

# **SOAP1**

## **Sleep-Disordered Breathing, Obesity and Pregnancy, Protocol 1 (SOAP1)**

### **Manual of Operations and Procedures**

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## 1. About this Manual

The purpose of this Manual of Operations and Procedures (MOP) is to provide clear, consistent, accurate and complete instructions for carrying out the Sleep Disordered Breathing, Obesity and Pregnancy, Protocol 1 (SOAP1) study. While the MOP incorporates some content from the Protocol for reference, the focus here is on implementation. More details about the background, rationale, hypothesis, aims, outcome measures and models of statistical analysis are included in the Protocol.

The DCC is responsible for keeping the MOP up to date, in consultation with the PI and co Investigators. Revisions are tracked (see Table 1, below) and new versions are distributed to study personnel, in electronic format, for reference. In some cases, MOP changes are also documented in Operations Memos.

**Table 1: MOP Revisions**

Version	Initials	Date	Summary of change(s)
1.0	JWB	3/12/15	<ul style="list-style-type: none"> <li>Published manual</li> </ul>
1.1	JWB	3/30/15	<ul style="list-style-type: none"> <li>Added info about unblinding</li> </ul>
1.1.1	JWB	3/30/15	<ul style="list-style-type: none"> <li>Updated Appendix D with screen shot of Dashboard and instructions for Unblinding (UB) form</li> </ul>
1.1.2	JWB	3/31/15	<ul style="list-style-type: none"> <li>Added info about browser compatibility to Appendix D</li> </ul>
1.1.3	JWB	4/14/15	<ul style="list-style-type: none"> <li>Added informed consent form to Appendix A</li> </ul>
2.0	JWB	6/1/15	<ul style="list-style-type: none"> <li>Updated list of measures</li> <li>Reformatted entire document</li> <li>Added info about MF, MV (per OpsMemo 2)</li> </ul>
2.1	JWB	6/3/15	<ul style="list-style-type: none"> <li>Corrected funding source</li> <li>Updated clinical management section (e.g., video shown during Visit 1)</li> </ul>
3.0	JWB	10/19/15	<ul style="list-style-type: none"> <li>Modified inclusion/exclusion criteria to reflect protocol changes (per OpsMemo 4, 5)</li> </ul>
4.0	JWB	2/16/16	<ul style="list-style-type: none"> <li>Restructured entire document (new chapter titles, headers)</li> <li>Added more detail about procedures related to recruitment, screening, clinic visits, and delivery/post delivery</li> <li>Added content about IDSMB reports</li> <li>Updated list of protocol deviations to include administrative error</li> <li>Clarified that PI abstracts charts for participants with complications and all CPAP participants; study coordinator does the rest</li> <li>Modified section on adverse events</li> </ul>
4.1	JWB	2/24/16	<ul style="list-style-type: none"> <li>Clarified definition and reporting of adverse events, including adverse pregnancy outcomes</li> <li>Made other edits per study team</li> </ul>
4.2	JWB	3/1/16	<ul style="list-style-type: none"> <li>Updated section on Clinic Visits to revised updated orders</li> <li>Inputted edits from N-CTRC</li> </ul>

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4.3	JWB	6/14/16	<ul style="list-style-type: none"> <li>• Made minor edits to Study Overview and Clinical Management sections to align with 5/12/16 IDSMB report</li> <li>• Updated Appendices</li> </ul>
4.4	JWB	9/29/16	<ul style="list-style-type: none"> <li>• Updated chapter 4.2 and 5.6 to reflect change in chart abstractions procedure</li> <li>• Updated 3.2 to reflect personnel change (study coordinator) and clarify clinical team's responsibilities</li> <li>• In 5.4, added instructions for putting new CPAP machines into service</li> <li>• Removed references to CTTC throughout</li> <li>• Updated Appendix A to reflect personnel change (study coordinator) and add OSU personnel</li> <li>• Updated Appendix B to reflect personnel change (CTSI)</li> <li>• Replaced consent forms in Appendix C</li> <li>• Updated Appendix D to reflect personnel change (study coordinator); also made formatting changes to NTCR general orders</li> <li>• Updated Appendix E with current version of forms</li> </ul>
4.5	JWB	11/30/16	<ul style="list-style-type: none"> <li>• Added discussion of internal reports to section 8.4</li> <li>• Replaced "DSMB" with "IDSMB" throughout document</li> <li>• Updated Appendix B to include new IDSMB member and IDSMB coordinator</li> <li>• Updated Appendix C with new consent forms for main study and ancillary study</li> <li>• Updated Appendix E with most recent set of forms</li> </ul>
5.0	JWB	2/6/17	<ul style="list-style-type: none"> <li>• Inserted "Institutional" before "Data &amp; Safety Monitoring Board" throughout document</li> <li>• Updated Table 2: Data Collection Points, Related Forms and Delegation of Responsibility in Section 5 (Clinical management) to include the new Consent Documentation (CD) form and clarify delegation of responsibility for form completion</li> <li>• Revised Section 5.1 (Recruitment and Screening) to more accurately reflect current practices</li> <li>• Revised Section 5.2 (Clinic visits) to reflect new procedures designed to reduce missing data and monitor CPAP equipment</li> <li>• Updated Section 5.6 (Delivery/Post-Delivery) to reflect current procedure for unblinding and removed conflicting instructions in Appendix F (Electronic Data Entry System)</li> <li>• Revised Section 8.1 (Data Privacy and Security) to reflect new procedures and removed for storing study documents</li> <li>• In Appendix D (Clinical Scripts, Orders, Protocols, and Instructions), replaced instructions regarding the Delivery Specimen (DS) form with a reference to the form, which includes instructions</li> <li>• Updated Appendix E with the current set of forms</li> </ul>

## Sleep-Disordered Breathing, Obesity and Pregnancy, Protocol 1 (SOAP1)

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6.0	JMW	7/24/17	<ul style="list-style-type: none"> <li>• Replaced SOAP with SOAP1 throughout MOP</li> <li>• Updated section 5.2 to include reference to "note to file" about sleep specialist referrals for controls with AHI&gt;5 at Visit 2</li> <li>• Corrected information in Section 5.7 about timing of CPAP Survey (completed after Delivery, not during Visit 2)</li> <li>• Modified Section 5.8 to note that, in addition to CPAP Survey (CS), DSMB Outcomes (DO) form must be completed prior to unblinding</li> <li>• Replaced "Neuroscience Clinical and Translational Research Center (N-CTRC)" with "Sleep and Behavior Neuroscience Center (SBNC)" throughout MOP, to reflect name change</li> <li>• Replaced forms in Appendix E with updated versions and added form instructions</li> <li>• Updated data manager's name and email address, to reflect name change, and updated EDC address in Section 3.3 and appendices A and F</li> </ul>
7.0	JMW	9/22/17	<ul style="list-style-type: none"> <li>• Updated Section 5, Table 2 to include specimens collected during clinic visits 1 and 2 or at delivery, and then processed later, in batches</li> <li>• Updated Section 5.6 to provide additional information about specimens collected at delivery</li> <li>• Added Section 7.5, Missing Data Codes</li> <li>• Added Section 11: Other Study Documents and deleted all appendices</li> </ul>

## 2. Study Overview

Sleep-Disordered Breathing, Obesity and Pregnancy, Protocol 1 (SOAP1) is a prospective observational study of the interplay between sleep-disordered breathing (SDB), obesity and cardiovascular risk factors in pregnancy. Our central hypothesis is that SDB is an effect modifier that increases maternal cardiovascular risk and placental hypoxic injury in obese pregnant women, and that CPAP treatment during pregnancy results in an improved cardiovascular risk and placental profile. To test this hypothesis, our cohort includes obese women with and without SDB. Refer to the table below and sections 1.1-1.4 for a discussion of the protocol. Modifications to this protocol are made only with approval from the IRB and IDSMB.

After a screening process, eligible participants are scheduled for two clinic visits, one during the second trimester (14-20 6/7 weeks) and the other during third trimester (28-31 6/7 weeks). Each visit begins with a questionnaire followed by an overnight polysomnogram (PSG). The following morning, clinical measurements are taken, maternal bloods are collected, and a uterine artery Doppler is performed. Participants with severe apnea at the first clinic visit (i.e., AHI estimate  $\geq 50$ ) are withdrawn from the study. Those without SDB (i.e., AHI estimate  $< 5$ ) are assigned to a control group for observation only. Participants with SDB (i.e., AHI estimate 5-49) are randomly assigned to receive an autotitrating CPAP machine or a sham unit. Autotitrating units coordinate air-flow delivery with effort, providing the lowest pressure necessary to maintain upper airway patency. Sham units, meanwhile, have been modified to deliver air without pressure. Assignment is "double blinded," i.e., neither participants nor members of the clinical research team know which units are autotitrating versus sham. All CPAP units include a modem that transmits data back to the study team. After delivery, SDB participants are unblinded, modems are removed, sham units are replaced with active ones, and referrals to sleep specialists are provided so that appropriate follow-up treatment can be arranged. Data collection points and related forms are discussed in Chapter 5.

### **3. Organization**

#### **3.1. Leadership**

The principal investigator (PI) is Francesca Facco, MD, a maternal fetal medicine specialist and assistant professor in the Department of Obstetrics, Gynecology & Reproductive Sciences in the School of Medicine at the University of Pittsburgh. Dr. Facco's research has focused on sleep and pregnancy, with past projects including a prospective observation survey, retrospective chart review, case-control study, and prospective cohort study. She works closely with co-investigators and clinical and data management personnel (see below) to ensure that the study is being conducted in accordance with operations and procedures outlined in this manual. Dr. Facco also communicates with the Institutional Review Board (IRB) and Institutional Data and Safety Monitoring Board (IDSMB, see below), seeking their input/approval on proposed modifications and keeping them apprised of any serious adverse events and protocol violations that occur.

Co-investigators include:

- Carl Hubel, PhD, Department of Obstetrics, Gynecology & Reproductive Sciences, School of Medicine, University of Pittsburgh
- W. Tony Parks, MD, Department of Pathology, School of Medicine, University of Pittsburgh
- Patrick Stollo, MD, FCCP, FAASM, UPMC Sleep Medicine Center, Department of Pulmonary, School of Medicine, University of Pittsburgh
- Stephen R. Wisniewski, PhD, Graduate School of Public Health, University of Pittsburgh

#### **3.2. Clinical Team**

Clinical management and data collection are handled by Victoria Lopata, BSN, RN (study coordinator) and Christiana Ekekwe, MPH (research assistant) at Magee-Womens Hospital, part of the University of Pittsburgh Medical Center (UPMC). Their responsibilities include recruiting and screening participants, scheduling visits, collecting blood specimens, completing many of the forms, and working with the DCC to deal with data that are missing, out of range, or illogical through the "edits" process (see 8.2, below).

Sleep studies are conducted by technicians at the Sleep and Behavioral Neuroscience Center (SBNC) located at Western Psychiatric Institute and Clinic (WPIC), also part of UPMC.

Delivery specimens are handled by the obstetric sterile processing unit (OSPU) at Magee.

#### **3.3. Data Coordinating Center**

The Epidemiology Data Center (EDC), in the Graduate School of Public Health, is serving as the Data Coordinating Center (DCC), under the direction of Dr. Stephen Wisniewski, co-director of the EDC and a SOAP co-investigator, and assisted by staff members Heather Eng, Jason Lyons, and Jenny Wolsk.

The DCC's responsibilities include:

- Developing and maintaining the web-based data collection system, including forms, with input from the PI, co-PIs, and clinical team
- Developing and updating the MOP, with input from the PI, co-PIs, and clinical team

- Maintaining the system for random assignment of participants and labelling of CPAP equipment (active versus sham)
- Reviewing data for logical inconsistencies and missing or delinquent data and reporting any findings to the clinical team for prompt resolution
- Generating reports for the IDSMB and IRB
- Conducting site visits
- Analyzing data and publishing results, with clinical investigators

### **3.4. Institutional Data and Safety Monitoring Board (IDSMB)**

The Institutional Data and Safety Monitoring Board (IDSMB) includes experts in obstetrics and gynecology, sleep medicine, and biostatistics. To avoid conflicts of interest, IDSMB members have no other involvement in the study. Refer to the appendix for a current roster.

The IDSMB's responsibilities include:

- Reviewing the research protocol, informed consent documents and plans for data and safety monitoring
- Evaluating the progress of the study, including periodic assessments of data quality and timeliness; participant recruitment, accrual and retention; participant risk versus benefit, adverse events, and unanticipated problems; and other factors that could affect study outcomes
- Considering factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the participant safety or the ethics of the study
- Providing technical assistance and serving as a resource to the PI on issues related to study conduct, enrollment, sample size and/or data collection
- Making recommendations to the PI concerning continuation, termination or other modifications based on observed beneficial or adverse effects
- Reviewing reports of serious adverse events and protocol violations

The IDSMB meets at least once every six months by phone, with additional meetings convened as needed (e.g., if a safety concern arises). The chairperson is the safety officer, serving as the contact person for reports of serious adverse events and protocol violations. "Open" (masked) reports to the IDSMB are prepared by the DCC, in consultation with the PIs and co-PIs. The DCC also compiles "closed" (unmasked) books which show data by treatment arm (active CPAP versus sham), including the following adverse fetal/neonatal outcomes: preterm birth < 32 weeks gestation; severe growth restriction (birth weight < 3rd percentile); intrauterine fetal demise; and neonatal death before discharge from the hospital. Closed books, reviewed during closed sessions, are used by the IDSMB to determine whether the study should continue as planned or be modified or terminated.

