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Sleep Breathing Substudy Manual of Operations

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1. INTRODUCTION

1.1 Overview of the Main Study

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) established the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) to study women for whom the current pregnancy will lead to their first delivery (nulliparas). Nulliparas comprise about 40% of pregnant women in the United States. Because no information is available from previous pregnancy outcomes to guide assignment of risk or mitigating interventions, adverse pregnancy outcomes in nulliparas are especially unpredictable. The underlying mechanisms of adverse pregnancy outcomes such as preterm birth, preeclampsia, and fetal growth restriction are interrelated and therefore will be evaluated as part of the study. The goals of the study are to 1) determine maternal characteristics, including genetics, epigenetics, and physiological response to pregnancy as well as environmental factors that influence and/or predict adverse pregnancy outcome; 2) identify specific aspects of placental development and function that lead to adverse pregnancy outcome; and 3) characterize genetic, growth, and developmental parameters of the fetus that are associated with adverse pregnancy outcome.

The information gained will benefit women who are pregnant or who are considering pregnancy and their health care providers. In addition, the knowledge will support future research aimed at improving outcomes for this critical group of at-risk women who are currently understudied.

The nuMoM2b investigators, in partnership with NICHD staff, developed one protocol that satisfies the goals of the study. NuMoM2b is a prospective cohort study of a racially, ethnically, and geographically diverse population of 10,000 nulliparous women, aged 13 and over, with viable singleton gestations. Study participants are recruited and screened for eligibility through public and private prenatal clinics associated with eight participating clinical sites across the country, some of which include subsites. Informed consent is obtained from eligible women and their parent or guardian if necessary. An ultrasound is required to confirm that the project estimated gestational age is less than or equal to 13 weeks and 6 days (13^6 weeks) using CRL and to confirm viability of a singleton gestation with no obvious malformations before a woman is enrolled to the study. Recruitment began in late September 2010, with a ramp-up period of three months. Recruitment at full operational levels is 15 months, starting in January 2011.

Participants are assessed during their pregnancy at 6^0 through 13^6 weeks gestation (Visit 1), 16^0 through 21^6 weeks gestation and at least four weeks after the first assessment (Visit 2), and 22^0 through 29^6 weeks gestation and at least four weeks after the second assessment (Visit 3). At each of these three visits, data are obtained through clinical measurement; personal interview; self-administered questionnaires; collection of blood, urine, and cervico-vaginal fluid samples; and clinical and research ultrasounds. Participants undergoing chorionic villus sampling (CVS) or amniocentesis are asked for consent to collect additional sample for study purposes. If the pregnancy is lost before 20^0 weeks gestation, a sample of the products of conception is collected if possible. At delivery, the participant is interviewed and maternal blood, cord blood, placenta samples, fetal membrane samples and an umbilical cord sample are obtained. Medical charts are abstracted near the beginning of the study and again around delivery to obtain information about medical conditions and diagnoses and medications. Medical charts are abstracted after delivery to obtain data related to prenatal care, antepartum hospitalizations,

labor and delivery, and maternal and neonatal outcomes. All biological specimens are sent to a central repository for later analysis.

Ancillary studies of subsets of the 10,000 enrolled women may be initiated during the course of the study. The study of *Sleep Disordered Breathing during Pregnancy and Risks to Cardiovascular Health* (abbreviated as the Sleep Breathing Substudy) is the first of the ancillary studies to reach fruition under nuMoM2b. The funding for this substudy is provided by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH).

1.2 Background on Sleep Disorders

1.2.1 Sleep Apnea

What is sleep apnea? Sleep Apnea (also referred to as obstructive sleep apnea syndrome (OSA), sleep apnea-hypopnea (SAHS), sleep disordered breathing (SDB)) is a condition characterized by loud disruptive snoring, snorting/gasping (during sleep), and daytime sleepiness. These symptoms result from abnormal breathing during sleep occurring as a result of intermittent (<1 minute) and repetitive (>5 hour) collapse or partial collapse of the throat (upper airway tissues). When the throat totally collapses (obstructs), ***breathing completely stops (momentarily),*** and an ***apnea*** occurs. When the throat partially collapses, a ***hypopnea*** (or partial obstruction) occurs ***(breathing continues but is diminished)***. In order to resume breathing after a complete or partial throat obstruction, the body sends signals to the lungs and chest to breathe harder. Eventually (usually only seconds), enough force is developed to open the throat muscles, allowing normal breathing to resume. As the throat tissues are pulled open, a *loud snort* or *gasp* may result. *Snoring* may be heard as the throat tissues vibrate during breathing through a partially blocked throat.

Why does this occur? Normal breathing depends on many factors, including airway (bronchial) size and function, lung tissue factors, the lung's blood supply, and breathing muscles (chest, diaphragm, and throat). The brain controls many of the lung's activities. While we are awake, the brain usually sends the appropriate signals to the muscles of the chest and the throat, maintaining normal breathing. However, during sleep, many of the throat muscles relax too much. When this happens, especially in people with a small throat opening (from big tonsils, a big tongue, fat, or a small jaw), a partial or complete throat collapse (hypopnea or apnea) may occur.

In whom does this occur? Not too long ago, sleep apnea was thought to be a rare condition. Now that doctors know more about it, and have access to sleep laboratories (where sophisticated monitoring equipment aids in making this diagnosis), many people are being diagnosed. Moreover, epidemiologists (scientists who study diseases and risk factors in communities) have begun measuring sleep and breathing in large numbers of people in the community. Because of this, we now know that sleep apnea is quite common (perhaps as common as high blood pressure). It is estimated that between 2 and 10% of adults have sleep apnea. Sleep apnea occurs in people of all ages. It may be most common, however, in the elderly, occurring in >25% of some surveys of the elderly. It also occurs in both men and women, although, at least during middle age, men are more likely to be affected than women. Although one of the biggest risk factors for sleep apnea is obesity, thin people may also have sleep apnea.

How does sleep apnea affect a person? Most of the consequences of sleep apnea are due to three phenomena: snoring, sleep disruption, and irregular breathing. One of the most troubling

consequences of sleep apnea is the snoring and loud breathing noises that can disturb the sleep of the affected person as well as his/her bed-partner. This may cause embarrassment and marital discord. The intermittent disruptions to sleep also interfere with the brain's normal sleep pattern- causing "arousals," and reducing the amount of sleep time spent in deep sleep and REM (Rapid Eye Movement or "dream") sleep. This may prevent "restorative" sleep, causing the person to feel sleepy and irritable during the day, and, possibly, "slowing" the person (physically and mentally). The breathing irregularities often cause the body's oxygen levels to drop. The drops in oxygen levels are thought to cause to stress on the heart, and possibly contribute to high blood pressure, to other heart ailments (heart attacks, angina, irregular heart rhythms) or stroke. However, very few studies have carefully examined these issues.

How is sleep apnea diagnosed? Sleep apnea is diagnosed in people who have symptoms of snoring, snorting, and sleepiness, using an overnight sleep study (with measurement of breathing and brain activities; polysomnography) that shows repetitive periods of obstructed breathing. During sleep, every apnea and hypopnea that lasts at least 10 seconds (and usually also is associated with some drop in oxygen or change in brain waves [arousals]) is counted. If the total number of apneas and hypopneas per hour of sleep is greater than a given threshold (5 to 20, according to local physician practices), a diagnosis of sleep apnea is made.

How is sleep apnea treated? Several fairly simple things are usually recommended to improve breathing during sleep: weight loss (if overweight), sleep posture (side rather than back), nasal decongestants, avoidance of alcohol, and good sleep habits (regular bed/awake times, sufficient sleep time, etc). People who are symptomatic often are prescribed a breathing aid, nasal CPAP (continuous positive airway pressure), a bedside device that blows air, under pressure, through the nose into the mouth, acting as a pneumatic stent, keeping the throat open. People who are prescribed this wear a small plastic mask over their nose (to permit the passage of this air). It is recommended that this machine be used nightly. Other therapies include surgery (tonsillectomy or "UPP"- uvulopalatopharygoplasty - a procedure where excess throat tissue is removed) and dental devices that bring the jaw forward. There is a great deal of controversy, however, concerning the role of specific treatments in people who do not complain of excessive daytime sleepiness.

1.2.2 Insomnia

What is insomnia? Insomnia refers to problems initiating (getting to) or maintaining sleep, including early morning awakenings. Chronic insomnia (lasting $\geq$ one month) affects about 10% of people; however, 30 to 50% of people have suffered from insomnia from time to time. Insomnia may be found in 40% of elderly (>65% years). Insomnia rarely presents as an isolated condition ("primary insomnia") and more commonly is associated with underlying medical (e.g., arthritis, chronic lung problems, renal failure) or psychological (e.g., anxiety, depression, and responses to life stress) conditions. In the elderly, pain from physical problems is a common cause of insomnia. People with insomnia often complain of daytime sleepiness and poor waking function. People who regularly sleep < 6 hours per night also may be at increased risk for death compared to people who get 7 to 8 hours of sleep per night.

How is insomnia diagnosed? Diagnosis of insomnia usually requires a careful medical history. Sometimes a 7 day sleep diary along with actigraphy (to measure movement and estimate sleep-wake time) is useful. Sometimes an overnight sleep study is needed to rule out other conditions that may disrupt sleep, including sleep apnea and periodic limb movement disorder (PLMD). If an overnight sleep study (PSG) is done, some typical findings in participants with insomnia are: a long sleep latency (long period of awake before sleep onset; e.g., > 30

minutes), low sleep efficiency (low percentage of time asleep compared to time in bed; e.g., < 65%), and long period of REM sleep (> 30% of sleep time).

How is insomnia treated? Treatments for insomnia vary according to its cause, including treatment of any underlying medical and psychological conditions and efforts at improving sleep hygiene (following regular and healthy sleep habits). Sometimes behavioral-cognitive therapy or medications are needed.

1.2.3 Periodic Leg Movements Disorder

Periodic leg movement disorder (PLMD) is characterized by repetitive stereotypical movements, usually of the legs, but sometimes of the arms, that occur during sleep. Most of the movements individually last 0.5 to 5 seconds and recur every 20 to 40 seconds in clusters that can last minutes or hours. Often the big toe extends and ankle dorsi-flexes. With movements, there are often "arousals" –or lightening of sleep or even awakening. PLMD is fairly rare in younger people, but may occur in > 40% of the elderly. Many people with PLMD also have restless leg syndrome (RLS) – a syndrome where the subject reports feeling "creeping or crawling" sensations in the legs-especially while resting. PLMD may be a cause of insomnia and/or daytime sleepiness. Much, however, is not known about PLMD.

1.2.4 Glossary of Pertinent Sleep Terms

Table 1-1 lists sleep terms that may be used during this study and provides definitions of those terms.

Table 1-1. Pertinent Sleep Terms

Term	Definition
Alpha rhythm	EEG rhythm, usually with frequency of 8-12 Hz. in adults; most prominent in the posterior areas; present most markedly when the eyes are closed; attenuated during attention, especially visual. (Characteristic of relaxed wakefulness with the eyes closed.)
Alpha wave	Individual component of an alpha rhythm.
Amplifier	An electronic instrument used to increase the strength of an incoming signal.
Apnea	Period ($\geq$10 seconds) with no airflow.
Apnea/Hypopnea Index (AHI)	Number of apneas + hypopneas per hour of sleep.
Artifact	A non-biological signal that appears in an EEG or sleep recording; or a signal that interferes with the derivations being recorded.
Beta rhythm	EEG rhythm with a frequency higher than 12 cps. Can be increased by certain medications
Bioelectric potentials	Electrical changes originating from living tissue.
Bipolar derivation	Signals obtained by comparing voltages from 2 electrodes.
Body movement	Scored during any sleep stage when a phasic increase in the amplitude of the EMG lead of 1 sec or longer is accompanied by muscle artifact in an EEG or EOG trace.
Canthus	Corner of the eye (plural: Canthi)

Term	Definition
C3	A symbol of the International 10-20 electrode system, identifying left central electrode placement site.
C4	A symbol of the International 10-20 electrode system, identifying right central electrode placement site.
Cz	A symbol of the International 10-20 electrode system, identifying a central electrode placement site.
Central Apnea (Hypopnea)	Cessation (or reduction) of respiratory effort $\geq$ 10 secs
Channel	The linear (signal) output of an amplifier
Collodion	An ether-based substance used for gluing electrodes to the scalp. Not used in this protocol
Delta Rhythm	EEG rhythm with frequency of 4 Hz. or less.
Delta Sleep	Sometimes used as a synonym for stages 3 and 4 sleep.
Delta Wave	EEG wave with duration of .25 sec. or more
Derivation	Recording from a pair of leads.
Drowsy sleep	Sometimes used as a synonym for stage 1 sleep.
Duration of a wave	Time interval from beginning to end of a waveform.
Electrical silence	Absence of electrical activity.
Electroencephalogram (EEG)	A record of the electrical activity of the brain.
Electromyogram (EMG)	A record of the electrical activity of muscles.
Electrooculogram (EOG)	A record of the electrical activity of eye movements.
Frequency	The number of complete cycles of a waveform within 1 second. Defined in Hz.
Gain	Voltage ratio of amplifier input to output.
Ground electrode	Electrode (or pair of electrodes) connected directly to the polysomnograph to provide for electrical safety or artifact reduction.
Hertz (Hz)	Cycles per second; a measure of frequency.
Hypopnea	Decrease in airflow or thoracic effort (usually <50% of baseline) for $\geq$10 seconds; partial airflow obstruction.
Impedance	Opposition to the passage of alternating current (AC).
Inductive Plethysmography	Method for measuring changes in circumference.
Inion	A bony protuberance at the base of the skull.
K complex	An EEG waveform having a well-delineated negative sharp wave immediately followed by a positive component; duration exceeds 0.5 seconds; waves of 12-14 Hz. (sleep spindles) may or may not constitute a part of the complex; generally maximal over vertex regions; occurring during sleep either spontaneously or in response to sudden (usually auditory) stimuli. (Characteristic of stage 2 sleep.)

Term	Definition
Lead	Term used to denote a single electrode.
Light sleep	Sometimes used as a synonym for stage 1 and stage 2 sleep.
Location	Physical site, or area.
Low-voltage EEG	EEG consisting of cerebral activity of 20 μV or less.
Montage	Combination of multiple derivations.
Morphology	The shape (form) of a wave.
REM sleep	Rapid Eye Movement, the dream-stage of sleep. A relatively low-voltage, mixed-frequency EEG in conjunction with episodic rapid eye movements and a low-amplitude EMG.
Obstructive apnea (hypopnea)	Absence (reduction) in air exchange despite respiratory effort lasting ≥10 seconds.
Ohm	Unit of electrical resistance or impedance.
Ohmeter	A device used to measure impedance in a circuit.
Oximeter	Sensor that emits infrared light band transmitted across tissue (e.g., nail, earlobe), to detect hemoglobin oxygen saturation.
Mastoid	Bony process behind the ear.
Nasion	Indentation above the bridge of the nose.
Piezoelectric	A crystal that generates electrical current when subjected to movement. Used in some respiratory bands and leg movement sensors.
Polysomnograph	Multichannel instrument used to record physologic parameters during sleep.
Preauricular point	Small indentation in front of, slightly above, cartilage flap (tragus) of ear canal.
Quiet sleep	Sometimes used as a synonym for stages 3 and 4 sleep.
Random	Occurring at inconstant time intervals.
Respiratory Disturbance Index (RDI)	Number of respiratory disturbances (apneas plus hypopneas per hour of sleep). Synonym for AHI.
Rhythm	Periodicity or recurrence of a wave.
Saw-tooth waves	Notched wave forms in vertex and frontal regions that sometimes occur in REM sleep.
Sleep spindle	A waxing and waning wave form with a frequency of 12-14 Hz., most prominent in stage 2 sleep.
Slow-wave sleep	Sometimes used as a synonym for stages 3 and 4 sleep.
Stage 1 sleep	Relative low-voltage, mixed-frequency EEG without rapid eye movements; slow rolling eye movements are often present; vertex sharp waves may be seen; EMG activity is not suppressed.
Stage 2 sleep	12-14 Hz. sleep spindles and K complexes on a background of relatively low-voltage, mixed-frequency EEG activity.

Term	Definition
Stage 3 sleep	Moderate amounts (20%-50%) of high amplitude (75 μV or greater), slow-wave (2 Hz. or slower) EEG activity.
Stage 4 sleep	Predominance (greater than 50%) of high-amplitude (75 μV or greater), slow-wave (2 Hz. or slower) EEG activity.
Thermocouple	Sensor measuring changes in temperature with inspiration and expiration, used to assess airflow.
Theta activity:	Series of waveforms with durations of .14 to .25 sec. (May be seen in stage 1 or REM sleep).
Theta rhythm	EEG rhythm with a frequency of more than 4 Hz to less than 8 Hz.
Theta wave	EEG wave with duration of .14 to .25 sec.
Topography	Distribution of activity with respect to anatomic landmarks. (Synonym: spatial distribution).
Transducer	Devise used to convert non-electrical physiological variables into electrical signals.
Unilateral	Occurring on one side of the head or body.
Vertex sharp wave	Sharp wave, maximal at the vertex and negative in relation to other areas (often occurring during later portions of stage 1 sleep).
Wave	Any transient change of potential difference in the EEG.

1.3 Sleep Breathing Substudy Objectives

This Sleep Breathing Substudy seeks to evaluate whether sleep disordered breathing (SDB) may be a risk factor for adverse pregnancy outcomes. The objective is to evaluate the impact of SDB on cardiovascular and metabolic outcomes in pregnancy using both subjective (questionnaire) and objective (portable apnea monitoring) measures of sleep.

1.4 Overview of the Sleep Breathing Substudy

The association between cardiovascular disease (CVD) risk and untreated adult SDB is well established; with SDB associated with a 2-3 fold increased risk of incident hypertension, coronary artery disease, diabetes, arrhythmia, stroke, and all-cause mortality.[1-5] Mounting evidence indicates that adding SDB treatment to usual care for CVD risk factors can moderate blood pressure, improve glycemic control, and decrease incident CVD events.[6-11] Accumulating data indicate that SDB symptoms are reported by nearly 30% of women during pregnancy,[12-16] and that self-reported SDB symptoms are associated with an increased frequency of gestational high blood pressure, preeclampsia, gestational diabetes, and other adverse pregnancy outcomes.[17-19] In addition, the pathophysiological profile of SDB resembles that of maternal cardiovascular and metabolic disease indicators, including elevated sympathetic tone, oxidative stress, systemic inflammation, insulin resistance, and hyperlipidemia.[20-25] Together, these findings indicate that SDB may be a potentially unrecognized health risk in women during pregnancy. This study is designed to determine the prevalence of SDB in pregnancy and the relationship between SDB phenotype with maternal cardiovascular and metabolic disease.

Both objective and subjective measures of sleep disordered breathing are evaluated. Questionnaire-based subjective measures of sleep quality are obtained from the entire cohort of 10,000 women at study Visits 1 (6^0 to 13^6 weeks gestational age) and 3 (22^0 to 29^6 weeks

gestational age) as part of the main study. In addition, for the entire cohort of the main study, clinical measurements such as weight, height, and blood pressure are measured in early (8^0-13^6 weeks), mid- (16^0-21^6 weeks) and later pregnancy (22^0-29^6 weeks) and neck circumference is measured in early pregnancy (6^0-13^6 weeks).

A subgroup of 3630 women are recruited to the Sleep Breathing Substudy at study Visit 1. These women participate in objective sleep assessments with unattended, in-home 7-channel polysomnography after study Visits 1 and 3. Participants completing Visit 1 for the main study by 13^6 weeks project estimated gestational age may be enrolled in the Sleep Breathing Substudy as long as the sleep breathing assessment can be completed by the morning of 15^0 weeks project estimated gestational age. Assessments are considered acceptable if they contain a minimum of 2 hours of oximetry and either nasal pressure or one respiratory band. Assessments containing less than the minimal requirements are not a repeat assessment is requested. Repeat assessments for Visit 1 must also be completed by the morning of 15^0 weeks project estimated gestational age. Assessments may be repeated only once for the visit. Similarly, all sleep breathing assessments and repeat assessments around the time of nuMoM2b Visit 3 must be completed between 22^0 weeks project estimated gestational age and the morning of 31^0 weeks project estimated gestational age. Even if a participant enrolled in the Sleep Breathing Substudy around the time of Visit 1 was not able to provide a valid Visit 1 sleep breathing assessment, she should be asked to complete a sleep breathing assessment for Visit 3. However, all participants must be enrolled in the substudy around the time of Visit 1.

1.5 Sleep Breathing Substudy Hypotheses

1.5.1 Primary Aim and Hypotheses

Sleep disordered breathing (SDB) is a risk factor for adverse pregnancy outcomes among nulliparas.

Primary Aim: To evaluate the relationship between SDB and the development of preeclampsia.

Primary Hypothesis: Early pregnancy SDB is an independent risk factor for preeclampsia.

Secondary Hypothesis: Late pregnancy SDB is an independent risk factor for preeclampsia.

1.5.2 Sub-Aims and Hypotheses

Sub-Aim 1: To evaluate the relationship between SDB and the development of other cardiovascular and metabolic complications of pregnancy (gestational hypertension and gestational diabetes).

Sub-Hypothesis 1a:	Early pregnancy SDB is an independent risk factor for gestational hypertension.
Sub-Hypothesis 1b:	Late pregnancy SDB is an independent risk factor for gestational hypertension.
Sub-Hypothesis 1c:	Early pregnancy SDB is an independent risk factor for gestational diabetes.
Sub-Hypothesis 1d:	Late pregnancy SDB is an independent risk factor for gestational diabetes.

Sub Aim 2: Estimate prevalence of and trends in SDB among women during pregnancy.

Sub-Hypothesis 2a:	SDB will be more common in certain subgroups of pregnant women (i.e., obese and overweight women).
Sub-Hypothesis 2b:	The prevalence of SDB increases as pregnancy progresses.

Sub-Aim 3 (exploratory): Define the SDB phenotype(s) in pregnancy most strongly associated with maternal CV and metabolic disease (preeclampsia, gestational hypertension, and gestational diabetes).

Sub-Hypothesis 3a:	There will be a substantial correlation between severity of SDB, manifested by increasing apnea hypopnea index (AHI, number of events per hour of sleep), index of O_2 desaturation events of 3% (ODI3) and 4% (ODI4) per hour, and/or a higher proportional O_2 desaturation per event (ODI/AHI ratio), and the frequency/severity of preeclampsia, gestational hypertension, and gestational diabetes.
Sub-Hypothesis 3b:	Obstructive sleep apnea will be more strongly associated with the above adverse outcomes than central sleep apnea.

1.5.3 Other Exploratory Aims

Exploratory Aim 1: To evaluate the relationship between SDB and fetal growth.

Exploratory Aim 2: To evaluate the relationship between SDB and preterm birth (both spontaneous and iatrogenic).

Exploratory Aim 3: To evaluate the relationship between objectively measured SDB and subjectively assessed symptoms of SDB in pregnancy.

1.6 Sleep Breathing Substudy Definitions

1.6.1 Measures of Sleep Disordered Breathing

SDB is defined as an apnea-hypopnea index (AHI) of ≥ 5. Apneas and hypopneas will be scored according to the alternative AASM criteria (requiring a 3% desaturation to identify hypopneas).

Other SDB variables / phenotypes that will be examined include but are not limited to the following:

- AHI as a continuous variable
- AHI as a categorical variable – no (AHI <5), mild (5≤ AHI <15), and moderate to severe SDB (AHI ≥15)
- ODI3 and ODI4 (oxygen desaturation index [number of desaturation events per hour] defined by 3% and 4% desaturation from baseline, respectively) as continuous variables
- Time spent at oxygen saturation <90% and <92%
- Nadir of oxygen desaturations
- ODI (3 and 4)/AHI

- Central versus obstructive apnea index (AI).

1.6.2 Primary Pregnancy Outcome for the Substudy

Preeclampsia is the primary outcome of the Sleep Breathing Substudy. The main study defines preeclampsia as follows:

Preeclampsia

Preeclampsia is defined by events occurring through 14 days postpartum. Definitions below are provided for four groups of participants defined by hypertension and proteinuria status before 20^0 weeks gestation. The two groups with pre-existing proteinuria are subgrouped according to the magnitude of the baseline proteinuria as total 24-hour urine protein excretion of <300 mg or ≥300 mg .

Group 1 - Women who do not have pre-existing hypertension or proteinuria before 20^0 weeks gestation

The diagnosis of preeclampsia requires the development of new onset hypertension at ≥ 20^0 weeks gestation plus one of the following:

- preeclamptic proteinuria,
- thrombocytopenia (<100,000/mm^3), or
- pulmonary edema.

Group II - Women with pre-existing proteinuria and normal blood pressure before 20^0 weeks gestation

Group IIa – Baseline proteinuria <300

The diagnosis of preeclampsia requires the development of new onset hypertension at ≥ 20^0 weeks gestation plus one of the following:

- preeclamptic proteinuria,
- thrombocytopenia (<100,000/mm^3), or
- pulmonary edema.

Group IIb – Baseline proteinuria ≥300

The diagnosis of preeclampsia requires the development of new onset hypertension at ≥ 200 weeks gestation plus one of the following:

- sudden increase in proteinuria (5 times the baseline value, or 2 times a baseline value of ≥5000 mg/24 hours)
- thrombocytopenia (<100,000/mm^3),
- serum aspartate aminotransferase (AST) concentration ≥ 100 IU/L,
- severe headache, or

- epigastric pain,.

Group III – Women with <u>pre-existing hypertension but no proteinuria before 20^0 weeks gestation</u>

The diagnosis of preeclampsia requires the presence of one of the following:

- preeclamptic proteinuria or
- thrombocytopenia (<100,000/mm^3).

Group IV – For women with <u>both pre-existing hypertension and proteinuria before 20^0 weeks gestation</u>

Group IVa – Baseline proteinuria <300.

The diagnosis of preeclampsia requires the presence of one of the following:

- preeclamptic proteinuria or
- thrombocytopenia (<100,000 /mm^3).

Group IVb – Baseline proteinuria ≥300

The diagnosis of preeclampsia requires one or more of the following:

- worsening hypertension, as shown by: two diastolic BPs ≥ 110 mm Hg taken four hours apart in the week before delivery plus one of the following:
  - ◊ severe headache,
  - ◊ epigastric pain, or
  - ◊ sudden increase in proteinuria (5 times the base-line value, or 2 times a baseline value of >5000 mg/24 hours)
- thrombocytopenia (<100,000/mm^3), or
- serum aspartate aminotransferase (AST) ≥100 U/L,

where:

1. The diagnosis of ***chronic (pre-existing) hypertension*** will be made if the patient meets the criteria for ***hypertension*** (blood pressure is ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic on two (2) occasions at least 6 hours apart or has a single elevated blood pressure of ≥140 mmHg systolic or ≥90 mmHg diastolic with subsequent antihypertensive medication therapy) before pregnancy or before 20^0 weeks gestation
2. ***Proteinuria:*** The 24-hour urine collection is the definitive test for proteinuria and supersedes all previous urinary dipstick values. The diagnosis of proteinuria will be made if the total 24-hour urine protein excretion value is ≥ 150 mg, or if there is ≥ 2+ proteinuria on dipstick or a protein-creatinine ratio ≥0.15 (150 mg/g) if a 24-hour urine is not available.

<u>Baseline Proteinuria:</u> Proteinuria occurring <u>before 20^0 weeks gestation,</u>

a. **<u>Baseline proteinuria ≥ 150 and <300</u>** indicates that there is baseline proteinuria, but the criteria for baseline proteinuria ≥300 have not been met.

b. **Baseline proteinuria ≥300** indicates that there is baseline proteinuria and the total 24-hour urine protein excretion value is ≥300 mg, **or** if there is ≥2+ proteinuria on dipstick or a protein-creatinine ratio ≥0.3 (300mg/g) if a 24-hour urine is not available.

The occurrence of ≥2+ proteinuria on dipstick before 20^0 weeks gestation without other available urine protein measurements will be considered baseline proteinuria ≥300.

Preeclamptic Proteinuria: The diagnosis of preeclamptic proteinuria will be made if, at ≥20^0 weeks gestation, the total 24-hour urine protein excretion value is ≥300 mg, **or** if there is ≥2+ proteinuria on dipstick or a protein-creatinine ratio ≥0.3 (300mg/g) if a 24-hour urine is not available.

Women will also be determined to have **preeclampsia** if they have a diagnosis of either of the following:

- ***Eclampsia:*** defined a seizure without another known cause during pregnancy through 14 days postpartum.

- ***HELLP syndrome:*** defined as 1) hemolysis evidenced by a) serum total bilirubin ≥ 1.2 mg /dL (20 µmol /L), b) serum lactate dehydrogenase (LDH) ≥ 600 IU/L, or hemolysis on peripheral smear, **AND** 2) serum aspartate aminotransferase (AST) ≥ 100 IU/L, **AND** 3)°thrombocytopenia (<100,000 /mm^3).

For definitions of all other pregnancy outcomes refer to the protocol and manual of operations from the main study.

1.7 Substudy Documents

A number of documents describe the project activities and provide information relevant to implementation of the Sleep Breathing Substudy. Among the most important of these documents are:

- The Sleep Breathing Substudy Protocol (**Appendix A**) – The substudy protocol broadly describes all activities of the study.

- Consent/Assent Forms – Each site uses the model forms (**Appendix B**) to develop site specific, and sometimes hospital specific, versions of the consent forms for the Sleep Breathing Substudy. The locally tailored forms are approved by local IRBs.

- Sleep Breathing Substudy Questionnaires (**Appendix C**) – There are a number of data forms that pertain to this substudy. They include:

  - Revised Sleep Questionnaire Visit 1 and Revised Sleep Questionnaire Visit 3 are administered as part of the main study. They were originally issued as Forms V1F and V3F. These forms were revised for purposes of the Sleep Breathing Substudy and have been reissued as Forms V1L and V3L.

  - Sleep Monitoring Following Visit 1 (V1K) and Sleep Monitoring Following Visit 3 (V3K) are completed by the participant at home on the morning following a night of monitoring.

  - Sleep Breathing Substudy Evaluation Visit 1 (E1A) and Sleep Breathing Substudy Evaluation Visit 3 (E3A) completed by study staff reviewing sleep assessments prior

to sending the data to the Sleep Reading Center. The completed form is sent to the Sleep Reading Center with the assessment data for which it was completed.

- Sleep Breathing Substudy SRC QS Visit 1 (E1B) and Sleep Breathing Substudy SRC QS Visit 3 (E3B) are completed by the staff at the Sleep Reading Center who are reviewing the assessment to document the quality of the data submitted.

- Administrative forms related to the substudy include: Substudy Protocol Deviations (A33), Substudy Adverse Event (A34), Substudy Withdrawal (A35), and Sleep Breathing Substudy Consent Elements (A61).

- Sleep Breathing Substudy Certification Materials (**Appendix D**):

  - Brief Overview of Training Procedures

  - Training Agenda

  - PowerPoint Training Slides – Updated after training to reflect changes in procedures.

  - Training Video

  - Practical Exam for PSG Tech Certification (SC01) documents observation of a polysomnographer (PSG) technician during training for the Sleep Breathing Substudy – either at central training by Sleep Reading Center staff or during local training by a site staff member certified by the Sleep Reading Center. A copy of the completed form is retained at the Sleep Reading Center.

  - Written Exam for PSG Tech Certification (SC02) completed by each site staff member seeking PSG technician certification for the nuMoM2b Sleep Breathing Substudy to demonstrate knowledge of the protocol and procedures for the Sleep Breathing Substudy. A copy of the completed form is returned to the Sleep Reading Center for scoring and is retained at the Sleep Reading Center.

- Tools for the Sleep Breathing Substudy (**Appendix E**):

  - Model Participant Recruitment Brochure for the Sleep Breathing Study – This brochure was developed to introduce potential participants to the substudy. This brochure is tailored by each clinical site with appropriate contact information on the back page.

  - Informational Brochure on Sleep – This brochure provides general information about healthy sleep and is available on the NHLBI website at the following link: http://www.nhlbi.nih.gov/health/public/sleep/healthy_sleep_atglance.pdf. It will be given to all participants enrolling in the Sleep Breathing Substudy.

  - Sleep Breathing Assessment Instructions – These instructions (INFO 10) explain how to put on and take off the sleep monitor, complete the questionnaire, and send the device and accompanying materials back to the study site. Site staff uses this sheet when explaining the study and send a copy home with the monitoring device.

  - Model Urgent Referral Letter – This letter will be used by clinic staff to promptly notify a participant's physician if her study findings indicate severe levels of sleep

disordered breathing and certain other conditions that may warrant further investigation.

- Sample tracking logs for monitoring Embletta Gold unit use and maintenance.
- nuMoM2b sheet template (file that end with the extension **.esst**) for REmLogic-E (available on Web or from SRC only)
- Recruitment Tool providing information about recruitment and answers to frequently asked questions.

Additional study-wide documents available for the main study can be found on the nuMoM2b project website.

1.8 Substudy Timeline

The timeline for the Sleep Breathing Substudy is as follows:

- September 2010 – Sleep Breathing Substudy funded by NHLBI.
- August 2010 – The Sleep Breathing Committee of nuMoM2b formed to develop the protocol and other substudy materials.
- January 2011 – Materials submitted to IRBs for approval.
- January 2011 – Central training, followed by training at the clinical sites by key staff trained centrally.
- Late January 2011 – Study roll out as site staff are trained and IRB approvals are obtained.
- January 2011 – August 2012 – Participant recruitment and follow-up.

