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Dear Dr. Facco,

On Friday January 20, 2017, the Institutional Data and Safety Monitoring Board (IDSMB) of the Office of Clinical Research (OCR), Health Sciences held a teleconference to discuss the proposed modification for your study entitled "Sleep Disorder Breathing, Obesity and Pregnancy (SOAP) Study" IRB Number: PRO13080159.

The DSMB supports your proposed study modification. The proposed modification will not change subject safety and will still continue to contribute meaningful data.

We look forward to your next study update in May 2017.

Sincerely,

Rachel J Givelber MD

Rachel Givelber, MD
Chair of the IDSMB Committee

Request: Modify design (pertinent to Aims 2 and 3) so that the arms are auto-CPAP vs an attention control instead of sham CPAP.

In summary, we propose this swap occur after we have randomized 45 individuals under the current design with a plan to randomize another 36 individuals after we switch to the unblinded and unmasked design. Those not randomized to CPAP would be informed of their SDB diagnosis, both verbally and also in a handout/letter. This proposed change in the control arm is being proposed because we believe it will enhance compliance with CPAP. The request is NOT being made based on any safety or risk considerations regarding the current vs. proposed modified design. We strongly believe that both sham-CPAP and attention control are safe and appropriate, and that this proposed modification would not impact subject safety.

I have discussed this proposed change with the study co-Investigators and the data coordinating center and have gotten approval from the DSMB(attached). I recognize that this is a major protocol change that will require NIH/NHLBI approval and am writing this letter to formally request approval. As part of this request we have outlined a detailed rationale and analytical plan that takes this proposed change into consideration. Attached to this letter is also a revised Protection of Human Subjects From that addresses this proposed modification, with Track Changes to highlight the edits.

Rationale:

Currently our study, in part, consists of a randomized controlled trial of Auto-CPAP vs. Sham CPAP in pregnancy. As of 2/14/17, we have screened 309 participants, enrolled 228, randomized 43 to auto-CPAP or sham CPAP, and assigned 96 to the control group for observation only. We are very pleased with our study recruitment and data collection processes. We are recruiting on schedule and have excellent retention. The over-arching goals of my study were to provide mechanistic insights on how SDB impacts pregnancy and to provide preliminary/feasibility data to inform the practical and scientific aspects of a CPAP and pregnancy trial. For the latter, I would like to continue to make iterative changes to the protocol to understand best practices to optimize CPAP use in pregnancy as part of a clinical trial. To improve compliance to CPAP among randomized subjects, we have added a monetary incentive and we have demonstrated a positive effect from this modification, but, given recent data from other sleep cohorts, I remain wary about how having a sham arm may be hindering compliance. My co-investigators and I are requesting approval for this modification because we believe that it will enhance the scientific value of our study data. The CPAP trial component of our study (Aims 2 and 3 outlined below) is a pilot study not designed to definitively determine effectiveness, but rather determine the feasibility and acceptability of a CPAP trial in pregnancy and see if a treatment effect is possible to consider for a larger study. To that end, we strongly believe that any modification that leads to increased adherence to treatment will be of great value.

Since the initiation of this study more data has been published regarding trial methodology in sleep apnea related research and my co-investigators and I are motivated to use this data to enhance our study. We have done an extensive literature search and have reviewed all the compliance data from medium and large CPAP trials published to date. In our review, we have concluded that sham-CPAP, while theoretically an ideal control, is not a true placebo when it comes to blinding, and its use in trials negatively impacts compliance. An analysis of adherence in the largest randomized controlled trial using sham CPAP (APPLES) reported that 55.2% of those randomized to active therapy guessed their allocation correctly whereas 70.0% of those randomized to sham CPAP guessed correctly ($p<0.001$). Regardless of actual allocation, those who guessed they were on active treatment had higher hours of adherence than those who guessed they were on sham (4.65 h ± 2.10 h vs. 2.65h±2.22 H, $P<0.001$).[1] Furthermore there is no evidence to suggest that this approach poses any additional risks to subjects compared to sham-CPAP. Several large trials of CPAP

have employed a similar design, pointing to the suitability of such a design to sleep experts and journal editors, alike.[2,3] Most notably, a similar attention-control design (e.g., usual care) was used as the alternative to active treatment in Sleep Apnea Cardiovascular Endpoints (SAVE) study was very recently published in New England Journal of Medicine. [4]