### **3.5. Human Research Protection Office (HRPO)**

The University of Pittsburgh's Human Research Protection Office (HRPO), formerly the Institutional Review Board, is charged with ensuring that research involving human subjects is conducted in safe, ethical and scientifically-sound ways. Prior to beginning the SOAP1 study, the PI secured approval from the HRPO (see appendix for letter of approval). For the duration of the study, renewal requests must be submitted annually and amendment requests must be approved before any changes to the Protocol are



implemented. The HRPO also requires that the PI report serious adverse events and protocol violations (see chapter 8) through the Online Submission for Institutional Reviews System (OSIRIS).

### **3.6. Funding/Support**

Sources of support for this study include:

- National Heart, Lung, and Blood Institute (1R01HL120354-01A1 grant)
- The University of Pittsburgh's Building Interdisciplinary Research Careers in Women's Health (K12HD043441 grant)
- Phillips Respironic (sham CPAP devices provided on loan at no cost)
- The Department of Obstetrics and Gynecology at the University of Pittsburgh's School of Medicine (additional funds provided, as needed)

## 4. Startup Requirements

### 4.1. Checklist

- Funding secured from NHLBI (PI)
- IDSMB approval obtained (PI)
- HRPO approval obtained (PI)
- Clinical protocols developed for recruitment, screening and treatment of participants (DCC, PI)
- Data collection forms developed (DCC, PI)
- Electronic data collection, entry and management systems developed and tested (DCC)
- Randomization procedures developed and tested (DCC)
- Training and certification materials developed (DCC)
- List of key personnel identified by name, affiliation, title, email address and phone number (PI)
- Completion of training and certification by study personnel (Clinical Team, see below)
- Conflict of interest disclosure(s) filed with the DCC (Leadership, Clinical Team, DCC, see below)

### 4.2. Training and Certification

The DCC provides training for clinical team members, to ensure quality and reliability of data and appropriate documentation of study progress and outcomes.

Topics include:

- Data collection forms
- Electronic data management system
- Randomization and CPAP assignment
- CPAP compliance tracking and incentive payments
- Adverse events and protocol deviations/violations
- Missed visits and missing forms
- Missing, out of range, or illogical data

Chart abstraction training entails abstracting two charts already abstracted by Dr. Facco and reviewing any discrepancies with Dr. Facco.

At the conclusion of training, the DCC certifies clinical team members who demonstrate proficiency. Refresher training is scheduled, as needed, and recertification required, if appropriate.

Over the course of the study, the PI is expected to notify the DCC about new hires so that training and certification can be provided in a timely manner.

### 4.3. Conflict of Interest Disclosure

The PI and all co-investigators are required to disclose any ties to companies or individuals that could create conflicts (or dualities) of interest for the study. Disclosure statements are renewed annually and filed with the DCC.

## 5. Clinical Management

Clinical personnel recruit, screen and enroll participants, coordinate treatment, obtain specimens, and collect data at certain time points using forms developed or modified by the DCC for this study (see Table 2, below, and sections 5.1-5.6). Forms are included as an appendix to this MOP.

**Table 2: Data Collection Points, Related Forms and Delegation of Responsibility**

Form	Screening (EGA 6-19 6/7 wks)	Clinic Visit 1 (EGA 14-20 6/7 wks)	Home Visit	Clinic Visit 2 (EGA 28-31 6/7 wks)	Delivery/ Post Delivery	Other Time- point
Screening Questionnaire (SC)	RA					
Consent Documentation (CD)	RA					
Contact Information (CI) <sup>1</sup>	RA					
Initial Interview (II)	RA					
Sleep Log (SL)	[give]	[return]				
Sleep Questionnaire (SQ)		PARTICIP.		PARTICIP.		
Sleep Study 1 (SS1) <sup>2</sup>		SBNC   COORD.		SBNC   COORD.		
Randomization Log (RAND) <sup>1</sup>		SBNC				
Home Visit (HV) <sup>1,3</sup>			SBNC   COORD.			
Sleep Study 2 (SS2) <sup>2</sup>		SBNC   COORD.		SBNC   COORD.		
Maternal Bloods (MB)		COORD.		COORD.		
Uterine Artery Doppler (UA)		PI		PI		
Delivery Specimens (DS)					OSPU	
IDSMB Outcomes (DO) <sup>3</sup>					COORD.	
CPAP Survey (CS) <sup>3</sup>					PARTICIP.	
Unblinding (UB) <sup>3</sup>					COORD.	
Chart Abstraction (CA)					COORD. <sup>4</sup>	
Adverse Event (AE)	<----- COORD. (as needed) ----->					
Protocol Deviation (PD)	<----- COORD. (as needed) ----->					
Withdrawal (WD)	<----- COORD. (as needed) ----->					
Missed Visit (MV)	<----- COORD. (as needed) ----->					
Missing Form (MF)	<----- COORD. (as needed) ----->					
Other Data	Screening (EGA 6-19 6/7 wks)	Clinic Visit 1 (EGA 14-20 6/7 wks)	Home Visit	Clinic Visit 2 (EGA 28-31 6/7 wks)	Delivery/ Post Delivery	Other Time- point
Maternal blood <sup>5</sup>		Gallagher		Gallagher		
Placenta <sup>5</sup>					Parks	
Placental biopsies <sup>6</sup>					PI	
Cord blood and plasma <sup>6</sup>					PI	

<sup>1</sup> Completed on paper only; not part of the electronic Data Management System

<sup>2</sup> In the electronic Data Management System, each of the Sleep Study forms (visits 1 and 2) is split into two forms: Sleep Study PM (SSP) and Morning Sleep Study (SSA)

<sup>3</sup> Applies only to CPAP participants

<sup>4</sup> In consultation with PI

<sup>5</sup> Processed later, in batches

<sup>6</sup> Stored for future studies

### 5.1. Recruitment and Screening

To identify potential participants for the SOAP1 study, the research assistant (RA) reviews prenatal medical records on the EPIC system and approaches women who meet basic inclusion criteria (i.e., aged 18 or older, 6-20 weeks pregnant, and obese) during their prenatal appointments to ascertain their

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interest. This requires cooperation from the healthcare provider and his/her staff, so the PI reaches out to them to let them know about the study before their patients are approached.

Meanwhile, some women find out about the study on their own through Pitt+Me (pittplusme.org), a searchable database designed for individuals who are interested in getting involved in research; flyers or pamphlets posted throughout Magee-Womens Hospital (MWH); a slide displayed on the plasma screens in the lobby and near the elevators; or word of mouth. If they decide to contact the study team, they are prescreened in person or by phone.

The RA maintains a list of individuals who identify themselves or are approached and follows up with those who are interested during subsequent prenatal visits until a formal screening visit takes place. Repeated contact helps to ensure that those who ultimately enroll understand what is involved and are committed to completing the study.

During the formal screening visit, the RA confirms that the individual has not already been screened during this pregnancy or enrolled during a previous pregnancy long enough to complete the first sleep study, both of which are exclusion criteria. Next, a study ID is generated and a Screening (SC) form is completed, in person or by phone, to review the other exclusion criteria<sup>1</sup>:

- A history of sleep apnea, insomnia, diabetes, heart disease, or lupus
- Prior use of a CPAP device
- Use of a breathing machine at night
- Currently pregnant with twins or higher order multiples (criterion added 6/1/15)
- Use of a sleeping aid more than once in the past month

### **Instructions: ID Generation**

1. Create a new record on the electronic data entry system (REDCap). A 4-digit number will automatically be assigned. If REDCap is not accessible, refer to the clinical data management tool developed by Jack Doman to determine the next consecutive 4-digit number.
2. Add a dash ("-") followed by the participant's first and last initials to create her ID (e.g., 1034-HB).

The SC is based on self-report; the RA does not refer to medical records or other sources to verify the accuracy of participant responses.

If the individual is found to be eligible, additional information is collected about sleep characterization and then details about the study are provided, including the timeline, the randomization process, potential risks and benefits, and the importance of compliance. Prior to seeking informed consent, which must be done in person, the RA reminds the individual that there is no obligation to participate or penalty for declining to participate, and that her care will not be compromised if she chooses not to participate or enrolls and subsequently leaves the study. Prospective participants must sign the consent form in order to proceed. The consent process is documented on the Consent Documentation form.

If informed consent is obtained, Contact Information (CI) is collected on a paper form and stored in a secure place at the study office; it is not entered into the electronic data entry system (REDCap). Next, an Initial Interview (II) is completed with questions about lifestyle, use of medications, prior pregnancies, and medical history, and self-reported estimated gestational age is confirmed by reviewing

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<sup>1</sup> Inclusion and exclusion criteria have changed over the course of the study.

the participant's medical record. Finally, the participant is given a 7-day Sleep Log (SL) along with instructions about how to record bedtimes, wake-up times, naps, and other information. Participants are expected to bring the completed SL when they come for Clinic Visit 1, which takes place 14-20 6/7 weeks EGA, so they need to receive the SL at least one week before then.

### **5.2. Clinic Visits: PSG, Maternal Bloods, Uterine Artery Doppler**

There are two overnight clinic visits, one scheduled during the second trimester (14-20 6/7 weeks EGA) and the other during the third trimester (28-31 6/7 EGA). Both take place at the Sleep and Behavioral Neuroscience Center (SBNC). The instructions below are consistent with orders prescribed by the PI (see Appendix).

Prior to the each visit, the coordinator review the participant's medical record to identify any medications that have been prescribed as well as diagnoses or symptoms that could affect her participation. Participants receive a reminder by phone, text, or email (based on personal preferences noted on the Contact Information form) of the coming visit and instructions to bring all medications with them. This is especially important for participants with hypertension. For the first visit, participants are also instructed to bring their completed Sleep Log (SL).

Each clinic visit begins in the evening when the participant arrives at the SBNC, usually 7-8PM. Components include:

- Collection of the Sleep Log (SL) (Visit 1 only). The participant receives the SL from the coordinator during screening, completes it on paper, and returns it to SBNC.
- Administration of a Sleep Questionnaire (SQ). The SQ covers general work and sleep patterns, sleep habits, snoring and sleep apnea. It is administered online. SBNC personnel complete the first part and the participant completes the rest. SBNC personnel are permitted to provide assistance, if requested by the participant, but should not rephrase questions. Prior to submitting, SBNC are asked to review the form for completeness and encourage the participant to fill in any blanks.
- Presentation of a short video followed by mask fitting. The PI created a video about the study which describes sleep apnea and continuous positive airway pressure (CPAP) machines. After the video, the participant is fitted for a CPAP mask. Mask type and size are recorded in the progress notes in case the participant turns out to be a candidate for randomization.
- Completion of the Sleep Study PM (SSP) form. Weight is measured (this is not self-reported) and, after at least five minutes of rest, blood pressure is measured three times, with five minutes between measurements. Any readings >140/90 should be reported immediately to the medical contact.
- "Wire up." Small electrodes are placed on the participant's scalp, face, and legs so that technologists can monitor her air flow, body movements, heart rate, and oxygen saturation while she sleeps.
- Completion of the Sleep Study AM (SSA) form. During the night, SBNC personnel review the participant's polysomnography (PSG) data to calculate an apnea-hypopnea index (AHI) estimate, using AASM 2012 rules. The AHI estimate at the first visit determines eligibility for randomization (see below). If a sleep study is not completed successfully – either because a participant refuses or there is a medical reason or technical problem – SBNC personnel should report this on the SSA and also notify the Study Coordinator. (Note: sleep studies are formally scored later on but these scores are recorded on the SBNC's "Harmony System," not REDCap.)
- Randomization and assignment of CPAP machine (Visit 1 only). Participants with an AHI estimate 5-49 and who agree to be randomized are assigned a CPAP machine for the treatment phase of the

study (see “Randomization,” below). The assignment date, unit number, and mask style and size are recorded on the SSA. SBNC personnel should review CPAP use and care instructions, included in the case, with the participant.

- Clinical measurements, bloodwork and uterine artery ultrasound. After the PSG, participants are escorted by the Study Coordinator back to Magee. Clinical measurements (vitals, height, weight and waist, hip and neck circumference) are taken using the SOAP1 Tanita Protocol (see Appendix), along with three measures of blood pressure, and recorded on the SSA; fasting blood is drawn for cardiovascular risk profiles and documented on the Maternal Blood (MB) form; and a uterine artery (UA) Doppler is performed. Blood is processed and then stored for future batched testing. The Study Coordinator also takes this opportunity to review the Sleep Log, to see if there are any unusual responses, and the Sleep Questionnaire, to see if any responses are missing, asking the participant for clarification or additional information, as appropriate. In addition, for during visit 2, the Study Coordinator asks CPAP participants whether all of the equipment is the same as what was originally issued and confirms that all components are still correctly labeled.