This timeline will be revised if needed to reflect the pace of recruitment in the nuMoM2b study.

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2. SLEEP BREATHING SUBSTUDY ORGANIZATION AND FUNDING

2.1 Overview and Sleep Breathing Committee

The Sleep Disordered Breathing during Pregnancy and Risks to Cardiovascular Health Study (Sleep Breathing Substudy) is an ancillary study of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b). While the main study is funded through the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD) to study the mechanism and prediction of adverse pregnancy outcomes in nulliparas, this ancillary study is funded by the National Heart Lung and Blood Institute (NHLBI). The funded clinical sites, the Data Coordinating and Analysis Center (DCAC), and the Sleep Reading Center form a cooperative network in scientific partnership with NHLBI and NICHD to conduct this prospective substudy of the prevalence of sleep disordered breathing (SDB) in pregnancy and the relationships between SDB phenotype and maternal cardiovascular and metabolic disease.

Much of the work of designing and overseeing the Sleep Breathing Substudy is accomplished through the Sleep Breathing Committee, a committee under the Steering Committee of nuMoM2b. The Sleep Breathing Committee includes at least one representative from each of the clinical sites, NICHD, NHLBI, the Sleep Reading Center, and the DCAC. Members of the committee have expertise in sleep disorders, sleep measurement, pulmonary function, obstetrics, biostatistics, and data management. This committee designs all of the study materials, which are submitted to the nuMoM2b Steering Committee for review and approval. Both the nuMoM2b Steering Committee and the Sleep Breathing Committee monitor recruitment and implementation of the Sleep Breathing Substudy. The Sleep Breathing Committee makes recommendations to the Steering Committee if changes in procedures become necessary.

This chapter describes the study organization, roles, and funding for the Sleep Breathing Substudy.

2.2 Participating Organizations

2.2.1 NICHD

NICHD's role in nuMoM2b is to oversee the activities of the clinical sites and the DCAC; to ensure that these research sites are responsive to the original goals; to collaborate with study investigators in the design and conduct of the study protocol; and to coordinate the financial aspects of the study. One or more NICHD Project Scientists and a Program Official collaborate with nuMoM2b clinical site and DCAC staff and oversee nuMoM2b activities. Specifics regarding the role of NICHD for the main study appear in the Manual of Operations for the main nuMoM2b study.

As part of their overall role, the NICHD nuMoM2b project scientists are active members of the Sleep Breathing Committee, offering input to study design and implementation. Additionally, they facilitate funding for the substudy by passing the funding NHLBI provides to support substudy activities at the DCAC, the clinical sites, and the Sleep Reading Center, through the nuMoM2b grant to the DCAC for appropriate distribution.

2.2.2 NHLBI

In addition to providing funding for this substudy, the NHLBI has a representative on the Sleep Breathing Committee. This representative provides technical expertise related to sleep breathing studies. Additionally, NHLBI monitors study progress against benchmarks for substudy progress.

2.2.3 Clinical Sites

Eight clinical sites, encompassing a total of 18 subsites, constitute the study sites of the nuMoM2b consortium. The clinical sites are Case Western Reserve University, Columbia University, Indiana University, Magee-Women's Hospital, Northwestern University, University of California Irvine, University of Pennsylvania, and University of Utah. All sites are participating in the Sleep Breathing Substudy. The nuMoM2b site Principal Investigators are responsible for study administration at their respective institutions. In addition, an investigator from each site has been appointed to the Sleep Breathing Committee, and this investigator closely monitors the substudy activities at his or her site.

The clinical site staffs ensure that the substudy protocol and its related consent forms are reviewed and approved by their individual institutional human subjects review boards. Moreover, they are responsible for identifying potential participants for the substudy, obtaining informed consent, enrolling nuMoM2b participants to the substudy, and carrying out activities described in the Sleep Breathing Substudy protocol and this Manual of Operations. They are also responsible for ensuring that all data collection procedures are completed fully and accurately, that data are obtained and transmitted to the DCAC and the Sleep Reading Center in a timely manner, and that error correction requests are answered. Staff involved with collecting, reviewing or transmitting sleep assessment data must be certified by the Sleep Reading Center prior to obtaining or reviewing sleep breathing assessment data at the site.

Clinical site investigators who are involved in the substudy work with the NHLBI and NICHD project scientists, the DCAC and the Sleep Reading Center in the review of study data and in the presentation and publication of the study results (including data analysis, abstract and manuscript development, preparation and review).

2.2.4 Data Coordinating and Analysis Center

The Data Coordinating and Analysis Center (DCAC) is located at RTI International. The DCAC is responsible for biostatistical design, designing a system for the uniform capture and transmission of data to the DCAC, quality control of the data, data management, and interim and final data analysis. The DCAC actively participates in deliberations of the Sleep Breathing Committee, in development of materials for the substudy, and in the capture and analysis of the study and substudy data. The DCAC also generates periodic data management reports that assess recruitment, protocol adherence, completeness of data collection, and timeliness and quality of data collection. The DCAC receives funding for the ancillary study, establishes subcontracts with the clinical sites and Sleep Reading Center to facilitate base funding for this substudy, and administers capitation payments to the clinical sites for participation in this substudy.

2.2.5 Sleep Reading Center

The Sleep Reading Center (SRC), led by Dr. Susan Redline at Brigham and Women's Hospital, was identified and recommended by the Sleep Breathing Committee and selected by vote of the Steering Committee. It is responsible for the following activities during this substudy:

- Leading/contributing substantially to the development of a manual of operations for the substudy.
- Leading a central training session to instruct the nuMoM2b study staff from each clinical site on the use of the home sleep breathing assessment monitoring device, the instructions required to study participants, and the transmission of data to the Sleep Reading Center.
- Conducting any follow-up training that may be needed to ensure the collection of high quality readings from each sleep breathing assessment.
- Conducting an initial review of each data recording within 14 days of receipt and generating an alert for any adverse readings, consistent with the alert criteria specified in the protocol, to both the DCAC and the clinical site for follow up referral.
- Conducting an in depth analysis of each data recording for use in aggregated data analysis.
- Providing the DCAC access to an FTP site that is updated weekly or monthly, as applicable and needed for the project, for download of results that have accumulated at the Sleep Reading Center.
- Monitoring the quality of the readings performed by Sleep Reading Center staff.
- Participating in nuMoM2b Sleep Breathing Committee conference calls and meetings by Dr. Redline or her designee.
- Collaborating as needed with the Sleep Breathing Committee and/or nuMoM2b Steering Committee.
- Providing a written report at quarterly intervals to the DCAC that includes the following elements:
  - Number of studies received to date
  - Number of studies passing quality standards to date
  - Number of studies reported as adverse
  - Number of studies fully analyzed to date
  - Problems identified with the clinical sites in use of equipment or data transmission to Sleep Reading Center.

In summary, Sleep Reading Center staff oversee study quality and training, participate in analyses and manuscript preparation; oversee the performance of the scorers, provide training and support to sites; oversee the overall flow of data from the sites and to the DCAC; and generate periodic monitoring reports.

2.3 Advisory and Safety Monitoring Board

The Advisory and Safety Monitoring Board (ASMB), that advises the nuMoM2b Steering Committee in the development of research protocols, reviews the protocol and other materials for the Sleep Breathing Substudy and helps monitor substudy progress and safety. The Advisory and Safety Monitoring Board was chosen by the NICHD. To adequately review this ancillary study, sleep experts were added to the Board to supplement the existing expertise in

obstetrics, perinatology, genetics, perinatal pathology, biostatistics, epidemiology, and neonatology. The Chairperson of the nuMoM2b Steering Committee, the Principal Investigator of the DCAC, and the NICHD and NHLBI Project Scientists attend Advisory Board meetings to provide information as needed. Additional members of the nuMoM2b Steering Committee or the Sleep Breathing Committee may participate based on the need for specific expertise. Each member of the ASMB has one vote.

2.4 Funding

Funding for the Sleep Breathing Substudy is provided by NHLBI through the DCAC grant. The DCAC establishes subcontracts with each of the eight clinical sites to cover base costs of study oversight, attendance at central training, and other administrative requirements. Additionally, the clinical sites receive capitation costs for each sleep breathing assessment that is completed. Finally, the DCAC negotiates and establishes a subcontract with the Sleep Reading Center to cover the services detailed in **Section 2.2.5**.

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3. SITE PREPARATIONS

3.1 Overview

This chapter describes the steps each clinical site must make to prepare for and manage the Sleep Breathing Substudy of nuMoM2b. The preparations described in this study are in addition to the preparations described in Chapter 3 of the nuMoM2b Manual of Operations for the main study.

3.2 Required Approvals, Subcontract, and Account

Clinical sites need to have the following approvals, subcontract, and account in place for the Sleep Breathing Substudy:

- All approvals required for the nuMoM2b protocol;
- IRB approval for the Sleep Breathing Substudy from clinical sites and subsites that enroll participants into the substudy;
- A subcontract with RTI providing base funding for the substudy; and
- An account with Embla Systems, based in Broomfield, Colorado, for purchase of the supplies required for the sleep assessments.

Documentation related to these items should be maintained in secure files in the local nuMoM2b offices. Copies of the documents granting IRB approvals, FWA #s, and locally approved IRB Forms should be sent to the Data Coordinating and Analysis Center (DCAC), which is required to maintain a file of approvals for all sites. IRB approvals must be renewed at least annually.

3.3 Staff Roles, Training and Certification Requirements Specific to the Sleep Breathing Substudy

3.3.1 Clinical Site Staffing

In addition to the roles and responsibilities described in the nuMoM2b Manual of Operations for the main study, including those of the Principal Investigator, who has oversight of all aspects of nuMoM2b including the Sleep Breathing Study, each site must have the following staff for the Sleep Breathing Substudy:

- An investigator who participates in Sleep Breathing Committee conference calls and meetings, helps design and review materials for the Sleep Breathing Substudy, monitors local implementation of the substudy, and participates in analysis and publication of resulting data.
- A coordinator or other staff member centrally trained and certified in the procedures related to the sleep breathing assessment using the Embletta Gold device and other procedures related to the Sleep Breathing Substudy. This staff member initially will be responsible for training and certifying local site staff in substudy procedures, interacting with the Sleep Reading Center and the DCAC, and ensuring that procedures related to urgent referrals are followed appropriately. Should all centrally trained staff leave the site, a locally trained and

certified staff member may be designated to train and certify new staff joining the study team.

- Other locally trained clinical site staff may be assigned various tasks related to the substudy. Tasks related to use of the monitor, interaction with participants, and review and transfer of data require local training and certification by the Sleep Reading Center. These tasks include the following: recruiting participants for the Sleep Breathing Substudy; preparing devices for each breathing assessment and ensuring that the devices are in good working order; explaining the procedures to participants when deploying equipment; receiving devices and materials returned to the clinical sites or subsites; reviewing, processing, and transmitting recordings and other data to the Sleep Reading Center; preparing urgent referral letters; and performing other administrative duties related to the ancillary study. These duties may be performed by the staff member who was centrally trained and certified as a Sleep Breathing Substudy technician. Other site staff may be trained by a certified site staff member and certified by the Sleep Reading Center to perform some or all of the duties of a technician under his or her oversight.

- Administrative staff who ensure that needed supplies are available and perform other duties that do not require interaction with participants or acquisition or review of the sleep assessment data.

3.3.2 Sleep Reading Center Staffing

The roles and responsibilities of staff at the Sleep Reading Center include:

- Investigators who oversee study quality, training and certification, and participate in analyses and manuscripts.

- Chief Polysomnologist who oversees the performance of the scorers, provides training to sites; and supports sites with their efforts.

- Scorers who review and score data from the breathing studies and respond to questions from site staff regarding equipment and implementation of the study.

- Administrative staff who oversee the overall flow of data, coordinate communications, and generate routine reports.

- A Systems Administrator who sets up files, develops and implements a file transfer protocol; and manages data storage and backup.

3.3.3 DCAC Staffing

The roles and responsibilities of staff at the DCAC for the Sleep Breathing Substudy include:

- The DCAC Principal Investigator serves as a member of the Sleep Breathing Committee. The PI oversees all activities of the DCAC related to the Sleep Breathing Substudy. She also coordinates activities with the Sleep Reading Center staff to develop all materials for the substudy and to oversee its implementation. She will oversee analysis of the substudy data and participate in dissemination of study results.

- Investigators provide input to analysis sections of the study protocol, provide analysis of study results, and develop programs to capture activities related to capitation payments.

- Coordinators work with staff at the Sleep Reading Center to develop study materials, deploy equipment and supplies, and ensure adequate on-going communication between the clinical sites and the Sleep Reading Center.

- A financial analyst implements and oversees subcontracts with the clinical sites and the Sleep Reading Center, facilitates payment of capitation funding to the sites, and orders equipment and initial supplies from Embla.

- Programmers develop the system to capture and manage data for the substudy.

3.3.4 DCAC and Sleep Reading Center Staff Relation to Clinical Sites

Clinical site staff members directly correspond with both staff at the Sleep Reading Center and at the DCAC.

Sleep Reading Center staff will be most knowledgeable about issues related to the sleep breathing assessments and related data, quality of the sleep breathing assessments, and issues with the Embletta Gold hardware and software. It is requested that site staff copy DCAC coordinators when contacting the staff at the Sleep Reading Center about these issues so that DCAC staff can monitor issues and facilitate responses when possible.

DCAC staff will be most knowledgeable about consent, the data management system and keyed data, capitation payments, and the relationship between the Sleep Breathing Substudy and nuMoM2b.

3.3.5 Required Training/Certifications

Briefly, the following training and certifications are required for this study:

- Ethics – as for all NIH studies, any staff having contact with participants or their data are required to have ethics training related to the involvement of subjects in human research. This training should be conducted and documented locally.

- Central training and certification of at least one coordinator at each site as a Sleep Breathing Substudy technician. This individual subsequently trains other local local staff who are certified by the Sleep Reading Center to perform specific aspects of substudy activities with oversight. If the centrally trained technician leaves the site, another certified staff member may be appointed to train local staff.

3.4 Equipment, Materials, and Tools

3.4.1 Equipment and Related Supplies

The DCAC purchased all equipment for this substudy and purchased the supplies required to conduct the first 1000 of 7260 anticipated sleep studies. In addition, the DCAC negotiated favorable pricing with the vendor (Embla Systems) for each site to purchase additional supplies and replacement parts as necessary.

The equipment purchased for the Sleep Breathing Substudy, with the discounted rates negotiated for initial purchase, includes the following:

Item order number	Item Description	Price
1030404	Embletta Gold RLE XS ENU NSAM (includes Embletta Gold devices, Embletta XPOD Oximeter with finger probe, XactTrace Locks for Thorax and Abdomen, XactTrace belts (65.6 ft.), Download cable, Battery Rechargers, Embletta System Cases, RemLogic-E software agreement and CD, RemLogic-E Release Notes and Installation Instructions, Embletta Gold Patient Hook-up DVDs, Disp Solid Gel and Snap Electrodes)	$2,100.00
1421020	XactTrace Lock - Abdomen	$60.00
1421022	XactTrace Lock - Thorax	$60.00
1431004	Nonin Soft Sensor - medium	$180.50
1431000	Oximeter Flex Sensor 8000J	$89.00

Each site must establish an account with Embla Systems in Colorado providing authorization to place orders for supplies and required to obtain the preferred pricing. The list of consumable supplies and replacement equipment required for the Sleep Breathing Substudy and the reduced prices negotiated for the items are as follows:

Item order number	Item Description	Price
1420002	Nasal Cannulas 15in (50/pkg)	$75/pkg
1421000	XactTrace Belt 65.6ft/roll	$25/roll
1421020	XactTrace Lock - Abdomen	$60.00 ea.
1421022	XactTrace Lock - Thorax	$60.00 ea.
1431004	Nonin Soft Sensor - medium	$180.50 ea.
1431000	Oximeter Flex Sensor 8000J	$89.00 ea.
1410500	Disposable Electrodes Solid Gel (30/pkg)	$8/pkg
1431500	Flexiwraps for 8000JFW (25/pkg)	$18/pkg
1412000	Alcohol Prep Pads (200/pkg)	$2.20/pkg

To place an order with Embla for the Sleep Breathing Substudy, please contact:

Kristen Phillips
Customer Service Representative
Office: 303-962-1788
Fax: 775-860-5726
Toll Free: 888-662-7632

www.embla.com
www.shopembla.com

Reference “promotion code” **nuMoM2b** to obtain the preferred pricing documented above.

Warranty periods for various items of equipment are given in the following table. Items not listed have no warranty. The warranty period begins when the equipment is delivered to either RTI or directly to the sites.

Item #	Item Description	Warranty Period
1421020	XactTrace Lock – Abdomen	12 Month Warranty
1421022	XactTrace Lock – Thorax	12 Month Warranty
1430000	Oximeter Emblet/Embla7000 XPOD	24 Month Warranty when shipped with system, 12 Month Warranty when purchased individually
1431000	Oximeter Flex Sensor 8000J	3 Month Warranty
2003005	Embletta Gold	24 Month Warranty
2020303	USB Download Cable – EG	12 Month Warranty
2030104	Embletta Gold Pwr Supp US	12 Month Warranty

3.4.2 Materials

A complete list of documents developed for the Sleep Breathing Substudy and the location where originals can be accessed appears in **Section 1.7** of this document. Sites must ensure that copies of the following materials are available to staff conducting the study:

- Consent/Assent Forms – Version approved by the local IRB.
- Sleep Breathing Substudy Questionnaires
  - Revised Sleep Questionnaire Visit 1 and Revised Sleep Questionnaire Visit 3 (administered as part of the main study).
  - Sleep Monitoring Following Visit 1 (V1K) and Sleep Monitoring Following Visit 3 (V3K) (completed by the participant at home on the morning following a night of monitoring).
  - Sleep Breathing Substudy Evaluation Visit 1 (E1A) and Sleep Breathing Substudy Evaluation Visit 3 (E3A) (completed by study staff reviewing sleep assessments prior to sending the data to the Sleep Reading Center).
  - Substudy Protocol Deviations (A33),
  - Substudy Adverse Event (A34),
  - Substudy Withdrawal (A35), and

- Sleep Breathing Substudy Consent Elements (A61).

- Model Participant Recruitment Brochure for the Sleep Breathing Study – Copies distributed to potential participants.

- Informational Brochure on Sleep – This brochure is given to all participants enrolling in the Sleep Breathing Substudy.

- Sleep Breathing Assessment Instructions – These instructions (INFO 10) explain how to put on and take off the sleep monitor, complete the questionnaire, and send the device and accompanying materials back to the study site. Site staff uses this sheet when explaining the study and send a copy home with the monitoring device.

3.4.3 Certification Materials

The following materials are used when certifying local staff as sleep technicians. Originals of these materials are all located on the nuMoM2b Website in Appendix D of this manual. Staff should be provided copies of these materials or access to the Study materials on the website when undergoing training.

- Brief Overview of Training Procedures

- Training Agenda

- PowerPoint Training Slides – Updated after training to reflect changes in procedures.

- Training Video

- Practical Exam for PSG Tech Certification (SC01) documents observation of a polysomnographer (PSG) technician during training for the Sleep Breathing Substudy – either at central training by Sleep Reading Center staff or during local training by a site staff member certified by the Sleep Reading Center. A copy of the completed form is retained at the Sleep Reading Center.

- Written Exam for PSG Tech Certification (SC02) completed by each site staff member seeking PSG technician certification for the nuMoM2b Sleep Breathing Substudy to demonstrate knowledge of the protocol and procedures for the Sleep Breathing Substudy. A copy of the completed form is returned to the Sleep Reading Center for scoring and is retained at the Sleep Reading Center.

3.4.4 Other Tools

In addition to the materials described above, select tools are maintained on the study website in Appendix E of this document for use during the Sleep Breathing Substudy. These include

- Model Urgent Referral Letter – This letter will be used by clinic staff to promptly notify a participant's physician if her study findings indicate severe levels of sleep disordered breathing and certain other conditions that may warrant further investigation. It is completed using information provided by the Sleep Reading Center.

- Sample tracking logs for monitoring Embletta Gold unit use and maintenance.

- nuMoM2b sheet template (file that end with the extension **.esst**) for REmLogic-E (available on Web or from SRC only)

- Recruitment Tool providing information about recruitment and answers to frequently asked questions. This document may be used during training and serves as a reference to staff recruiting participants for the substudy.

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4. SCREENING AND ENROLLMENT

4.1 Recruitment

Participants to the Sleep Breathing Substudy must be enrolled in the main nuMoM2b study. Eligibility criteria for the Sleep Breathing Substudy are captured as part of the nuMoM2b Maternal Interview Visit 1. However, women may be recruited to the Sleep Breathing Substudy at any time through 13^{6} weeks gestational age, which is the endpoint for the nuMoM2b Visit 1. A recruitment brochure is available to introduce potential participants to the substudy. As with the main study, women may be consented to the Sleep Breathing Substudy before it is known if they are fully eligible, although consent should occur only after a participant has consented to participate in nuMoM2b. For example, a woman may be consented for the substudy immediately after she has consented to participate in the main study.

A brochure containing general information on healthy sleep should be given to all women who agree to be in the Sleep Breathing Substudy. Some sites may also choose to give this brochure to all women participating in nuMoM2b or make it available in waiting rooms where participants are being recruited. For this purpose, a good information brochure on Healthy Sleep at a Glance is provided. This brochure originated from the NHLBI website at the following link: http://www.nhlbi.nih.gov/health/public/sleep/healthy_sleep_atglance.pdf. It is available on the nuMoM2b website in both English and Spanish.

A recruitment tool containing an example of language that might be used when recruiting a participant to the Sleep Breathing Substudy and a list of frequently asked questions with appropriate answers appears in Appendix E.

4.2 Inclusion/Exclusion Criteria

The Sleep Breathing Substudy plans to enroll 3,630 of the 10,000 women participating in nuMoM2b. The substudy involves objective sleep breathing assessments with unattended, in-home, limited channel polysomnography. Inclusion and exclusion criteria for the substudy are those for the main study, with the following exceptions:

- Women who are currently using positive airway pressure (PAP) therapy are excluded from the Sleep Breathing Substudy. Although we expect this number to be small, the number so excluded is tracked through the maternal interview in order to accurately assess the prevalence of SDB during pregnancy.

- Women with severe asthma who have been on continuous oral steroid therapy for more than 14 days are excluded, because marked respiratory impairment may limit the interpretation of SDB assessments.

- Women with conditions requiring oxygen supplementation are excluded.

4.3 Screening Procedures

Eligibility criteria for the Sleep Breathing Substudy are captured as part of the Maternal Interview Visit 1 (Form V1A), Section D, items D14-D16. However, these criteria may be

reviewed informally before the maternal interview is conducted to assess potential eligibility. To be eligible for the substudy, a nuMoM2b study participant completing Visit 1 must:

- Answer “No” to D14, use of a positive airway pressure machine during sleep. In this question, we are looking for any use of a machine providing positive airway pressure through a facial or nasal mask while a participant sleeps. Examples of these breathing machines include continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP®), and variable positive airway pressure (VPAP™) machines. Use of a simple humidifier during sleep does not exclude a participant from the study.

- Answer “No” to D15, asthma **OR** answer “Yes” to question D15 and “No” to D15a (use of oral steroids) OR answer “Yes” to D15, “Yes” to D15a, and “No” to either D15a1 (daily use) or D15a2 (taken for more than 14 days).

- Answer “No” to D16, receive oxygen therapy.

After administering Form V1A, study staff should review the answers to the above items to ensure eligibility for the Sleep Breathing Substudy before enlisting a nuMoM2b participant into the substudy. Informed consent for the Sleep Breathing Study must be obtained before any substudy procedures are performed. As noted earlier, informed consent may have been obtained before it was known if the woman was fully eligible for the substudy.

4.4 Obtaining Informed Consent

4.4.1 Explaining the Substudy

4.4.1.1 Overview

The goal of the informed consent process is to explain the substudy and its risks and benefits to a potential Sleep Breathing Study participant and her parent or guardian if she is a minor and gain agreement for enrollment into the substudy. Detailed information about the informed consent process is contained in the Manual of Operations for the nuMoM2b main study.

Before participation in the Sleep Breathing Substudy may begin, written informed consent must be obtained from the subject who has the legal right to consent for herself and from a legal guardian if she cannot legally consent. Written informed assent also must be obtained from the subject who does not have the legal authority to consent to this research and whose guardian has consented that she may participate. Written consent and assent, if applicable, are obtained by clinical site personnel who are knowledgeable of the substudy and who have knowledge and training in the consent process and in issues related to the protection of human subjects.

A series of model consent forms for the Sleep Breathing Substudy are developed (described below and appearing in **Appendix B**). Each clinical site adapts these forms for local use and the site-specific forms are approved by local IRBs. In some cases, specific subsites require further local modifications, so multiple versions of a form may exist within a nuMoM2b clinical site. These forms are available in English and some sites translate local versions into Spanish. The nuMoM2b coordinator and other recruitment staff must be familiar with all versions of the consent forms in use at the site or subsite and be able to select the most appropriate form or forms for each potential participant.

The model consent forms used for the Sleep Breathing Substudy and information regarding their use are as follows:

- **CN05a – Model Participant Consent for Sleep Breathing Assessments:** Use a version of this form to consent a participant for the Sleep Breathing Substudy when she is able to consent for herself according to state law. The subject, the individual obtaining consent, and a witness sign this form.

- **CN05b – Model Legal Guardian Consent for Sleep Breathing Assessments:** Use a version of this form to obtain consent for a participant in the Sleep Breathing Substudy from a parent or guardian when the participant cannot legally consent for herself according to state law. A parent or guardian, the individual obtaining consent, and a witness sign this form. It is always used in conjunction with Form CN05c below.

- **CN05c – Model Participant Assent for Sleep Breathing Assessments:** Use a version of this form to assent the participant for the Sleep Breathing Substudy when she cannot legally provide consent for herself according to state law. The participant, the individual obtaining consent, and a witness sign this form. It is always used in conjunction with CN05b above.

Appropriate forms, CN05a, CN05b and CN05c, must be signed and on file before performing any Sleep Breathing Substudy research procedures or collecting any substudy data beyond the screening data obtained as part of the main nuMoM2b Study.

4.4.1.2 The Informed Consent Process

When obtaining informed consent for the Sleep Breathing Substudy, ample time should be provided for a potential participant to read and understand the consent form and to ask questions. If a potential participant and/or legal guardian (if applicable) cannot read and the IRB approves, the consent form may be read aloud or an audio-tape of the consent form and a tape player may be provided. Written translations and formal interpreters for conducting informed consent in languages other than English may be available at a clinical site, consistent with local IRB requirements and approvals.

A woman who consents to the Sleep Breathing Substudy is thanked and given a copy of the signed consent form for her personal records (see **Section 4.4.2** on Documenting Consent). If a nuMoM2b participant refuses to consent to the substudy, thank her for her time and leave contact information so that she can contact the nuMoM2b office if she has questions.

4.4.1.3 Information to be covered with a Potential Participant

When reviewing the Sleep Breathing Assessments consent form with the participant, all of the following information needs to be discussed with the her and, if needed, her parent or guardian.

- **Name of the study:** nuMoM2b Sleep Breathing Assessments Substudy. Make it clear that she is being asked to participate in a research study.

- **The Principal and Investigator, Co-Investigators, and Research Coordinator**

- **Funding agency:** the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development and the National Heart, Lung and Blood Institute, both parts of the U.S. National Institutes of Health.

- **Purpose of the study:** To find out how often nulliparous women have breathing problems during sleep and whether these problems make it more likely to have problems with pregnancy.

- **Number of study participants:** About 3630 nuMoM2b participants from across the nation, including about <NUMBER> from <LOCAL SITE>.

- **Reason she is eligible for the study:**

  – She is in the nuMoM2b study.

  – She does not have a breathing problem during sleep that requires treatment with a positive airway pressure (PAP) machine. We are looking for any use of a machine providing positive airway pressure through a facial or nasal mask while a participant sleeps. Examples of these breathing machines include continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP®), and variable positive airway pressure (VPAP™) machines. Use of a simple humidifier does not exclude the participant from the study.

  – She does not have any other breathing problem that is severe, such as severe asthma.

  – She does not have a medical condition for which she is being given oxygen.

- **Study procedures:** Give enough detail so that the participant (guardian) understands what happens to her if she consents and is eligible. The description should distinguish between standard care and study related procedures.

  – She will wear a simple sleep monitor on two nights during her pregnancy, once around the time of her first nuMoM2b study visit and again around the time of her third nuMoM2b study visit. The monitor records information about breathing, how fast her heart is beating, and how well her body is getting oxygen while sleeping.

  – Each time, she will complete a 5-minute questionnaire about her sleep on the morning after she wears the sleep monitor.

  – Each time she will be asked to return the sleep monitor and the questionnaire to the site (by mail in a postage-paid envelope that is provided, by drop off, or by courier).

  – We may ask her to redo an assessment if we did not get a good recording.

- **The expected length of study participation:** Study participation will take 2 nights.

- **Risks to participation:** Cover the following points:

  – The study is safe.

  – Any discomforts will be minor, such as irritation from the adhesive sensors.

- **Benefits of participation** (depends on local consent form)

  – She will not receive any direct personal benefit from participation in the breathing assessment.

  – We may tell her provider if we happen to see a major problem during the breathing assessment.

  - We may learn more about how breathing during sleep affects birth outcomes for nulliparous women.
- **Participation is voluntary and does not cost anything:** If she chooses to participate, she can leave or withdraw from the study or choose not to answer one or more of the questions or do the breathing assessment with no penalties and without affecting her regular health care.
- **She will receive $50 each time the monitor is returned after an assessment.**
- **Measures in place to protect the participant's privacy:**
  - Study ID: Names are not used with study data. Records linking the participant to her study ID number are stored in a locked file.
- **How to contact the PI, coordinator, or IRB**.
- Signing the consent form indicates agreeing to participate in the study.
- She (guardian) is given a copy of the signed form for her records.
- She (guardian) can withdraw consent at any time without penalty. Point to the contact information for the person(s) to contact to withdraw from the study.
- She (guardian) understands that this research may include storing and using data in other research studies. This is not required to be in the study.
- She (guardian) can take her time to make a decision about being in the study.
- She (guardian) can ask questions to help understand what is being agreed to.

4.4.2 Documenting Consent

4.4.2.1 Written, Signed Forms

Once the subject (guardian) has agreed to participate in the study, ask another individual to come into the room to witness the subject's signature. This does not have to be a project staff person. Note that the witness is merely witnessing the signature, not the entire consent process.

Ask the participant (guardian) to initial each page of the consent form and to sign the consent form at the end of the consent section and on additional pages to allow Sleep Breathing Substudy data to be stored for other researchers if she agrees. Next, the person obtaining consent should sign the forms and print his/her name and title on the form. If an interpreter was used to facilitate consent, the interpreter should sign the form. If no interpreter was used, print the letters "NA" in the space provided. Finally, the witness is asked to sign both pages of the form to indicate that the subject willingly participated in the consent process and signed the form.

Repeat the procedure with the assent form if appropriate.

Thank the participant for agreeing to be in the substudy and give her a copy of the signed form or forms. The original signed copy is kept in a locked file at the clinical site with other

confidential information on the participant and, if required, a copy is placed in her medical record.

4.4.2.2 Form A61: Consent for Sleep Breathing Assessments – Question-by-Question Instructions

The Consent for Sleep Breathing Assessments (Form A61) is completed on all women deemed eligible for the Sleep Breathing Substudy as documented on the Maternal Interview Visit 1 (Form V1A, Section D, questions 14-16). The form is used to document approach, consent, and selection for the substudy. Some women may be approached for consent prior to eligibility being fully determined and subsequently found to be ineligible. A form should be completed on these women as well to document this effort.

Question-by-Question specifications for completing Form A61 follow. Instructions for entering header information apply to all substudy forms and appear in **Section 5.2**.

Section A. Approach

A61A01 Record whether or not informed consent and assent (if applicable) were administered for sleep breathing assessments. "Administered" means that you approached a woman and went over the consent form, whether or not she agreed to participate. This can be done at any time after the participant has agreed to be in nuMoM2b, and may be done before eligibility is documented on the Maternal Interview Visit 1. In particular, this question documents reasons for not administering consent to participants who were eligible for the study according to the answers to the Maternal Interview Visit 1, Form V1A, Section D, questions 14-16.

If "**Yes,**" then Skip to Section B.
If "**No,**" check the reason(s) informed consent was not administered in the remainder of Section A then STOP. At least one reason should be checked. The form is complete at the end of Section A.

A61A01a Check this response if staff certified for the Sleep Breathing Substudy were not available at the time that consent for the study needed to be administered.

A61A01b Check this response if staff certified for the Sleep Breathing Substudy were not available to provide instructions on equipment use.

A61A01c Check this response if no Embletta Gold equipment were available at the time the participant should have been consented.

A61A01d Check this response if the participant could not provide consent alone and the guardian was not present.

A61A01e Check this response if the woman and/or her guardian were physically or emotionally unable to provide consent or otherwise take part in the substudy.

A61A01f Check this response if staff deemed that the woman or her guardian were not reliably able to return equipment to the site.

A61A01g Check this response if the woman was not approached for consent because recruitment efforts were intentionally slowed or stopped.

A61A01h Check this response if consent was not administered to the woman or her guardian for a reason not listed above. If this box is checked, record the reason the consent was not administered in the blank provided for that purpose.