This brings me to our request; we would like to change the RCT design (Aims 2 and 3) so that the arms are auto-CPAP vs an attention control. We would like to make this swap after we have randomized 45 individuals under the current design with a plan to randomize another 36 individuals after we switch to the unblinded and unmasked design. Those not randomized to CPAP would be informed of their SDB diagnosis, both verbally and also in a handout/letter. They would be informed that currently there are no treatment guidelines for SDB in pregnancy (a reiteration of wording from the consent form). We would offer some general sleep hygiene advice about getting regular and sufficient sleep and discuss how some women may get some alleviation from snoring by sleeping on their side, which some experts recommend for all pregnant women after 20 weeks gestation. We would conclude the letter by stating that if they have significant sleep disturbance or daytime sleepiness that they are concerned about that they should talk to their doctor about pursuing clinical testing. Contact information for a local sleep specialist would also be included.

Special Considerations:

A. Outcome Ascertainment

The main outcome measures of our study are outlined in Table 1 with a description of how unblinding/unmasking the control arm may impact ascertainment. In summary, we feel that the impact of unblinding/unmasking the participants, Dr. Facco and her research staff would be minimal as the individuals performing the ultrasound assessments and blood analyte measurements would remain blinded.

Chart abstraction would be carried out by unblinded study staff but the outcomes of interest for abstraction are clinically well defined and abstraction requires ascertainment of diagnoses (e.g., gestational diabetes, preeclampsia) along with supportive documentation (e.g. lab tests, blood pressures) so this would limit the potential for bias.

Table 1 Study Outcome Measures and Vascular Domain, Angiogenic Domain, Metabolic Domain		
Variable	Rationale	Considerations for unblinding/unmasking
Vascular Domain		
Primary Measure: Uterine artery Doppler mean pulsatility index	Several studies have demonstrated that uterine artery Doppler studies early in gestation are predictive of the development of preeclampsia later in pregnancy.[5] The pulsatility index, alone or combined with notching, is the most predictive Doppler index.	Uterine artery Dopplers will continue to obtained and quantified by blinded sonographers. Dr. Facco and her study staff will
Angiogenic Domain		
Primary measure: sFLT/PIGF ratio	Ischemic trophoblasts have been shown to increase production of anti-angiogenic proteins (sEng, sFlt1) and reduce production of angiogenic proteins (PIGF). Several investigators have reported that significant differences in these angiogenic factors predate the clinical manifestations of preeclampsia by several weeks to months and correlate with disease severity. [6-9] The predictive value is more specific for ratios than for individual factors. [10]	Dr. Hubel and his lab will remain blinded to treatment ascertainment even after the proposed change. All blood analyses will be conducted by his lab in a blinded fashion.
Metabolic Domain		
Primary measure: Homeostasis model assessment of insulin resistance (HOMA-IR)	Mid-trimester insulin resistance, even in the absence of clinical gestational diabetes, has been associated with an increased risk of subsequent preeclampsia.[11-13]	Dr. Hubel and his lab will remain blinded to treatment ascertainment even after the proposed change. All blood analyses will be conducted by his lab in a blinded fashion.

The DSMB reports that we provide, currently unblinded in closed session, would now become unblinded. However, the safety outcomes we have been asked to ascertain in these reports are well defined and are not subject to ascertainment bias:

1. Preterm birth < 32 weeks gestation
2. Severe growth restriction (Birth weight < 3rd percentile)
3. Intrauterine fetal demise
4. Neonatal death before discharge from the hospital

A copy of our DSMB outcome form has also been attached to this letter.

B. Analysis Plan by Aim

Aim 1: To examine the influence of SDB on a pregnancy-specific cardiovascular risk profile

Analysis modification plan: This protocol change would not require any changes to this analysis plan as this analysis is based on baseline data from all SDB positive subjects regardless of randomization to treatment or compliance with treatment.