Eating is permitted until midnight. After midnight, only water is permitted until after fasting blood has been collected in the morning. Ideally, participants are asleep by 11PM but no specific good night time (GNT) has been established for the study.

An AHI estimate is calculated at both visits. At Visit 1, the AHI estimate determines group assignment (see 5.3, below). At Visit 2, participants who are in the Control Group and who have an AHI estimate of 5 or higher are given a referral to a sleep specialist (documented by the Study Coordinator as a "note to file").

Data are entered directly into REDCap, using the study laptop at the SBNC. If REDCap is not accessible, SBNC personnel enter data on a paper form and then give the paper form to the Study Coordinator the following morning so that the data can be entered into REDCap and/or visually verified, if it has already been entered by then. Visual verification is required for all forms completed on paper and is done by a different staff person or at least a day later, if done by the same staff person.

### **5.3. Randomization**

A participant’s AHI estimate from the first clinic visit determines whether she is randomized, assigned to the control group for observation only, or withdrawn from the study.

Participants with an AHI estimate below 5 are assigned to the control group. They are not randomized.

Participants with an AHI estimate of 50 or higher are referred to a sleep specialist and withdrawn from the study. They are not randomized.


Participants with an AHI estimate 5-49 who agree to randomization receive an autotitrating- or sham-CPAP machine. Autotitrating units coordinate air-flow delivery with effort to provide the lowest pressure necessary to maintain upper airway patency. Sham units have a hidden leak. This is a double-blind study, so neither participants nor clinical personnel are supposed to know which CPAP machines are active versus sham. The DCC stores randomization assignments separately; they are not part of the electronic Data Management System.

**Table 4: AHI Estimates, Study Assignment, and Instructions for SBNC**

AHI Estimate	Assignment	Instructions for SBNC
<5	Control	Tell participant that she does not have sleep apnea so she will not be in the treatment part of the study. Do <u>not</u> randomize.
5-49	CPAP ("Case")	Tell participant that she is eligible for the treatment part of the study and ask if she agrees to be randomized. If she agrees, proceed with randomization (see Instructions, below). If she does not agree: 1) do <u>not</u> randomize; 2) notify Study Coordinator immediately.
≥50	Withdrawn	Tell participant that she has a degree of sleep apnea that requires attention and let her know that the Study Coordinator will follow up to provide a referral to a sleep specialist. Notify Study Coordinator immediately. Do <u>not</u> randomize.

**Instructions: Randomization**

- 1) Refer to the Randomization Log, stored in the supply room with the CPAP machines at the SBNC.



**SOAP**

RANDOMIZATION LOG

This log should remain with unassigned CPAP units

CPAP UNIT NUMBER	TAKEN BY	DATE TAKEN	ASSIGNED TO [SOAP ID]
<b>C001</b>	_____	__/__/__	_____ - _____
<b>C002</b>	_____	__/__/__	_____ - _____
<b>C003</b>	_____	__/__/__	_____ - _____

- 2) Refer to the Randomization Log, stored in the supply room with the CPAP machines at the SBNC.
- 3) Select the next consecutive CPAP unit number from the list. It is important not to skip any rows.
- 4) Select the CPAP carrying case that matches the number from the log. Open the case to make sure the unit number on the machine, elbow bag and elbow all match. If they do not match, or if any component is missing, make a note on the Randomization log, select the next consecutive CPAP unit number, and notify the Study Coordinator immediately.
- 5) Complete the Randomization log with your initials, the date, and the participant's SOAP1 ID. Record the same information, plus the CPAP unit number, mask type and size, on the SSA.
- 6) Pick up the mask that the participant was fitted for the night before and attach the elbow located inside the CPAP case.
- 7) Train the participant on proper CPAP usage, cleaning, etc.
- 8) Give the CPAP case to the participant.

**5.4. CPAP Equipment**

The PI is responsible for obtaining active and sham CPAP machines and elbows along with cases and modems. The DCC assembles units in batches, at the request of the PI, attaching modems and labeling components. The coordinator brings the units to the SBNC for distribution to eligible participants at Clinic Visit 1.

## Sleep-Disordered Breathing, Obesity and Pregnancy, Protocol 1 (SOAP1)

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Each CPAP unit has a built-in hard drive that stores up to six months of data, a removable memory card that stores up to one year of data, and a modem configured to transmit data electronically. Data are transmitted to a secure, password-protected website ([encoreanywhere.com](http://encoreanywhere.com)) and are reviewed regularly by the PI to assess compliance and determine if the participant is eligible for incentive payments (see “Participant Compensation,” below). Data are accurate in real time only if modems are working properly. Otherwise, there may be a lag until data from the memory cards are transmitted.

### **Instructions: Labeling CPAP Machines**

- 1) The PI requests machines from the manufacturer, along with active and sham elbows, and notifies the DCC when they arrive.
- 2) To keep the clinical staff blinded, the DCC assembles kits – including the CPAP machine, a modem, and elbow – and labels all of the parts with the circuit number. Kits are stored in canvas bags.
- 3) The Clinical Team delivers the labeled kits to WPIC.

### **5.5. Home Visit and Weekly Calls/Texts**

CPAP participants are scheduled for a follow-up Home Visit (HV) by study personnel to try to address potential barriers to CPAP utilization. There is no defined window but, ideally, the visit occurs within two weeks of randomization. Additional visits may be scheduled, if needed. In addition to the home visit, the coordinator attempts to contact participants weekly by phone, text and/or email, depending on preferences recorded on the Contact Information (CI) form, to remind them to continue to use their CPAP machine.

### **5.6. Delivery/Post-Delivery**

To ensure that Magee is prepared for SOAP deliveries, the Study Coordinator uses UPMC's Augr website to report medical record numbers (MRNs) of patients who are participating in the study, adding new enrollees and removing those who have already delivered or been withdrawn. In addition, she emails the same information directly to the Magee Obstetric Sterile Processing Unit (OSPU), as a backup measure. At delivery, cord blood is collected, placental biopsies are taken, and the placenta is sent to the Pathology Department, as documented by the OSPU on the Delivery Specimen (DS) form. If the OSPU is not staffed at the time of delivery, or the participant delivers at a non-study hospital, it is possible that specimen will not be collected.

The Pathology Department prepares and stores slides of the placenta for future analysis by Dr. Parks, a study co-PI. Cord blood and plasma are stored by the OSPU, for possible future analysis.

For randomized participants, the coordinator documents IDSMB Outcomes (D0), administers a CPAP Survey (CS), consults the DCC to be Unblinded (UB) about the status of the CPAP unit (active versus sham), unblinds the participant, and, if sham, exchanges her unit with an active one, ideally before she leaves the hospital. In addition, a referral to a sleep specialist is provided, as appropriate, so that follow-up treatment can be arranged.



### Process: Unblinding

1. The Study Coordinator notifies the DCC when she is ready to be unblinded. This should not happen until the DSMB Outcomes (DO) form and CPAP Survey (CS) have been completed.
2. The DCC provides the circuit number of the machine that was issued and the unit type (active or sham).
3. After confirming that the circuit number matches, the Study Coordinator unblinds the participant and collects the modem.
4. If the unit is sham, the Study Coordinator exchanges the unit with an active one, recording the serial number of the active unit replacement, and replaces the sham elbow with an active elbow.

Within four weeks of delivery, a Chart Abstraction (CA) is completed to document lab results and other data related to admission and delivery, labor, maternal complications during pregnancy, postpartum complications, pregnancy outcomes, neonatal care, infant status, etc. CAs are completed by a trained chart abstractor. Prior to entry into REDCap, the following CAs must be reviewed by Dr. Facco:

- All CPAP participants
- For non CPAP participants:
  - If delivery occurred before 34 weeks
  - If Yes to any part of section G
  - If Yes to any part of section H
  - If Yes to M1, M2 or M4
  - If Yes to any part of section P

### 5.7. Participant Compensation

All participants are eligible to receive up to \$550 for completing the following procedures:

- PSG (clinic visits 1 and 2):  $\$150 \times 2 = \$300$
- Maternal bloods (clinic visits 1 and 2):  $\$50 \times 2 = \$100$
- Uterine artery Doppler (clinic visits 1 and 2):  $\$75 \times 2 = \$150$

In addition, CPAP participants are eligible for the following payments:

- CPAP compliance incentive:  $\$10/\text{week}^2$
- CPAP survey (delivery/post-delivery): \$25
- CPAP return (delivery/post-delivery): \$40

The coordinator uses the web-based WePay™ card payment system to disburse payments to participants. In addition, free parking is provided at Magee and WPIC, for sleep studies.

#### Instructions: WePay

1. Log on at <https://wepay.upmc.com/WP>
2. Select "Make a Payment"
3. Pick a known participant or search for or create a new participant
4. Activate a new card for new participants or select the payment card for return participants
5. Enter compensation, reimbursement and participant ID
6. Select "Continue" to print a receipt for the participant

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<sup>2</sup> Compliance is defined as using the CPAP a minimum of 4 hours per day for at least 5 out of 7 days.

## 6. Events

### 6.1. Adverse and Serious Adverse Events, including Adverse Pregnancy Outcomes

Over the course of any study, there is always a risk of an adverse event, defined as the unintended worsening of a participant's signs or symptoms. AEs are characterized in terms of study-relatedness, expectedness, and seriousness.

The SOAP1 informed consent form includes a list of AEs considered both "study related" and "expected":

- Minor discomfort associated with wearing the belt, nasal cannula and/or finger pulse oximeter during the ApneaLink Home Sleep Monitoring
- Mild bleeding, bruising, and/or soreness (infrequent; occurs in 1%-10% of people) during blood draws. Other risks include fainting and/or infection (rare; occurs in less than 1%)
- Rash or chafing at the site of the monitors, probes and/or electrodes during the PSGs
- Brief and/or minor discomfort associated with CPAP use (e.g., minor skin discomfort from the mask, nasal stuffiness, runny nose, nosebleed, eye discomfort)
- Rash or chafing at the site of the uterine artery Doppler abdominal US probe

For this study, adverse pregnancy outcomes (APOs) are also considered "expected," even though they are not on the informed consent form, because they can, theoretically, happen in any pregnancy. Examples include miscarriage, preterm birth, severe growth restriction, intrauterine fetal demise, and neonatal death before discharge. To determine whether APOs are study-related requires unmasking so this is handled by the IDSMB (see below).

An AE is considered serious if:

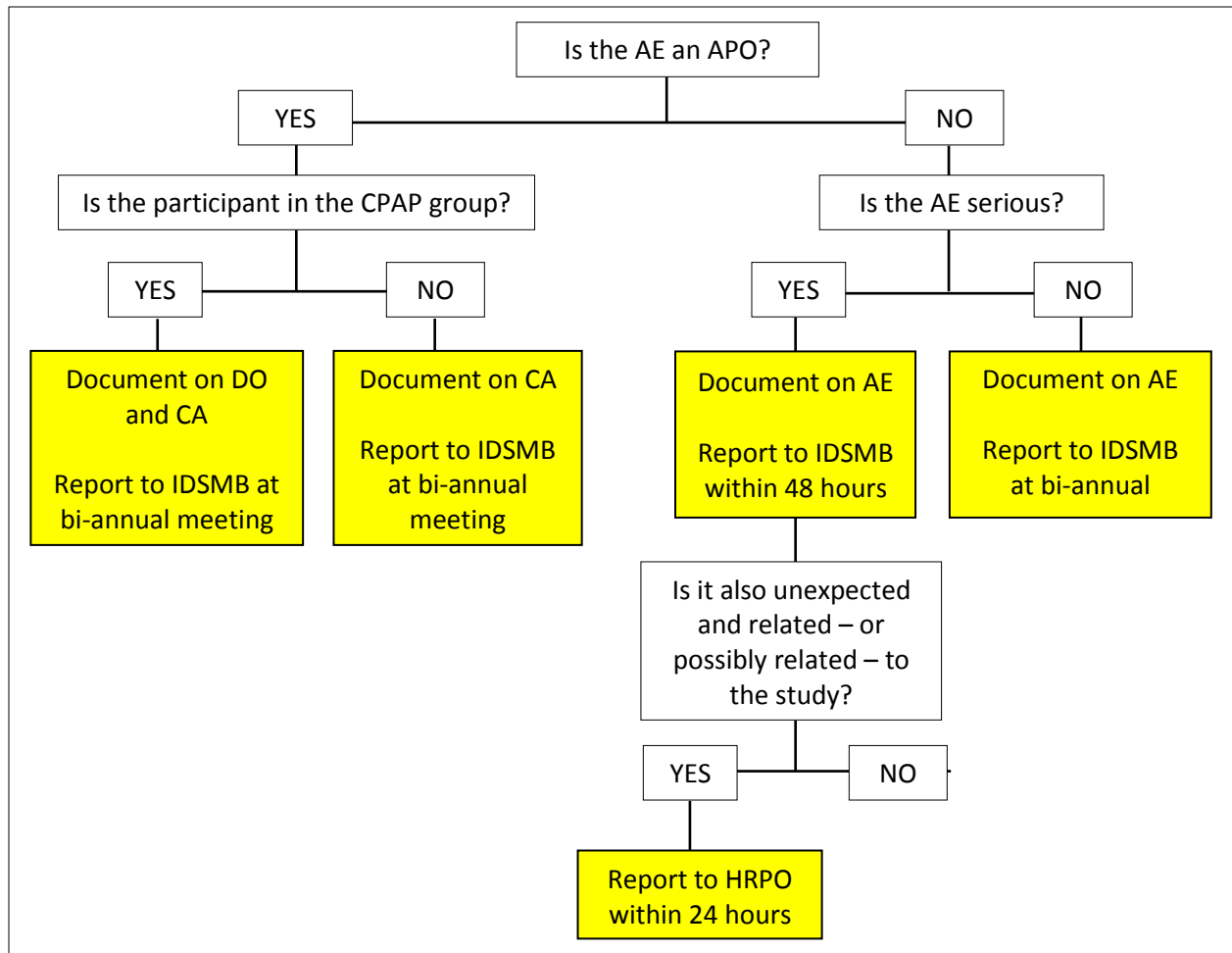
- it is life threatening;
- it results in death, hospitalization (initial or prolonged), or disability or permanent damage; or
- an intervention is required to prevent permanent impairment/damage.