Section B. Consent

A61B01 Record the date the informed consent administration was completed in mm/dd/yyyy format. This corresponds to the last signature date on the consent form. If both consent and assent were required and these forms have a different date, use the last date, which corresponds to the date when administration of informed consent was complete.

A61B02 Check the box next to "Yes" or "No" to indicate whether participant and guardian (if applicable) agreed to participate in the Sleep Breathing Assessment Study.

If "**Yes,**" then answer A61B03.
If "**No,**" STOP, the form is complete.

A61B03 Check the box next to "Yes" or "No" to indicate whether participant and guardian (if applicable) agreed to the sleep breathing assessment results being kept in NIH databases for future research.

Section C. Selection

A61C01 Record whether the woman was found ineligible for the study after agreeing to consent. This might happen because she did not appear for nuMoM2b study visit 1, she did not complete the Maternal Interview Visit 1 during nuMoM2b study Visit 1, or because she completed the Maternal Interview Visit 1, but the responses to Section D, Items D14-D 16 indicated that she was ineligible for the substudy (see **Section 4.3** above).

If "**Yes,**" STOP, the form is complete.
If "**No,**" continue to question A61C02 below.

A61C02 When you reach this question, the participant has consented to the study and meets all eligibility criteria. However, it is still possible that the woman is not selected to participate in the substudy. Record whether the woman was selected for the sleep breathing assessments by study staff.

If "**Yes,**" STOP, the form is complete. If the woman ends up not getting the equipment after being selected for the study by study staff, complete a Substudy Withdrawal form, Form A35, to document the reason the participant did not take part.
If "**No,**" check at least one reason that the woman was not selected to participate in the study in questions A61C02a – A61C02f below.

A61C02a Check this response if staff certified for the Sleep Breathing Substudy were not available to provide instructions on equipment use.

A61C02b Check this response if no Embletta Gold equipment were available at the time the participant should have been consented.

A61C02c Check this response if the woman was determined to be physically or emotionally unable to take part in the substudy.

A61C02d Check this response if staff deemed that the woman could not reliably return equipment to the site.

A61C02e Check this response if the woman was not asked to take part in the study because recruitment efforts were intentionally slowed or stopped.

A61C02f Check this response if study staff did not select an eligible woman for the substudy for a reason that is not listed above. If this box is checked, record the reason the woman was not selected for the substudy in the blank provided for that purpose.

Table of Contents

5. FORMS FOR THE SLEEP BREATHING SUBSTUDY

5.1 Overview

Several of the forms designed for the nuMoM2 be study have been modified to collect data required for the Sleep Breathing Substudy and a number of new forms have been designed specifically for the substudy. This chapter describes these form modifications and forms and describes how to complete the forms for this substudy.

5.1.1 nuMoM2b Forms Associated with this Substudy

The following nuMoM2b study forms were modified to include data elements required for this substudy:

- **V1A: Maternal Interview Visit 1** – Items 14 thorugh 16 were added to Section D of the Jauary 17, 2011 version of this form to capture the data required to confirm eligibility for this substudy. Use of the answers to these questions as part of substudy screening procedures is described in **Section 4.3** of this manual.

- **V1B: Clinical Measurements Visit 1** – Item 7, Section A, was added to this form to collect neck circumference at Visit 1. Instructions for obtaining this measurement appear in Chapter 11 of the nuMoM2b Manual of Operations.

- **Take Home Sleep Questionnaires** – Forms V1F and V3F are Sleep Questionnaires that were part of the take home packages after Visits 1 and 3 respectively since the beginning of nuMoM2b. These questionnaires have been substantially revised in light of the new Sleep Breathing Substudy and were reissued as Forms V1L: Revised Sleep Questionnaire Visit 1 and V3L: Revised Sleep Questionnaire Visit 3 on January 17, 2011. Track change versions of these questionnaires have been placed on the nuMoM2b website to indicate changes between the original forms and the reissued forms. Many of the changes reflect new instructions and time frame references for answers to existing questions. However, at both visits, questions were added related to sleep position, numbers of times the participant wakes up or gets out of bed during the night, and on use of a breathing machine at night. For Visit 1 only, the five questions on snoring and sleep apnea were duplicated and asked in relation to before the participant became pregnant and again in relation to the four weeks before Visit 1. Specifications for these forms appear in Chapter 10 of the nuMoM2b Manual of Operations.

Since all of these forms are discussed elsewhere, they are not discussed further in this chapter.

5.1.2 Forms Developed for the Sleep Breathing Substudy

The following forms were developed for the Sleep Breathing Substudy:

Self-Administered Forms Completed at Home

- **Form V1K: Sleep Monitoring Following Visit 1** – This short questionnaire is completed by participants at home on the morning after they wear the monitor during their sleep following study Visit 1.

- **Form V3K: Sleep Monitoring Following Visit 3** – Similar to V1K, this short questionnaire is completed by participants at home on the morning after they wear the monitor for a night following study Visit 3.

Administrative Forms

- **Form A61: Sleep Breathing Study Consent Elements** – An administrative form that documents consent and subsequent participation in the substudy.

- **Form A33: Substudy Protocol Deviations** – This administrative form was developed to track protocol deviations in any of the ancillary studies for nuMoM2b. It will be modified when new substudies are added to nuMoM2b.

- **Form A34: Substudy Adverse Event** – This administrative form was developed to track adverse events in any of the ancillary studies for nuMoM2b. It will be modified when new substudies are added to nuMoM2b.

- **Form A35: Substudy Withdrawal** – This administrative form was developed to track withdrawal from any of the ancillary studies for nuMoM2b. It is not completed if the participant withdraws from nuMoM2b, as completion of Form A05 indicating withdrawal from nuMoM2b also indicates withdrawal from all substudies associated with the study. This form will be modified when new substudies are added to nuMoM2b.

Evaluation Forms

- **Form E1A: Sleep Breathing Substudy Evaluation Visit 1** – Site staff complete this form to document local evaluation of the quality of each Visit 1 sleep assessment. The completed form is sent to the Sleep Reading Center with the assessment data for scoring.

- **Form E3A: Sleep Breathing Substudy Evaluation Visit 3** – Site staff complete this form to document local evaluation of the quality of each Visit 3 sleep assessment. The completed form is sent to the Sleep Reading Center with the assessment data for scoring.

Sleep Certification Forms

- **Form SC01: Practical Exam for PSG Tech Certification** – This form documents qualitative knowledge of training and certification topics covered during training for the Sleep Breathing Substudy. It is completed for all participants and kept on file at the Sleep Reading Center.

- **Form SC02: Written Exam for PSG Certification** – This form is completed by each site staff member seeking certification. It is sent to the Sleep Reading Center for Scoring and is kept on file there.

After first providing some general information about how to complete form headers and how variables are named in the DCAC databases, the remainder of the chapter includes question-by-question instructions on how to complete the Sleep Breathing Substudy forms briefly described in this section.

5.2 General Instructions on Form Header Information

An example of a form header is given here:

nuMOM2b Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-be	**REVISED* SLEEP QUESTIONNAIRE VISIT 1** Version 03 / January 17, 2011	**Form V1L** Page 1 of 9
Study ID	**Staff ID**	**Date Form Completed**
__ __ __ __ __ __ __ __	__-__-__ __ __ .....__ __ /__ __ /__ __ __ __ mm dd yyyy	

The header for each of the forms contains 2 lines of information. The first line identifies the study, form name, version number and date, gives a short form identifier, and lists the page number and number of pages in the form. This part of the header does not require any entries by a substudy staff member.

The second line of each header identifies the study participant, the staff member who completed or finalized the form, and the date the form was completed (finalized). Since pages of a paper form may become separated or lost, the Study ID is written on the front of every physical sheet of a form. The Staff ID and the date the form was completed are written on the front page of a form at a minimum. **To protect a participant's confidentiality, never write her name on a data form.** Additional information about these entries follows.

5.2.1 Study ID

Participants are identified in the study database that is maintained by the Data Coordinating and Analysis Center (DCAC) with an 8-digit study ID. The study ID serves to link the data for an individual within the database and is consistent across the main study and all substudies in which the woman participates. The study ID is a unique number assigned to a subject during screening for the main study with no direct identifier of the subject. The format of the study ID is as follows: the first digit of the study ID identifies the clinical site; the second digit identifies the subsite (if applicable, otherwise coded 1), digits 3-7 represent a sequential number within the subsite, beginning with 00001; and digit 8 is a character check digit. There are eight study sites, numbered 1-8. These sites and their subsites are listed in **Table 5-1** by number and name.

Table 5-1: Clinical Site and Subsite Numbers and Names

[1] Case Western Reserve University
1-1 Case Western Reserve University
1-2 Ohio State University
[2] Columbia University
2-1 Columbia University
2-2 Christiana Care Health System
[3] Indiana University (no subsites)
3-1 Indiana University
[4] Magee-Women's Hospital
4-1 Magee-Women's Hospital
4-2 West Penn Allegheny Health System
[5] Northwestern University (no subsites)
5-1 Northwestern University
[6] University of California Irvine
6-1 UC-Irvine
6-2 Long Beach Memorial Medical Center
6-3 Fountain Valley Regional Medical Center
[7] University of Pennsylvania
7-1 University of Pennsylvania
7-2 Pennsylvania Hospital
[8] University of Utah
8-1 University of Utah HSC
8-2 LDS Hospital
8-3 McKay Dee Hospital
8-4 Utah Valley Regional Medical Center
8-5 Intermountain Medical Center

An example of a study ID for a mythical site 9, subsite 1, is: 9100017S.

The Study IDs assigned by the clinical site staff at the time of initial screening are used for the Sleep Breathing Substudy. Any hard copy records with both a study ID and a participant's name are kept with other confidential information in a secure location with limited access to clinical site staff involved in the nuMoM2b Study. The name of the participant is never entered into a study database.

5.2.2 nuMoM2b Staff ID at Clinical Sites

Each clinical site staff member submitting data to the project, including staff certified as a Sleep Breathing Study Technician, is assigned a nuMoM2b Staff ID number. The Staff ID also is used on reports to the Sleep Reading Center. Staff IDs are 5 digits in length. The first two digits indicate the site and subsite (see **Table 5-1** for specification of these digits). The last three digits identify the staff member within the subsite.

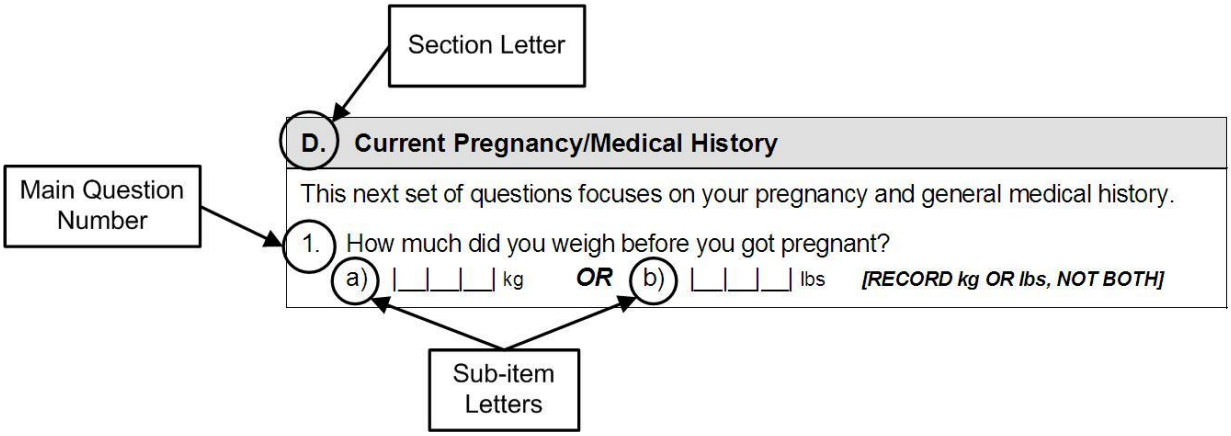
5.2.3 Date Form Completed

The date the substudy form was completed is entered into the header in the format mm/dd/yyyy.

5.3 Question Naming Structure

The nuMoM2b Data Management System (DMS) associates a unique variable name with every data element in the database. Each variable name corresponds to a unique data element on the specific hard copy data collection instrument and the question number is used to derive the variable name. The name in the database is used to specify the variables in the specifications in this manual. This practice will help staff identify information in the DMS as it relates to the forms and will prove useful if it becomes necessary to correct a response to a data element.

In this manual, questions on forms generally can be identified following the pattern of: Form identifier / section letter / 2-digit main question number / sub-item letter / number (i.e., letter, number, letter, number, etc.). In other words, the first three or 4 letters and numbers correspond to the form identifier in the header, and the next letter corresponds to the section of the form where the question or data element is located. The immediately following two-digit number is the main question number, followed by a letter, which identifies the sub-part or sub-item of the main question. In some cases, the sub-item also has subparts that are designated by numbers. For example, in the Maternal Interview Visit 1 (Form V1A) question-by-question specifications, the sub-items for the first question in section D as shown below are designated V1AD01a and V1AD01b.



When the data items are organized in a table with a finite number of rows, identifying the question requires identification of the row and column. For instance, in Section E of the Maternal Interview Visit 2 (Form V2A), the user may input information about up to, but no more than 6 family relations with diabetes (Section E, Question 4, Sub-part a with primary numbering V2AE04a as described above). The question numbers for each cell of this table are provided below in squiggly brackets.

a) For each family member, tell me the relation to you and whether the diabetes was diagnosed as a child or as an adult.

Family Member

a) Family Relation	b) Diabetes Onset 01=Juvenile	02=Adult
1. |__|__| {V2AE04a1a}	☐01	☐02 {V2AE04a1b}
2. |__|__| {V2AE04a2a}	☐01	☐02 {V2AE04a2b}
3. |__|__| {V2AE04a3a}	☐01	☐02 {V2AE04a3b}
4. |__|__| {V2AE04a4a}	☐01	☐02 {V2AE04a4b}
5. |__|__| {V2AE04a5a}	☐01	☐02 {V2AE04a5b}
6. |__|__| {V2AE04a6a}	☐01	☐02 {V2AE04a6b}

Codes for Family Relation
01=Participant's mother
02= Participant's father
03= Participant's brother/half-brother
04= Participant's sister/half-sister

These question numbers are used in the question-by-question specifications to describe the intended responses for a column of data (e.g., the question numbers for column 'a. Family Relation' are specified together in the question-by-question specifications using the nomenclature 'V2AE04a1a to V2AE04a6a').

5.4 Self-Administered Sleep Breathing Substudy Forms

5.4.1 V1K: Sleep Monitoring Following Visit 1

5.4.1.1 General Instructions

Each participant will fill out a *Sleep Monitoring Following Visit 1* questionnaire after their home assessment using the Embletta Gold. This form will be provided to the participants when they receive their Embletta Gold device. All Study ID, Staff ID and date information will be completed by a site staff member before the form is given to the participant. The participant completes the questions related to her night's sleep.

5.4.1.2 Question-by-Question Specifications

The questions on the *Sleep Monitoring Following Visit 1* form all relate to the participant's sleep. This form should be filled out the morning after the first study.

Section A. Time Spent Sleeping

V1KA01 "What time did you go to bed last night (time the lights went out)?" Alternate wording: What time did the participant get in bed and begin attempting to fall asleep? This is not the time the participant *thinks* they actually first fell asleep.

V1KA02 "What time did you wake up this morning?" Alternate wording: What time did the participant first remember waking up in the morning? She may remember waking up multiple times, but this question is looking for the *first* time.

V1KA03 "What time did you get out of bed this morning?" Alternate wording: What time did the participant get out of bed and "start their day"? If they get back in bed and go back to sleep, this is the *final* time they got out of bed for the rest of the day.

V1K04 "How long did you sleep last night?" This is the participant's estimation of how much total sleep she thinks she got during the night recorded as total hours and minutes.

Section B. Sleep Quality

V1KB01 "Compared to your usual night's sleep during pregnancy, how well did you sleep last night?" The participant should choose the one descriptor that describes how much better or worse she slept while wearing the Embletta, compared to a normal night's sleep since becoming pregnant.

Question B2 asks "How much discomfort, if any did the following parts of the monitor cause you?" The participant should put a check in the box of one answer for each item on the list describing the level of discomfort it caused them that night. The items on the list are as follows:

V1KB02a the "plastic piece around your ears and nose" (cannula)

V1KB02b "the belts around your chest and waist" (respiratory belts)

V1KB02c "the three sticky pads" (ECG), and

V1KB02d "the finger piece" (oximeter.)

Question B3 asks the participant to rate her sleep last night by checking a number from 1 to 5 on each of 3 scales. The participant is presented with three scales from 1 to 5 and asked to mark the box that best describes their sleep the night before. The three scales areas follow:

V1KB03a Light (1) to Deep (5),

V1KB03b Short (1) to Long (5), and

V1KB03c Restless (1) to Restfull (5).

Question B4 concerns sleeping positions. The participant is asked, "What position did you…?" The participant is given a list of 7 different positions and "don't remember" and is asked to note in which position did she

V1KB04a go to sleep in last night (the night of monitoring,

V1KB04b sleep in for the majority of the night, and

V1KB04c wake up in after the night of monitoring.

V1KB05 "How often did you wake up during the night?" The participant should give her best estimate of the number of times she woke up during the night.

V1KB05 "During the night, how often did you have to get out of bed?" The participant should give her best estimate of the number of times she physically got out of bed during the night (for example, to use the toilet, to get something to eat).

5.4.2 V3K: Sleep Monitoring Following Visit 3

5.4.2.1 General Instructions

The questions on the *Sleep Monitoring Following Visit 3* form all relate to the participant's sleep and should be filled out the morning after their second study. The form is similar to V1K, but is completed after the second sleep study, rather than the first.

5.4.2.2 Question-by-Question Specifications

The questions on this form are the same as those on the *Sleep Monitoring Following Visit 1* form. See **Section 5.4.1.2** for details about how to complete specific questions. Note that the variable names for this questionnaire start with V3K rather than V1K as in the prior section.

5.5 Administrative Forms

5.5.1 Form A61: Consent for Breathing Assessments

Question-by-question specifications for this form appear in **Section 4.4.2.2** of this manual.

5.5.2 Form A33: Substudy Protocol Deviations

5.5.2.1 Overview and Definitions

This form is designed to collect protocol deviations for all nuMoM2b substudies. The Substudy Codes table is updated each time an additional substudy is added to nuMoM2b. Protocol deviations related to the main nuMoM2b protocol should be recorded on Form A03.

A protocol deviation is any variance from a written protocol. Form A33, Substudy Protocol Deviations, is completed for every episode in which procedures specified in a nuMoM2b substudy protocol are not carried out or are carried out incorrectly. A protocol deviation is considered significant and labeled a protocol violation if the action affects the participant's rights, safety, or welfare and/or the integrity of the data.

The following actions are labeled protocol violations for a substudy:

- Failure to obtain and/or document informed consent prior to any substudy procedures;
- Failure to obtain and/or document HIPAA Authorization of Disclosure prior to use of medical records for a substudy;
- Enrollment of an ineligible woman into the substudy; Note: Enrollment occurs when the first substudy procedure beyond screening commences.
- Breach of confidentiality.

These situations are reported to the local IRB and the DCAC as soon as study personnel are aware of the violation. The DCAC provides protocol violation reports to NICHD and the RTI IRB.

As a substudy progresses, protocol deviations may arise that need to be evaluated as to the significance with respect to participant's rights, safety, or welfare and/or the integrity of the data. When such circumstances arise, the protocol deviation is reported to the DCAC immediately for review and resolution. Documentation is maintained at the DCAC for each instance.

Periodic monitoring reports produced by the DCAC include a cumulative list of protocol deviations that have occurred on each substudy, and a list of those labeled protocol violations.

5.5.2.2 Question-by-Question Specifications

Complete the Substudy Protocol Deviations Form as soon as possible and no later than 1 week after recognition of a substudy protocol deviation. The header is completed as described in **Section 5.2**.

Section A. Details on Deviation(s)

A33A01 Record the date when the protocol deviation(s) occurred in the format mm/dd/yyyy.

A33A02 Enter codes from the Substudy Codes table at the bottom of the page into A33A02a, A33A02b, and A33A02c to indicate the substudy(ies) in which the deviation occurred. If the deviation pertains to fewer than three substudies, leave the remaining fields blank. Code "01" is used for the Sleep Breathing Substudy.

For Question 3, check the appropriate box or boxes to document the type(s) of substudy deviation(s) that occurred on this date. Choices are as follows:

A33A03a Check this box if site staff failed to obtain appropriate informed consent and / or assent on a woman prior to conducting substudy procedures.

A33A03b Check this box if site staff failed to obtain HIPAA authorization of disclosure on a woman prior to obtaining information for the substudy from medical records.

A33A03c Check this box if site staff enrolled an ineligible participant into a substudy. (a person is "enrolled" when the first substudy procedure beyond screening occurs.) IF A33A03c is checked, specify the reason the participant was ineligible in 50 characters or less in the space provided (A33A03c_SP).

A33A03d Check this box if site staff identified a breach of participant confidentiality.

A33A03e Other, check this box if the identified protocol deviation does not fit under any of the above choices. IF A03A03e is checked, specify the reason the participant was ineligible in 50 characters or less in the space provided (A33A03e_SP).

A33A04 Describe circumstances surrounding the substudy protocol deviation in greater detail. Up to 500 characters may be entered into the data system for this field. Identify the participant by Study ID number. **Do not include the name of the participant or other identifying information in the description.** If the explanation exceeds 500 characters, check the "Yes" box for A33A05 and send a narrative summary to the DCAC. Also, call a DCAC site coordinator to discuss the situation.

A33A05 The DCAC may request further documentation in narrative format or the site may choose to send additional information to the DCAC. Check the box next to "Yes" or "No" to indicate whether a narrative summary was sent to the DCAC.

5.5.3 Form A34: Substudy Adverse Event

Participant safety always takes priority above all else. Assurances of participant safety are made through informed consent procedures, responsibilities for participant confidentiality, adherence to HIPAA regulations, and close monitoring and reporting of adverse events.

Form A34 is used to report adverse events for any nuMoM2b substudy. Adverse events related to the main nuMoM2b study are reported on Form A04 rather than this form.

5.5.3.1 Definitions

NuMoM2b is an observational study obtaining data and specimens. The methods used for clinical measurements, ultrasounds specimen collections, and other related procedures fall under protocols for routine, often obstetric, care. The procedures for the main study are all considered minimal risk, as are the breathing assessments conducted under the protocol for this substudy.

It is projected that approximately 12% of the participants will experience adverse pregnancy outcomes, and severe sleep breathing disturbances may be identified in 5% of all cases. These outcomes would traditionally fall under the definition of an adverse event. Due to the expected frequency and the observational nature of the study, traditional adverse event reporting does not apply.

Given this background, adverse experiences are expected to be rare. However, each clinical site is responsible for reporting adverse events to their local IRBs and the DCAC. Also, each site reports adverse events as is required by the specific IRB applicable to that site or the hospital in which the adverse event occurs.

The adverse events that will be monitored and reported during this study include the following:

- Rash (or skin irritation from electrodes, tape or monitoring equipment.

Hospitalizations will be monitored, but not considered adverse events as virtually all participants are expected to be hospitalized for delivery.

5.5.3.2 Monitoring / Detection

An Adverse Event (AE) can be detected at any time. However, most AEs for this substudy will be detected shortly after a sleep breathing assessment.

NuMoM2b staff monitor the occurrence of the listed adverse events for each study participant over the period of active study participation, from enrollment through discharge after the delivery hospitalization. Procedures are as follows.

- All participants are provided with contact information and instructions about how to contact study personnel to report any concerns or serious events that occurred outside of the clinical setting.

- Participants are queried about any concerns (medical or otherwise) during the scheduled contacts. Before each contact with a study participant, a clinical site staff member reviews the participant's accumulating study record to ensure familiarity prior to engaging the participant in conversation.

- Missed expected and rescheduled visits or due dates are monitored weekly and followed-up by telephone call.

5.5.3.3 Reporting

Each site is responsible for fulfilling all IRB requirements for reporting adverse events. Data collection allows for monitoring the adverse events listed above. These events must be reported within 24 hours of identification.

The clinical site PIs are responsible for ensuring that the appropriate local IRB(s) and the Data Analysis and Coordinating Center (DCAC) are notified within the appropriate time frame. The completed adverse event forms along with additional laboratory findings or other documentation are submitted to the DCAC as specified here. The study participant records that are submitted are identified by study ID number only, and all other identifying information is stripped from the forms.

Upon receipt, the DCAC disseminates the report to the NICHD Project Officer and Project Scientists within 72 hours of notification. The DCAC PI and NICHD review each reported adverse event. Cumulative adverse event data also are reviewed by the Advisory and Safety Monitoring Board at periodic intervals during the study. The DCAC prepares reports of the study for review by this Board.

5.4.3.4 Question-by-Question Specifications

Complete the Adverse Event form within 24 hours of recognition of any adverse event that must be reported centrally or to your local IRB. FAX the completed form to the Principal Investigator at the DCAC within 24 hours of recognition of the adverse event, and key the form into the data management system. The header is completed as described in **Section 5.2**.

Section A: Details on Event

A34A01 Record the date the event occurred in the format mm/dd/yyyy. If the event occurred over multiple days record the date when the event started.

A34A02 Record the date when the event was resolved. If the adverse event has not been resolved within 72 hours, enter -4 in all parts of the date field. This will indicate that the date is temporarily missing and will be completed once known.

A34A03 Enter codes from the Substudy Codes table at the bottom of the page into A34A03a, A34A03b, and A34A03c to indicate the substudy(ies) in which the deviation occurred. If the deviation pertains to fewer than three substudies, leave the remaining fields blank. Code “01” is used for the Sleep Breathing Substudy.

A34A04 Enter one or more adverse event codes from the table at the bottom of the page on lines A34A04a, A34A04b, or A34A04c, or check the box in A34A04d to indicate that an event other than those listed in the adverse event coding list occurred. If the box in A34A04d is checked, specify the event in 50 characters or less in the space provided (A34A04d_SP. Other reportable events are at the discretion of the local research staff, consistent with local IRB reporting requirements.

A34A05 Record “Definitely”, “Possibly” or “Not at all” to indicate if, in the opinion of the clinical site PI, the event was related to study participation.

A34A06 Record a description of the event in 500 characters or less. Be sure to cover all major points leading up to the event and how it was resolved. **Do not include the participant’s name or other identifying information in the description.**

A34A07 Depending on the circumstances surrounding the event, the DCAC may request further documentation in narrative format or the clinical site staff may choose to send the DCAC additional information. Check “Yes” or “No” to indicate whether a narrative summary was sent to the DCAC. This will alert the DCAC that the narrative has been sent and help link the narrative to this form. In the summary, identify the participant by study ID number. **Do not include the participant’s name or other personal identifying information in the summary.**

5.5.4 Form A35: Substudy Withdrawal

5.5.4.1 General Instructions

Withdrawals from the nuMoM2b study and/or its various substudies are documented so that these events can be monitored by the DCAC and reported to various groups including the

Steering Committee, IRBs, and Scientific Advisory and Safety Board. Understanding reasons why participants are withdrawing as the study or substudy progresses can allow the investigators to make modifications to the protocol, if necessary, to improve the level of participation and retention of participants.

This administrative form was developed to track withdrawal from any of the ancillary studies for nuMoM2b. It is not completed if the participant withdraws from nuMoM2b, as completion of Form A05 indicating withdrawal from nuMoM2b also indicates withdrawal from all substudies associated with nuMoM2b. This form will be modified when new substudies are added to nuMoM2b.

5.5.4.2 Question-by-Question Specifications

Complete the Withdrawal Form for any participant who is lost or withdrawn from the Sleep Breathing Substudy prior to completion of the second sleep breathing assessment following Study Visit 3. The form should be completed within 1 week of learning about the loss or withdrawal. The header is completed as described in **Section 5.2**.

Section A. Study Withdrawal

A35A01 Record the date of withdrawal using the format mm/dd/yyyy.

A35A02 Enter codes from the Substudy Codes table at the bottom of the page into A35A02a, A35A02b, and A35A02c to indicate the substudy(ies) in which the deviation occurred. If the deviation pertains to fewer than three substudies, leave the remaining fields blank. Code “01” is used for the Sleep Breathing Substudy.

Check one or more boxes in Question A03 to indicate who withdrew the participant from the study:

A35A03a Check this box to indicate that the participant withdrew herself from the substudy,

A35A03b Check this box to indicate that the participant's legal guardian withdrew the participant from the substudy,

A35A03c Check this box to indicate that the participant's primary health care provider withdrew the participant from the substudy,

A35A03d Check this box to indicate that the clinical site staff withdrew the participant from the substudy. If site staff are unable to get in touch with a woman after sufficient effort and the woman has not completed study participation, check this response. Similarly, if the woman dies during the course of study participation, check this box to indicate that she is being withdrawn by the study coordinator.

A35A03e Check this box to indicate that another person withdrew the participant from nuMoM2b. If this box is checked, use 50 characters or less to specify who withdrew the participant in the space provided (A35A03e_Other).

Check one or more boxes in Question A04 to indicate all of the reasons that the participant is withdrawn from the substudy.

A35A04a Check this answer if the participant is unable to continue substudy participation due to medical condition. If this is the case, please specify the medical condition and any other relevant information in 50 characters or less in the space provided (A35A04a_Other).

A35A04b Check this answer if the participant withdrew consent. If this answer is checked, specify in 50 characters or less the reason the participant gave for withdrawing consent for the substudy (A35A04b_Other).

A35A04c Check this answer if the participant's guardian withdrew consent for the participant to be in the study. If this answer is checked, specify in 50 characters or less the reason the participant's guardian gave for withdrawing consent for the substudy (A05A03g_Other).

A35A04d Check this box if a reason for withdrawal from the substudy does not fit under any of the above answer choices. If this answer is chosen, specify the reason for withdrawal in 50 characters or less in the space provided (A35A04d_Other).

A35A05 Describe the circumstances surrounding the withdrawal from the substudy including the condition of the participant (and, if delivered, her baby) at the time of withdrawal in 500 characters or less.

5.6 Evaluation Forms

5.6.1 Form E1A: Sleep Breathing Substudy Evaluation Visit 1

5.6.1.1 General Instructions

This form is completed by study staff upon reviewing a recently collected sleep breathing assessment following Visit 1. This is not the official quality review form, but assists the scorer at the Sleep Reading Center in reliably reviewing the sleep breathing assessment for final scoring and quality. Form E1A is filled out using times from the participant's *Sleep Monitoring Following Visit 1* form and information based on what the site staff member sees upon a quick review of the study in RemLogic-E. The study staff member who performed the demonstration for the participant should have their staff ID recorded at the top of the form. When Form E1A is completed, it is added to the zipped folder containing the sleep breathing assessment data and sent via FTP to the Sleep Reading Center for scoring. These procedures are described in **Sections 6.8 and 6.9** of this manual.

5.6.1.2 Question-by-Question Specifications

Form E1A is divided into two sections: *Information Related to Sleep Breathing Assessment* and *Site Evaluation of Recording.*

A. Information Related to Sleep Breathing Assessment

E1AA01 Date Study Recording Initiated (format: mm/dd/yyyy). This is the date that the participant attempted to record data for a sleep breathing assessment. This is not necessarily the date of the visit during which the participant is instructed on use of the Embletta and receives their unit for overnight recording.

E1AA02 The Unit ID is the 3 digit unit ID number unique to each Embletta. This number is on the bag and on a label on the back of the Embletta. Make sure these two numbers match. This number is used also in RemLogic-E to identify the Embletta Gold device used for the sleep breathing assessment described.

E1AA03 Record the number of minutes a staff member spent talking with the participant when the device was issued to explain the proper placement, hookup, removal and paperwork associated with the Embletta Gold for the sleep breathing substudy.

E1AA04 Record the time that the participant turned off the lights, got into bed and began attempting to fall asleep. This is *not* the time the participant thinks they actually fell asleep. This time is copied from Form V1K, Section A, Question 1.

E1AA05 Record the time that the participant first remembers waking up in the morning. This time is taken from form V1K, Section A, Question 2.

B. Site Evaluation of Recording

This section begins with five yes or no questions about the overall quality of the sleep breathing assessment data that will help the site staff in identifying problem studies in case equipment needs troubleshooting or a participant needs to be asked to repeat her overnight study. There is also space for staff to provide an explanation for "No" answers. The five questions in greater detail are:

E1AB01 "Is the participant ID on the recording correct? Does it match the ID on the paperwork?" In RemLogic-E, in the "Recordings" panel on the left side is the patient's information properly entered identifying information is displayed in the order: Study ID (8 character)-Visit Number (1 in this case)-Demonstration Date, Staff ID (5 digit), Unit ID (3 digit). Note that a hyphen separates each of the components of the ID (Study-Visit-Date). An example of a possible identifier is: **9100017S-1-01042011, 91123 (001)**. Check to make sure that all these identifier numbers match any numbers on their paperwork. If any discrepancies are found contact any study staff involved to correct this identifying information before sending files to the Sleep Reading Center.

E1AB02 "Are there signals on each of the channels (i.e., no flat-lined signal[s])?" This question is addressing whether there is a signal on each channel that looks appropriate for the type of data involved? Some channels such as position, gravity and snore may appear as a flat-lined signal for long periods of time, but this is normal. In these cases the site staff member just needs to verify that those signals are not flat for the **entire** recording, which is indicative of problems with the hookup or equipment. All respiratory channels should display a sinusoidal curve of varying frequency and amplitude. The SpO2 and pulse channels should be largely flat with some variation that corresponds with changes on respiratory channels. SpO2 and pulse should also display values with realistic ranges (85-99% for SpO2 and 50-130 bpm for pulse.) Finally, the EKG channel should have a waveform with distinct P waves and QRS complexes when viewed on a 30 second page (time scale is changed in the upper right corner of RemLogic-E). Additional information about this review is provided in **Section 6.8**.

