such study has already been conducted in 8 participants with obesity and identified a 20% improvement in insulin sensitivity.

Potential Benefits: There is no direct benefit to the volunteers but knowledge may be gained that will benefit others. Participants will, however, receive some information about their health.

Payment for Participation: If participant completes all 14 days of the study, they will receive $350 for the time spent in the clinic. Conversely, if the participant completes the mid-intervention visit (Day 7) but does not complete the post-intervention visit (Day 14), the participant will receive $175. And finally, if the participant enrolls in the study but does not complete the mid-intervention visit (Day 7) or beyond, the participant will receive $50. This compensation is in line with all the other studies conducted at the Pennington Biomedical Research Center and will be mailed within 4 weeks of study completion.

Financial Obligations of the Subjects: None

Emergency Care and Compensation for Research-Related Injury: No form of compensation for medical treatment is available from the Pennington Biomedical Research Center. In the

event of injury or medical illness resulting from the research procedures the research volunteer will be referred to a treatment facility. The Pennington Biomedical Research Center is a research facility and provides medical treatment only as part of research protocols. Should a volunteer require medical treatment, community physicians and hospitals must provide them to him/her.

Appendix (see below on pages 13 and 14)

The Food and Drug Administration (FDA) has reviewed this submission and responded to our request for a risk determination for the proposed study. FDA has determined that this proposed clinical investigation is a non-significant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812). See FDA letter attached.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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June 22, 2015

ERIC RAVUSSIN, Ph.D.
ASSOCIATE EXECUTIVE DIRECTOR FOR CLINICAL SCIENCE
PENNINGTON BIOMEDICAL RESEARCH CENTER
6400 PERKINS ROAD
BATON ROUGE, LA 70808-4124

Re: Q150541 – Study Determination for the Proposed Study titled, "Effect of 2-Week Nightly Moderate Hypoxia On Glucose Tolerance In Individuals With Type 2 Diabetes"
Dated: April 7, 2015
Received: April 14, 2015

Dear Dr. Eric Ravussin:

The Food and Drug Administration (FDA) has reviewed your submission, dated April 7, 2015, requesting a risk determination for the proposed study titled, "Effect of 2-Week Nightly Moderate Hypoxia On Glucose Tolerance In Individuals With Type 2 Diabetes". FDA has determined that your proposed clinical investigation is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812).

An IDE application is not required to be submitted to, or approved by, FDA for a NSR study. A NSR study is, however, subject to the abbreviated requirements described in § 812.2(b) of the IDE regulation. The abbreviated requirements stipulate that the sponsor of the investigation must label the device in accordance with § 812.5; obtain institutional review board approval of the investigation as a NSR study; ensure that each investigator obtains informed consent from each subject under the investigator's care; comply with the monitoring requirements of § 812.46; maintain records required under § 812.140(b)(4) and (5) and file the reports required under § 812.150(b)(1) through (3) and (5) through (10); and ensure that participating investigators maintain the records required by § 812.140(a)(3)(i) and file the reports required under § 812.150(a)(1), (2), (5) and (7).

Under the abbreviated IDE requirements, a sponsor must also comply with the prohibitions against promotion and other practices as identified in § 812.7. According to this section of the regulation, the sponsor of a NSR study, investigator, or any person acting for or on behalf of the sponsor or investigator is prohibited from promoting or test marketing the investigational device until after FDA has approved the device for commercial distribution; commercializing the device by charging a price greater than that necessary to recover the cost of manufacture, research, development, and handling; unduly prolonging the investigation; and representing the investigational device as being safe or effective for the purposes for which it is being investigated.

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Please note that, if in the future you submit an application under sections 505, 515, or 520(m) of the FDCA (21 USC §§ 355, 360(e), or 360(j)(m)), or under section 351 of the PHS Act (21 U.S.C. § 262), or you submit a report under section 510(k) of the FDCA (21 USC § 360(k)), the application or submission must be accompanied by a certification that all applicable requirements of section 402(j) of the PHS Act (42 USC § 282(j)) have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC § 282(j)(5)(B). Additional information regarding the certification is available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM164819.pdf . Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trial(s) is available at the Protocol Registration System website (http://prsinfo.clinicaltrials.gov/).

If you have any questions, please contact Paula Caposino at (301) 796-6160.

Sincerely yours,

Katherine Serrano -S

For: Courtney H. Lias, Ph.D.
Director
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