Serious adverse events (SAEs) that are unexpected and related, or possibly related, to the study must be reported by the PI to the University of Pittsburgh HRPO as soon as possible but no more 24 hours after discovery. SAE reporting is done online through the HRPO's OSIRIS electronic submission system.

Meanwhile, every non-APO SAE, irrespective of relatedness and expectedness, must be reported by the PI to the chair of the IDSMB and NHLBI staff, within 48 hours of discovery.

Miscarriages are documented on a Withdrawal (WD) form; all other APOs are documented during Chart Abstraction (CA) following delivery. For CPAP participants, APOs are also documented on the IDSMB Outcomes (DO) form. All other AEs are documented on Adverse Event (AE) forms. AE and APO data are pulled for weekly internal "Events" reports and are also included in bi-annual reports to the IDSMB. IDSMB reports are unmasked so that members can determine study-relatedness (e.g., evidence of a deleterious effect of sham-CPAP treatment on the fetus) and consider whether the study needs to be modified or even terminated. Documentation and reporting requirements are summarized in the Diagram 1, below.

**Diagram 1: Documenting and Reporting AEs and SAEs, including APOs**



## 6.2. Protocol Violations and Deviations

Protocol violations are defined as departures from accepted clinical research practices or SOAP1 Study protocol or procedures that pose a risk to participant safety, adversely affect data quality and the integrity of the major scientific goals of the study, and/or involve a significant and repeated breach of participants’ privacy. Protocol violations include, but are not limited to:

- failure to obtain or document informed consent prior to study procedures
- randomization of an ineligible participant
- assignment of incorrect CPAP unit
- failure to report serious adverse events appropriately
- breach of confidentiality
- unmasking of participant or staff

By the nature of their definition, protocol violations are considered the most serious class of departure from the study protocol.

## Sleep-Disordered Breathing, Obesity and Pregnancy, Protocol 1 (SOAP1)

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All protocol violations must be reported on a Protocol Deviation/Violation Form (PD). In addition, within seven days, the site PI must develop an action plan, indicating how the problem has been/will be corrected and reoccurrences prevented. This action plan must be sent to the University of Pittsburgh HRPO and forwarded, along with responses from the HRPO, to the DCC.

Protocol deviations are defined as departures from SOAP1 Study protocol or procedures that do not pose a risk to subject safety, do not adversely affect the integrity of the major scientific goals of the study, and do not involve a significant and repeated breach of participant privacy. Protocol deviations include, but are not limited to:

- failure to obtain appropriate source documentation
- mistimed procedures or visit (e.g., conducting a clinic visit outside of the window outlined in the protocol)
- failure to collect a specimen or perform a test specified in the Protocol
- administrative error

All protocol deviations must be reported on a Protocol Deviation/Violation Form (PD). If a pattern of repeated protocol deviations emerges and it appears that data quality could be compromised or participant safety jeopardized, the PI is expected to investigate to determine whether a protocol violation applies.

### **6.3. Withdrawals**

Participants can withdraw or be withdrawn at any time. No further data are collected after the date of withdrawal but data already collected for study purposes, including biological samples, remain in the database and are used for analysis. Withdrawals are recorded on the Withdrawal (WD) form and included in reports compiled for monthly study team meetings and bi-annual IDSMB meetings.

In addition to the reasons listed on the WD, missing Clinic Visit 1 is grounds for withdrawal because randomization takes place at that visit. After randomization, intention to treat principles apply, i.e., participants remain in the study for observation even if they are unable to complete one or more components of the study or CPAP needs to be discontinued.

## **7. Data Collection**

Study personnel are expected to enter all data directly into the SOAP1 electronic data entry system (REDCap) at the time of capture. The only exceptions are the Contact Information (CI) form, Randomization Log (RAND), and Home Visit (HV) form, all of which are completed only on paper and not entered into REDCap, as well as the Sleep Log (SL) and Chart Abstraction (CA), which are completed on paper prior to being entered into REDCap.

A complete set of forms are included in the Appendix, for reference, along with form instructions and the SOAP1 REDCap User Guide.

### **7.1. Self-Assessments**

Forms marked as “Participant” in the table of forms are self-assessments (e.g., Sleep Questionnaires, CPAP survey). Study personnel are permitted to provide technical assistance to help participants complete forms, including reading the forms to them and recording responses on their behalf, but should not rephrase questions.

After a participant completes a self-assessment, Study personnel are expected to review the form for completeness and, if any field is blank, attempt to obtain a response from the participant.

If a participant refuses to complete a self-assessment form, study personnel should offer assistance and encouragement. If these attempts fail, a Missing Form (MF) form should be completed (see below).

### **7.2. Other Forms**

Aside from the self-assessment forms, all other forms are completed by study personnel, including interview-based forms (e.g., SC, II), procedure forms (e.g., MB, UA), and administrative forms (e.g., AE, PD).

With interview-based forms, study personnel should follow the prompts but are permitted to rephrase questions, if necessary, to obtain valid responses from participants.

### **7.3. Paper Forms and Visual Verification**

The DCC provides study personnel with printable PDFs of blank forms, as a backup, in case REDCap is not accessible. The participant’s ID must be written on every page, along with any other header fields (e.g., form date, staff initials). Paper forms should be stored securely at study sites, to protect participants’ confidentiality, and separate from any identifying information (e.g., names, medical record numbers). The DCC reviews paper forms during site visits (see “Data Quality,” below).

If a response on a paper forms needs to be changed, the original response should be crossed out and the new response written beside it, along with the initials of the staff person inputting the change and the date of the change. If there is a corresponding electronic version, that should be updated, too. REDCap automatically tracks who makes changes and when they are made so that information does not need to be entered online.

## Sleep-Disordered Breathing, Obesity and Pregnancy, Protocol 1 (SOAP1)

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If there is a corresponding electronic version, the paper form should be entered into REDCap as soon as possible. Visual verification is required with all paper forms, to ensure accuracy and completeness. Visual verification must be performed by a different staff person or, if by the same person, at least 24 hours later. The Study Coordinator verifies forms completed at the SBNC since these are public surveys and can't be retrieved by SBNC personnel once they have been submitted.

### 7.4. Missed Visits and Missing Forms

If a participant misses a visit and there is no opportunity to reschedule within the window (e.g., SBNC has no makeup appointments available), or the participant attends a visit but one or more forms is not completed during the visit, the Clinical Team is expected to complete a Missed Visit (MV) or Missing Form (MF) form, as appropriate. The purpose of documenting missed and incomplete visits is to alert the DCC not to expect data. A missed or incomplete visit that meets the criteria for a protocol deviation should also be documented on a PD form.

### 7.5. Missing Data Codes

In general, fields should not be left blank on a data collection form. Instead, the following missing data codes should be used:

Description	Date Value	Time Value	Numeric Value	Character Value
Not applicable	2/2/1802	98:00:00	-2	N/A
Participant does not know	3/3/1803	97:00:00	-3	Unk
Participant refuses to answer	4/4/1804	96:00:00	-4	Ref
Missing forever (e.g., test not done, result not in chart, question left blank and opportunity to respond has passed)	5/5/1805	95:00:00	-5	ND
Below the level of detection	N/A	94:00:00	-6	BLD
Above the level of quantification	N/A	93:00:00	-7	ALQ

### **8. Data Management**

The Clinical Team uses an internal system (“Jack’s system”) to manage clinical data, including keeping track of upcoming participant visits. The DCC has access to this system, too, but generally uses it only to prepare a monthly report for the Magee obstetric sterile processing unit (OSPU) of participants who have not delivered yet.

CPAP data, stored online at [encoreanywhere.com](http://encoreanywhere.com), are reviewed regularly by the PI to assess compliance. She has configured her account so that it does not display data that could unmask her (e.g., minimum pressure). The DCC has access to these data through a separate account.

The SBNC uses the Harmony System to manage clinical data, including formal AHI scores.

Management of all research data is handled by the DCC. Responsibilities include developing and updating data collection forms, training personnel in data collection and entry procedures, creating SAS programs to import data from REDCap, compiling data reports, and overseeing regulatory reporting.

Refer to Chapter 9 for information about Data Collection.

#### **8.1. Data Privacy and Security**

Study personnel are expected to maintain the security and confidentiality of participant data. To this end, three folders are maintained for each participant’s paper documents, all of which are stored in separate locked cabinets:

- A folder for documents that refer to her only by her study ID, with no identifiable data (i.e., most of the study forms)
- A folder for documents that refer to her by her study ID but also include some identifiable data (e.g., II, CA (which includes admission and discharge dates), requests for appointments at the SBNC (which include appointment date)
- A folder for documents that include her name (e.g., CI, ultrasounds, requests for ultrasound appointments)

Receipts for payments and compliance (which are identified by study ID), meanwhile, are kept in a separate locked cabinet.

Some identifiable data is stored on the electronic data system (REDCap) but access is restricted to authorized users with appropriate credentials. Data extracted by the DCC, meanwhile, are stored in secure password-protected servers maintained by the University of Pittsburgh.

In keeping with the University of Pittsburgh HRPO-approved consent procedures, participant records must be destroyed seven years after the completion of the study.

#### **8.2. Data Quality**

Data quality begins with training in data collection and entry procedures conducted by the DCC for study personnel.

## Sleep-Disordered Breathing, Obesity and Pregnancy, Protocol 1 (SOAP1)

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In addition, throughout the study, the DCC scans data sets to look for missing data, range violations, and logical and chronological discrepancies. Results are compiled in a weekly “Edits” report that is forwarded to study personnel, so they can fix errors or request bypasses (see Instructions, below)

### **Instructions: Edit Bypass Requests**

1. Open the MS Excel document attached to the weekly “Edits” report.
2. Resize columns, as needed, to view all of the data. Codes are as follows:
  - Visits: 0=Screen/Enroll | 1=Visit 1 | 2=Visit 2 | 3=Delivery/Post Delivery.
  - Edit checks: 1=Missing | 2=N/A | 3=Out of Range | 4=Dependent | 5=Illogical.
3. For each edit, fix on REDCap OR request a bypass by completing the last 3 columns for that item on the report
  - Bypass Request Date – date of request
  - Bypass Code – 1= correct as is (for range checks only) | 2 = missing forever | 3=other, specify
  - Bypass Reason – required for bypass code 3; otherwise optional
4. If you are requesting any bypasses, return the report to the DCC by email or fax as soon as possible. Bypass requests can be submitted in batches, while you continue to work on other edits. Edits that are bypassed will not show up in subsequent edit reports.

The DCC compiles several other reports for study personnel, to help them track progress and identify potential problems that could affect data quality, including:

- “Accrual and Retention” – the number of participants who have completed each phase of the study (screening, randomization, delivery) or been withdrawn.
- “Forms Status” – a comparison of forms expected versus completed, pending completion, missed, or delinquent (neither received nor reported missing)
- “Events” – the number of adverse events, serious adverse events, and protocol deviations/violations reported in recent weeks
- “Edits Status” – the number of edits identified in the last week, and how many have been resolved

Finally, the DCC conducts monitoring visits annually to monitor the quality of data collection processes and assess security of confidential records and informed consent procedures. DCC personnel review documentation, observe operations, and interview study personnel to verify that:

- human subjects’ rights are being protected;
- conduct is in compliance with the currently approved protocol; and
- study data are accurate, complete and verifiable from source documentation.