E1AB03 "Is each channel mostly clear of artifact (thick, fuzzy lines)?" Each channel should look as described in the question above, but artifact may occur. Intermittent artifact is very common with participant movement but should only occur in short corresponding sections. Long stretches of unusual looking signals are indicative of a problem sensor or suboptimal hookup. Respiratory artifact will typically involve jagged, inconsistent signals that occur during what appears to be sleep. Respiratory signals should be relatively clean, sinus curves that vary in frequency and amplitude. Artifact on the SpO2 channel will typically manifest itself as signal dropouts where the channel goes from values in the 90's to a value of 0 and back frequently. SaO2 dropout is also expected during movement, but not at any point during sleep. Artifact on EKG is typically caused by loose or bad leads and will cause the signal to become "fuzzy." Individual waves should be easily discernible

on the EKG channel on a nice sharp waveform. Lastly, the position sensor's artifact will make it appear that the participant is rapidly changing positioning during the night, with spikes and wild variation on the position channel. Additional information about artifact appears in **Section 6.8**.

E1AB04 "Are there at least 2 hours of recorded data?" Answer "Yes" if there are at least 2 hours of "sleep" data viewable in RemLogic-E. Each channel should have a reliable signal that is mostly clear of artifact and is calm for at least 2 hours between "time to bed" and "wake time." If there are several hours of clear signals before the participant goes to bed and the waveforms "settle down," but then they shortly go bad this is not usable for scoring. In order to pass a study and begin scoring, it needs to have at least 2 hours of relatively calm signal after the participant has gone to bed.

E1AB05 "Are there at least 2 hours of oximetry data?" During the 2 hours of usable data as described in the last question, there needs to be a reliable SaO2 signal for the sleep breathing assessment to be scored. The SaO2 channel should display a consistent signal with minimal dropouts (zeros) and display values in a realistic range (85-99%, varying with breathing effort).

E1AB06 "If less than 2 hours of recorded oximetry **and** either nasal pressure or one respiratory band data is observed check here to indicate study failed, send in failed study with paperwork, and repeat study." A sleep breathing assessment must have at least 2 hours of good data with concurrent oximetry and oneor more of nasal pressure, abdomen, or thorax to be scored. Leave this question blank for studies that are not failed due to less than 2 hours of usable data.

E1AB07 The final section of the *Sleep Breathing Substudy Evaluation Visit* form is a space for any relevant comments about the study from the reviewing staff. Good comments include:

Difficulties involved explaining the hookup to the participant.

Problems a participant reported regarding the time when she attempted to hook herself up.

Descriptions of any environmental conditions at the participant's home that could have affected recording (e.g., animals sleeping in the bed, an emergency during the night).

Problems with signals seen in RemLogic-E, and actions being taken to troubleshoot and/or fix them.

Anything else that the RA thinks the scorer should be aware of when interpreting the study.

It is always best to have more information for scoring unusual studies, so, when in doubt about whether information will be useful, write a comment to be safe.

5.6.2 Form E3A: Sleep Breathing Substudy Evaluation Visit 3

5.6.2.1 General Instructions

This form is completed by study staff upon reviewing a recently collected sleep breathing assessment following Visit 3. This is not the official quality review form, but assists the scorer at the Sleep Reading Center in reliably reviewing the sleep breathing assessment for final scoring and quality. Form E3A is filled out using times from the participant's *Sleep Monitoring Following Visit* 3 form and information based on what the site staff member sees upon a quick review of the study in RemLogic-E. The study staff member who performed the demonstration for the participant should have their staff ID recorded at the top of the form. When Form E3A is completed, it is added to the zipped folder containing the sleep breathing assessment data and sent via FTP to the Sleep Reading Center for scoring. These procedures are described in **Sections 6.8 and 6.9** of this manual.

5.6.2.2 Question-by-Question Specifications

Form E3A is divided into two sections: *Information Related to Sleep Breathing Assessment* and *Site Evaluation of Recording.*

A. Information Related to Sleep Breathing Assessment

E3AA01 Date Study Recording Initiated (format: mm/dd/yyyy). This is the date that the participant attempted to begin recording data for a sleep breathing assessment. This is not necessarily the date of the visit during which the participant is instructed on use of the Embletta and receives their unit for overnight recording.

E3AA02 The Unit ID is the 3 digit unit ID number unique to each Embletta. This number is on the bag and on a label on the back of the Embletta. Make sure these two numbers match. This number is used also in RemLogic-E to identify the Embletta Gold device used for the sleep breathing assessment described.

E3AA03 Record the number of minutes a staff member spent talking with the participant when the device was issued to explain the proper placement, hookup, removal and paperwork associated with the Embletta Gold for the sleep breathing substudy.

E3AA04 Record the time that the participant turned off the lights, got into bed and began attempting to fall asleep. This is *not* the time the participant thinks they actually fell asleep. This time is copied from Form V3K, Section A, Question 1.

E3AA05 Record the time that the participant first remembers waking up in the morning. This time is taken from form V3K, Section A, Question 2.

B. Site Evaluation of Recording

This section begins with five yes or no questions about the overall quality of the sleep breathing assessment data that will help the site staff in identifying problem studies in case equipment needs troubleshooting or a participant needs to be asked to repeat her overnight study. There is also space for staff to provide an explanation for "No" answers. The five questions in greater detail are:

E3AB01 "Is the participant ID on the recording correct? Does it match the ID on the paperwork?" In RemLogic-E, in the "Recordings" panel on the left side is the patient's information properly entered identifying information is displayed in the order: Study ID (8 character)-Visit Number (3 in this case)-Demonstration Date,

Staff ID (5 digit), Unit ID (3 digit). Note that a hyphen separates each of the components of the ID (Study-Visit-Date). An example of a possible identifier is: **9100017S-3-01042011, 91123 (001)**. Check to make sure that all these identifier numbers match any numbers on their paperwork. If any discrepancies are found contact any study staff involved to correct this identifying information before sending files to the Sleep Reading Center.

E3AB02 "Are there signals on each of the channels (i.e., no flat-lined signal[s])?" This question is addressing whether there is a signal on each channel that looks appropriate for the type of data involved? Some channels such as position, gravity and snore may appear as a flat-lined signal for long periods of time, but this is normal. In these cases the site staff member just needs to verify that those signals are not flat for the **entire** recording, which is indicative of problems with the hookup or equipment. All respiratory channels should display a sinusoidal curve of varying frequency and amplitude. The SpO2 and pulse channels should be largely flat with some variation that corresponds with changes on respiratory channels. SpO2 and pulse should also display values with realistic ranges (85-99% for SpO2 and 50-130 bpm for pulse.) Finally, the EKG channel should have a waveform with distinct P waves and QRS complexes when viewed on a 30 second page (time scale is changed in the upper right corner of RemLogic-E). Additional information about this review is provided in **Section 6.8**.

E3AB03 "Is each channel mostly clear of artifact (thick, fuzzy lines)?" Each channel should look as described in the question above, but artifact may occur. Intermittent artifact is very common with participant movement but should only occur in short corresponding sections. Long stretches of unusual looking signals are indicative of a problem sensor or suboptimal hookup. Respiratory artifact will typically involve jagged, inconsistent signals that occur during what appears to be sleep. Respiratory signals should be relatively clean, sinus curves that vary in frequency and amplitude. Artifact on the SpO2 channel will typically manifest itself as signal dropouts where the channel goes from values in the 90's to a value of 0 and back frequently. SaO2 dropout is also expected during movement, but not at any point during sleep. Artifact on EKG is typically caused by loose or bad leads and will cause the signal to become "fuzzy." Individual waves should be easily discernible on the EKG channel on a nice sharp waveform. Lastly, the position sensor's artifact will make it appear that the participant is rapidly changing positioning during the night, with spikes and wild variation on the position channel. Additional information about artifact appears in **Section 6.8**.

E3AB04 "Are there at least 2 hours of recorded data?" Answer "Yes" if there are at least 2 hours of "sleep" data viewable in RemLogic-E. Each channel should have a reliable signal that is mostly clear of artifact and is calm for at least 2 hours between "time to bed" and "wake time." If there are several hours of clear signals before the participant goes to bed and the waveforms "settle down," but then they shortly go bad this is not usable for scoring. In order to pass a study and begin scoring, it needs to have at least 2 hours of relatively calm signal after the participant has gone to bed.

E3AB05 "Are there at least 2 hours of oximetry data?" During the 2 hours of usable data as described in the last question, there needs to be a reliable SaO2 signal for the sleep breathing assessment to be scored. The SaO2 channel should display a consistent signal with minimal dropouts (zeros) and display values in a realistic range (85-99%, varying with breathing effort).

E3AB06 "If less than 2 hours of recorded oximetry **and** either nasal pressure or one respiratory band data is observed check here to indicate study failed, send in failed study with paperwork, and repeat study." A sleep breathing assessment must have at least 2 hours of good data with concurrent oximetry and oneor more of nasal pressure, abdomen, or thorax to be scored. Leave this question blank for studies that are not failed due to less than 2 hours of usable data.

E3AB07 The final section of the *Sleep Breathing Substudy Evaluation Visit* form is a space for any relevant comments about the study from the reviewing staff. Good comments include:

Difficulties involved explaining the hookup to the participant.

Problems a participant reported regarding the time when she attempted to hook herself up.

Descriptions of any environmental conditions at the participant's home that could have affected recording (e.g., animals sleeping in the bed, an emergency during the night).

Problems with signals seen in RemLogic-E, and actions being taken to troubleshoot and/or fix them.

Anything else that the RA thinks the scorer should be aware of when interpreting the study.

It is always best to have more information for scoring unusual studies, so, when in doubt about whether information will be useful, write a comment to be safe.

5.7 Forms for Staff Certification

5.7.1 Form SC01: Practical Exam for PSG Tech Certification

5.7.1.1 General Instructions

This form will be used to document training and to certify new staff members as technicians prepared for their duties for the nuMoM2b Sleep Breathing Substudy. Each section is reviewed during training with the staff member seeking certification. The form is signed and dated by a member of the Sleep Reading Center staff, another investigator authorized to train during central training, or a local staff member who was trained at central training and fully certified by Sleep Reading Center staff. No training should take place at sites until the trainer at the site has been fully certified by the Sleep Reading Center. A copy of this form is sent to the Sleep Reading Center after completion to be reviewed and archived.

5.7.1.2 Question-by-Question Specifications

The name and 5 digit Staff ID of the staff member being certified as a technician goes in the header of the form. When the practical exam is completed, it is signed and dated at the top of the form by a staff member who was previously certified by the Sleep Reading Center. Each section should be completed individually with care taken to make sure the staff member seeking certification demonstrates an understanding of each sub topic listed, and then initialed and dated by both the trainer and trainee.

5.7.2 Form SC02: Written Exam for PSG Tech Certification

5.7.2.1 General Instructions

This form is used to test the knowledge each staff member seeking certification has of the protocol for the nuMoM2b Sleep Breathing Substudy. Completion of the written exam with a passing score is required to certify a staff member as a new technician for data collection. This from must be submitted to the Sleep Reading Center along with their Practical Exam and recorded certification study for review before a technician can be certified. The form is archived at the Sleep Breathing Center and in local staff training records.

5.7.2.2 Question-by-Question Specifications

The trainee's name and 5-digit Staff ID are written in the header of the exam. Upon completion of the exam, it is signed and dated by the local trainer and sent to the Sleep Reading Center for scoring. The written exam is a standard exam with 20 questions requiring the trainee to circle the one most correct answer to each question.

Table of Contents

6. SITE RESPONSIBILITIES FOR SLEEP BREATHING SUBSTUDY ASSESSMENTS

6.1 Overview

Full in-laboratory polysomnography (PSG) is the gold standard for the objective measurement of sleep, sleep related breathing and sleep related movements; however it is often not feasible to use full in-laboratory PSG for large sleep related studies given the cost and limited availability of sleep laboratory space. Recently, a number of portable sleep apnea monitoring devices have become available that avoid some of the limitations of in-laboratory PSG. After discussion with the nuMOM2b Sleep Breathing Committee, it was determined to perform sleep monitoring using the Embletta-Gold device (Embla, Broomfield, CO), a pocket-sized digital recorder. This device contains the three critical sensors that are recommended as validated sensors for measuring sleep apnea: nasal pressure (measuring airflow, needed for detecting apneas and hypopneas and episodes of lesser airflow limitation); thoracic and abdominal inductance plethysmography (measuring respiratory effort for distinguishing central from obstructive apneas and as a back-up for the nasal pressure signal); and finger pulse oximetry (to quantify level of oxygen desaturation). In addition, snoring sounds and a bipolar ECG are collected. The Embletta system was used by the HomePap study, a clinical trial of 430 subjects (including inner city minorities) who were instructed at a research exam on how to use the device, including self-applying sensors at home. A majority of these studies were graded as excellent or outstanding quality, suggesting the feasibility of this low-burden approach, with overall failure rates of 5 to 6%. This device is currently in use by the HeartBEAT study, an NHLBI-funded multisite clinical trial. For this study, failure rates of approximately 5 to 6% are seen (mostly due to oximetry), again using the device after a short demonstration in the clinic and with self-application.

Clinical site personnel instruct the participant on proper placement of the various device sensors during a study visit, and participants are asked to wear the device for one night in early pregnancy, and then again for one night in late pregnancy. To allow time to conduct sleep breathing assessments for participants recruited late in the Visit 1 study window, participants completing visit 1 for the main study by 13^6 weeks project estimated gestational age may be enrolled in the Sleep Breathing Substudy as long as the sleep breathing assessment can be completed by the morning of 15^0 weeks project estimated gestational age. Assessments will be considered acceptable if they contain a minimum of 2 hours of oximetry and either nasal pressure or one respiratory band. Assessments containing less than the minimal requirements will not be processed for scoring and the Sleep Reading Center will notify the site coordinator via e-mail to request a repeat assessment from the participant. Repeat assessments for Visit 1 must also be completed by the morning of 15^0 weeks project estimated gestational age. Assessments may be repeated only once for the visit. Similarly, all sleep breathing assessments and repeat assessments around the time of nuMoM2b Visit 3 must be completed between 22^0 weeks project estimated gestational age and the morning of 31^0 weeks project estimated gestational age. Even if a participant enrolled in the Sleep Breathing Substudy around the time of Visit 1 was not able to provide a valid Visit 1 sleep breathing assessment, she should be asked to complete a sleep breathing assessment following Visit 3. However, all participants must be enrolled in the substudy around the time of Visit 1.

At the time of each sleep assessment visit, application of sensors is demonstrated by trained certified staff, with participants asked to demonstrate their understanding of application. Participants are shown how to apply the device before bedtime, and are provided an instruction sheet and a staff phone number to use if questions arise during application or monitoring. Each

participant is provided a monitor to use within the subsequent 48 hours. Arrangements are made to retrieve or return the monitor by mail, drop off, or pickup. Care is taken to have the participant use the monitor while following routine habits. Once the device is returned, the sleep study information is downloaded using the appropriate software and transmitted to the Sleep Reading Center (SRC).

6.2 Recorder Components and Substudy Supplies

The Embletta Gold consists of the digital recorder and a series of sensors used to capture the information on breathing, oxygen levels, heart rate, snoring, and body position of interest to the study. A summary of the Embletta Gold recorder and associated components is shown below.

The nasal cannula, EKG wet gel electrodes, Flexiwraps for oximeter, and XactTrace belts are intended for single participant contact only and must be discarded after use.

Each participant kit assembled should contain the following:

Table 6-1 Embletta Gold Supplies for Participant

Embletta Gold Specific Supplies	Description
	**Embletta Gold (reusable):** A pocket-sized digital recording device designed to record patient sleep study data for the purpose of subsequent display and manual diagnosis of sleep-disordered breathing, such as obstructive sleep apnea.
	**Black storage bag (reusable):** Carries Embletta Gold including sensors and paperwork
	**EKG Snap-On leads (1 Orange, 1 Black, 1 Green; reusable):** 2 leads required to record 1 channel EKG (1 orange lead for EKG+, and 1 black lead for EKG-) and 1 green required for Participant Ground site (PGND)
	**Oximeter (reusable):** Connects the Embletta Gold to Oximeter flex sensor

Oximeter Flex Sensor (reusable): Used to measure the degree of oxygen saturation of the circulating blood. Connects to Oximeter

Elastic Strap (reusable): One of 3 sizes fitted to the participant to be used to fasten the Embletta on the participant.

XactTrace Locks for Thoracic and Abdominal belts (blue and yellow; reusable): Fastens XactTrace belts together.

XactTrace Thoracic and Abdominal belts (disposable, cut to fit): Used to measure the patient's chest/abdominal movements.

EKG Wet Gel Electrodes(disposable): Solid gel LM/EKG electrodes; Circular shape; Diameter 4.8 cm (1.9 in); Single-use; Latex free; Hypoallergenic; To be used with snap-on leads. **Qty: 3 plus 1-2 extra**

Flexiwraps for Oximeter (disposable): Designed for use with the Oximeter Flex Sensor. Preferred application site is the index finger. **Qty: 1 plus 1-2 extra**

Nasal Cannula (disposable): Latex free, used to measure airflow. The cannula can also detect snoring sounds. Connects to the luer lock on the Embletta Gold. **Qty: 1**

Alcohol Prep Pads (disposable): Used to prepare and clean electrode sites. **Qty: 4 plus 1-2 extra.**

No picture available

Re-Sealable Plastic Bag, such as Ziploc Bag (disposable): Used to keep sensors separate and untangled when participant takes Embletta Gold unit home. **Qty: 6**

Medical Tape (disposable): Can be used to secure cannula to participant's face.

Table 6-2 Additional Supplies Needed

General Sleep Study Supplies	General Sleep Study Dispensing Supplies
• Instruction Sheet – INFO 10 • Mailer Envelope or Courier Instructions	• Measuring Tape • Labels for Embletta Gold case Supplies for Disinfection • Caviwipes (or similar anti-bactericidal) • Disposable surface protector (i.e., underpad) • Scissors • Latex-free gloves

6.3 Training and Certification

6.3.1 Training Materials

These include this substudy Manual of Operations including its appendices, extra copies of forms, a certification packet, PowerPoint presentations, and a training video. These will be available in the private area on the nuMoM2b website. In addition, an Embletta Gold device and accompanying equipment and supplies as detailed in this chapter are needed for demonstration and practice.

6.3.2 Training

Every collection site must have at least one (1) study coordinator or research assistant who is responsible for overseeing the Sleep Breathing Substudy data collection at central training. This staff member is the first staff member at each site to certify for sleep breathing assessment data

collection and then becomes responsible for training and oversight of any additional staff members who certify for providing instruction to participants or to perform other tasks related to collection of sleep breathing assessments data at the site. The certifying staff member need not actually perform every required task but will be responsible for the acceptable completion of each task.

Sleep collection training requires a staff member (often called the technician in this manual) to become familiar with the purpose of the nuMOM2b Sleep Breathing Substudy, the purpose of sleep breathing monitoring and relevance to the overall study goals; how to use the sleep monitor hardware and software; how to transmit data to the SRC; how to maintain relevant study documents; interpret unit-generated quality control checks; routine maintenance checks and other unit troubleshooting methods; and how to act on identified Urgent Sleep Alerts.

6.3.3 Certification

6.3.3.1 Site Technician Training and Certification

Certification requirements include:

- completion of a written exam;
- completion of a practical exam, which includes observation by a Sleep Reading Center approved investigator or staff member or a centrally trained and certified clinical site staff member to evaluate the ability of the staff member to initialize and download the studies and to clearly explain the use of the portable sleep monitoring device; and
- documentation of a successful transmission of a high quality study and associated paperwork to the SRC.

Staff are required to demonstrate proficiency in using the sleep monitor for collection and transmitting data by submitting one (1) acceptable night time recording on a volunteer. This serves both as part of the staff certification and as practical experience in using the equipment in the study environment. Certification studies also allow for verification that sensors and equipment are functioning properly before being used on a study participant. Centrally certified Sleep Breathing staff are permitted to train others at the local level. Additional staff trained locally must complete the certification process before performing these duties at the site. A checklist for training on site is provided to ensure that staff members who have not attended central training have the same basic understanding of collecting sleep data as those who attended central training. This checklist must be signed by the trainee and the certified technician and submitted to the SRC as part of the certification process.

To be considered acceptable for certification the sleep recording must:

- have good quality signal on each channel (i.e., all sensors must work and be relatively free from artifact) for at least 4 hours of monitoring time;
- include proper naming of the study recording (including the Study ID, Staff ID, and Unit ID);
- include a completed Sleep Breathing Substudy Evaluation Visit 1 or Visit 3 form (E1A or E3A); and
- be successfully downloaded and transmitted to the SRC.

6.3.3.2 Maintaining Certification

After initial certification, sleep certification can be maintained by performing successful data collection and transmission of a minimum of one (1) study per month. Signal and study codes, specific to each staff member and monitor will be summarized and reported on a monthly basis to the nuMOM2b Steering Committee and the Sleep Breathing Committee. These reports identify individual staff members who do not meet pre-defined levels of performance. If needed, the SRC will lead periodic Sleep Breathing Substudy Quality Control calls to facilitate dissemination common information related to problems identified and to discuss solutions to those problems (e.g., optimizing presentation of equipment to pregnant women). A practice study is defined as successful data collection (at least 2 hours in length) on a non-participant volunteer and transmission of the resulting data to the SRC.

6.3.3.3 Device Certification

In addition to staff certification, sites are required to perform at least one practice study with each Embletta Gold device and transmit the resulting data to the SRC before using the device on a study participant. This ensures that faulty devices are not used for sleep breathing assessments on participants.

If a device has a failed assessment during the substudy or a device is repaired, at least one successful practice study on a volunteer must be done with the device before it is used for any additional substudy assessments on participants.

6.3.3.4 Adding New Site Staff or Devices

Tech and unit IDs allow for quality tracking. If a site has added a new staff member, the main liaison for the site must first notify the SRC with the following information:

- Staff member name
- Staff ID
- Email Address
- Phone Number

SRC staff will log this information into a contacts database for future reference. All techs and units must be certified before performing work on the nuMoM2b study (see **Section 6.3.3.1** and **Section 6.3.3.3**).

6.4 Overview of Activities and Timeline for a Sleep Breathing Assessment

Table 6-3 provides information about the activities and timeline associated with a sleep breathing assessment for a particular participant.

Table 6-3 Activities and Timeline for a Sleep Breathing Assessment

Time Frame	Activities
Before the Study Visit (1 to 2 days prior to the Study Visit)*	• Prepare the Embletta Gold device. • Fully charge battery (2 hours and 15 minutes) and verify that Embletta Gold is clean and disinfected • Verify necessary sleep study supplies in the Embletta bag • Upload Participant information to the device • Place Participant Study ID labels on Form V1K: Sleep Monitoring Form Following Visit 1 or Form V3K: Sleep Monitoring Form Following Visit 3 and place in bag
Participant Study Visit	• Describe purpose of sleep study/obtained informed consent (if not already done) • Demonstrate basic unit parts and how to use • Measure and cut elastic respiratory bands for proper band size • Provide and review written instructions for hooking-up the device and for return of unit, including Form V1K: Sleep Monitoring Form Following Visit 1 or Form V3K: Sleep Monitoring Form Following Visit 3 • Log Monitor Number, Date and Participant ID • Arrange monitor retrieval • *(If patient first consented at the Study Visit, do the last 2 steps described under “Before the Study Visit” now)
Upon Return of Sleep Monitor (Morning after Use or when Received)	• Verify Form V1K: Sleep Monitoring Following Visit 1 or Form V3K: Sleep Monitoring Following Visit 3 and Forms V1L or V3L, the main study Revised Sleep Questionnaires, are complete and accurate. Phone participant if necessary to complete. • Remove, discard disposables, and clean unit. • Download and save assessment data. • Review assessment data; complete Sleep Breathing Substudy Evaluation Visit 1 (or 3), Form (E1A or E3A), as appropriate. • Inform (email) the SRC if possible Urgent Referrals are identified. • Take appropriate troubleshooting actions if needed in response to quality messages generated at download. • Reformat Embletta Gold – (enter new participant information). • Recharge Embletta Gold. • Add new disposable supplies to Embletta Gold bag (based on who’s coming in next).
Data Transmittal (24 to 48 hrs. after receipt of monitor)	• Transmit sleep file to SRC. • Confirm SRC receipt on website.

Time Frame	Activities
Reports	• Check website for sleep reports and quality summaries. • Follow-up on Urgent Sleep Alerts.

6.5 Initial Embla Installation Procedures

RemLogic software needs to be installed on an accessible and secure computer. Each recording device (Embletta Gold) needs to be initially configured so it is recognized by the software. This section describes those procedures.

6.5.1 Installing RemLogic E software

RemLogic-E is a polygraphy application program that assists in the preparation, downloading, and reporting and analysis of Embletta recordings.

Prerequisites

Before installing or upgrading to RemLogic-E 1.2, some operating system components may need to be updated. Following is a list of operating system prerequisites:

Windows XP Professional

- Visual C++ 32-bit runtime
- Windows XP Service Pack 3
- .NET Framework 2.0, Service Pack 1
- The following files are prerequisites only if you want to burn CDs and DVDs on a computer with Windows XP. If you will not burn CDs or DVDs, the files are not required
  - Windows Image Mastering API (KB932716, version 2) (Microsoft IMAPI Hotfix)
  - Windows Feature Pack for Storage (32-bit) IMAPI Update for Blu-Ray® (Microsoft IMAPI Feature Pack)

Windows Vista Business/Windows Vista Home Premium

- Visual C++ 32-bit runtime
- Windows Vista Service Pack 2

Windows 7

- Visual C++ 32-bit runtime (32-bit and 64-bit operating systems)
- Visual C++ 64-bit runtime (64-bit operating systems only)
- Windows 7 Service Pack 1

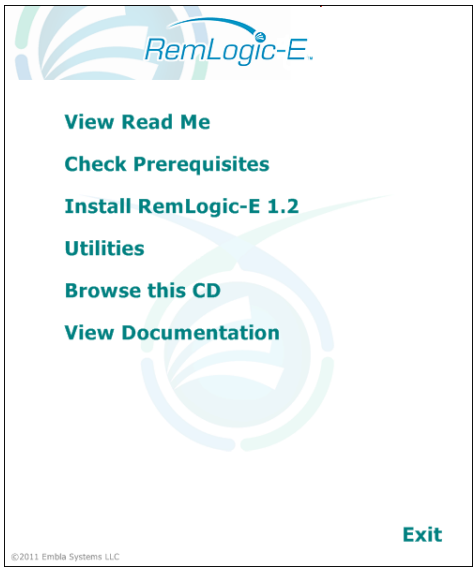
These components, with the exception of Update for Microsoft Office 2003 (KB907417) and Windows Service Packs, can be installed from the RemLogic-E 1.2 Installation CD.

To verify and install prerequisite components:

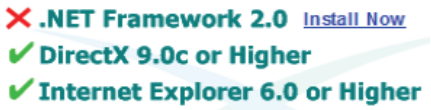
1. Close all programs and log on with administrator privileges.

2. Insert the RemLogic-E 1.2 installation CD into the CD-ROM drive.

3. On the Welcome screen, click **Check Prerequisites**. A green check mark will appear to the left of components included in the install.



Missing components will display a red “x” on the left and an **Install Now** link on the right.



4. Click **Install Now** and follow the setup instructions to install missing components.

5. Repeat this procedure for all missing prerequisite components. The computer may need to be restarted during or following the installation process.

To install RemLogic-E 1.2:

1. Close all programs and log on with administrator privileges.

2. Insert the RemLogic-E 1.2 Installation CD into the CD-ROM drive.

3. On the Welcome screen (see above), click **Install RemLogic-E 1.2**.

4. The RemLogic-E 1.2 Installation Wizard is displayed. Do one of the following:

    - If you are installing RemLogic-E 1.2 and not upgrading from RemLogic-E 1.1 (or earlier), click **Next**.
    - If you are upgrading from RemLogic-E 1.1 (or earlier), click **Next**, then proceed to step 6.

5. On the Choose Setup Type screen, click the radio button next to the **Typical** installation option, and then click **Next**.

6. Click the arrow to the left of the install component labeled **Data Management Module** and select the option **Entire feature will be unavailable.** Click **Next**.

7. Click **Install**. A status bar is displayed.

8. Click **Finish** to exit the Installation Wizard, and click **Exit** to close the welcome screen.

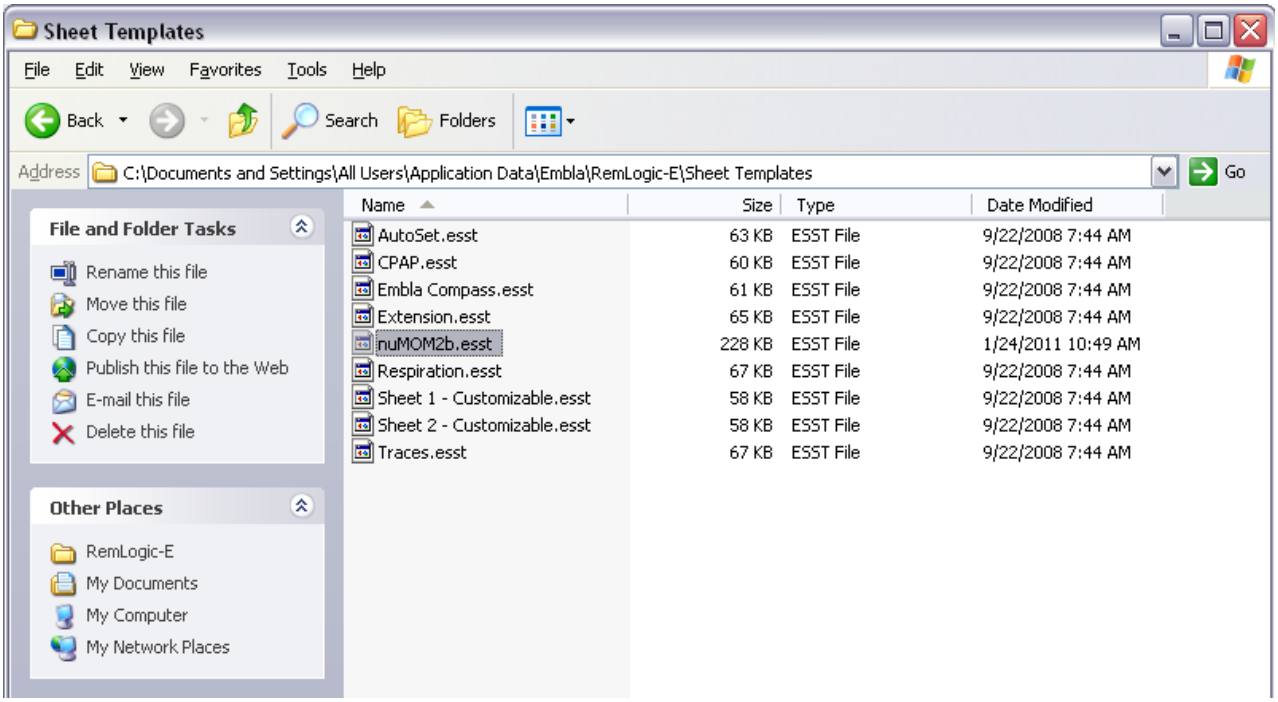
9. Restart the computer.

To insert pre-made sheet templates into RemLogic-E:

All sites will receive the nuMOM2b sheet template file via email from the SRC. Sites may request additional copies of the sheet template file from the SRC, as well. **Sites upgrading to RemLogic-E 1.2 from RemLogic-E 1.1 may not need to repeat this process.**

1. With RemLogic-E closed, copy the nuMOM2b sheet template files (files that end with the extension **.esst**) including any overview sheets to the following folder: These files are available on the nuMoM2b website with the other tools for the substudy.