Aim 2: To perform a randomized controlled trial of autotitrating- CPAP versus sham-CPAP in pregnancy to examine the impact of CPAP treatment during pregnancy on cardiovascular risk and describe adherence to treatment

Analysis modification plan: Our original sample size calculation for our trial called for a total of 68 subjects, 34 subjects in the active CPAP arm and 34 subjects in the sham CPAP arm. We are now proposing to increase our total N to 81. We would end recruitment in the active vs. sham trail when we have recruited a total of 45 participants. We would then start enrolling women to an active CPAP vs. sleep hygiene with the goal of recruiting 36 more participants' total (18 to active CPAP; 18 to sleep hygiene).

Aim 3: Explore interplay between SDB, CPAP and evidence of maternal vascular disease and chronic fetal hypoxia by evaluating the placental profile of obese women with and without SDB

Analysis modification for Aim 3 would follow the same construct outlined for aim 2, substituting the placental prolife as the outcome of interest.

C. Analysis Plan

The analysis plan for the original aim would remain the same, **importantly this modification would have no effect on the detectable effect size or power calculation for Aim 1 as presented in our original application.**

The plan for the revised Aim 2 and 3 will follow in kind:

In summary, analyses would begin by describing the baseline characteristics by randomly assigned treatment group. Either parametric (t-test) or nonparametric (Wilcoxon test) analyses would be used to compare continuous characteristics and chi-square tests would be used to compare discrete characteristics across randomly assigned treatment groups. The analyses would be carried out based on intention to treat, but exploratory analyses would be conducted on the per protocol subgroup. The treatment effects of sleep hygiene *vs.* active CPAP on the vector of cardiovascular risk factors would be compared with multivariate analysis of variance (MANOVA). If differences in baseline characteristics are observed, the characteristics would be included in the MANOVA to control for the potential confounding effects. This analytic plan would be repeated in the per-protocol subgroup. The MANOVA model would be fit with main effects for treatment group and an indicator of the level of compliance as well as the two-way interaction. Additionally, ANOVA and X^2 analyses would be used to examine intergroup differences between Time 1 and Time 2 assessments among all the groups. The assumptions of all analyses (e.g., normality of residuals) would be investigated. If assumptions are violated, transformations of the data would be investigated. If adequate transformations cannot be identified, nonparametric approaches would be utilized.

The revised design would have two impacts on the study design. First, would be a reduction in power of the first comparison. The second would be the size of the effect that can be estimated in the modified design analysis; the detectable effect size would be larger (1.52, assuming 80% power, a type I error rate of 0.05, a two-sided alternative hypothesis, with four outcomes variables in the MANOVA). However, given that Aim 2 and 3 are designed as a pilot study, the size of the effect should not be a concern since the goal of the study is not to definitively determine effectiveness, but rather determine the feasibility of a CPAP trial in pregnancy and see if a treatment effect is possible to consider for a larger study. To that end, any modification that leads to increased adherence to treatment would be of great value to this study, as well as future investigations.

D. Budget

We are not requesting any additional funding. We will be able to execute this modification, including enrolling the additional study participants beyond our original sample size, under the constraints of our current budget.

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10. Lim JH, Kim SY, Park SY, Yang JH, Kim MY, Ryu HM. Effective prediction of preeclampsia by a combined ratio of angiogenesis-related factors. *Obstet Gynecol.* Jun 2008;111(6):1403-1409.

11. Hauth JC, Clifton RG, Roberts JM, et al. Maternal insulin resistance and preeclampsia. *Am J Obstet Gynecol.* Apr 2011;204(4):327 e321-326.

12. Parretti E, Lapolla A, Dalfra M, et al. Preeclampsia in lean normotensive normotolerant pregnant women can be predicted by simple insulin sensitivity indexes. *Hypertension.* Mar 2006;47(3):449-453.

13. Sierra-Laguado J, Garcia RG, Celedon J, et al. Determination of insulin resistance using the homeostatic model assessment (HOMA) and its relation with the risk of developing pregnancy-induced hypertension. *Am J Hypertens.* Apr 2007;20(4):437-442.