A subset (10%) of participant records is randomly selected for thorough auditing. Site visit reports are sent to the PI and also included in IDSMB reports.

### **8.3. Data Freezes**

The DCC freezes datasets, as well as the programs used to import them into SAS, at least once a month, for future reference.



### 8.4. Reporting

The DCC produces internal reports to keep study personnel informed about progress, data quality, and outcomes. Reports are distributed by email and/or at monthly team meetings. Examples include:

- Accrual and Retention – summary of participants by status, including screened, eligible, consented, completed first sleep study, randomized, completed second study, withdrawn, and delivered; distributed at monthly SOAP team meetings.
- Visit window closing – list of participants with a visit window closing in the next week; emailed weekly to SOAP team
- Delivery specimen reports: information about collection of cord blood DNA and plasma, placental biopsies, and placenta; emailed after delivery to Marcia Gallagher and Ron Jaffe.
- Withdrawal report: reminder to update EHRs and cancel any outstanding orders for participants who are withdrawn; emailed to SOAP team after withdrawal.

The DCC also prepares bi-annual reports for the IDSMB, in consultation with the PI. Topics include:

- study progress, including an assessment of data quality
- enrollment, screen failures, and outcomes
- adverse and serious adverse events
- protocol deviations/violations and modifications

In closed IDSMB reports, data are reported by treatment arm (i.e., active CPAP versus sham).

IDSMB reports are submitted annually to the University of Pittsburgh HRPO at the time of renewals.

Upon completion of the study, the DCC will make deidentified data and appropriate documentation available to the National Heart, Lung and Blood Institute of the National Institutes of Health.

## 9. Publications and Authorship

Publications refer to manuscripts, abstract, and presentations or posters at conferences. Prior to initiating any publication, a written summary including the topic, background (one paragraph), hypothesis, the target publication venue, and deadline must be submitted to the PI for review. The submission must occur within three months of any deadline to ensure adequate time for review and analyses.

All publications must include the PI and co-PI as authors.

The PI has adopted the following guidelines for authorship, based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, authored by the International Committee of Medical Journal Editors:

- To qualify as an author, an individual must have contributed to the conception and design of the work or to data collection and interpretation and must have played an important role in drafting and approving the final publication.
- The order of authorship should be a joint decision of the coauthors. Authors should be prepared to explain the order in which authors are listed.
- Every publication should have a primary author who assumes responsibility for all aspects of the publication, including accuracy of the data, authorship, and approval of the final draft by all authors. This individual also agrees to handle correspondence and respond to inquiries.
- Other contributors should be listed in the acknowledgments rather than as authors.

## **10. Ancillary Study: Autoscoring (Home PSG)**

The purpose of the Autoscoring (Home PSG) Ancillary Study is to better understand how well home sleep testing for sleep apnea compares to in-laboratory tests. The Clinical Team is recruiting 20-30 SOAP1 participants who are in the control group and have completed Clinic Visit 2, to wear an ApneaLink home sleep monitor for one night before giving birth. There is a separate consent form. Participants are eligible to receive \$50 for completing a sleep assessment of a good recording that provides valid data. Participants may be asked to repeat the assessment if valid data are not recorded. There is no payment for a repeat assessment.

The PI is Francesca L. Facco, MD, Assistant Professor, Department of Obstetrics, Gynecology & Reproductive Sciences, University of Pittsburgh. Dr. Facco is also the PI for the main SOAP1 study.

Co PIs are Carl Hubel, PhD, Associate Professor, Department of Obstetrics, Gynecology & Reproductive Sciences, Magee-Womens Research Institute; W. Tony Parks, MD, Associate Professor of Pathology, University of Pittsburgh, Magee Womens Hospital; and Patrick J. Strollo, Jr., MD, Professor of Medicine, Clinical Director, Sleep Disorder Program, UPMC – Montefiore. These individuals are also co-investigators for the main SOAP1 study.

The clinical staff includes Victoria Lopata, BSN, RN, Study Coordinator, Magee-Womens Hospital of UPMC; and Christiana Ekekwe, MPH, Research Assistant, Magee-Womens Hospital of UPMC.

Sources of support include Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and Phillips Respironics.

## **11. Other Study Documents**

Study Personnel (Z:\Facco:\SOAPforms8\_19\_2014)

IDSMB Roster (REDCap file repository)

Informed Consent Forms (Z:\Facco:\SOAPforms8\_19\_2014)

Clinical Scripts, Orders, Protocols and Handouts (Z:\Facco:\SOAPforms8\_19\_2014)

Data Collection Forms, with Instructions (REDCap file repository)

Electronic Data Entry System (REDCap) User Guide (REDCap file repository)

\* "Z" drive is accessible only by authorized personnel in Magee's Maternal and Fetal Medicine Department

# **SOAP2**

## **Sleep-Disordered Breathing, Obesity and Pregnancy, Protocol 2 (SOAP2)**

### **Manual of Operations and Procedures**

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Version 3.0, Rev. 09/22/17

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## 1. About this Manual

The purpose of this Manual of Operations and Procedures (MOP) is to provide clear, consistent, accurate and complete instructions for carrying out part 2 of the Sleep Disordered Breathing, Obesity and Pregnancy Study (SOAP2). While the MOP incorporates some content from the Protocol for reference, the focus here is on implementation. More details about the background, rationale, hypothesis, aims, outcome measures and models of statistical analysis are included in the Protocol.

The DCC is responsible for keeping the MOP up to date, in consultation with the PI and co Investigators. Revisions are tracked (see Table 1, below) and new versions are distributed to study personnel, in electronic format, for reference. In some cases, MOP changes are also documented in Operations Memos.

**Table 1: MOP Revisions**

Version	Initials	Date	Summary of change(s)
1.0	JMW	6/19/17	<ul style="list-style-type: none"> <li>Published manual</li> </ul>
2.0	JMW	7/5/17	<ul style="list-style-type: none"> <li>Clarified the randomization process in Section 5.</li> <li>Added information about NICOM data to sections 2, 3 and 5</li> <li>Added scripts, orders and handouts to Appendix D</li> <li>Added forms to Appendix E</li> <li>Added "Protocol 2" to header throughout MOP and appendices</li> <li>Added Dr. Hauspurg to Appendix A</li> <li>Updated Appendix F to reflect changes on REDCap</li> </ul>
2.1	JMW	7/20/17	<ul style="list-style-type: none"> <li>Table of forms updated to show Apnea Survey is completed by Study Coordinator (via participant interview)</li> <li>Updated section 5.2 to include reference to "note to file" about sleep specialist referrals for controls with AHI&gt;5 at Visit 2</li> <li>Added "Understanding your CPAP machine", "CPAP set up instructions", "NICOM Variables", and "Delivery Specimen Collection Protocol" to Appendix D</li> <li>Added Form Instructions to Appendix E, along with updated consolidated set of forms</li> <li>Added "REDCap instructions for SBNC Personnel" to Appendix F</li> </ul>
3.0	JMW	9/18/17	<ul style="list-style-type: none"> <li>Updated Section 5, Table 2 to include specimens collected during clinic visits 1 and 2 or at delivery, and then processed later, in batches</li> <li>Replaced references to "Evening Sleep Study" and "Morning Sleep Study" with "Sleep Study" in Section 5.2</li> <li>Updated Section 5.6 to provide additional information about specimens collected at delivery</li> <li>Added Section 7.5, Missing Data Codes</li> <li>Added Section 10: Other Study Documents and deleted all appendices</li> </ul>

### **2. Study Overview**

Part 2 of the Sleep-Disordered Breathing, Obesity and Pregnancy Study (SOAP2) is the continuation of a prospective observational study of the interplay between sleep-disordered breathing (SDB), obesity and cardiovascular risk factors in pregnancy. Our central hypothesis is that SDB is an effect modifier that increases maternal cardiovascular risk and placental hypoxic injury in obese pregnant women, and that CPAP treatment during pregnancy results in an improved cardiovascular risk and placental profile. To test this hypothesis, our cohort includes obese women with and without SDB. Refer to the table below and sections 1.1-1.4 for a discussion of the protocol. Modifications to this protocol are made only with approval from the IRB and IDSMB.

After a screening process, eligible participants are scheduled for two clinic visits, one during the second trimester (14-20 6/7 weeks) and the other during third trimester (28-31 6/7 weeks). Each visit begins with a questionnaire followed by an overnight polysomnogram (PSG). The following morning, clinical measurements are taken, maternal bloods are collected, a uterine artery Doppler is performed, and non-invasive cardiac output monitoring (NICOM) is performed to measure cardiac function and output.

Participants with severe apnea at the first clinic visit (i.e., AHI estimate  $\geq 50$ ) are withdrawn from the study. Those without SDB (i.e., AHI estimate  $< 5$ ) are assigned to a control group for observation only. Participants with SDB (i.e., AHI estimate 5-49) are randomly assigned to receive CPAP or general sleep hygiene information. CPAP units include a modem that transmits data back to the study team. Data collection points and related forms are discussed in Chapter 5.



### **3. Organization**

#### **3.1. Leadership**

The principal investigator (PI) is Francesca Facco, MD, a maternal fetal medicine specialist and assistant professor in the Department of Obstetrics, Gynecology & Reproductive Sciences in the School of Medicine at the University of Pittsburgh. Dr. Facco’s research has focused on sleep and pregnancy, with past projects including a prospective observation survey, retrospective chart review, case-control study, and prospective cohort study. She works closely with co-investigators and clinical and data management personnel (see below) to ensure that the study is being conducted in accordance with operations and procedures outlined in this manual. Dr. Facco also communicates with the Institutional Review Board (IRB) – overseen by the Human Research Protection Office (HRPO, see below) – and the Institutional Data and Safety Monitoring Board (IDSMB, see below), seeking their input/approval on proposed modifications and keeping them apprised of any serious adverse events and protocol violations that occur.

Co-investigators include:

- Carl Hubel, PhD, Department of Obstetrics, Gynecology & Reproductive Sciences, School of Medicine, University of Pittsburgh
- W. Tony Parks, MD, Department of Pathology, School of Medicine, University of Pittsburgh
- Patrick Strollo, MD, FCCP, FAASM, UPMC Sleep Medicine Center, Department of Pulmonary, School of Medicine, University of Pittsburgh
- Stephen R. Wisniewski, PhD, Graduate School of Public Health, University of Pittsburgh

#### **3.2. Clinical Team**

Clinical management and data collection are handled by Victoria Lopata, BSN, RN (study coordinator) and Christiana Ekekwe, MPH (research assistant) at Magee-Womens Hospital, part of the University of Pittsburgh Medical Center (UPMC). Their responsibilities include recruiting and screening participants, scheduling visits, collecting blood specimens, completing many of the forms, and working with the DCC to deal with data that are missing, out of range, or illogical through the “edits” process (see 8.2, below).

NICOM data are collected by the study coordinator for future processing by Alisse Hauspurg, MD, a Maternal-Fetal Medicine Fellow at Magee.

Sleep studies are conducted by technicians at the Sleep and Behavioral Neuroscience Center (SBNC, formerly the Neuroscience Clinical and Translational Research Center) located at Western Psychiatric Institute and Clinic (WPIC), also part of UPMC.

Delivery specimens are handled by the obstetric sterile processing unit (OSPU) at Magee.

#### **3.3. Data Coordinating Center**

The Epidemiology Data Center (EDC), in the Graduate School of Public Health, is serving as the Data Coordinating Center (DCC), under the direction of Dr. Stephen Wisniewski, co-director of the EDC and a SOAP2 co-investigator, and assisted by staff members Jenny Wolsk, Heather Eng and Jason Lyons.

The DCC's responsibilities include:

- Developing and maintaining the web-based data collection system, including forms, with input from the PI, co-PIs, and clinical team
- Developing and updating the MOP, with input from the PI, co-PIs, and clinical team
- Maintaining the system for random assignment of participants (CPAP versus Sleep Hygiene)
- Reviewing data for logical inconsistencies and missing or delinquent data and reporting any findings to the clinical team for prompt resolution
- Generating reports for the IDSMB and IRB
- Analyzing data and publishing results, with clinical investigators

### **3.4. Institutional Data and Safety Monitoring Board (IDSMB)**

The Institutional Data and Safety Monitoring Board (IDSMB) includes experts in obstetrics and gynecology, sleep medicine, and biostatistics. To avoid conflicts of interest, IDSMB members have no other involvement in the study. Refer to the appendix for a current roster.

The IDSMB's responsibilities include:

- Reviewing the research protocol, informed consent documents and plans for data and safety monitoring
- Evaluating the progress of the study, including periodic assessments of data quality and timeliness; participant recruitment, accrual and retention; participant risk versus benefit, adverse events, and unanticipated problems; and other factors that could affect study outcomes
- Considering factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the participant safety or the ethics of the study
- Providing technical assistance and serving as a resource to the PI on issues related to study conduct, enrollment, sample size and/or data collection
- Making recommendations to the PI concerning continuation, termination or other modifications based on observed beneficial or adverse effects
- Reviewing reports of serious adverse events and protocol violations

The IDSMB meets at least once every six months by phone, with additional meetings convened as needed (e.g., if a safety concern arises). The chairperson is the safety officer, serving as the contact person for reports of serious adverse events and protocol violations. Reports are prepared by the DCC, in consultation with the PIs and co-PIs, and distributed to IDSMB members, through the Clinical Translational Science Institute (CTSI, see below) at least one week prior to each meeting.