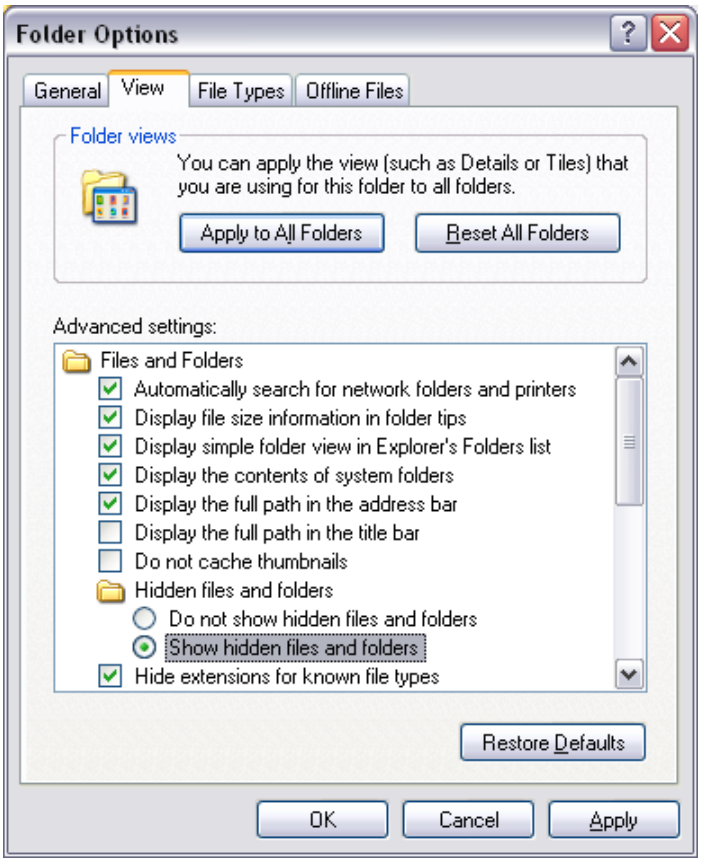
   C:\Documents and Settings\All Users\Application Data\Embla\RemLogic E\Sheet Templates



2. If you are unable to see the Application Data folder within the All Users folder then show hidden folders as follows:

   From the **Tools** menu of the All Users folder select **Folder Options**

   On the **View** tab choose “Show hidden files and folders” within the advanced settings as shown:



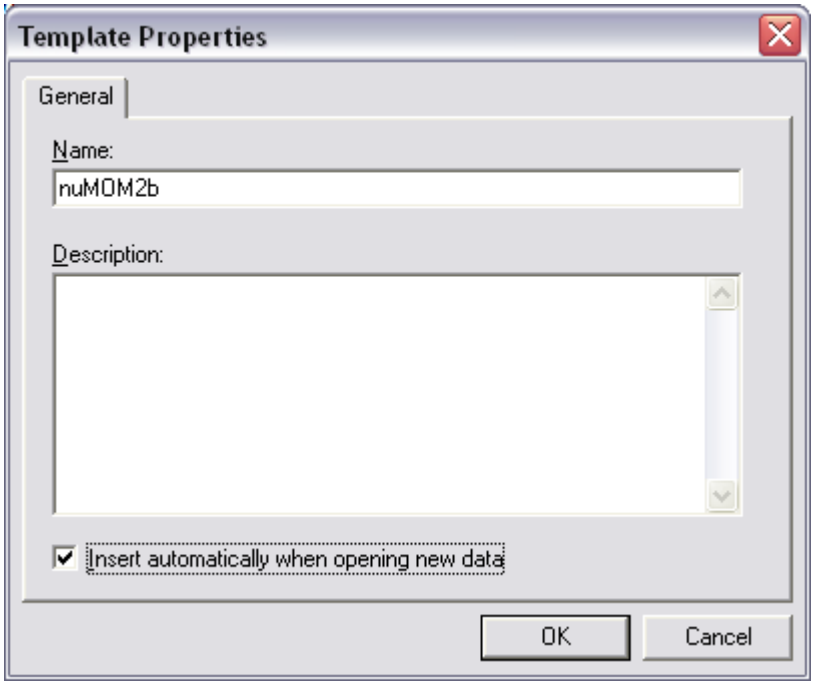
   Click **Apply** then click **OK**. The Application Data folder will now appear and can be browsed.

3. Open RemLogic-E and the sheet templates will be available and (if set as default) will insert automatically into any recording that is downloaded.

4. To set the nuMOM2b template as the default template, select **View** then **Templates…**

   Select the nuMom2b template and click **Edit…**

Check the box labeled “Insert automatically when opening new data” (as shown below), click **OK**, and then **Close**.

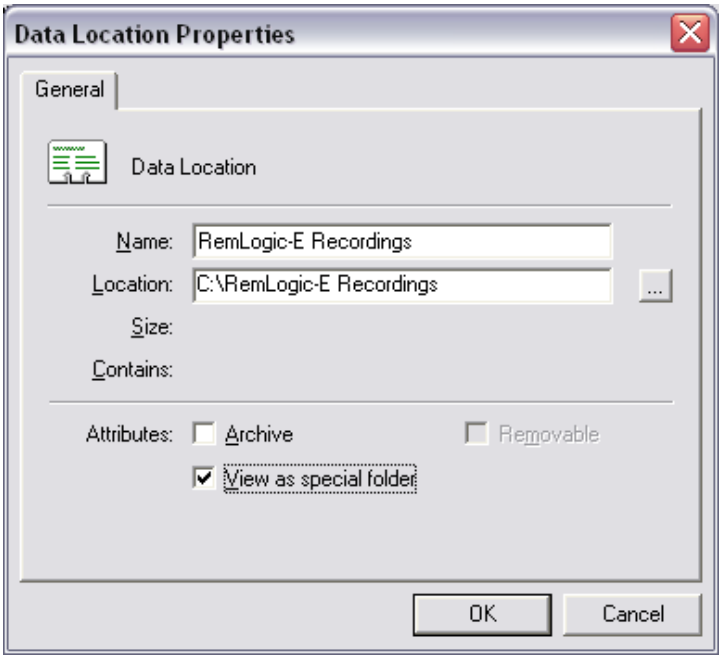


To specify how data files are managed in Windows Explorer using RemLogic-E:

1. With RemLogic-E open, from the Tools menu select Options…

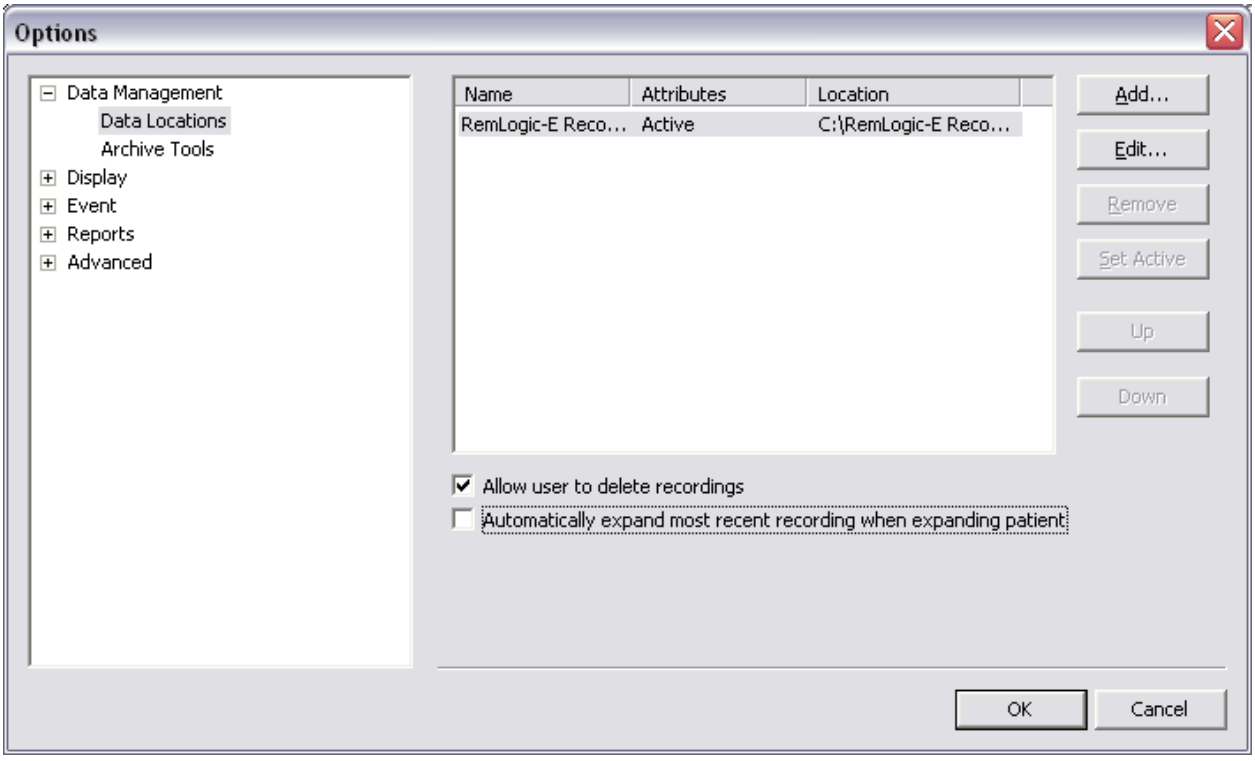
2. Select the **+** sign next to the **Data Management** Heading to expand it, then select **Data Locations**. Select the default data location called “RemLogic-E Recordings” and click **Edit**…

3. Under Attributes, select View as special folder then click OK.



Downloads will now be stored and organized in accordance with the file's participant information.

4. Upon returning to the previous screen, select **Allow user to delete recordings** (as shown below):



6.5.2 Configuring Each Device to Be Recognized by the RemLogic-E Software

Note: Each computer that will be used for initializing or downloading Embletta studies needs to be configured to recognize each Embletta device. The following steps should be followed the first time any Embletta is used in association with a "new" computer.

1. Open RemLogic-E.

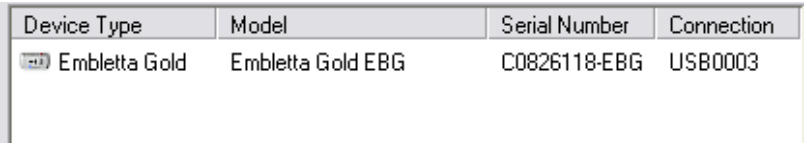
2. Connect the isolated USB download cable to the Embletta Gold connection port (located to the right of the device status lights).

3. Connect the isolated USB download cable connector to a computer USB port. The New Device Wizard will automatically detect the new device.

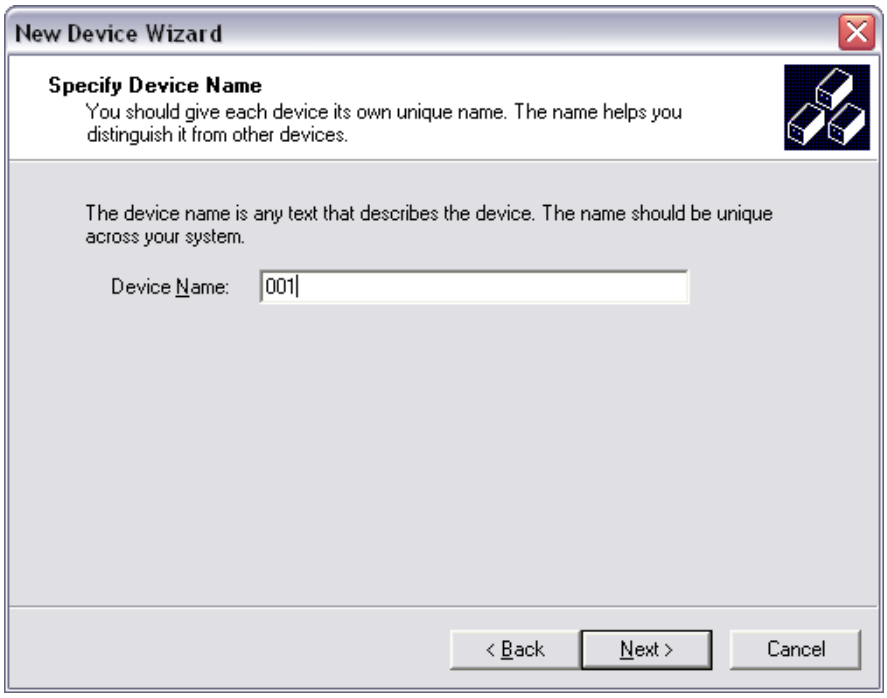
   *The wizard for adding new hardware may also be automatically executed by Windows. If this happens, **do not** allow Windows to search for new drivers. Select for the device to be automatically detected in the second window of the wizard.*

4. Click **Next** to continue.

5. Select the Embletta Gold device, and then click **Next**.



6. Enter the three-digit ID for the new device using the device ID label on the back of the device, and then click **Next**. An overview of device properties is displayed.



7. Click **Finish** to close the wizard.

6.6 Preparations before the Visit

6.6.1 Preparing the Embletta Unit for an Individual Sleep Breathing Assessment

When possible, prior to the participants' arrival for the clinic visit the technician/coordinator should prepare the Embletta Gold for data collection and gather a complete packet of supplies, instruction sheets, and data forms to be given to the participant at the Study Visit.

Preparation of the sleep monitor requires the Embletta Gold device to be fully charged, the participant identification information to be uploaded and the storage case prepared with appropriate supplies and labeling.

Before programming the Embletta Gold for a Sleep Breathing Substudy recording:

- Charge the battery for 2 hours and 15 minutes or until the charge is full.
- Ensure that the computer that interfaces with the Embletta has been configured (**see 6.5.2**)

- Verify that the participant information has been entered
- Check that all supplies and labels have been packed and affixed correctly

6.6.2 Charging the Batteries

After download of a prior study, allow 2 hours and 15 minutes of battery charging time before resetting for a new participant.

Green LED	Red LED
Flashes each half-second when fast charging	Flashes when the batteries need to be recharged
Glows steadily when charge completed	

The built-in batteries of the Embletta Gold are charged by connecting the recorder to the voltage adaptor provided with the device.

To charge the batteries:

1. Plug the adaptor into the electrical outlet.
2. Plug the voltage adaptor into the 26-pin connection port on the Embletta Gold (located to the right of the status lights – see **Figure 6-1** below).
3. To fully charge the Embletta Gold batteries, leave the device connected to the charger for **2 hours and 15 minutes**
4. When the Embletta Gold is fully charged, the *battery* indicator light on the device will display green. The Embletta Gold can now be disconnected from the voltage adaptor.

Notes on Battery Use

- The batteries provide a minimum recording duration of 8 hours when **re-charged** for 45 minutes from any battery state; however, a full battery charge can take up to 2 hours and 15 minutes. Once fully charged, the unit will make one attempt to restart the charge to ensure that it is at full capacity. If left plugged into the outlet, the charger will not attempt to recharge unless the charger is reseated into the outlet. Thus, leaving the units plugged in for several days does not ensure that the unit has a full charge when used. If the unit has not been touched for two days or more, replug the unit into the charger and the outlet and fully charge it again before it goes out with a participant. The green light on the unit will flash while the unit is charging and goes solid green when the battery is full. This recharge may only take 30 to 45 minutes. Note that any time you replug in a charger, the green light will flash for a short while as the unit determines whether the battery is full. When fully charged, the batteries can power the Embletta Gold for a minimum of 24 hours of recording.
- Rechargeable batteries should be charged soon before each recording as they do not maintain their electrical charge for long periods like non-rechargeable batteries. Embletta Gold devices left unused for more than a week should be recharged prior to use.

- A USB cable is provided with the Embletta Gold to connect the device to the computer for programming and downloads. This cable also sends a trickle charge to the built-in batteries. This trickle charge will keep fully-charged batteries "topped up" while the recorder is connected to the computer.

- When the Embletta Gold is not connected to the computer via serial or USB cable, or to the voltage adaptor, the device will switch to **sleep mode** after several minutes of inactivity to save power. Pressing the **Start** button will activate the status light.

- In **sleep mode**, the batteries will maintain their charge for approximately two weeks.

- The battery service lifetime is at least 500 studies, based on an average recording duration of 8 hours. This corresponds to 2 years of use at 250 studies per year. Contact the Sleep Reading Center and the DCAC if a battery needs to be replaced.

Warnings on Battery Use

- **Never use an AC voltage adaptor other than the one provided** for the Embletta Gold for recharging the Embletta Gold batteries. Doing so could severely damage the Embletta Gold and present risks to operator and participant safety.

- **Do not use the battery charger when the Embletta Gold is attached to the participant**. The Embletta Gold may get warm during charging, and the battery charger cord may present a tripping hazard.

6.6.3 Entering Participant Information

Connect the Embletta Gold to the acquisition computer with the isolated USB download cable.

To connect the Embletta Gold to a desktop computer:

1. Connect the USB download cable to the Embletta Gold connection port (located to the right of the device status lights – see **Figure 6-1** below).

2. Connect the USB download cable connector to a computer USB port.

Enter Participant Information:

1. Double-click the RemLogic-E icon.

2. On the Operations sheet, click **Patient Information**.

3. The Participant Information dialog opens. On the various tabs, enter the necessary information:

4. Enter the Staff ID (5 digits) in the **First** box.

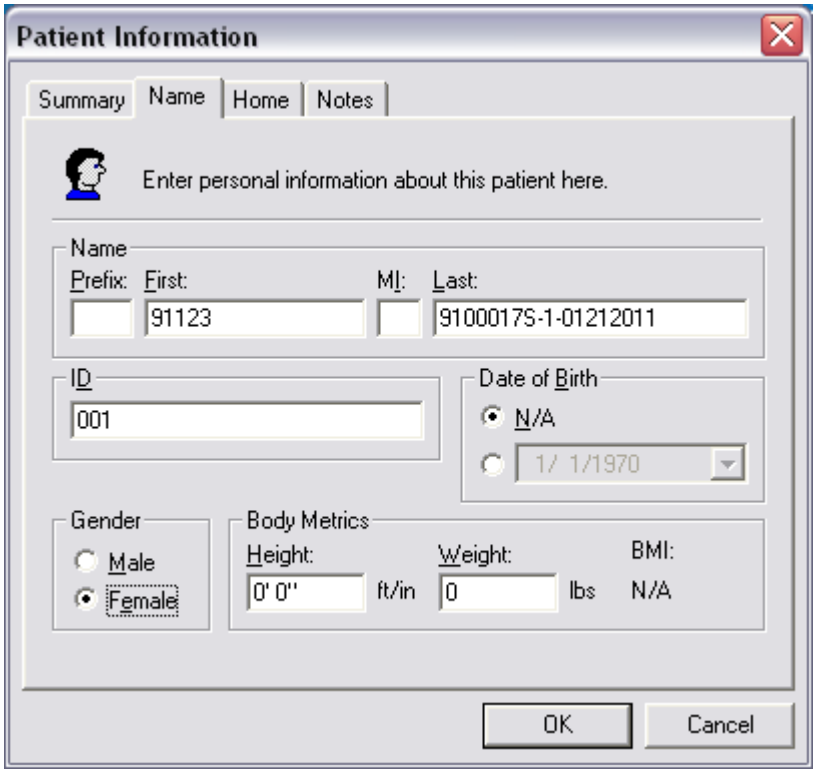
   Note: This should be the ID of the staff member who demonstrates the hookup to the participant.

5. The **Last** box should contain: [Participant's Study ID (8 characters)] – [Visit # (1 or 3)] – [Date of the demonstration (mmddyyyy)] (e.g., 9100017S-1-01212011)

6. The Unit ID number for the Embletta Gold device (3 digits) will be entered in the **ID** box.

For Example: **Study ID -** 9100017S **Visit -** 1 **Date of Demonstration -** January 21, 2011
Staff ID - 91123 **Unit ID -** 001

First : 91123 **Last:** 9100017S-1-01212011 **ID:** 001

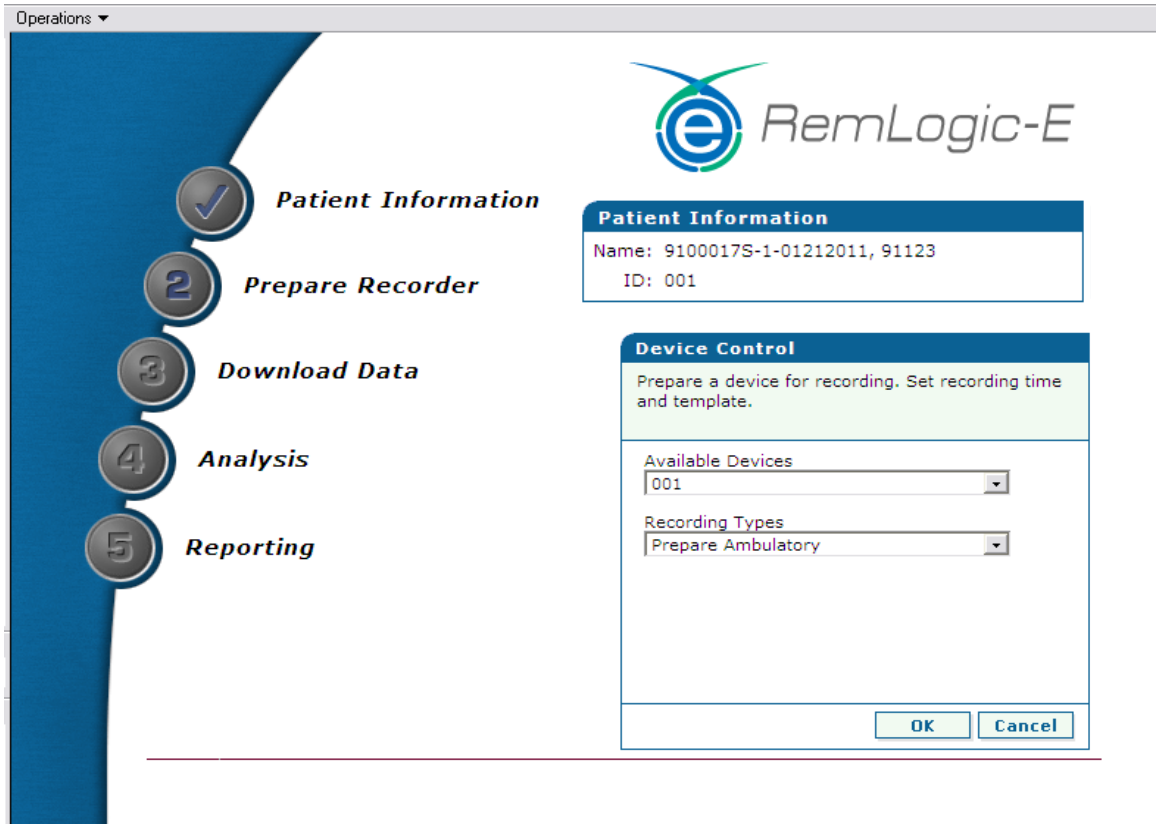


Leave the other fields on this screen blank. Do not use any other identifying data on this screen.

Prepare the Recorder to Perform a Sleep Study:

1. Check that the prior study already had been downloaded.
2. Double click the RemLogic-E icon

3. On the Operations sheet, click **Prepare Recorder**. The Device Control table is displayed to the right, below the Patient Information table (as shown).



4. From the Available Devices drop-down list, select the monitor ID that will be used.

5. From the Recording Types drop-down list, select **Prepare Ambulatory**, and then click **OK**.

6. Click **Add**.

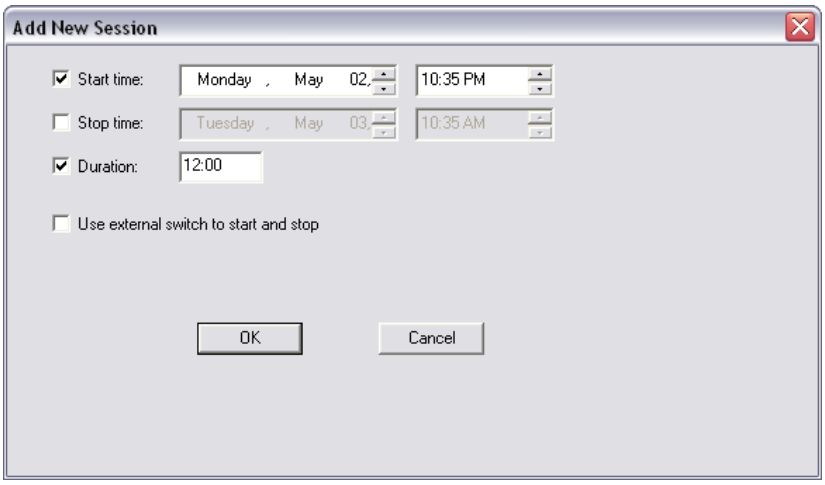
7. Determine whether the Embletta will be programmed to start automatically or will be initiated manually by the participant. If the participant indicates a willingness to use the Embla within the next two nights, then the unit is programmed to begin recording one hour before her reported bedtime for each of the two subsequent nights. Programming the unit to start on each of two nights provides some flexibility—the unit can record even if not used one of these two nights. If the participant cannot use the unit within the next two nights, it is recommended that an alternative time be identified for distributing the unit so it can be used within a two night timeframe. In rare occasions, it may not be possible for the participant to commit to use the unit within the subsequent two nights, and it may not be easy to reschedule the distribution of the sleep monitor. In these occasions, the participant may be instructed to manually begin the recording.

   Preferred Approach for Programming Start Times: To program the unit to automatically start recording at a specified time:

   Start time should be checked to pre-program the recording interval for **1 hour** before the participant's bedtime.

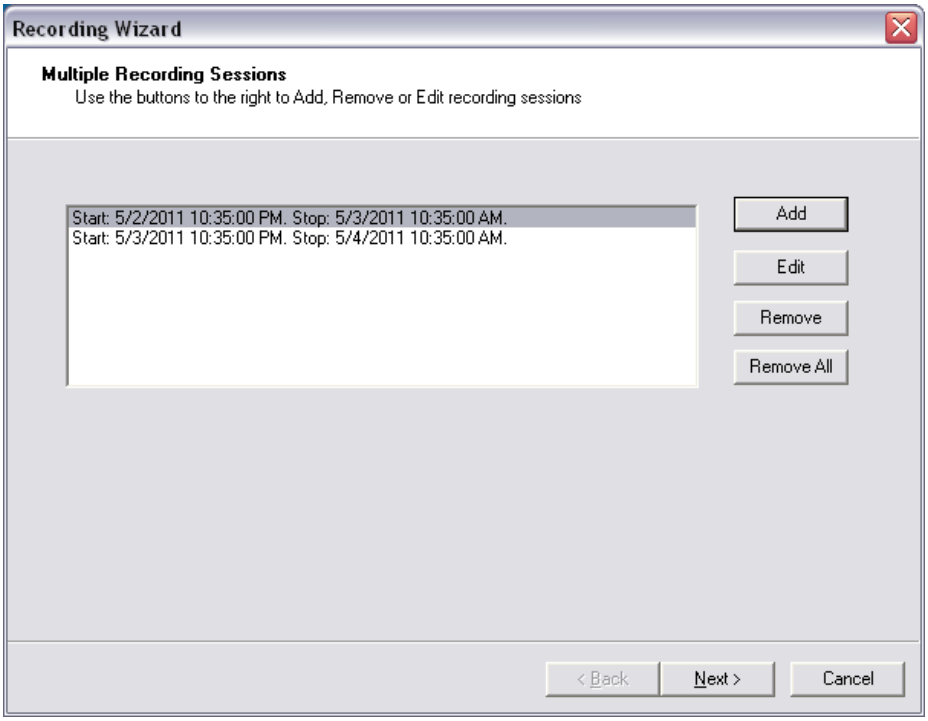
Stop time should be left unchecked or the study will end abruptly.

Duration should be checked and entered as "**12:00**"



Do not select the external switch to start and stop.

Select **Add** again and program another session for the following night using the same duration. This presets the unit to record for the two nights that the participant will have the chance to complete the sleep study.

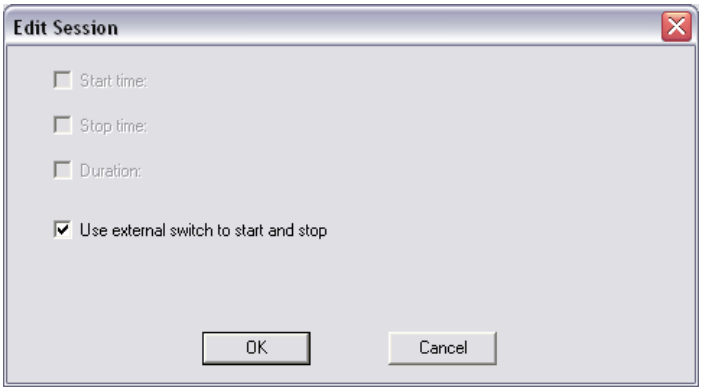


Alternative Approach for Initiating the Recording Start: Manual Start by the Participant:

Select "**Use external switch to start and stop**" ONLY.

To start a recording, the participant needs to use a small object to press and hold the **start** Start button on the Embletta until the green status light turns on. To stop the recording, the participant needs to press and hold the **start** button until the green status light turns off.

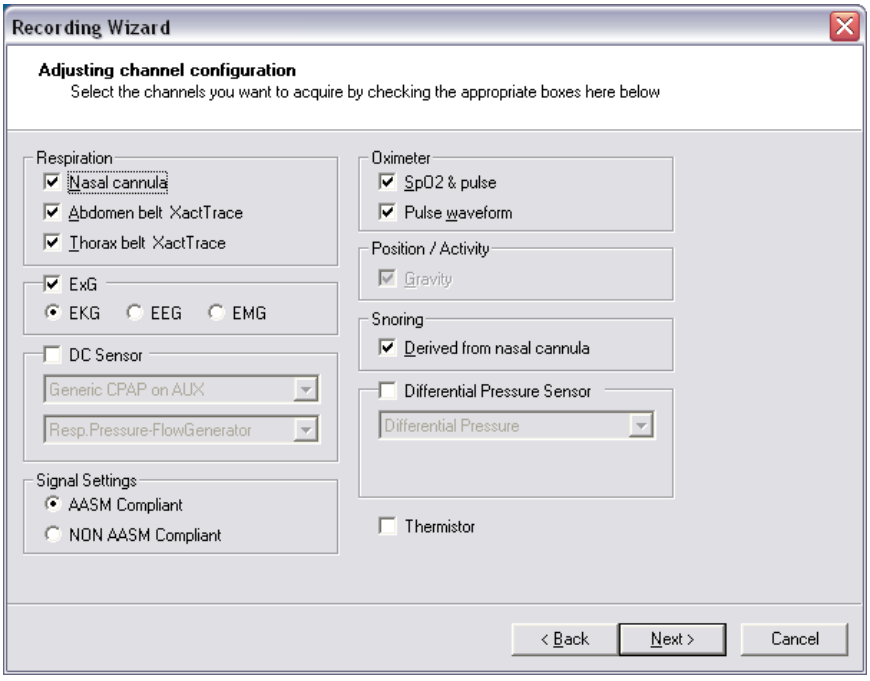
Start time, **Stop time**, and **Duration** options should now be unavailable as shown: Click **OK**.



8. Click **Next**

9. Select **Diagnostic study**, and then click **Next**.

10. Adjust channel configuration to match the one shown below by selecting the signals that should be recorded and “AASM Compliant” under signal settings, and then click **Next**.



11. Confirm that the correct participant Study ID and study type were entered and match the paperwork. Click **Finish**.

12. A progress bar is displayed and a buzz sounds while the memory of the Embletta is cleared. The Embletta shows a double-flashing yellow status light.

13. Wait until an information dialog box is displayed. Confirm that the Embletta has been correctly programmed, and then click **OK**.

14. Disconnect the USB download cable from the Embletta Gold. The device status light will stop blinking and the Embletta Gold will start recording in accordance with Recording Wizard specifications. Disconnect the USB cable from the setup computer.

6.6.4 Preparing the Embletta for Participant Use

The Embletta consists of the following sensors:

- Elastic Strap
- XactTrace belts and locks
- EKG and PGND leads
- Nasal cannula
- Oximeter

Additional supplies needed include alcohol wipes, the flexi-wrap adhesive and medical tape.

Each set of sensors is colored coded and attached to the recorder as shown below:

Table 6-4 Embletta Gold Input Color Code (from left to right)

Color	Sensor	Connector Type
Blue	Thoracic Respiratory Effort	2 pin touch-proof
Yellow	Abdominal Respiratory Effort	2 pin touch-proof
White	**(Not used in this study)**	2-pin touch-proof
Gray	**(Not used in this study)**	N/A
Brown	Oximeter	3 pin touch-proof
	(Not used in this study)	1/8 inch hose barbs
	(Not used in this study)	1/8 inch hose barbs
	Nasal Cannula	Luer-Lock Female
Orange	EKG+	1-pin touchproof
Black	EKG-	1-pin touchproof
Green	Participant Ground (PGND)	1-pin touchproof

The Recorder should be configured as follows:

Figure 6-1 Embletta Gold Control Panel and Input Area Components

The following figure identifies the Embletta Gold recorder control panel (front panel) and input area components.

1. thoracic respiratory effort input
2. abdominal respiratory effort input
3. DC input
4. thermistor input
5. oximeter input
6. online input (AutoSet interface)
7. differential pressure sensors
8. pressure luer lock (flow sensor)
9. ExG sensor input (EMG, EKG, EEG)
10. patient ground (PGND)
11. event button
12. power button
13. test button
14. battery light
15. status lights
16. sensor lights
17. connection port

Table 6-5 Control Panel Buttons

Button	Description
Start 	• When the unit is set for manual recording, can be used by the participant to start and stop a recording. The button is disabled when a recording has been programmed to start at a specified time or immediately. • If the Embletta Gold is in sleep mode, pressing the Start button will wake the device (and activate the green status light).
Test 	• Initiates the signal test.
Event 	• Can be used by the participant to time-stamp events during a sleep study (e.g., pressing the Event button to indicate an event such as temporarily getting out of bed). **This button is not used for the nuMOM2b Sleep Breathing Substudy.**

Table 6-6 Control Panel Lights

Light	Description
Battery	• Green/red battery light, indicating the battery condition.
Status	• Yellow/green/red status light, indicating the status of the recorder.
Sensor	• Yellow sensor lights, indicating signal quality of the sensor inputs.

Note: A red status light and/or a red battery light indicate an error requiring immediate attention.

Step by Step Instructions for Configuring the Sensors:

1. Attach both EKG and the PGND gel electrodes to the snap wires, and plug them into their designated input locations on the Embletta Gold device. Enclose the ends of the three leads in three different re-sealable plastic bags.