### **3.5. Human Research Protection Office (HRPO)/ Institutional Review Board (IRB)**

The Institutional Review Board, overseen by the Human Research Protection Office (HRPO), is charged with ensuring that research involving human subjects is conducted in safe, ethical and scientifically-sound ways. Prior to beginning the SOAP2 study, the PI secured approval from the HRPO (see appendix for letter of approval). For the duration of the study, renewal requests must be submitted annually and amendment requests must be approved before any changes to the Protocol are implemented. The HRPO also requires that the PI report serious adverse events and protocol violations (see chapter 8) through the Online Submission for Institutional Reviews System (OSIRIS).

### **3.6. Clinical Translational Science Institute (CTSI)**

The Clinical Translational Science Institute (CTSI) oversees DSMBs for clinical trials that require oversight, and assists in ensuring safe conduct of the study. For SOAP2, the CTSI works with the PI, IDSMB chair, and DCC to schedule meetings, develop agendas, and distribute materials.

### **3.7. Funding/Support**

Sources of support for this study include:

- National Heart, Lung, and Blood Institute (1R01HL120354-01A1 grant)
- The University of Pittsburgh's Building Interdisciplinary Research Careers in Women's Health (K12HD043441 grant)
- The Department of Obstetrics and Gynecology at the University of Pittsburgh's School of Medicine (additional funds provided, as needed)

## 4. Startup Requirements

### 4.1. Checklist

- NHLBI approval obtained (PI)
- IDSMB approval obtained (PI)
- HRPO/IRB approval obtained (PI)
- Clinical protocols modified for recruitment, screening and treatment of participants (DCC, PI)
- Data collection forms modified (DCC, PI)
- Electronic data collection, entry and management systems modified and tested (DCC, Clinical Team)
- Randomization procedures developed and tested (DCC, Clinical Team)
- Training materials modified (DCC)
- List of key personnel updated (PI)
- Completion of training by study personnel (Clinical Team, see below)
- Conflict of interest disclosures on file with the DCC (Leadership, Clinical Team, DCC, see below)

### 4.2. Training and Certification

The DCC provides training for clinical team members, to ensure quality and reliability of data and appropriate documentation of study progress and outcomes.

Topics include:

- Data collection forms
- Electronic data management system
- Randomization
- CPAP compliance tracking and incentive payments
- Adverse events and protocol deviations/violations
- Missed visits and missing forms
- Missing, out of range, or illogical data

Chart abstraction training entails abstracting two charts already abstracted by Dr. Facco and reviewing any discrepancies with Dr. Facco.

At the conclusion of training, the DCC certifies clinical team members who demonstrate proficiency. Refresher training is scheduled, as needed, and recertification required, if appropriate.

Over the course of the study, the PI is expected to notify the DCC about new hires so that training and certification can be provided in a timely manner.

### 4.3. Conflict of Interest Disclosure

The PI and all co-investigators are required to disclose any ties to companies or individuals that could create conflicts (or dualities) of interest for the study. Disclosure statements are renewed annually and filed with the DCC.

## 5. Clinical Management

Clinical personnel recruit, screen and enroll participants, coordinate treatment, obtain specimens, and collect data at certain time points using forms developed or modified by the DCC for this study (see Table 2, below, and sections 5.1-5.6). Forms are included as an appendix to this MOP.

**Table 2: Data Collection Points, Related Forms and Delegation of Responsibility**

Form	Screening (EGA 6-19 6/7 wks)	Clinic Visit 1 (EGA 14-20 6/7 wks)	Home Visit	Clinic Visit 2 (EGA 28-31 6/7 wks)	Delivery/ Post Delivery	Other Time- point
Screening Questionnaire (SC)	RA					
Consent Documentation (CD)	RA					
Contact Information (CI) <sup>1</sup>	RA					
Initial Interview (II)	RA					
Sleep Log (SL)	[give]	[return]				
Sleep Questionnaire (SQ)		PARTICIP.		PARTICIP.		
Sleep Study (SS)		SBNC		SBNC		
Group Assignment (GRP)		COORD.				
Clinical Measurements (CM)		COORD.				
Maternal Bloods (MB)		COORD.		COORD.		
Uterine Artery Doppler (UA) <sup>3</sup>		COORD.		COORD.		
Home Visit (HV) <sup>1,2</sup>			SBNC	COORD.		
Delivery Specimens (DS)					OSPU	
IDSMB Outcomes (DO) <sup>2</sup>					COORD.	
Apnea Survey (AP) <sup>2</sup>					COORD.	
Chart Abstraction (CA) <sup>3</sup>					COORD. <sup>4</sup>	
Adverse Event (AE)	<----- COORD. (as needed) ----->					
Protocol Deviation (PD)	<----- COORD. (as needed) ----->					
Withdrawal (WD)	<----- COORD. (as needed) ----->					
Missed Visit (MV)	<----- COORD. (as needed) ----->					
Missing Form (MF)	<----- COORD. (as needed) ----->					
Other Data	Screening (EGA 6-19 6/7 wks)	Clinic Visit 1 (EGA 14-20 6/7 wks)	Home Visit	Clinic Visit 2 (EGA 28-31 6/7 wks)	Delivery/ Post Delivery	Other Time- point
NICOM <sup>4</sup>		Hauspurg		Hauspurg		
Maternal blood <sup>5</sup>		Gallagher		Gallagher		
Placenta <sup>5</sup>					Parks	
Placental biopsies <sup>6</sup>					PI	
Cord blood and plasma <sup>6</sup>					PI	

<sup>1</sup> Completed on paper only; not part of the electronic Data Management System

<sup>2</sup> Applies only to CPAP and Sleep Hygiene participants

<sup>3</sup> In consultation with PI

<sup>4</sup> Data collected and stored on NICOM machine by Study Coordinator then downloaded later by Dr. Hauspurg in batches and sent to DCC in MS Excel format

<sup>5</sup> Processed later, in batches

<sup>6</sup> Stored for future studies

### 5.1. Recruitment and Screening

To identify potential participants for the SOAP2 study, the research assistant (RA) reviews prenatal medical records on the EPIC system and approaches women who meet basic inclusion criteria (i.e., aged 18 or older, 6-20 weeks pregnant, and obese) during their prenatal appointments to ascertain their

## Sleep-Disordered Breathing, Obesity and Pregnancy, Protocol 2 (SOAP2)

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interest. This requires cooperation from the healthcare provider and his/her staff, so the PI reaches out to them to let them know about the study before their patients are approached.

Meanwhile, some women find out about the study on their own through Pitt+Me ([pittplusme.org](http://pittplusme.org)), a searchable database designed for individuals who are interested in getting involved in research; flyers or pamphlets posted throughout Magee-Womens Hospital (MWH); a slide displayed on the plasma screens in the lobby and near the elevators; or word of mouth. If they decide to contact the study team, they are prescreened in person or by phone.

The RA maintains a list of individuals who identify themselves or are approached and follows up with those who are interested during subsequent prenatal visits until a formal screening visit takes place. Repeated contact helps to ensure that those who ultimately enroll understand what is involved and are committed to completing the study.

During the formal screening visit, the RA confirms that the individual has not already been screened during this pregnancy or enrolled during a previous pregnancy long enough to complete the first sleep study, both of which are exclusion criteria. Next, a study ID is generated (see instructions, below) and a Screening (SC) form is completed, in person or by phone, to review the other exclusion criteria:

- A history of sleep apnea, insomnia, diabetes, heart disease, or lupus
- Prior use of a CPAP device
- Use of a breathing machine at night
- Currently pregnant with twins or higher order multiples (criterion added 6/1/15)
- Use of a sleeping aid more than once in the past month

### **Instructions: ID Generation**

1. Create a new record on the electronic data entry system (REDCap). A record ID (e.g., 81) will be automatically generated. Add 2000 to this record ID to generate the first part of the SOAP2 ID. If REDCap is not accessible, refer to the clinical data management tool developed by Jack Doman to determine the next consecutive 4-digit number.
2. Add a dash ("-") followed by the participant's first and last initials (using capital letters) to create her ID (e.g., 2081-AH).

The SC is based on self-report; the RA does not refer to medical records or other sources to verify the accuracy of participant responses.

If the individual is found to be eligible, additional information is collected about sleep characterization and then details about the study are provided, including the timeline, the randomization process, potential risks and benefits, and the importance of compliance. Prior to seeking informed consent, which must be done in person, the RA reminds the individual that there is no obligation to participate or penalty for declining to participate, and that her care will not be compromised if she chooses not to participate or enrolls and subsequently leaves the study. Prospective participants must sign the consent form in order to proceed. The consent process is documented on the Consent Documentation form.

If informed consent is obtained, Contact Information (CI) is collected on a paper form and stored in a secure place at the study office; it is not entered into the electronic data entry system (REDCap). Next, an Initial Interview (II) is completed with questions about lifestyle, use of medications, prior pregnancies, and medical history, and self-reported estimated gestational age is confirmed by reviewing

the participant's medical record. Finally, the participant is given a 7-day Sleep Log (SL) along with instructions about how to record bedtimes, wake-up times, naps, and other information. Participants are expected to bring the completed SL when they come for Clinic Visit 1, which takes place 14-20 6/7 weeks EGA, so they need to receive the SL at least one week before then.

### **5.2. Clinic Visits: PSG, Maternal Bloods, Uterine Artery Doppler**

There are two overnight clinic visits, one scheduled during the second trimester (14-20 6/7 weeks EGA) and the other during the third trimester (28-31 6/7 EGA). Both take place at the Sleep and Behavioral Neuroscience Center (SBNC, formerly the Neuroscience Clinical and Translational Research Center) at Western Psychiatric Institute & Clinic (WPIC, part of UPMC). The instructions below are consistent with orders prescribed by the PI (see Appendix).

Prior to the each visit, the Study Coordinator reviews the participant's medical record to identify any medications that have been prescribed as well as diagnoses or symptoms that could affect her participation. Participants receive a reminder by phone, text, or email (based on personal preferences noted on the Contact Information form) of the coming visit and instructions to bring all medications with them. This is especially important for participants with hypertension. For the first visit, participants are also instructed to bring their completed Sleep Log (SL).

Each clinic visit begins in the evening when the participant arrives at the SBNC, usually 7-8PM.

Components include:

- Collection of the Sleep Log (SL) (Visit 1 only). The participant receives the SL from the Research Assistant during screening, completes it on paper, and returns it to the SBNC.
- Administration of a Sleep Questionnaire (SQ). The SQ covers general work and sleep patterns, sleep habits, snoring and sleep apnea. It is administered online. SBNC personnel complete the first part and the participant completes the rest. SBNC personnel are permitted to provide assistance, if requested by the participant, but should not rephrase questions. Prior to submitting, SBNC personnel are asked to review the form for completeness and encourage the participant to fill in any blanks.
- Initiation of the Sleep Study (SS) form. Weight is measured (this is not self-reported) and, after at least five minutes of rest, blood pressure is measured three times, with five minutes between measurements. Any readings >140/90 should be reported immediately to the medical contact.
- "Wire up." Small electrodes are placed on the participant's scalp, face, and legs so that technologists can monitor her air flow, body movements, heart rate, and oxygen saturation while she sleeps.
- Completion of the Sleep Study (SS) form. During the night, SBNC personnel review the participant's polysomnography (PSG) data to calculate an apnea-hypopnea index (AHI) estimate, using AASM 2012 rules. The AHI estimate at the first visit determines eligibility for randomization (see below). If a sleep study is not completed successfully – either because a participant refuses or there is a medical reason or technical problem – SBNC personnel should report this on the SSA and also notify the Study Coordinator. (Note: sleep studies are formally scored later on but these scores are recorded on the SBNC's "Harmony System," not REDCap.)
- Randomization (Visit 1 only). Participants with an AHI estimate 5-49 and who agree to be randomized are randomized by the Study Coordinator to CPAP or Sleep Hygiene for the treatment phase of the study (see "Randomization," below). For those randomized to CPAP, the assignment date, unit number, mask type, and other details are recorded on Group Assignment (GRP) form, and

use and care instructions, included in the case, are presented. For those randomized to Sleep Hygiene, general information is provided.

- Clinical measurements, maternal bloodwork, uterine artery ultrasound and NICOM data. After the PSG, participants are escorted by the Study Coordinator back to Magee. Clinical measurements (vitals, height, weight and waist, hip and neck circumference) are taken using the SOAP2 Tanita Protocol (see Appendix), along with three measures of blood pressure, and recorded on the Clinical Measurement (CM) form; fasting blood is drawn for cardiovascular risk profiles and documented on the Maternal Blood (MB) form; and a uterine artery (UA) Doppler is performed. Blood is processed and then stored for future batched testing. Non-invasive cardiac output monitoring (NICOM) is performed to measure cardiac function and output over a small interval of time (5-10 minutes).
- The Study Coordinator also takes this opportunity to review the Sleep Log, to see if there are any unusual responses, and the Sleep Questionnaire, to see if any responses are missing, asking the participant for clarification or additional information, as appropriate. In addition, during visit 2, the Study Coordinator asks CPAP participants whether all of the equipment is the same as what was originally issued and confirms that all components are still correctly labeled.

At the SBNC, eating is permitted until midnight. After midnight, only water is permitted until after fasting blood has been collected in the morning. Ideally, participants are asleep by 11PM but no specific good night time (GNT) has been established for the study.

An AHI estimate is calculated at both visits. At Visit 1, the AHI estimate determines group assignment (see 5.3, below). At Visit 2, participants who are in the Control Group and who have an AHI estimate of 5 or higher are given a referral to a sleep specialist (documented by the Study Coordinator as a "note to file").

Data are entered directly into REDCap, using the study laptop at the SBNC. If REDCap is not accessible, SBNC personnel enter data on a paper form and then give the paper form to the Study Coordinator the following morning so that the data can be entered into REDCap and/or visually verified, if it has already been entered by then. Visual verification is required for all forms completed on paper and is done by a different staff person or at least a day later, if done by the same staff person.

### **5.3. Group Assignment and Randomization**

A participant's AHI estimate from the first clinic visit determines whether she is randomized, assigned to the control group for observation only, or withdrawn from the study. Participants with an AHI estimate below 5 are assigned to the control group. They are not randomized. Participants with an AHI estimate of 50 or higher are referred to a sleep specialist and withdrawn from the study. They are not randomized. Participants with an AHI estimate 5-49 who agree to randomization are randomized by the Study Coordinator to CPAP or Sleep Hygiene, based on a system developed by the DCC (see below).



**Table 4: AHI Estimates, Study Assignment, and Instructions for Study Coordinator**

AHI Estimate	Assignment	Instructions for Study Coordinator
<5	Control	Tell participant that she does not have sleep apnea so she will not be in the treatment part of the study. Do <u>not</u> randomize.
5-49	CPAP or Sleep Hygiene	Tell participant that she is eligible for the treatment part of the study and ask if she agrees to be randomized. If she agrees, proceed with randomization (see Instructions, below). If she does not agree, do not randomize. Instead, let her know she will be withdrawn from the study.
≥50	Withdrawn	Tell participant that she has a degree of sleep apnea that requires attention and provide a referral to a sleep specialist. Do <u>not</u> randomize.

**Instructions: Randomization**

- 1) Select the next consecutively numbered Randomization Envelope, provided by the DCC. It is important not to skip any numbers.
- 2) Prior to opening the envelope, confirm that it is Visit 1, the participant is willing to be randomized, and her AHI estimate is 5-49.
- 3) Open the envelope to reveal her randomization assignment and then follow the prescribed script, documenting the process as directed on the Group Assignment (GRP) form, on REDCap.
- 4) File the randomization assignment sheet in the participant's research study folder, as source documentation.

**5.4. CPAP Equipment**

The Clinical Team is responsible for obtaining CPAP machines with cases and modems and labeling them with circuit numbers (C200-C236). The coordinator brings the units to the SBNC for distribution to eligible participants at Clinic Visit 1.

Each CPAP unit has a built-in hard drive that stores up to six months of data, a removable memory card that stores up to one year of data, and a modem configured to transmit data electronically. Data are transmitted to a secure, password-protected website (encoreanywhere.com) and are reviewed regularly by the PI to assess compliance and determine if the participant is eligible for incentive payments (see “Participant Compensation,” below). Data are accurate in real time only if modems are working properly. Otherwise, there may be a lag until data from the memory cards are transmitted.

**5.5. Home Visit and Weekly Calls/Texts**

CPAP participants are scheduled for a follow-up Home Visit (HV) by study personnel to try to address potential barriers to CPAP utilization. There is no defined window but, ideally, the visit occurs within two weeks of randomization. Additional visits may be scheduled, if needed. In addition to the home visit, the Research Assistant attempts to contact participants weekly by phone, text and/or email, depending on preferences recorded on the Contact Information (CI) form, to remind them to continue to use their CPAP machine.

Sleep Hygiene participants do not have a Home Visit but they receive monthly reminders, by phone, text and/or email, depending on preferences recorded on the Contact Information (CI) form.

### 5.6. Delivery/Post-Delivery

To ensure that Magee is prepared for SOAP deliveries, the Study Coordinator uses UPMC's Augr website to report medical record numbers (MRNs) of patients who are participating in the study, adding new enrollees and removing those who have already delivered or been withdrawn. In addition, she emails the same information directly to the Magee Obstetric Sterile Processing Unit (OSPU), as a backup measure. At delivery, cord blood is collected, placental biopsies are taken, and the placenta is sent to the Pathology Department, as documented by the OSPU on the Delivery Specimen (DS) form. If the OSPU is not staffed at the time of delivery, or the participant delivers at a non-study hospital, it is possible that specimen will not be collected.

The Pathology Department prepares and stores slides of the placenta for future analysis by Dr. Parks, a study co-PI. Cord blood and plasma are stored by the OSPU, for possible future analysis.

For randomized participants, the Study Coordinator documents IDSMB Outcomes (DO), administers the Apnea Survey (AP), and collects the CPAP machine, if one was issued.

Within four weeks of delivery, a Chart Abstraction (CA) is completed to document lab results and other data related to admission and delivery, labor, maternal complications during pregnancy, postpartum complications, pregnancy outcomes, neonatal care, infant status, etc. CAs are completed by a trained chart abstractor. Prior to entry into REDCap, the following CAs must be reviewed by Dr. Facco:

- All CPAP participants
- For non CPAP participants:
  - If delivery occurred before 34 weeks
  - If Yes to any part of section 4
  - If Yes to 6.1, 6.2 or 6.4
  - If Yes to any part of section 10
  - If Yes to any part of section 16

### 5.7. Participant Compensation

All participants are eligible to receive up to \$550 for completing the following procedures:

- PSG (clinic visits 1 and 2):  $\$150 \times 2 = \$300$
- Maternal bloods (clinic visits 1 and 2):  $\$50 \times 2 = \$100$
- Uterine artery Doppler (clinic visits 1 and 2):  $\$75 \times 2 = \$150$

In addition, randomized participants are eligible for the following payments:

- Apnea survey (delivery/post-delivery): \$25
- CPAP compliance incentive (for CPAP participants only): \$10/week<sup>1</sup>
- CPAP return (for CPAP participants only) (delivery/post-delivery): \$40

The Clinical Team uses the web-based WePay™ card payment system to disburse payments to participants. In addition, free parking is provided at Magee and WPIC, for sleep studies.

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<sup>1</sup> Compliance is defined as using the CPAP a minimum of 4 hours per day for at least 5 out of 7 days.

**Instructions: WePay**

1. Log on at <https://wepay.upmc.com/WP>
2. Select "Make a Payment"
3. Pick a known participant or search for or create a new participant
4. Activate a new card for new participants or select the payment card for return participants
5. Enter compensation, reimbursement and SOAP2 ID
6. Select "Continue" to print a receipt for the participant

### 6. Events

#### 6.1. Adverse and Serious Adverse Events, including Adverse Pregnancy Outcomes

Over the course of any study, there is always a risk of an adverse event, defined as the unintended worsening of a participant's signs or symptoms. AEs are characterized in terms of study-relatedness, expectedness, and seriousness.

The SOAP2 informed consent form includes a list of AEs considered both "study related" and "expected":

- Minor discomfort associated with wearing the belt, nasal cannula and/or finger pulse oximeter during the ApneaLink Home Sleep Monitoring
- Mild bleeding, bruising, and/or soreness (infrequent; occurs in 1%-10% of people) during blood draws. Other risks include fainting and/or infection (rare; occurs in less than 1%)
- Rash or chafing at the site of the monitors, probes and/or electrodes during the PSGs
- Brief and/or minor discomfort associated with CPAP use (e.g., minor skin discomfort from the mask, nasal stuffiness, runny nose, nosebleed, eye discomfort)
- Rash or chafing at the site of the uterine artery Doppler abdominal US probe

For this study, adverse pregnancy outcomes (APOs) are also considered "expected," even though they are not on the informed consent form, because they can, theoretically, happen in any pregnancy. Examples include miscarriage, preterm birth, severe growth restriction, intrauterine fetal demise, and neonatal death before discharge. To determine whether APOs are study-related requires unmasking so this is handled by the IDSMB (see below).

An AE is considered serious if:

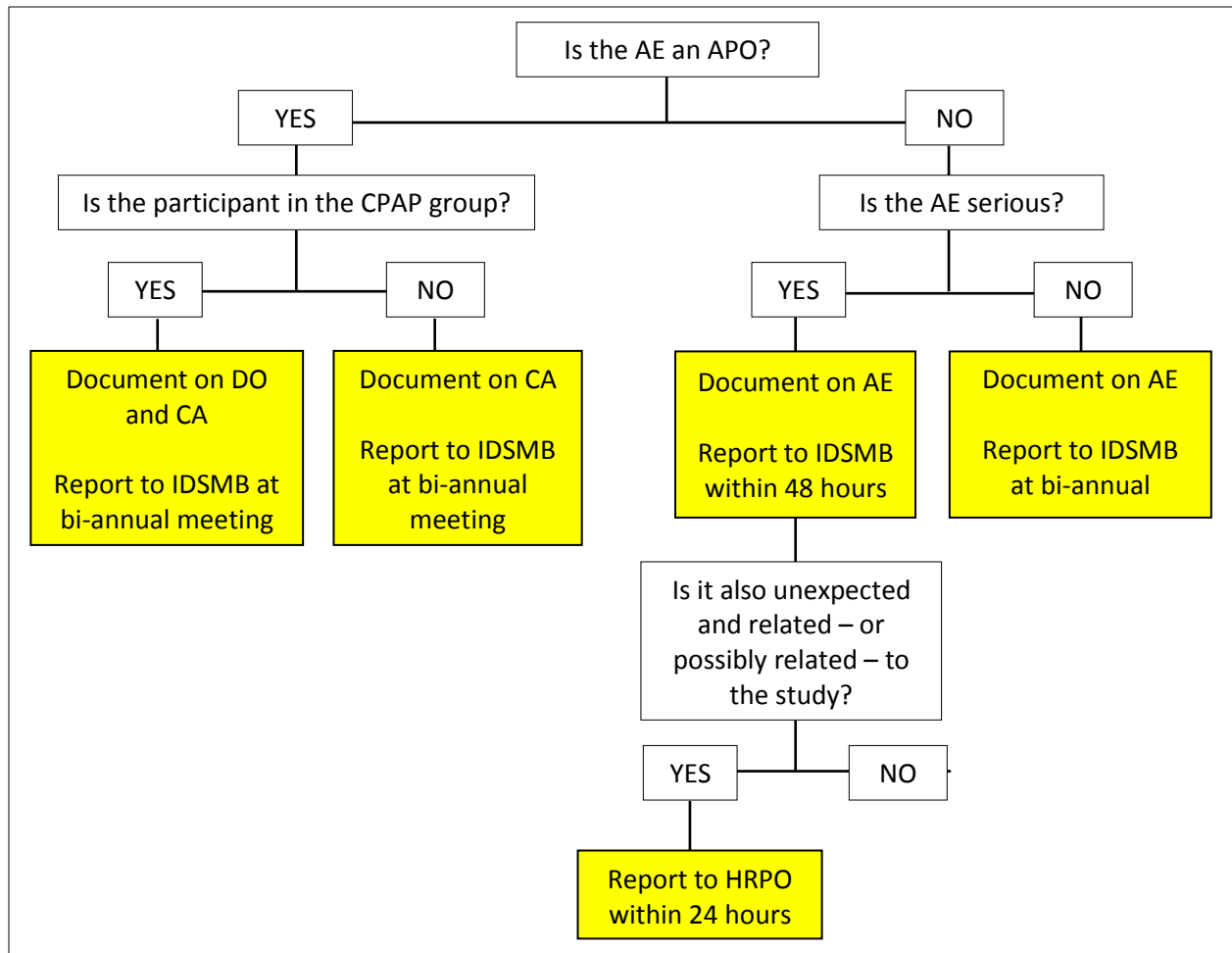
- it is life threatening;
- it results in death, hospitalization (initial or prolonged), or disability or permanent damage; or
- an intervention is required to prevent permanent impairment/damage.

Serious adverse events (SAEs) that are unexpected and related, or possibly related, to the study must be reported by the PI to the University of Pittsburgh HRPO as soon as possible but no more 24 hours after discovery. SAE reporting is done online through the HRPO's OSIRIS electronic submission system.

Meanwhile, every non-APO SAE, irrespective of relatedness and expectedness, must be reported by the PI to the chair of the IDSMB and NHLBI staff, within 48 hours of discovery.