2. Plug the nasal cannula into the device, and enclose the end of it in a fourth re-sealable plastic bag.

3. The oximeter is prepared by connecting the oximeter to the oximeter flex sensor, and then placing a new Flexiwrap on the sensor in application position.

   Wrap the connection between the oximeter and the oximeter flex sensor with medical tape to ensure that they remain connected for the entire 48 hours.

   To prepare the Flexiwrap in application position, place a new Flexiwrap pad with the printed side facing down on a flat surface, and partially peel off the paper backing to expose the adhesive area around the two cutout sections.

Place the sensor face-upon the Flexiwrap pad. The sensor's protrusions (two little squares should fit into the corresponding cutout sections of the adhesive pad and the wire should extend from the narrow end of the wrap). Re-cover the adhesive side of the pad by folding the paper backing back in place so it will be ready for the participant to use.

Enclose this sensor in a fifth re-sealable plastic bag.

4. The XactTrace belts must be custom fit for each participant, and can be measured over the participant's clothes (see instructions in **Section 6.7.2**). These belts are placed in the sixth and seventh plastic bags.

5. Have the Sleep Breathing Assessment Instructions (INFO 10) and Form V1K: Sleep Monitoring Following Visit 1 or Form V3K: Sleep Monitoring Following Visit 3 ready for the participant for home use and reference.

6. Place a participant Study ID label, on the questionnaires to ensure the monitor is dispensed to the correct participant. Record the participant ID in the Embletta Gold Tracking Log on the page for the device scheduled for use.

7. Plug in ALL of the sensor wires into Embletta Gold unit. Make sure that they are plugged in correctly and securely.

8. Ensure that the case contains alcohol swabs and medical tape for the participant to use.

6.7 Instructing the Participant in the Use of the Machinery

6.7.1 Overview

An example of a script that can be used to instruct the participant in the use of the device appears in **Appendix E** for training and reference purposes. A Recruiting Tool with a similar script and frequently asked questions and answers also appears in **Appendix E**.

When explaining how to use the equipment, technicians should remember that pregnant women are classified as a vulnerable population in human subjects' research and many precautions must be taken to ensure that the health of both the mother and the baby/fetus are protected. Take the time to remind the participant that the study is completely voluntary, and that she is welcome to stop participating at any time whatsoever.

Tell the participant that she should feel free to ask questions during any part of the demonstration. It is also important to convey a willingness to listen to any questions, comments, concerns that the participant may have, and to handle those concerns professionally and with respect.

A pregnant woman at any stage of pregnancy is undergoing a number of hormonal changes, and it is especially important to be sympathetic to her needs before, during, and after the demonstration. For instance, a woman may need to use the restroom, get a drink of water, or do something to make herself more comfortable before engaging in the demonstration.

During the demonstration, take care to assure the participant that the device does not hurt the baby/fetus. Encourage the participant to tell you if she feels uncomfortable with any part of the device hook-up. At the same time, try to ensure a successful recording by giving a thorough demonstration, and preparing the device properly for the participant.

It's often helpful to show the participant exactly where sensors should be located on their own body. With that said, **always** ask for permission from the participant before touching her at any time during the demonstration.

The participant may feel tired or may want to go home, so it is also important to make sure that the demonstration is thorough, but at the same time, can be carried out in a reasonable timeframe. Ideally, the demonstration should take no more than 25-30 minutes.

Skin Sensitivity. Research staff should **always** begin by asking if the participant has any allergies, whatsoever. Women have increased skin sensitivity during pregnancy and skin allergies, in particular, would be of concern. Even though it's rare, it is possible for women to have some redness on the skin after the sleep study, especially where the skin has been in contact with adhesive substances such as the location of the EKG electrodes, or where any medical tape has been placed. Most often, this redness or irritation clears on its own, but rare cases of an actual allergic reaction can occur.

Special Considerations during the Visit 3 Demonstration. The participant is further along in her pregnancy at this time, and may be considerably larger. Sometimes, the participant has difficulty standing for long periods of time, and it may be best to conduct the demonstration while she is seated. Pregnancy itself may be more cumbersome, so she might have more difficulty using the device at home. Make sure the belts are especially secure in their proper locations, especially the abdominal belt. The belt falling off of the stomach could greatly alter the belt signal, and give an inaccurate recording.

Women also may feel more congestion at this stage of pregnancy, and it is possible that they may feel more discomfort with wearing the nasal cannula than usual. If the participant expresses that they feel as if they cannot breathe with the cannula on during the demonstration, assure them that they should try to keep the nasal cannula to the best of their ability. It may also be helpful to address any difficulties that they had with the initial study and provide advice for solving those difficulties.

The site staff member (often referred to as the Technician below) should review the Sleep Breathing Assessment Instructions (INFO 10) with the participant and add a contact name and phone number on the first page that she can call if any alert sounds keep repeating and/or if s/he has questions.

After thanking her for agreeing to participate in the nuMOM2b Sleep Breathing Substudy assessments, show her the carrying case with a sleep monitor and all necessary setup supplies. Inform her that the carrying case contains the Sleep Breathing Assessment Instructions (INFO 10) that she may want to review. It explains how to hook up the device. Review the following steps that should occur before the participant gets ready to go to bed.

1. Ask the participant to review the form titled **Sleep Monitoring Following Visit 1** (or Visit 3; V1K or V3K). She will need to complete this form the morning after wearing the sleep monitor. She will need to remember things like when she went to sleep and woke up, her sleeping positions, and whether she got up during the night.

2. She should plan to bathe or shower before she puts the device on or after she takes it off. The monitor should not be worn in the bathtub or shower.

3. She should allow at least 30 minutes before bedtime to put on the sleep monitor.

4. Make sure that she knows who to contact if she has questions and knows how to contact that person.

6.7.2 Instructions for Putting the Sleep Monitor on before Sleeping

Review the following instructions about how to put the monitor on before going to sleep. Pull out the various items from the bag during the review so that the participant will have a clear understanding of how to use the equipment. Allow plenty of time for questions. The instructions which follow are also detailed on INFO 10.

Show the participant the basic parts of the unit. Cover the following items:

On/off switch	Elastic Strap	Nasal cannula
Event button	XactTrace belts and locks	Oximeter
Status lights	EKG and PGND leads	

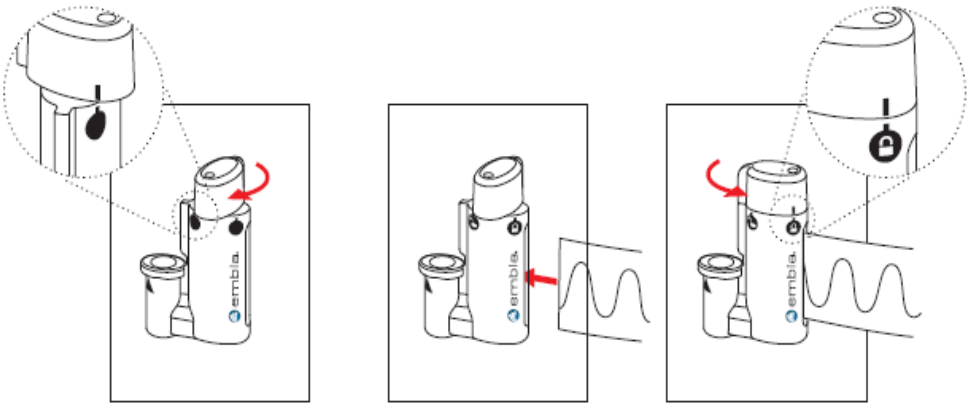
Custom fit the thoracic and abdominal belts for each participant as follows:

Custom Fitting the Thoracic Belt:

1. Encircle the XactTrace belt around the participant's chest just above the breast area and under the participant's arms. The belt should be cut about 4-6 inches short of your measurement to ensure that the belt stretches and prevents slippage during the night.

Note: It is important to use sharp scissors for a clean cut. The wire should not exceed the end of the belt, and the belt should never be cut at an angle (see figure below). Doing so could prevent the belt's signal from being recorded.

2. Insert and secure the cut ends of the belts into the belt lock with the **blue** connector according to the following steps:

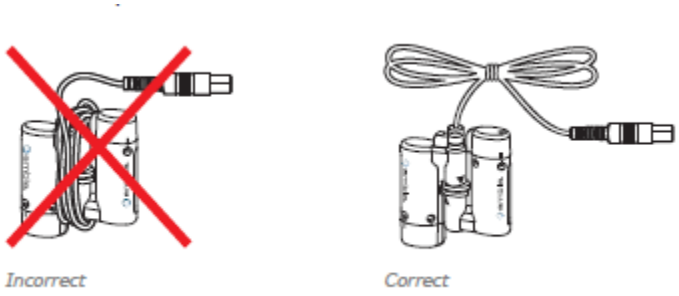


3. Turn the top end of the belt lock clockwise to open the catch. The white mark on the top should match the open lock symbol on the catch.

4. Insert the cut end of the belt into the catch. Ensure the end is positioned at the bottom of the catch.

5. Twist the top end of the belt lock counter-clockwise to close the catch. When the white mark on the top matches the closed lock symbol on the catch, the belt lock is properly closed.

6. To protect the sensor cable from damage, do not wrap the cable tightly around the belt lock as it may cause the cable to break.



7. Participants should be shown how to lock the end of the belt into the belt lock in case a belt falls out of its belt lock at night.

Custom Fitting the Abdominal Belt:

1. Prepare the abdominal belt in the same manner, only this time fitting the belt around the participant's stomach at the navel and using the belt lock with the **yellow** connector. Extra care should be taken to ensure the belt is secure.

<u>Demonstrate attachments of each of the following recording components:</u>

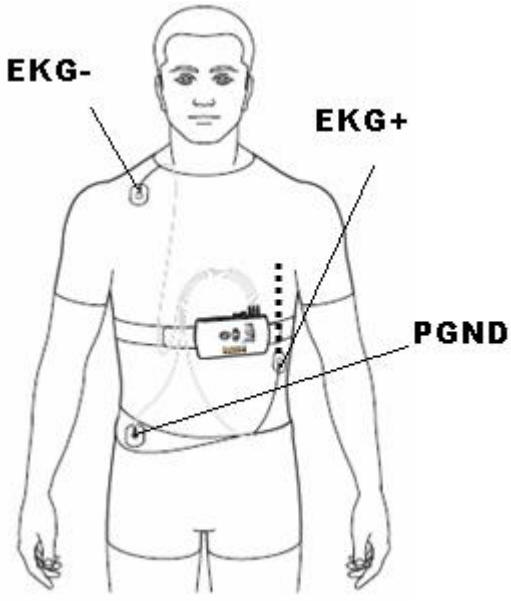
Attaching the Recorder

The Embletta Gold monitoring unit should be a little left of center over the participant's abdomen between the thoracic band and the abdominal band. Show how the unit is placed around the abdomen and looped through the other end of the device with the Velcro flap **facing out**. Demonstrate how to adjust the band so the unit is securely positioned and does not slide around. Explain that this will ensure that the sleep monitor acquires accurate signals all night long.

Attaching the EKG Sensors

The electrodes together transmit the bipolar signal required to record one channel of EKG, and for maximum patient safety and signal quality, a patient ground (PGND) is attached to the participant.

Remind the participant to clean each EKG and PGND electrode site with an alcohol prep pad in order to remove all excess skin oils. A circular wipe over a one inch area in each area should be sufficient. To account for skin sensitivity, make sure to tell the participant that they should clean the area of the electrode site gently. Scrubbing too hard could create irritation and/or redness, and could also make the sensor too uncomfortable to wear at night.



Instruct the participant on proper placement of the EKG leads by telling her that positive EKG electrode (EKG+), the **orange lead** which is connected to the **orange input** on the device, is on the **left** side (near her heart). Demonstrate that the location is in line with the left nipple should be placed just below the ribcage.

The negative EKG electrode, which is the **black lead** connected to the **black** input, is on the **participant's right** side. Show the participant that the electrode should be placed just below the right collar bone, halfway between the participant's neck and shoulder.

The PGND is the **green lead** connected to the **green input,** and is placed anywhere on the participant's **right** abdomen below the elastic strap.

Show the participant which locations to attach the EKG electrodes and then have her show you were she will place them.

Note: It may be helpful to label each EKG electrodes with small tags that say "right top" for the black wire; "left" for the orange; and "right bottom: for the green electrode.

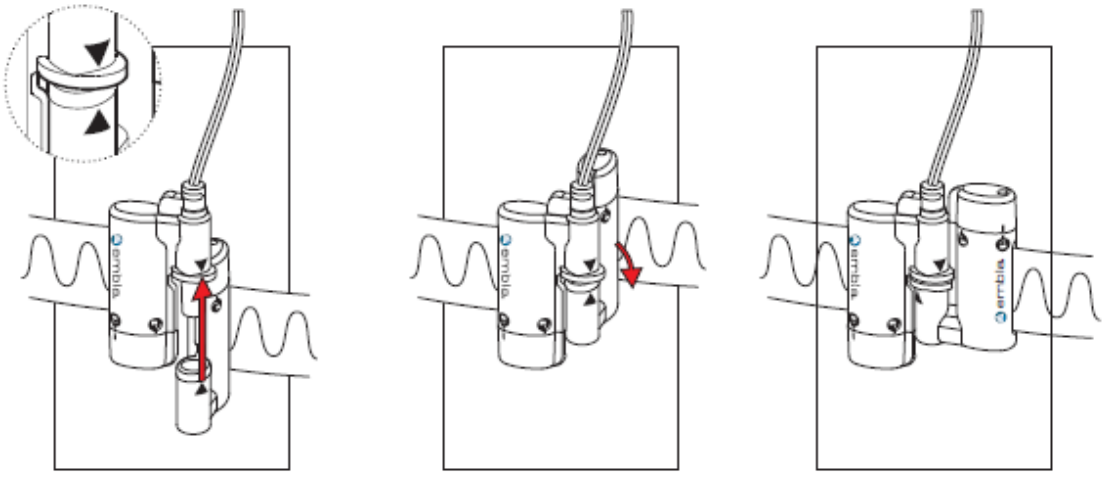
Attaching the XactTrace Single-Use Belts

The XactTrace belts are intended to be worn **over the participant's nightclothes.**

The blue and yellow sensor plugs should already be plugged into the appropriate color-coded inputs on the Embletta Gold. Follow the instructions above to measure the appropriate sized bands that go around the abdomen and chest.

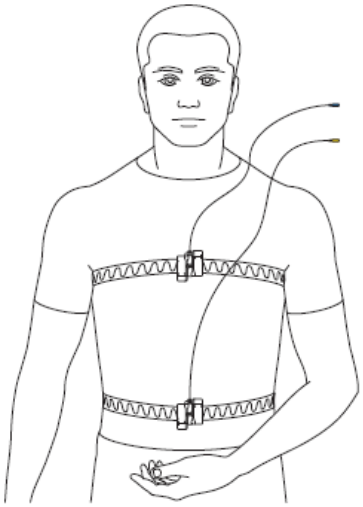
1. Show the participant how to disconnect the belt lock with the **yellow** connector and then place the belt around their **stomach** at the navel with the wires up.

2. Show them how to reconnect the two components of the black belt lock as shown below:



3. The participant should do the same for the second belt with the **blue** connector but instead place the belt around their **chest** under their arms, and just above the breast area with the wires up. They should then reconnect the second belt lock.

NOTE: Proper placement should ensure that the wires are at the **top** of the buckle for both belts as shown below:



Doing otherwise can reverse the polarity of the belt signal and could produce a highly inaccurate reading.

Additional Considerations: When placing the belts, it's important to account for the comfort of the participant while at the same time ensuring that the belts are secure enough that they will not move too much during the night, especially during the third visit when the participant is in her third trimester of pregnancy. Make sure to have the participant try on both belts once they are made. During this time, check to see the belts are secure. Always ask the participant if she feels any discomfort from wearing the belts, and if they need to be resized. Most often, the belts can be sized as normal, unless the participant says that the belt feels too tight. Have the participant demonstrate to you how to connect these sensors. Remind the participant to try to keep the bands dry. Suggest how to tuck the various wires can into the black elastic band keep them secure and tidy.

Placement of Cannula and Slip Tube Adjustment

Having a mirror during the demonstration is particularly helpful for cannula placement.

After the strap setting has been adjusted for the participant, explain that the nasal cannula will be placed in the nostrils to record breathing and possible snoring sounds during the night. Show how the cannula is placed in the nostrils with the tubing prongs curving downward to lay on the floor of the nares (**Figure 6-2a**). Then, show how the cannula tube must be looped over the ears ("cowboy" fashion) and subsequently positioned under the chin (**Figure 6-2b**). Instruct the participant that the slip tube should be adjusted to make sure that the cannula does not fall out of the nose. Demonstrate how the slip tube can be used to tighten or loosen the cannula tubing (**Figure 6-2c**) and explain if properly tightened it cannot be pulled out of the nose. Demonstrate proper positioning of the slip tube under the chin. Tell the participant to look in the mirror to see the proper placement of the unit and the cannula. Be sure to show how the participant how to apply a small piece of tape over the tubing on each side of the nose around the cheek area to further prevent the cannula from falling out of place. You may suggest that if her nose is stuffy,

she blow her nose before inserting the cannula and can remove and replace if she needs to blow her nose during the night.

Figure 6-2 Placement of the Nasal Cannula

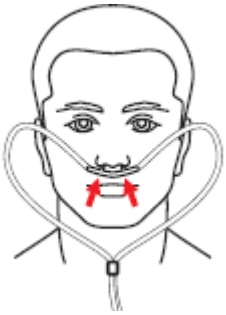


Figure 6-2a

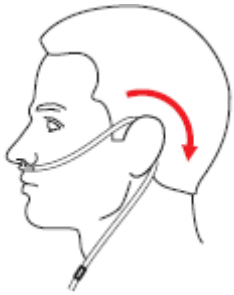


Figure 6-2b

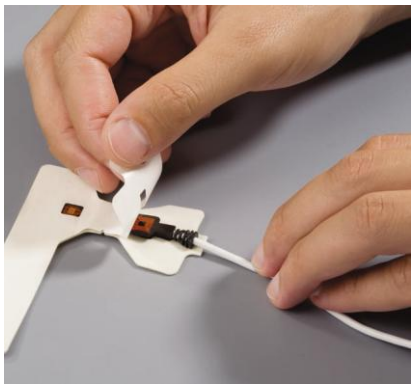
Figure 6-2c

Placement of Oximeter Flex Sensor

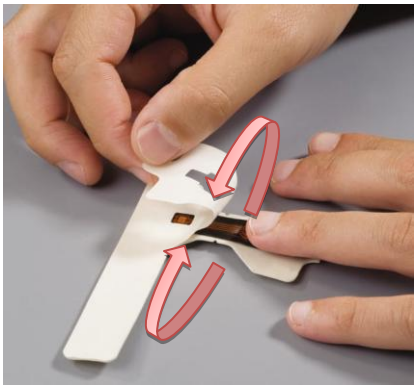
Identify the finger that will be used—any finger that can comfortably support the oximeter probe on the non-dominant hand is appropriate. Choosing a finger with short nails is preferred. Ask the participant to remove any nail polish or artificial nails on the finger that will be used. Demonstrate how to place the oximeter sensor without peeling the tape back and then review the procedures that will be used when she peels back the tape when using the sensor herself. If she seems to have problems understanding, you can use an extra flexi-wrap to go through the actual taping of the sensor, and then supply her with a fresh flexi-wrap.

The pictures below show how to put the oximeter flex sensor on the participant's finger.

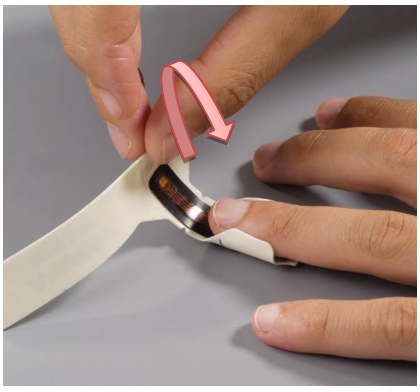
Figure 6-3 Placement of the Oximeter Sensor on the Participant's Finger



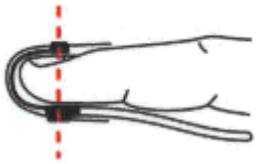
A. Place Oximeter and Flexiwrap pad on a flat surface. Peel off the paper half way—up to the two notches.



B. Place the fingertip just before the two notches. Fold the side flaps, attaching them to the sides of finger.

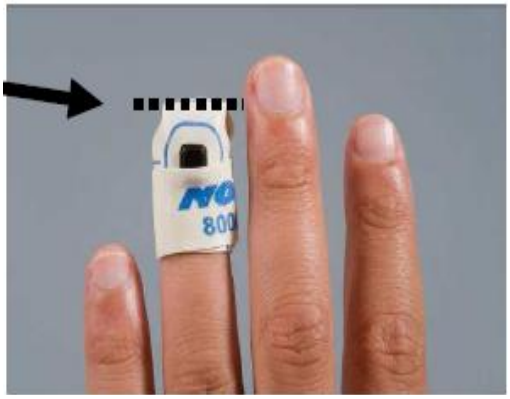


C. Remove the rest of the paper and fold the top flap over the finger.



D. Fold down the remaining side flap. Make sure the black squares are aligned with each other.

E. Gently wrap the long flap around the finger (not too tightly).



F. *Proper placement of the Oximeter*: Ensure that the "dotted line" is located at the tip of the finger.

Pre-Bedtime Check Instructions

Before going to bed the participant should check a few things in order to ensure a successful sleep study. She should check that the sensors are placed correctly and that the sensors are firmly connected to the Embletta Gold device. If one of the sensors has become disconnected, the participant should reconnect it into the proper color-coded input. Provide a phone number and instructions on whom to contact if questions arise.

Manual Start and Stop versus Automatic Recording

The Sleep Breathing Instruction Sheet (INFO 10) includes instructions on how to start and stop the device manually in boxes on pages 5 and 6. If the device is set to record automatically (preferred mode), cross out these two boxes with a large X on the instruction sheet so that the participant knows to ignore those instructions.

Instructions for manually starting the device follow. Make sure to review these with the participant if she needs to manually start and stop recording. Instructions for stopping the device appear on the instruction sheet (INFO 10).

For Studies That Have Been Programmed for Manual Starts ONLY: Demonstrating How to Start and End the Sleep Assessment

After getting into bed, the unit should be powered on. Show the participant how to should press and hold the **start** button 

until the green **status** light turns on. The participant may use a blunt object such as the tip of a writing pen, if needed. Check for a red light on the oximeter finger to ensure that it is properly connected.

Participants should be instructed to only remove and power off the monitor after rising for the day (see **Section 6.7.3,** Instructions for the Morning Following Monitoring). To stop the recording upon waking, press and hold the **start** button until the green **status** light turns off. Removing or powering off the monitor during the night may invalidate the study. It is important to collect as much usable/good-quality data as possible (at least 2 hours).

Review of Alarms

A red flashing status light or red battery light means immediate attention is required and the participant will need to contact the site. Make sure you provide contact information on the first page of the Sleep Breathing Assessment Instructions (INFO 10).

6.7.3 Instructions for the Morning Following Monitoring

Next review the instructions for when the participant takes the monitor off. Emphasize the importance of completing the Sleep Monitoring Visit 1 or Visit 3 Form as it is a critical part of interpreting the data. The instructions to be reviewed follow.

1. Remove the nasal cannula (tubing) from the face and place it in the resealable bag provided. **Do not unhook it from the unit.** Seal the bag to the extent possible.

2. Remove the FlexiWrap adhesive wrap from the finger and **throw it away**. Keep the wiring attached to the monitor.

3. Unsnap the ECG wires from the electrodes. Remove the sticky pads (electrodes) from the skin and **throw them away**. Suggest the participant use a wash cloth with warm water if the electrode sensors are difficult to pull off the skin.

4. Unhook the white belts and leave them attached to the unit.

5. After everything has been removed, place the unit, belts, connectors and tubing in the case with the equipment unit still attached. Inform the participant that there may be “indents” on the cheeks from the cannula, is normal and should disappear in a few hours.

6. **Complete the form** titled Sleep Monitoring Following Visit 1 (or Visit 3). The time the participant got into bed (time the Embletta Gold was turned on at night if done manually), and the time the participant woke up in the morning (time the Embletta was turned off if manual) should be noted on the Form V1K: Sleep Monitoring Following Visit 1 or Form V3K:

Sleep Monitoring Following Visit 3 sheet, the remainder of the items on the form should be answered, and the form should be placed in the bag with the Embletta Gold.

6.7.4 Instructions for Returning Materials to Clinical Site Staff

Review the instructions for returning the materials to the clinic. Give the participant the materials for packaging and mailing the portable monitoring device and other materials so that participants can return the device to the clinical site via self addressed mailers. Alternatively, arrangements may be made to retrieve the monitors by courier or for the participant to bring the bag to the site. Participant reimbursement is issued once monitors are returned. The instructions to review with the participant at this time are as follows:

1. Make sure that the device, belts, tubing, and wiring are in the carry case provided by the clinic. A check list is given below.

    - ☐ Sleep Device
    - ☐ Belts
    - ☐ Nasal Cannula (Tubing)
    - ☐ ECG Wires
    - ☐ Oximeter and Flex Sensor
    - ☐ Unused alcohol swabs and tape
    - ☐ Sleep Monitoring Form and Other Questionnaires

2. Ask the participant to place the carry bag, the completed Sleep Monitoring Form, and any other Take-Home forms that she needs to return in the pre-paid mailer provided, and ship it to the clinic. Alternately, discuss other arrangements for return or pick up of the bag, its contents and the questionnaires.

3. Return the package to the clinic.

Answer any remaining questions, repack all of the materials and supplies required for the assessment, and give them to the participant. Again make sure that the participant knows who to call with questions. Make sure that she knows that she will receive $50 by mail after the device is returned to the site. Thank her for taking the time to participate in this important study.

6.8 Procedures when the Package is Returned to Clinical Site Staff

6.8.1 Unpacking, Cleaning, and Disinfecting

Don gloves before setting the package containing the monitor and accompanying paperwork on a surface protector and opening it. Remove the paperwork and set it aside from the surface protector. Remove the plastic bag containing the nasal cannula from the unit. Discard the plastic bag and nasal cannula and inspect the monitor for signs of damage in case the corresponding sleep study has poor quality.

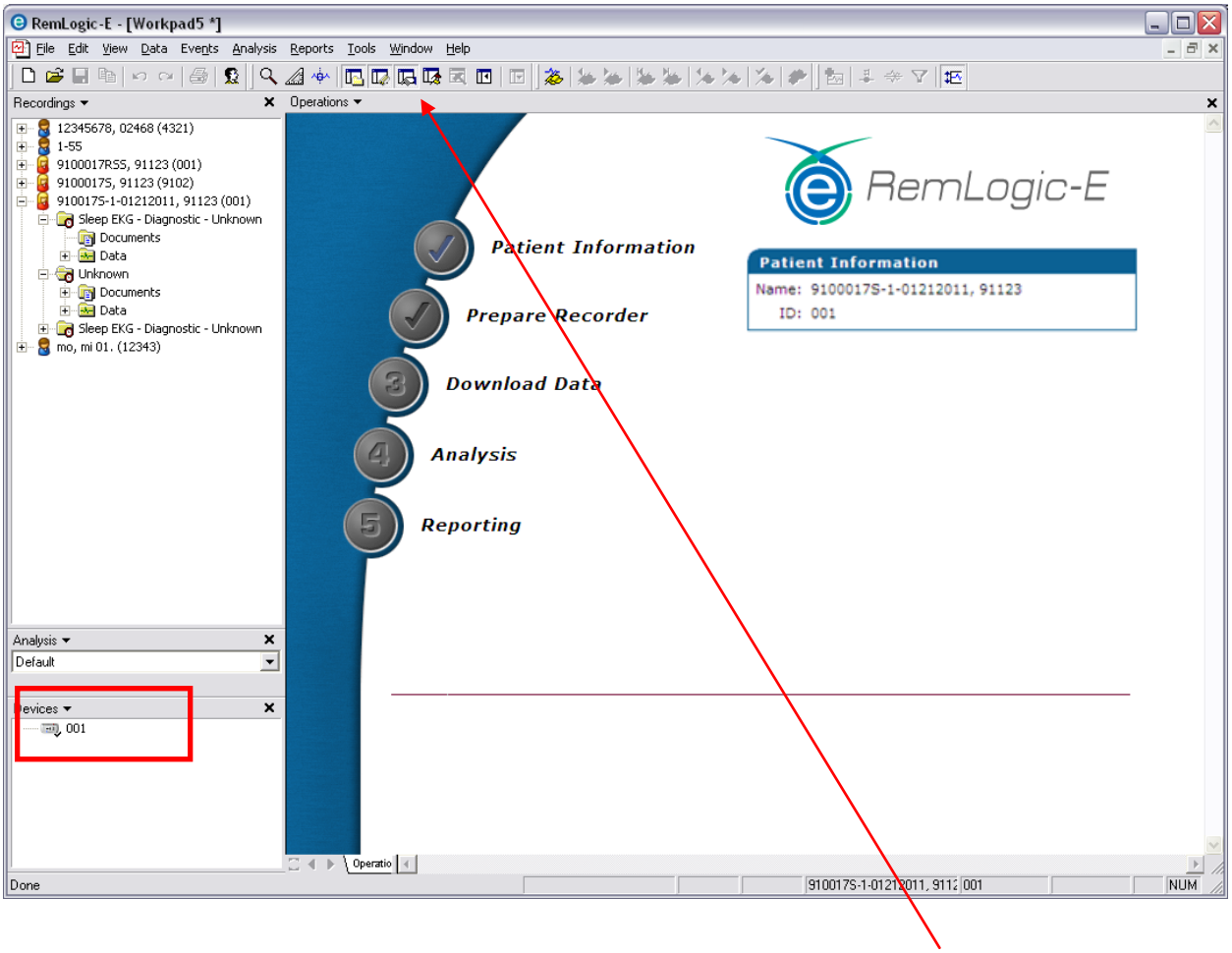
Use the CaviWipe towelette (or comparable bactericidal) to wipe the unit and all of the wires and sensors. During this cleaning, turn the towelette frequently. After all of the equipment has been disinfected, allow it to air-dry. Remove gloves, placing them with the dirty items on the protector.

Placing your hands under the protector, gather or roll it up to enclose all the dirty disposable items. Discard into the appropriate trash receptacle. Wash your hands before downloading the data.

6.8.2 Downloading Data

Carry the Embletta Gold and its paperwork to the downloading computer. Connect the Embletta Gold to the computer using the “Embla Isolated USB Interface” cable. From the computer desktop open the RemLogic-E software.

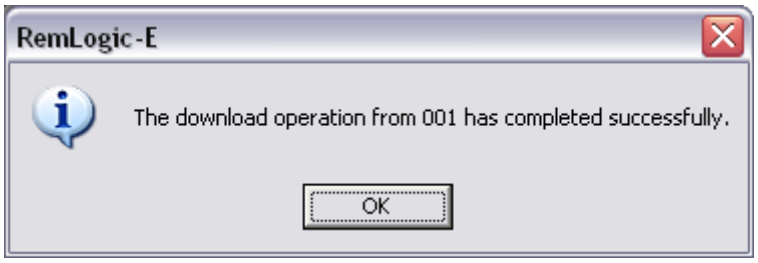
The Embletta Gold unit should appear as an icon in the lower left in the “Devices” window. The device should have a small check mark if it is ready for download.



If the “Devices” window is not visible turn it on using the “Toggle Devices” button.

Right click the Embletta’s device name and choose “**Stop**” to end recording and enable the data to be downloaded. REMlogic will prompt you that it is prepared in a recording mode. Click “**Yes**” to stop the recording. The small check mark next to the device name should now be gone.

Right click the device name again and click "**Download**," which should no longer be grayed out after stopping the Embletta. A progress bar should pop up indicating that the overnight recording is transferring from the Embletta, and then a popup stating that the download completed successfully.



Specifically, to download data into **RemLogic 1.2:**

1. Open **RemLogic 1.2** for Embletta.

2. Connect the Embletta to the computer with the USB cable or the serial download cable.

3. Click the **Download Data** button on the Operations sheet. Or Right-click the Embletta Gold icon in the device manager, and then click download. If the Embletta Gold is still in recording mode/pause mode, first click stop.