Miscarriages are documented on a Withdrawal (WD) form; all other APOs are documented during Chart Abstraction (CA) following delivery. For CPAP participants, APOs are also documented on the IDSMB Outcomes (DO) form. All other AEs are documented on Adverse Event (AE) forms. AE and APO data are pulled for weekly internal "Events" reports and are also included in bi-annual reports to the IDSMB. IDSMB reports are unmasked so that members can determine study-relatedness and consider whether the study needs to be modified or even terminated. Documentation and reporting requirements are summarized in the Diagram 1, below.

**Diagram 1: Documenting and Reporting AEs and SAEs, including APOs**



## 6.2. Protocol Violations and Deviations

Protocol violations are defined as departures from accepted clinical research practices or SOAP2 Study protocol or procedures that pose a risk to participant safety, adversely affect data quality and the integrity of the major scientific goals of the study, and/or involve a significant and repeated breach of participants’ privacy. Protocol violations include, but are not limited to:

- failure to obtain or document informed consent prior to study procedures
- randomization of an ineligible participant
- assignment of incorrect CPAP unit
- failure to report serious adverse events appropriately
- breach of confidentiality

By the nature of their definition, protocol violations are considered the most serious class of departure from the study protocol.

All protocol violations must be reported on a Protocol Deviation/Violation Form (PD). In addition, within seven days, the site PI must develop an action plan, indicating how the problem has been/will be

corrected and reoccurrences prevented. This action plan must be sent to the University of Pittsburgh HRPO and forwarded, along with responses from the HRPO, to the DCC.

Protocol deviations are defined as departures from SOAP2 Study protocol or procedures that do not pose a risk to subject safety, do not adversely affect the integrity of the major scientific goals of the study, and do not involve a significant and repeated breach of participant privacy. Protocol deviations include, but are not limited to:

- failure to obtain appropriate source documentation
- mistimed procedures or visit (e.g., conducting a clinic visit outside of the window outlined in the protocol)
- failure to collect a specimen or perform a test specified in the Protocol
- administrative error

All protocol deviations must be reported on a Protocol Deviation/Violation Form (PD). If a pattern of repeated protocol deviations emerges and it appears that data quality could be compromised or participant safety jeopardized, the PI is expected to investigate to determine whether a protocol violation applies.

### **6.3. Withdrawals**

Participants can withdraw or be withdrawn at any time. No further data are collected after the date of withdrawal but data already collected for study purposes, including biological samples, remain in the database and are used for analysis. Withdrawals are recorded on the Withdrawal (WD) form and included in reports compiled for monthly study team meetings and bi-annual IDSMB meetings.

In addition to the reasons listed on the WD, missing Clinic Visit 1 is grounds for withdrawal because randomization takes place at that visit. After randomization, intention to treat principles apply, i.e., participants remain in the study for observation even if they are unable to complete one or more components of the study or CPAP needs to be discontinued.

### **7. Data Collection**

Study personnel are expected to enter all data directly into the SOAP2 electronic data entry system (REDCap) at the time of capture. The only exceptions are the Contact Information (CI) form and Home Visit (HV) form which are completed only on paper and not entered into REDCap, as well as the Sleep Log (SL) and Chart Abstraction (CA), which are completed on paper prior to being entered into REDCap.

A complete set of forms are included in the Appendix, for reference, along with instructions and the SOAP2 REDCap User Guide.

#### **7.1. Self-Assessments**

Forms marked as “Participant” in the table of forms are self-assessments (e.g., Sleep Questionnaire). Study personnel are permitted to provide technical assistance to help participants complete this form, including reading the form to them and recording responses on their behalf, but should not rephrase questions.

After a participant completes a self-assessment, study personnel are expected to review the form for completeness and, if any field is blank, attempt to obtain a response from the participant.

If a participant refuses to complete a self-assessment form, study personnel should offer assistance and encouragement. If these attempts fail, a Missing Form (MF) form should be completed (see below).

#### **7.2. Other Forms**

Aside from the self-assessment form, all other forms are completed by study personnel, including interview-based forms (e.g., SC, II), procedure forms (e.g., MB, UA), and administrative forms (e.g., AE, PD).

With interview-based forms, study personnel should follow the prompts but are permitted to rephrase questions, if necessary, to obtain valid responses from participants.

#### **7.3. Paper Forms and Visual Verification**

The DCC provides study personnel with printable PDFs of blank forms, as a backup, in case REDCap is not accessible. The participant’s ID must be written on every page, along with any other header fields (e.g., form date, staff initials). Paper forms should be stored securely at study sites, to protect participants’ confidentiality, and separate from any identifying information (e.g., names, medical record numbers). The DCC reviews paper forms during site visits (see “Data Quality,” below).

If a response on a paper forms needs to be changed, the original response should be crossed out and the new response written beside it, along with the initials of the staff person inputting the change and the date of the change. If there is a corresponding electronic version, that should be updated, too. REDCap automatically tracks who makes changes and when they are made so that information does not need to be entered online.

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If there is a corresponding electronic version, the paper form should be entered into REDCap as soon as possible. Visual verification is required with all paper forms, to ensure accuracy and completeness. Visual verification must be performed by a different staff person or, if by the same person, at least 24 hours later. If the SBNC has to complete a form on paper and doesn't have an opportunity to verify it, the form should be given to the Study Coordinator for verification.

### 7.4. Missed Visits and Missing Forms

If a participant misses a visit and there is no opportunity to reschedule within the window (e.g., SBNC has no makeup appointments available), or the participant attends a visit but one or more forms is not completed during the visit, the Clinical Team is expected to complete a Missed Visit (MV) or Missing Form (MF) form, as appropriate. The purpose of documenting missed and incomplete visits is to alert the DCC not to expect data. A missed or incomplete visit that meets the criteria for a protocol deviation should also be documented on a PD form.

### 7.5. Missing Data Codes

In general, fields should not be left blank on a data collection form. Instead, the following missing data codes should be used:

Description	Date Value	Time Value	Numeric Value	Character Value
Not applicable	2/2/1802	98:00:00	-2	N/A
Participant does not know	3/3/1803	97:00:00	-3	Unk
Participant refuses to answer	4/4/1804	96:00:00	-4	Ref
Missing forever (e.g., test not done, result not in chart, question left blank and opportunity to respond has passed)	5/5/1805	95:00:00	-5	ND
Below the level of detection	N/A	94:00:00	-6	BLD
Above the level of quantification	N/A	93:00:00	-7	ALQ



### **8. Data Management**

The Clinical Team uses an internal system (“Jack’s system”) to manage clinical data, including keeping track of upcoming participant visits. The DCC has access to this system, too, but generally uses it only to prepare a monthly report for the Magee obstetric sterile processing unit (OSPU) of participants who have not delivered yet.

CPAP data, stored online at [encoreanywhere.com](http://encoreanywhere.com), are reviewed regularly by the Clinical Team to assess compliance.

The SBNC uses the Harmony System to manage clinical data, including formal AHI scores.

Management of all research data is handled by the DCC. Responsibilities include developing and updating data collection forms, training personnel in data collection and entry procedures, creating SAS programs to import data from REDCap, compiling data reports, and overseeing regulatory reporting.

Refer to Chapter 9 for information about Data Collection.

#### **8.1. Data Privacy and Security**

Study personnel are expected to maintain the security and confidentiality of participant data. To this end, three folders are maintained for each participant’s paper documents, all of which are stored in separate locked cabinets:

- A folder for documents that refer to her only by her study ID, with no identifiable data (i.e., most of the study forms)
- A folder for documents that refer to her by her study ID but also include some identifiable data (e.g., II, CA (which includes admission and discharge dates), requests for appointments at the SBNC (which include appointment date)
- A folder for documents that include her name (e.g., CI, ultrasounds, requests for ultrasound appointments)

Receipts for payments and compliance (which are identified by study ID), meanwhile, are kept in a separate locked cabinet.

Some identifiable data is stored on the electronic data system (REDCap) but access is restricted to authorized users with appropriate credentials. Data extracted by the DCC, meanwhile, are stored in secure password-protected servers maintained by the University of Pittsburgh.

In keeping with the University of Pittsburgh IRB-approved consent procedures, participant records must be destroyed seven years after the completion of the study.

#### **8.2. Data Quality**

Data quality begins with training in data collection and entry procedures conducted by the DCC for study personnel.

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In addition, throughout the study, the DCC scans data sets to look for missing data, range violations, and logical and chronological discrepancies. Results are compiled in a weekly “Edits” report that is forwarded to study personnel, so they can fix errors or request bypasses (see Instructions, below)

### **Instructions: Edit Bypass Requests**

1. Open the MS Excel document attached to the weekly “Edits” report.
2. Resize columns, as needed, to view all of the data. Codes are as follows:
  - Visits: 0=Screen/Enroll | 1=Visit 1 | 2=Visit 2 | 3=Delivery/Post Delivery.
  - Edit checks: 1=Missing | 2=N/A | 3=Out of Range | 4=Dependent | 5=Illogical.
3. For each edit, fix on REDCap OR request a bypass by completing the last 3 columns for that item on the report
  - Bypass Request Date – date of request
  - Bypass Code – 1= correct as is (for range checks only) | 2 = missing forever | 3=other, specify
  - Bypass Reason – required for bypass code 3; otherwise optional
4. If you are requesting any bypasses, return the report to the DCC by email or fax as soon as possible. Bypass requests can be submitted in batches, while you continue to work on other edits. Edits that are bypassed will not show up in subsequent edit reports.

The DCC compiles several other reports for study personnel, to help them track progress and identify potential problems that could affect data quality, including:

- “Accrual and Retention” – the number of participants who have completed each phase of the study (screening, randomization, delivery) or been withdrawn.
- “Forms Status” – a comparison of forms expected versus completed, pending completion, missed, or delinquent (neither received nor reported missing)
- “Events” – the number of adverse events, serious adverse events, and protocol deviations/violations reported in recent weeks
- “Edits Status” – the number of edits identified in the last week, and how many have been resolved

Monitoring is not conducted for this study.

### **8.3. Data Freezes**

The DCC freezes datasets, as well as the programs used to import them into SAS, at least once a month, for future reference.

### **8.4. Reporting**

The DCC produces internal reports to keep study personnel informed about progress, data quality, and outcomes. Reports are distributed by email and/or at monthly team meetings. Examples include:

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- Accrual and Retention – summary of participants by status, including screened, eligible, consented, completed first sleep study, randomized, completed second study, withdrawn, and delivered; distributed at monthly SOAP2 team meetings.
- Visit window closing – list of participants with a visit window closing in the next week; emailed weekly to SOAP2 team
- Delivery specimen reports: information about collection of cord blood DNA and plasma, placental biopsies, and placenta; emailed after delivery to Marcia Gallagher and Ron Jaffe.
- Withdrawal report: reminder to update EHRs and cancel any outstanding orders for participants who are withdrawn; emailed to SOAP2 team after withdrawal.

The DCC also prepares bi-annual reports for the IDSMB, in consultation with the PI. Topics include:

- study progress, including an assessment of data quality
- enrollment, screen failures, and outcomes
- adverse and serious adverse events
- protocol deviations/violations and modifications

IDSMB reports are submitted annually to the University of Pittsburgh HRPO at the time of renewals.

Upon completion of the study, the DCC will make deidentified data and appropriate documentation available to the National Heart, Lung and Blood Institute of the National Institutes of Health.

## 9. Publications and Authorship

Publications refer to manuscripts, abstract, and presentations or posters at conferences. Prior to initiating any publication, a written summary including the topic, background (one paragraph), hypothesis, the target publication venue, and deadline must be submitted to the PI for review. The submission must occur within three months of any deadline to ensure adequate time for review and analyses.

All publications must include the PI and co-PI as authors.

The PI has adopted the following guidelines for authorship, based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, authored by the International Committee of Medical Journal Editors:

- To qualify as an author, an individual must have contributed to the conception and design of the work or to data collection and interpretation and must have played an important role in drafting and approving the final publication.
- The order of authorship should be a joint decision of the coauthors. Authors should be prepared to explain the order in which authors are listed.
- Every publication should have a primary author who assumes responsibility for all aspects of the publication, including accuracy of the data, authorship, and approval of the final draft by all authors. This individual also agrees to handle correspondence and respond to inquiries.
- Other contributors should be listed in the acknowledgments rather than as authors.

## **10. Other Study Documents**

Study Personnel (Z:\Facco:\SOAPforms8\_19\_2014)

IDSMB Roster (REDCap file repository)

Informed Consent Forms (Z:\Facco:\SOAPforms8\_19\_2014)

Clinical Scripts, Orders, Protocols and Handouts (Z:\Facco:\SOAPforms8\_19\_2014)

Data Collection Forms, with Instructions (REDCap file repository)

Electronic Data Entry System (REDCap) User Guide (REDCap file repository)

\* "Z" drive is accessible only by authorized personnel in Magee's Maternal and Fetal Medicine Department