4. A progress bar will indicate the progress of the download.

Download is complete when the following message is displayed: The download operation from the Embletta has completed successfully

6.8.3 Study Quality Review

It is critical for all studies to be downloaded and reviewed soon after the monitor is returned to the clinical site. Timely review allows prompt identification of:

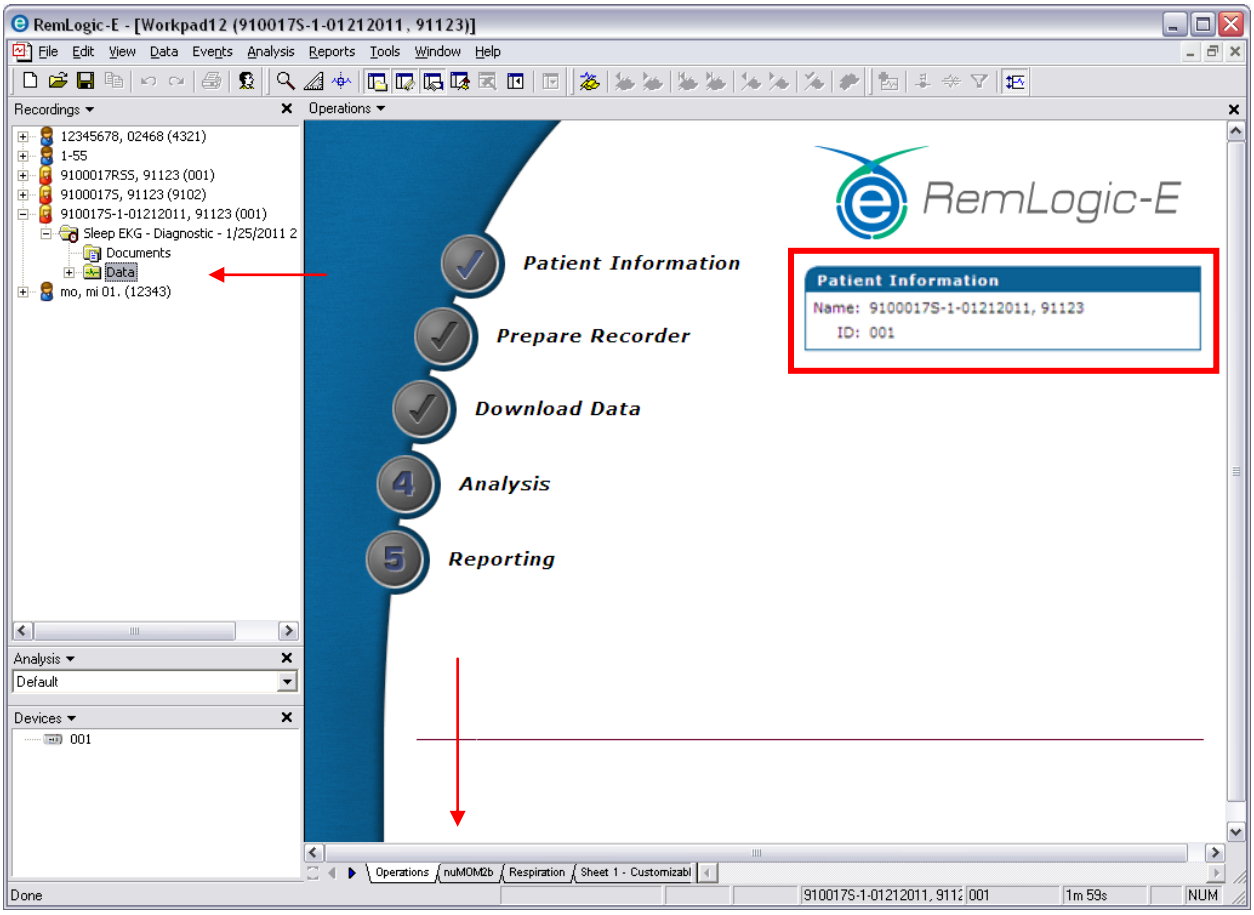
- "Failed" studies that require rescheduling

- Problem sensors and units that require troubleshooting/repair or replacement before being re-used on another participant

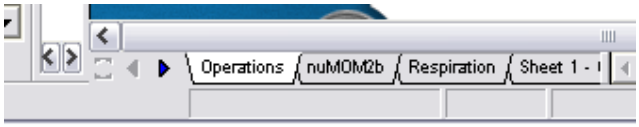
- Severe hypoxemia, heart rate irregularities and severe sleep apnea requiring triaged scoring at the SRC and physician Urgent Referral notification.

Immediately after downloading the study, the recorded sleep data should be displayed in the right panel, but may be hard to read in the default layout.

1. If the study is reviewed at a later time after download, the study can be located on the computer by clicking on the Participant ID-Visit#-Demonstration Date for the study of interest. After that click, the folder labeled **Data should be double clicked**. The participant's information should now appear in the Patient Information box located in the **Operations** sheet.



2. Located at the bottom of the workpad are tabs for the **Operations** sheet and the **nuMOM2b** sheet template:



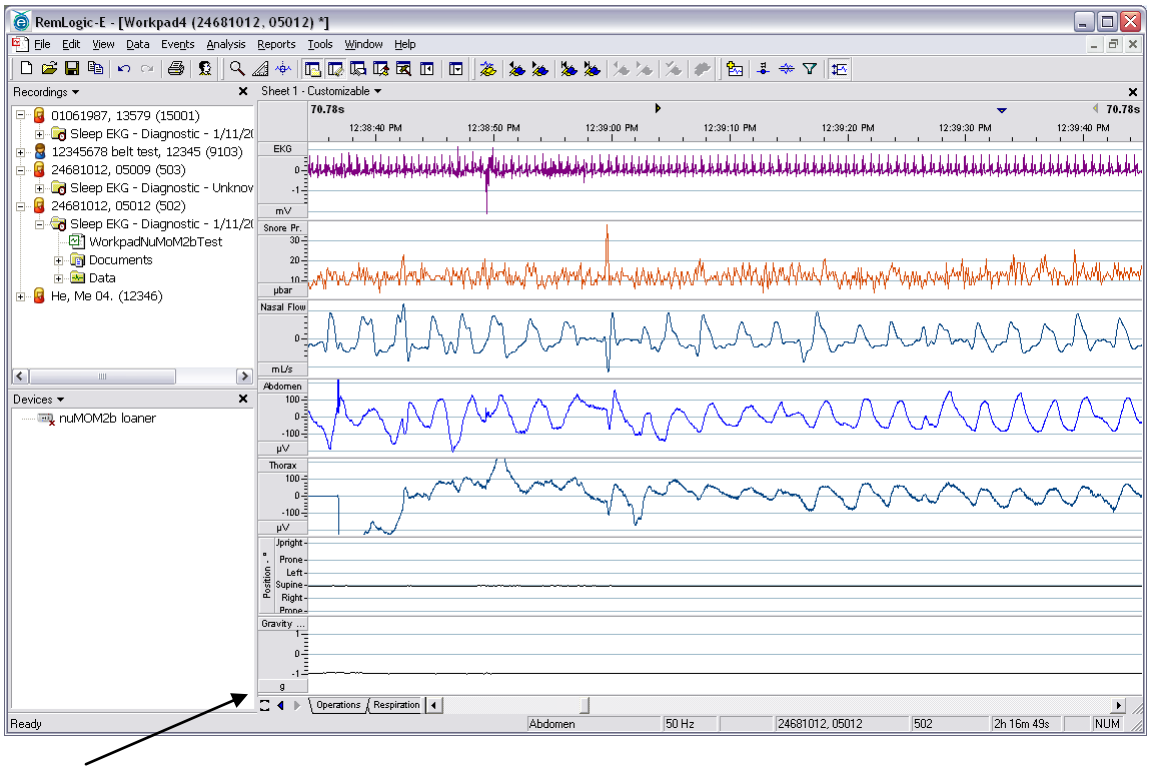
3. The **nuMOM2b** tab should be selected to view the downloaded study

4. The scroll bar at the bottom of the screen or your arrow keys can be used to view the signals.

5. Once the study is reviewed, the technician should complete E1A or E3A, Sleep Breathing Substudy Evaluation Visit 1 or Visit 3, as appropriate, to document whether any problems were seen. These procedures are described in **Sections 5.6.1 and 5.6.2** of this manual.

   Note: The staff ID of the study staff member who performed the demonstration for the participant should be recorded at the top of the form.

   You should be able to view 8 channels, or "traces," of data like below:

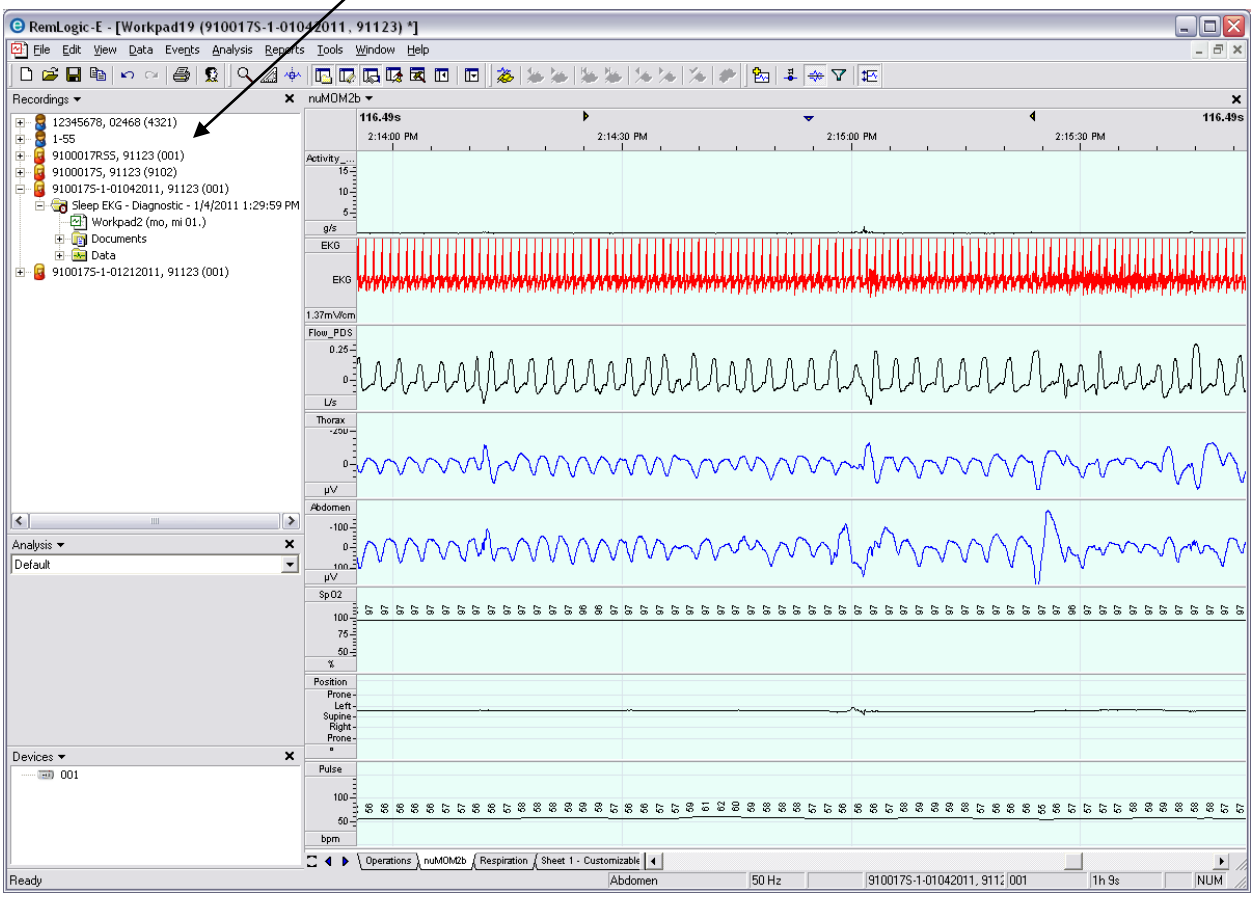


This button can be used to space the traces out evenly for easier viewing. Left click this icon in the lower left and select the maximum number of channels, which should be 8. You can also right click each waveform and select "Scale to Fit" if the data are scaled too large or too small to effectively review. Once this is done, the study is ready for quality review.

Once all channels of the study have been downloaded successfully, the Embletta Gold is safe to unplug. It can be unplugged from its USB cable and plugged into the C adapter to begin recharging the internal battery for the next participant.

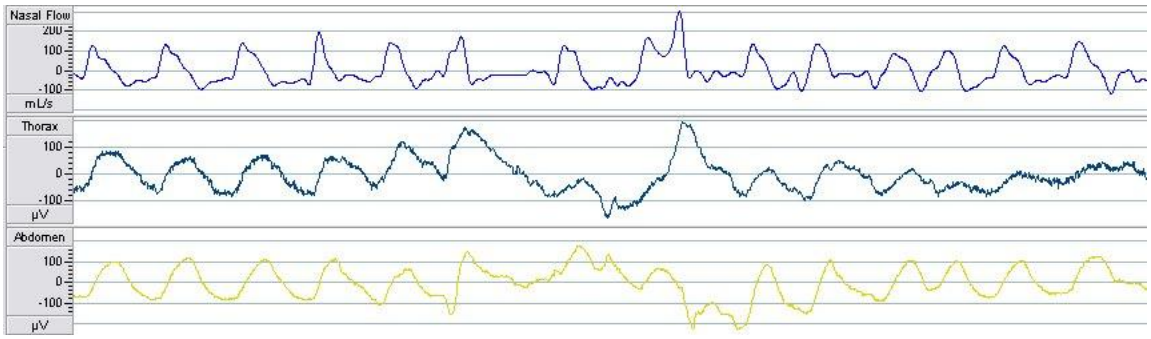
Viewing Signal Quality

The first item to verify is that the Study ID-Visit# -Demonstration Date, Staff ID, and Unit ID were entered correctly when the Embletta was first set up. To do this, within the left hand "Recordings" window, the study with the corresponding participant ID number should be located.

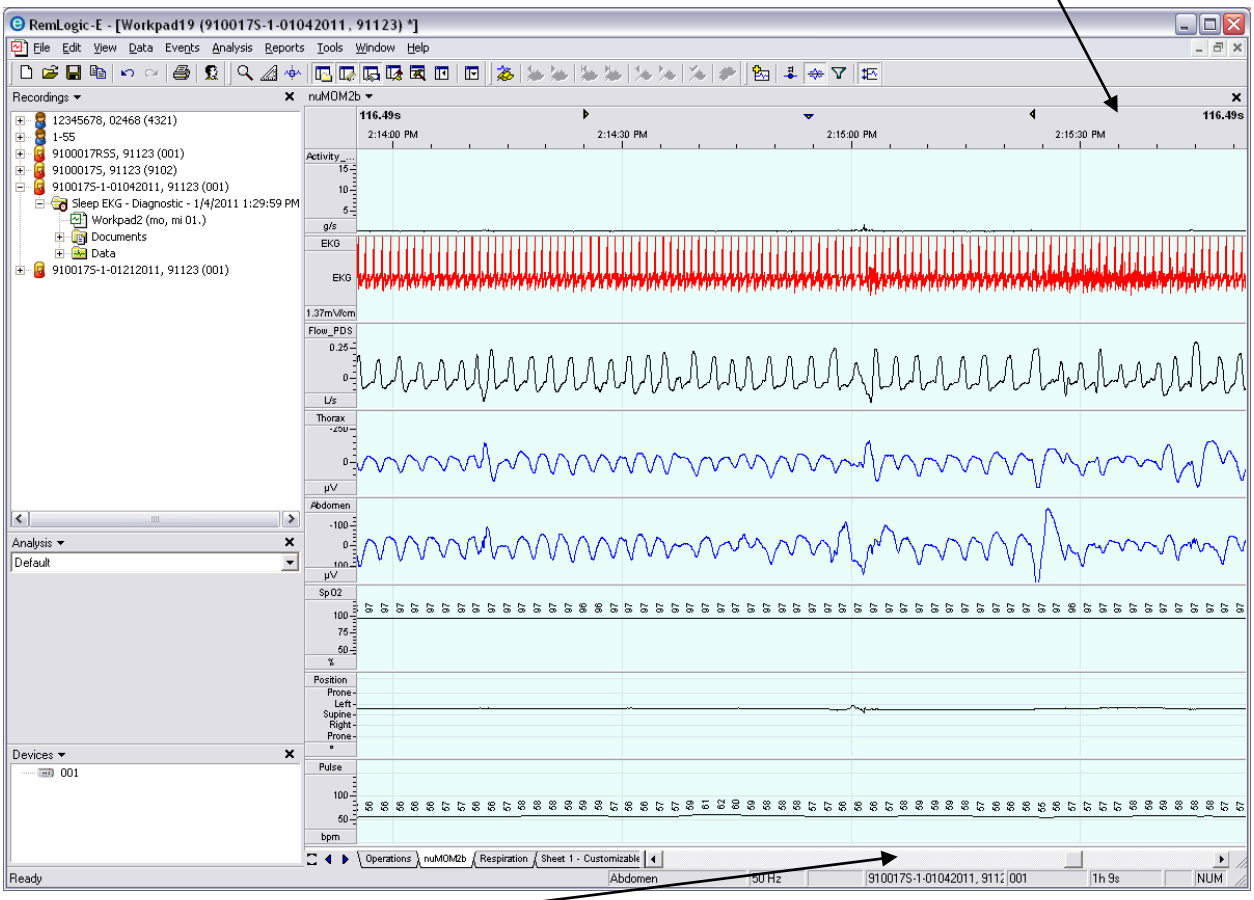


In this window the identifying information is displayed in the order: Study ID (8 character)-Visit Number (1 or3)-Demonstration Date, Staff ID (5 digit), Unit ID (3 digit). Note that a hyphen separates each of the components of the ID (Study-Visit-Date). An example of a possible study id is: **9100017S-1-01042011, 91123 (001)**.

Once this information is verified, each waveform should be viewed to ascertain that acceptable signals were collected. To do this, each channel should be checked to see if plausible waveforms are displayed. Some channels such as "position" and oxygen saturation may appear to be mostly flat line. The others should show evidence of fluctuation of generally smooth lines. Signals may appear irregular during wake and movement, but, if such irregularity covers a large portion of the study, it is likely that the information collected is unsatisfactory for analysis due to poor sensor placement, a broken sensor, or broken device. Below is an example of a relatively "clean" respiratory signal during wake.

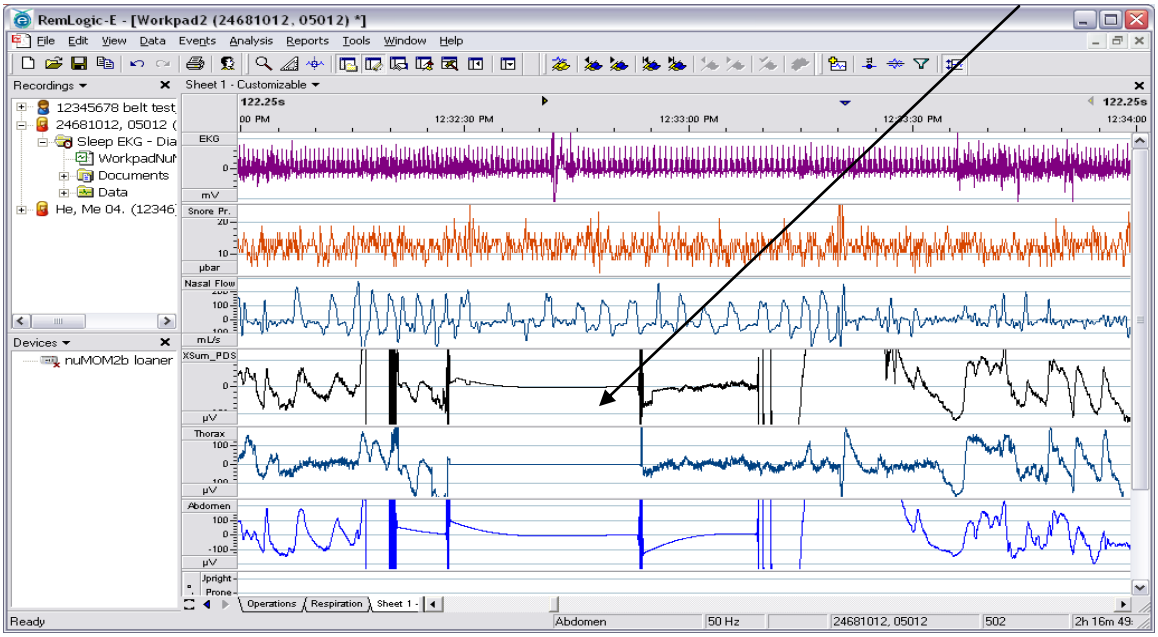


To assist with viewing the study, the time scale for viewing each “page” of the study may be varied. To do this, right click the time listed in the upper right and change it to a time that can be viewed easily on your monitor (e.g., 120 or 300 minutes).



The horizontal scroll bar at the bottom of the screen may be used to scroll through the study and evaluate signal quality. One can also page through the study one screen at a time using the arrow keys. The technician should record on the Study Evaluation Form information regarding signals that become a flat or erratic line, as this could indicate a broken lead or a disconnected cable. It is normal for most signals to go “bad” during wake and movement. It is important to note signals that go bad and stay bad for the rest of the night when all other signals look OK.

An example of signals during movement.



If all signals look good for a majority of the recording period: The Embletta device can be considered in acceptable working condition and ready for reuse for the next participant. At this point the tech completes form E1A (or E3A), Sleep Breathing Substudy Evaluation Visit 1 (or Visit 3). This form documents any comments regarding quality of the recording and any other pertinent information about the study and/or participant. This form is used by the scorer to verify that any issues the scorer sees were also witnessed by the technician at the site and to ascertain if any unusual circumstances occurred during the overnight recording process. Form E1A (or E3A), Sleep Breathing Substudy Evaluation Visit 1 (or Visit 3) asks for information regarding when the participant went to bed and woke up. This information should be transcribed from the form V1K (or V3K), Sleep Monitoring Following Visit 1 (or Visit 3) that is completed by the participant. If form V1K (or V3K), Sleep Monitoring Following Visit 1 (or Visit 3) is blank or missing, the technician should contact the participant to obtain this information.

If any problems are seen: The recorder should be examined again for any signs of damage, especially focusing on individual leads/sensors that correspond to the problem signals. Results of this visual inspection should be noted on Form E1A (or E3A), Sleep Breathing Substudy Evaluation Visit 1 (or Visit 3). Documentation should be made also of steps take to resolve or troubleshoot the problem.

The SRC prioritizes problem studies for troubleshooting review. Embletta Gold devices that have generated problem studies should not be used again until the cause of the problems has been identified. For example, if the participant indicates she shut off the unit early or never turned it on, it is most likely that the problems were participant and not recorder-related. Notes about issues like this are helpful so that the reviewer and scorer do not erroneously flag a unit as possibly broken. **Any Embletta Gold with a failed recording must be tested by study staff before its next use in the field.**

6.8.4 Reviewing Form V1K or V3K

At a convenient time, key the information from Forms V1K and V3K into the web-based data entry system used for the nuMOM2b study.

6.8.5 Providing Incentives to Participants

Once site staff receive the package from the participant with the device and related materials and ensure that a study was recorded, site staff will mail the $50 incentive to the participant to compensate for the time and effort she spent completing the study. The site will develop procedures for delivering this incentive in line with site-specific requirements.

6.8.6 Reformatting and Preparing the Embletta in RemLogic

Unplug the Embletta Gold from its AC adapter after the battery has had time to recharge. Plug the Embletta Gold into the computer and setup a new ambulatory study as described in **Section 6.6.** If any problems were seen during reviews of the last study prepare a different unit if available.

6.8.7 Re-prepping the Embletta Gold for the Participant

Prepare the Embletta Gold kit with all leads for the next participant as described in **Section 6.6.4**. Make note of and replace any questionable leads if they have not been proven working since their last quality review.

6.9 Sending Data to the Sleep Reading Center

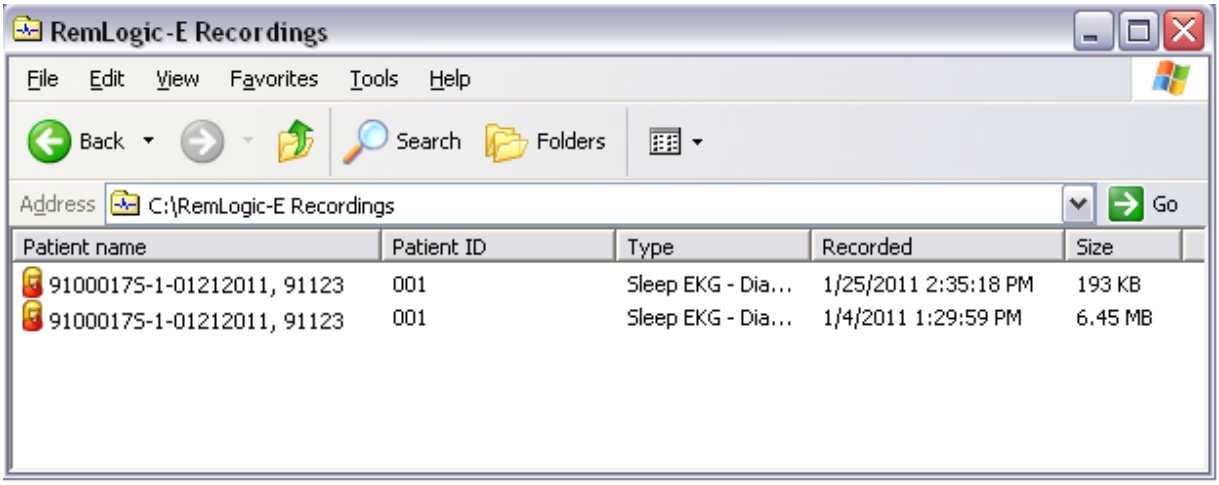
Sleep Breathing Substudy assessment data will be transmitted to the Brigham and Women's Hospital server at the Sleep Reading Center via FTP using FileZilla software. This allows for the sleep study files and data to be uploaded to the SRC FTP server over a secure SSL FTP server connection.

6.9.1 Preparing Data Packages for Transmission

The Form E1A (or E3A), Sleep Breathing Substudy Evaluation Visit 1 (or Visit 3) needs to be scanned and saved as a PDF document using methods available at the site. This document is packaged and sent with the corresponding sleep study data to the SRC in order to allow the scorer to properly review and score the data from the Embletta Gold.

If a site does not have the ability to scan documents the Form E1A (or E3A), Sleep Breathing Substudy Evaluation Visit 1 (or Visit 3) may be faxed to the Sleep Reading Center, **but this method is not preferred.** Sites are encouraged to work with DCAC coordinators and the Sleep Reading Center to establish a process for digitizing documents instead of sending them via fax. If needed, the Fax number for the SRC is (617) 278-6946.

To send the data, the RemLogic-E software is first closed. A file browser is used to navigate to the folders where the RemLogic-E recordings are saved. The default location is **C:\RemLogic-E Recordings**. RemLogic-E will save the studies in a special folder displaying Study ID-Visit #-Demonstration Date (see **Section 6.5.1**).

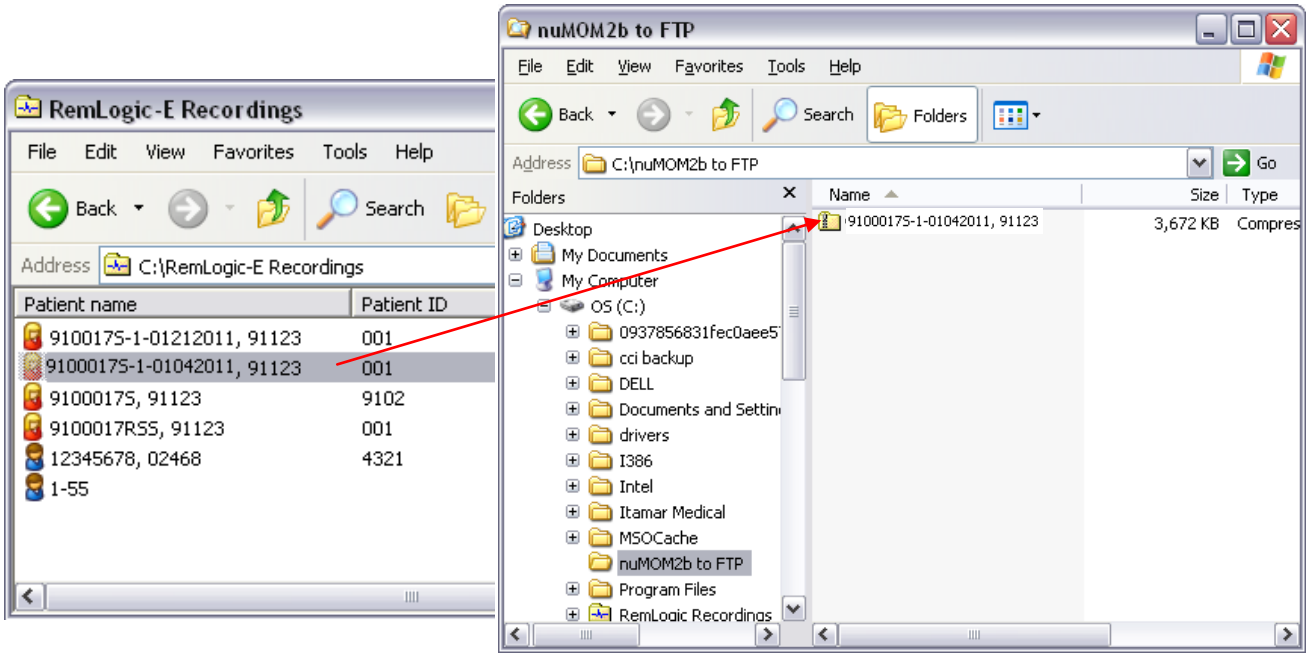


1. Before uploading any studies, a folder (e.g., nuMoM2b to FTP) is created on the computer's hard drive to store completed zip folders that are ready to be sent to the server.

   Once the folder has been created, the technician right-clicks inside the folder and selects **New ► Compressed (zipped) Folder**

2. This zip folder should be labeled: **[Study ID – Visit# – Demonstration Date]**

3. Drag and drop the study folder into the new zipped file. It may take several moments for all the files to be compressed and added to the new zip file.

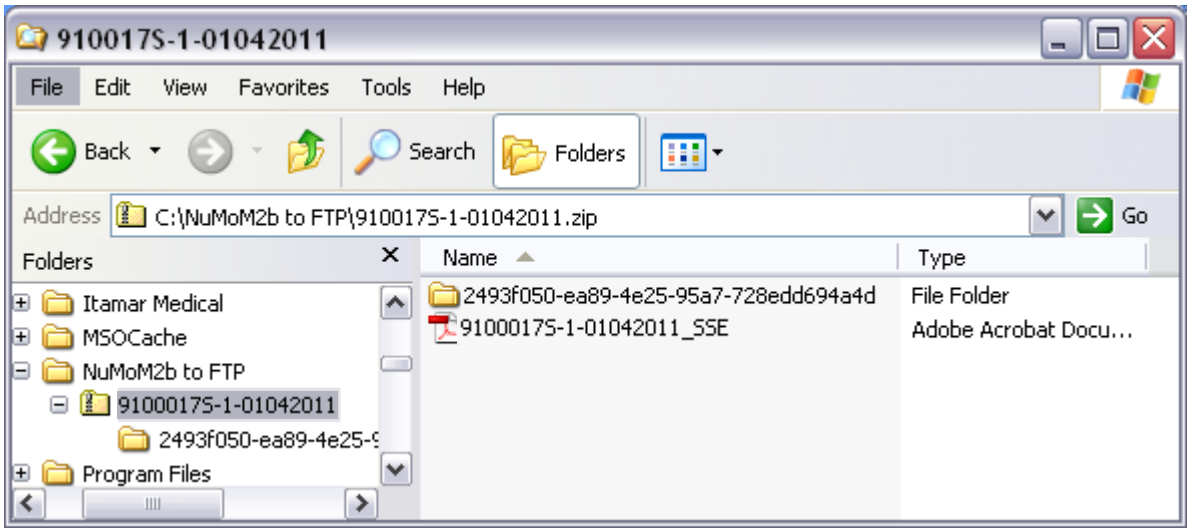


4. Locate a digital copy of the corresponding Form E1A (or E3A), Sleep Breathing Substudy Evaluation Visit 1 (or Visit 3) to be transmitted to the SRC

   Rename the electronic version of the form: **[Study ID – Visit# - Demonstration Date]_SSE** drag and drop the PDF file into the same study folder.

5. Right click the zipped folder and choose **Explore**.

6. A new explorer window will pop up, with the zip folder still highlighted. In the upper left, go to **File** and then **Add a Password**.



7. A dialogue box will pop up asking for a password to be entered and confirmed. The password to be entered will be provided separately by Sleep Reading Center staff and should be kept securely and never provided in correspondence with the file name. Reenter to confirm and click **OK. (Note that this is case sensitive).**

   The file is now ready to be transferred to the Sleep Reading Center via FTP.

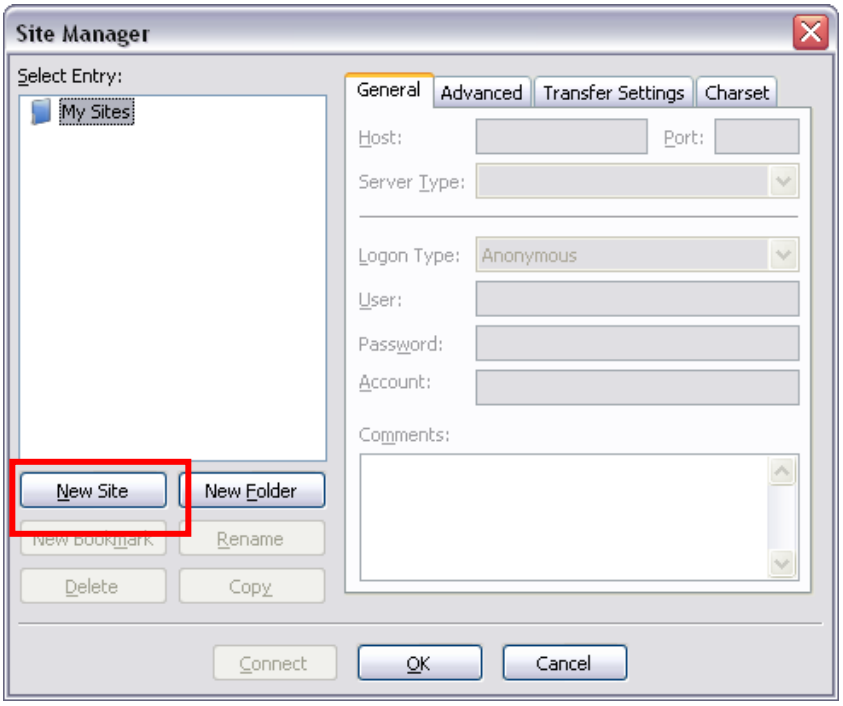
6.9.2 Transmitting Files via FTP using FileZilla

The software used to send study information to the reading center is FileZilla. If FileZilla is not already installed on the local computer, it can be downloaded and the installation run at:

http://filezilla-project.org/download.php

Once installed, open the program. Select **File ► Site Manager**

From there, select **New Site**



Under the **General** tab, fill in the following:

Host: phslxftp2.partners.org

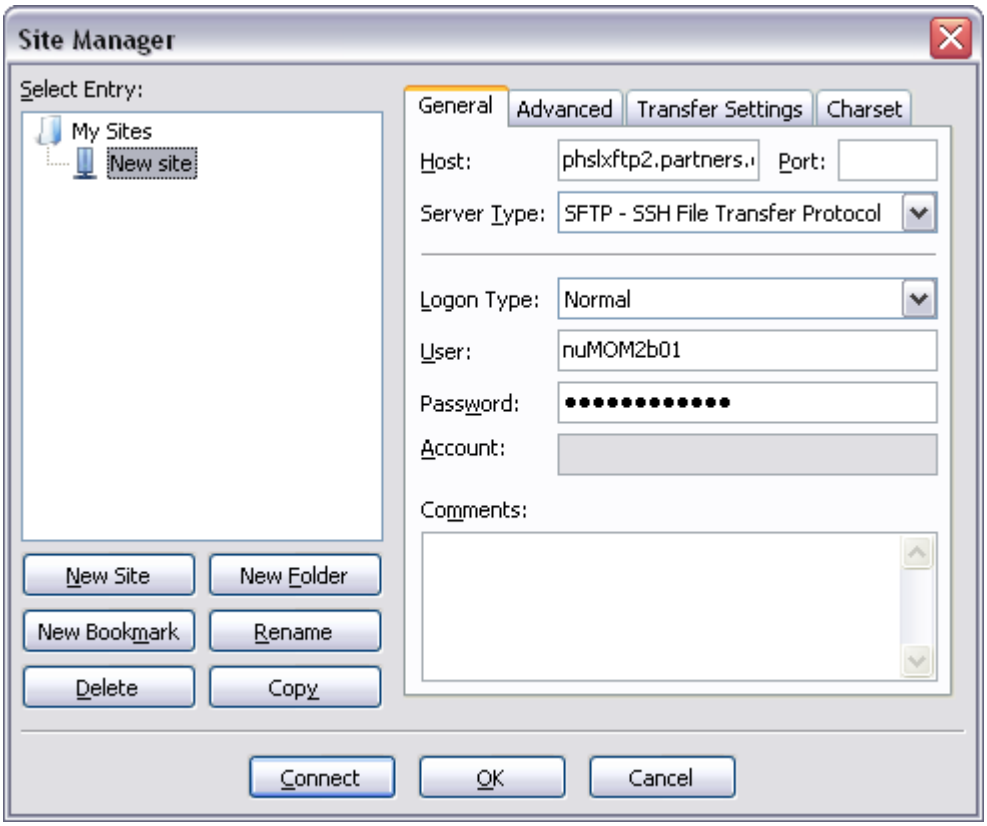
Port: (blank)

Servertype: SFTP – SSH File Transfer Protocol

Logontype: Normal

User: nuMOM2b01 (last two digits are site specific)

Password: to be provided to each site by the Sleep Reading Center

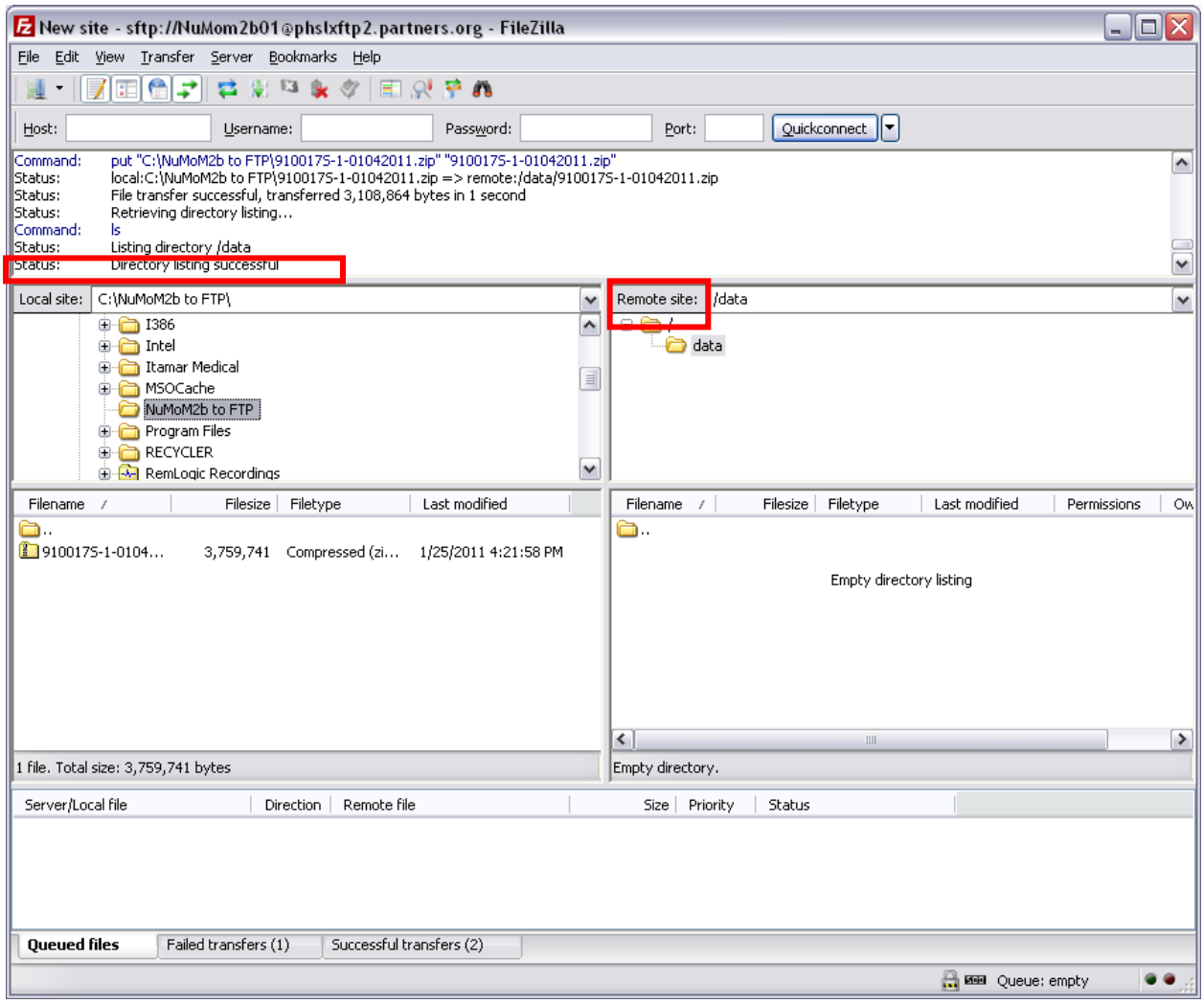


Select **Connect**.

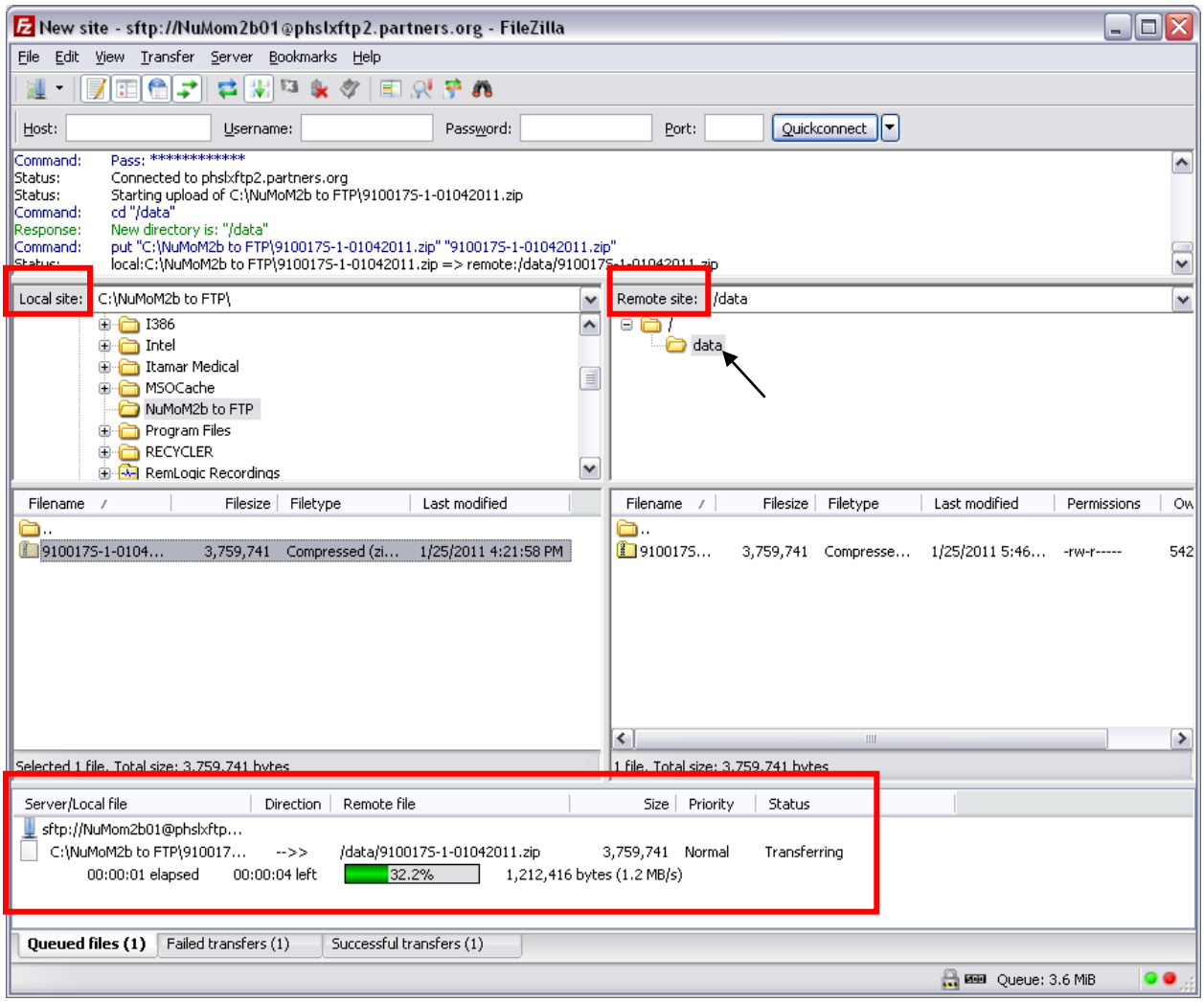
If all information was entered into site manager correctly FileZilla should connect to the remote server. There will now be text in the status window stating *directory listing successful.*

Remote Site will now list the directory on the FTP server. This may appear blank if no studies have been uploaded by the site yet.

The username and password will automatically route to the site's own folder on the server. Sites cannot see or access another site's data.



To send files, select the zipped study folders to send from the site computer (the **Local Site**) and drag and drop them to the Sleep Reading Center server (the **Remote Site**) in the **data** folder (as shown below). A status bar will pop up at the bottom while it transfers and the file should be visible in the remote site afterwards.



Transfer all future studies in the same manner by dropping them into the **Remote Site**. Once the study has been successfully sent to the SRC, FileZilla can be closed.

6.10 Feedback from the Sleep Reading Center

After receipt and review, each site will receive the following information from the SRC:

- Summary of Signal/Study Quality (including Pass/Fail status)
- Urgent Alert Identification and Physician Feedback reports for any studies triggering an Urgent Referral Alert (see **Section 6.11**).

Data from any studies flagged as a failed quality grade or noted to have marked drops in oxygen levels, or specific heart arrhythmia will receive priority scoring at the SRC, with reports generated within 2 business days of receipt. The SRC Manager contacts the site by phone or

email with information on possible equipment malfunction, participant acquisition problems (possibly requiring repeat studies), or urgent alerts (requiring timely feedback to the participant's physician). Reports for these studies are emailed to the site. A weekly report summarizing study quality and any urgent alerts is sent to each site.

All other studies are triaged for complete scoring at a later date. Finished, scored reports are transferred to the DCAC on a periodic basis.

The performance of each technician, monitor and site is reported to the Steering Committee and Sleep Breathing Committee monthly. Each study receives an overall study quality grade based on the artifact-free recording time that is present in the air flow (cannula), effort (respiratory bands) and saturation (SpO2) channels, which are considered key for scoring apneas and hypopneas. When monitoring quality, the minimal requirement for a "passed" study is 2 hours of artifact free data on the oximetry channel and on at least one respiratory channel (one band or nasal cannula.) Participants are asked to repeat studies that failed as soon as possible, and within 2 weeks of the initial attempt.

6.11 Urgent Referrals

6.11.1 Reasons Required

At this time, it is unknown what levels of sleep disordered breathing (SDB) severity or hypoxemia adversely influence pregnancy outcomes. It is for this reason that the nuMOM2b study has included a sleep breathing assessment as part of a substudy. Even in non-pregnant adults, the levels of SDB that confer an increased risk for adverse outcomes are unclear. It is also unclear which levels of SDB best respond to intervention. For example, some research indicates that it is predominantly adults with associated sleepiness in whom SDB treatment results in improved blood pressure. In general, SDB likely operates as a chronic exposure to increase risk for cardiovascular and metabolic diseases. Because SDB may fluctuate during pregnancy, it is also important to cautiously interpret the clinical significance of any measured level of SDB. Therefore, we identify only very severe levels of SDB as those that warrant prompt feedback, i.e., notification within 14 days of the sleep study, regardless of delivery date. After scoring at the Sleep Reading Center, studies that show an AHI >50 or severe hypoxemia (oxygen saturation of <90% for greater than 10% of the estimated sleep time) are identified. All studies meeting Urgent Referral criteria are reviewed by a Sleep Reading Center physician and the clinical site and DCAC are notified. In addition, other findings related to a sleep study may indicate the need for Urgent Referral. These include:

- Baseline oxygen saturation (prior to sleep onset) of <88%;
- Heart rate for more than 2 continuous minutes that is <40 or >150 beats per minute;
- The presence of a sustained wide complex rhythm ($\geq$3 consecutive beats) awake or asleep;
- Type 2 second degree and third degree atrioventricular block; and
- Atrial fibrillation and/or atrial flutter.

6.11.2 Urgent Referral Letter

Each site will identify an investigator who can interact with the participant's provider regarding the recommendations in the letter if needed. Upon notification that a participant's assessment

indicates the need for referral, this site investigator reviews the information. The patient's care provider is then notified of the results by phone and by letter so that arrangements for timely referral for full evaluation can be made.

Prompt feedback and/or urgent alerts that are noted as incidental findings on the sleep studies will not be considered adverse events since they likely reflect current health status and not a consequence of study participation.

An example of the urgent referral letter appears in **Appendix D**.

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7. SLEEP READING CENTER ACTIVITIES

7.1 Introduction

At the Sleep Reading Center, studies are first reviewed for technical quality and to identify Urgent Referrals (see **Section 6.7**). Review notes that require immediate action (data indicating a bad unit/sensor) and failures are sent to the site coordinator by email as these are identified.

Studies are considered acceptable if they contain a minimum of 2 hours of oximetry and either nasal pressure or one respiratory band during that time of good oximetry. Studies containing less than the minimal requirements are not scored, but quality codes are assigned to facilitate understanding problems in signal acquisition. For failed studies, the SRC notifies a designated staff member at the site via e-mail to request a repeat study from the participant. Quality grading of the study is documented using the SRC's quality control protocol (**Section 8.3**). The SRC scorer identifies any signal quality issues and provides recommendations for sensor replacements or adjustment. On a weekly basis, the site coordinator receives an electronic quality summary report indicating receipts, failures, study quality grades, and urgent referrals.

Sleep studies are scored using RemLogic© software by certified research sleep scorers. If needed to produce certain statistics, studies also will be imported as edf files and scored using customized Compumedics Profusion software. Each study undergoes manual editing, reviewing the stability of physiological signals and heart rate, and annotating defined windows of data to provide estimates of sleep and wake periods.

Although specific sleep staging cannot be done without an EEG, and thus the denominator used to quantify the AHI cannot be exactly estimated, sleep and wake states can be inferred from physiological measures derived from cardiopulmonary data. Dr. Redline has extensive experience using this methodology in other population-based studies. The approach for annotating estimated sleep time is to view all signals along with participant reported data on bed and wake times. Estimated sleep onset is marked based on a qualitative assessment that includes evidence of reduction in artifact across channels, reduction in heart rate, and assumption of rhythmic breathing. Estimated sleep offset is marked by appearance of sustained movement artifact, increased heart rate and patient report data. This approach normally provides an overall estimate of sleep time that is modestly higher, and thus, an AHI that is modestly lower, compared to estimates based on directly measuring sleep time.

The scorer manually annotates each respiratory event. Apneas are defined as a complete cessation of airflow for ≥ 10s. Hypopneas are defined in two ways: ≥ 30% reduction in nasal pressure signal excursions from baseline and associated ≥ 4% oxygen desaturation from pre-event baseline or ≥ 50% reduction in nasal pressure signal excursions and associated ≥ 3% oxygen desaturation. Additionally, events that meet the former hypopnea definition but are unassociated with desaturation are identified. Summary data generated include hours of recording and estimated sleep time, AHI, summary measures of heart rate and desaturation (% sleep time at saturation levels <90%, 80%, etc.), number of desaturation decreases of varying degree (ODI3, ODI4), and numbers and frequency of obstructive and central apneas. A semi-quantitative approach for quantifying airflow limitation and snoring is developed, pilot tested, refined, and utilized to explore the association of more subtle respiratory events with study outcomes.

7.2 Study Receipt

Upon receipt of studies at the Sleep Reading Center, the sleep assessment data are checked for accuracy. The receipt information includes: Subject ID, Study Date, date received via FTP, Embletta unit Number, and Staff (Technician) ID. If any discrepancy between the data contained on the Sleep Breathing Substudy Evaluation Visit 1 or Visit 3 (Form E1A or E3A) and the electronic sleep assessment file is noted, or if any data on a form are missing, an e-mail is sent to the site coordinator requesting clarification. The receipt date is entered in a database, and weekly receipt lists are sent to the to the site coordinator to confirm receipt of all studies.

A copy of the Sleep Breathing Substudy Evaluation Visit 1 or 3 (Form E1A or E3A) is sent to the Sleep Reading Center regardless of the quality or length of the recording. If there are no data at the time of download of the Embletta unit, the Sleep Study Evaluation form must still be sent. A note should be made on the form that no data were acquired on the Embletta at time of download. Short studies or problem studies that do not meet the criteria to be "passed" for scoring at preliminary review, also should be sent to Sleep Reading Center with any notes as to what troubleshooting was done, and whether the reason for the short study was determined. The Sleep Reading Center tracks all problems relating to lost sleep studies and must receive this paperwork on a regular basis. The problem studies are monitored, and, if any pattern is observed study wide, the Sleep Reading Center staff work to resolve the problem. These forms can be placed on the FTP server or can be faxed to the Sleep Reading Center.

7.3 Preliminary Review

The RemLogic Offline Analysis program is run at the Sleep Reading Center prior to review of studies by the Polysomnologist and final scoring to allow generation of reports and visualization of signals and graphic screens. After offline analysis of the record, the study is reviewed to determine any signal quality issues, possible monitor/electrode malfunctions, pass/fail status and possible Urgent Alert status indicating need for priority scoring.

To be classified as reliable sleep data, the record must contain at least 2 hours of fairly continuous (minimum of 20 minute consecutive epochs) scorable/reliable oximetry accompanied by one scorable respiratory channel (either airflow, thoracic, or abdominal belt) after reported bedtime. Studies containing less than the minimal requirements are not processed for scoring, and the site coordinator is notified via e-mail to request a repeat study from the participant. If the repeat study does not meet criteria, no attempt is made to repeat the study again at that visit.

7.4 Assignment of Studies – Urgent Alerts

Studies identified as potential urgent alerts are triaged for immediate scoring (within 2 business days). Once fully scored and determined to meet criteria for Urgent Alerts, a physician investigator at the Sleep Reading Center reviews the study. If an urgent alert is verified, it is logged into an Urgent Alert Log, and the site receives the full report and quality grades (Sleep Breathing Substudy SRC QS [Quality of Signal] Form E1B or E3B) within a week after final scoring is complete. All other studies are scored based on date received at the Sleep Reading Center via the FTP site.

Urgent Alert criteria include an AHI >50 or severe hypoxemia (oxygen saturation of <90% for greater than 10% of the estimated sleep time). In addition, other findings related to the sleep study may indicate the need for Urgent Referral. These include:

- Baseline oxygen saturation (prior to sleep onset) of <88%;

- Heart rate for more than 2 continuous minutes that is <40 or >150 beats per minute;
- The presence of a sustained wide complex rhythm (≥3 consecutive beats) awake or asleep;
- Type 2 second degree and third degree atrioventricular block; and
- Atrial fibrillation and/or atrial flutter.

7.5 In-Depth Analysis of Each Sleep Data Recording

7.5.1 Overview of Scoring

The RemLogic software is used to process and score the sleep recordings. Preliminary processing by the RemLogic software takes approximately 3 minutes, and, during this time, the SpO_2 and pulse rate are computed from the optical signals, and events are detected across all respiratory signals. The study is reviewed on 2 to 5 minute epoch length pages to identify and classify any respiratory events.

7.5.2 Summary of Scoring Process

Each study is manually scored in a single pass. During this pass, the scorer reviews the overall pattern in the data across the night's recording and reviews the RemLogic generated reports for any potential signal problems that were identified during processing. Using the Sleep Breathing Substudy SRC QS Visit 1 or Visit 3 Form (**E1B or E3B**), the scorer records the duration of the sleep period and documents if the study is less than 2 hours, which results in a failure of the study.

Review of Study Quality:

- The scorer reviews the channels and manually sets time of “analysis start” and “analysis stop.” If the study meets minimal passing criteria, the study is scored.

Scoring of the Sleep Study

- The respiratory signals from each study are reviewed on a 2-5 minute screen.
- The oxygen saturation channel is edited for artifact and respiratory events are marked manually according to the rules stated above using all signals.
- ECG is manually reviewed for abnormalities

After review, the Sleep Breathing Substudy SRC QS Visit 1 or Visit 3 Form (E1B or E3B) is filled out to document unusual patterns and signal/study quality grades. Feedback Reports are generated for studies that meet Urgent Referral Criteria. Reports are transmitted to the DCAC on a weekly basis. The raw and scored files and summary reports are saved to the Sleep Reading Center network drive and backed up on a nightly basis.

7.5.3 Lights Out and Lights On; Sleep Onset and Offset

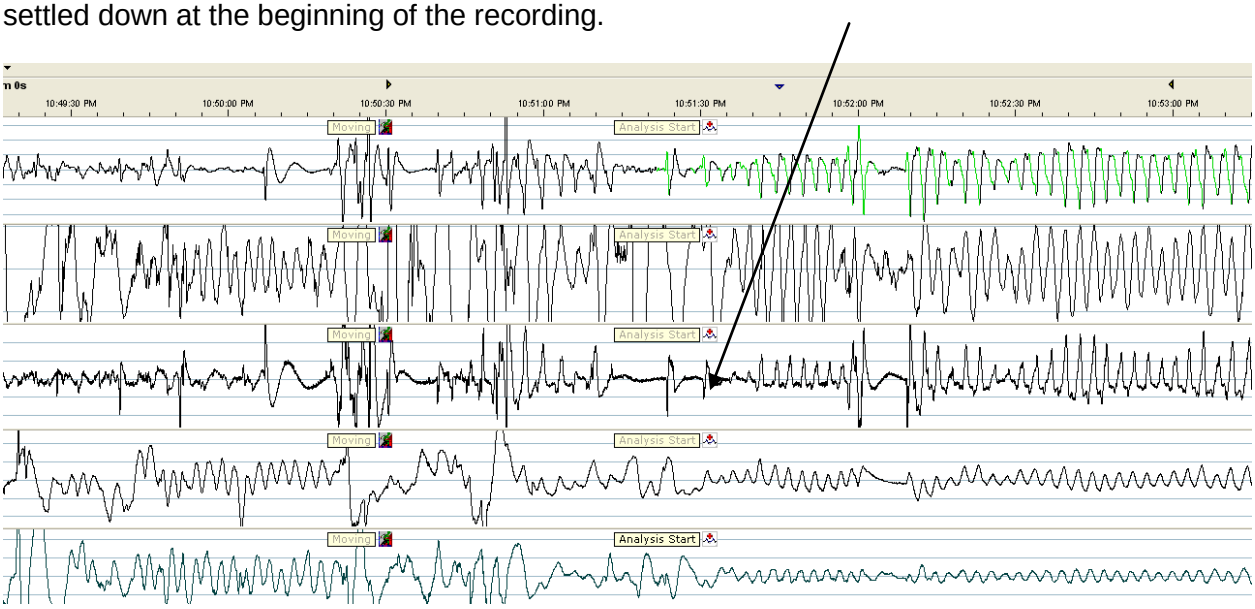
Lights Out and Lights On are documented on the SRC QS form based on data provided on the Sleep Breathing Substudy Evaluation Visit 1 or Visit 3 form completed at the site. If this information is unavailable, then Lights On and Lights Off correspond to the times the scorer estimates Sleep Onset and Sleep Offset. Sleep Onset is marked after lights out and when

movement decreases, breathing becomes more regular, and artifact decreases and is also usually associated with a decrease in heart rate. Sleep offset is identified with an increase in movement, changes in body position, irregular breathing, and increased heart rate.

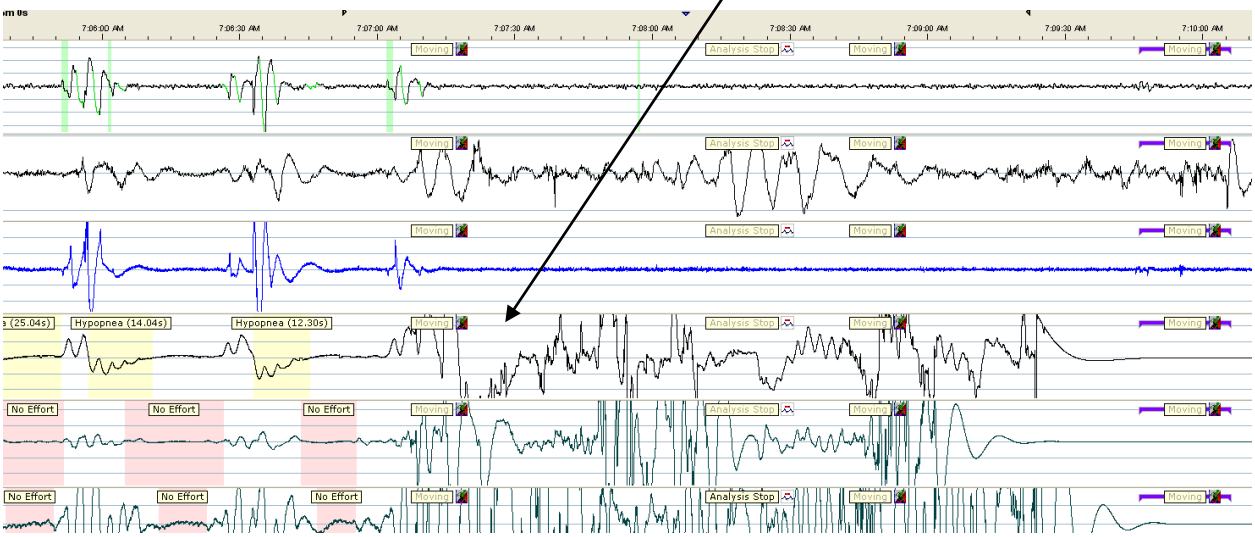
7.5.4 Analysis Start and Analysis Stop

The analysis start and stop events determine which parts of the recording are analyzed by the automatic analyzers. These events are marked in order to identify the analysis period.

When reviewing signals for analysis start, look for an area where it appears the participant has settled down at the beginning of the recording.



When reviewing signals for analysis stop, look for an area where it appears the participant has awoken before leads are being removed.



Once Analysis start and Analysis stop are marked, the scorer is ready to begin the Respiratory Analysis portion.

7.5.5 Sleep Duration and Quality of Signals

Each signal is reviewed for quality and a quality grade that gauges the duration of artifact free data is assigned for each channel. Any questionable or absent signal is noted in the QS report. An overall study quality grade is also assigned to reflect the absolute duration of artifact free signals for the four primary signals: nasal pressure (cannula), oxygen saturation (oximeter), and each respiratory effort belt.)

7.5.6 Respiratory Event Scoring

The scorer differentiates between 3 different categories of discrete respiratory events:

AASM Hypopneas are identified if ≥30% reduction of amplitude is visualized on either the nasal cannula or the respiratory SUM channel for a duration of at least 10 seconds and this reduction is associated with ≥4% oxygen desaturation. If the SUM and nasal cannula are not present, but a ≥30% reduction is seen on both belts (thoracic and abdominal) and is associated with ≥4% desaturation, then a hypopnea is scored. Discernable changes with desaturations that do not meet the rules of hypopnea are NOT scored as hypopneas. Identification of an AASM Hypopnea requires a minimum desaturation ≥4%.

AASM (Alternative) Hypopneas are identified if ≥50% reduction of amplitude is visualized on either the nasal cannula or the respiratory SUM channel for a duration of at least 10 seconds and this reduction is associated with ≥3% oxygen desaturation. If the SUM and nasal cannula are not present, but a 50% reduction is seen on both belts (thoracic and abdominal) and associated with ≥3% desaturation, then a hypopnea may be scored.

Other Hypopneas will be identified if ≥50% reduction of amplitude is visualized on either the nasal cannula or the respiratory SUM channel for a duration of at least 10 seconds and the associated oxygen desaturation is less than 3%.

Duration & Amplitude Criteria for Hypopneas

The beginning of a hypopnea is marked at the end of the last “normal” breath; the end of the event is identified as the beginning of the first breath that exceeds the amplitude of the first reduced breath used to mark the beginning of the event. Duration is based on a “trough to trough” marking lasting at least 10 seconds.

Contiguous respiratory events that have a single respiratory effort in the middle of two periods of absent efforts, each <6 seconds, **and** that are associated with a 3% or greater desaturation should be combined into a single Hypopnea event.

Amplitude reduction is estimated by comparing the amplitude of breaths within the event in question to the nearest area of regular breathing. In cases of severe SDB, this may not be possible. Care is taken not to consider resuscitative breaths as representative of normal breathing.

Obstructive Apneas. Acknowledging the limitations in reliably distinguishing apneas from hypopneas without thermistry, obstructive apneas will nonetheless be identified if the nasal pressure signal is completely flat for at least 10 seconds and scored regardless of associated desaturation.

Central Apneas will be identified if NO displacement is noted on both the chest and abdominal inductance channels. A minimum duration of ≥10 seconds is needed to score an apnea. Central

apneas will be scored when all signals are “flat” unless signal deflection is due to cardiogenic artifact. Identification of an apnea does not require a minimum desaturation.

Distinguishing Between Central and Obstructive Events

Only events with clear data from both the abdominal and chest signals can be potentially classified as central apneas. (Events where one or both of these channels are missing or contain artifact are considered hypopneas according to the above rules).

Often determining whether an apnea is central or obstructive is influenced by where the event is noted to begin and end. When unsure of where to mark the beginning and end of the event, the nasal pressure signal is used to identify the segment where airflow falls to zero and then rises above zero. Sometimes small efforts are seen following a completely flat area, followed by a large (“breaking”) breath. If a single non-artifactual deflection less than 25% of baseline breathing is seen at the beginning or the end of the period of flat signal, the event will be marked as central. (This recognizes that shortening the event slightly would make it a central event). However, if two or more consecutive small breaths less than 25% of baseline breathing (providing airflow is flat) are seen in the period in question, the event is marked as a hypopnea.

Exclusion of Respiratory Events

Single respiratory events that follow movement or a very large (sigh) breath ($\geq$150% of baseline effort) are not scored, unless they are part of a series of events. In these scenarios scoring of events begins with the second event in the series.

Nasal Flow Limitation

Nasal flow limitation is derived from the nasal cannula signal. A normal flow signal presents as a regular sinus rhythm and curve. Flow limitation may occur with increase upper airway resistance, not sufficient enough to cause discrete apneas and hypopneas. A regular sinus curve transforms into a signal that resembles a lowercase ‘H.” Periods of flow limitation are characterized according to the percentage of scored non-apneic/hypopneic respiratory data for which such a pattern was evident: 1) 0-10%; 2) 11 to 25%; 3) 26 to 50%; 4) 51 to 75% and 5) 76 to 100%.

7.5.7 RemLogic Software Analysis Process

1. Starting RemLogic: Double-Click the RemLogic Icon  on your desktop.

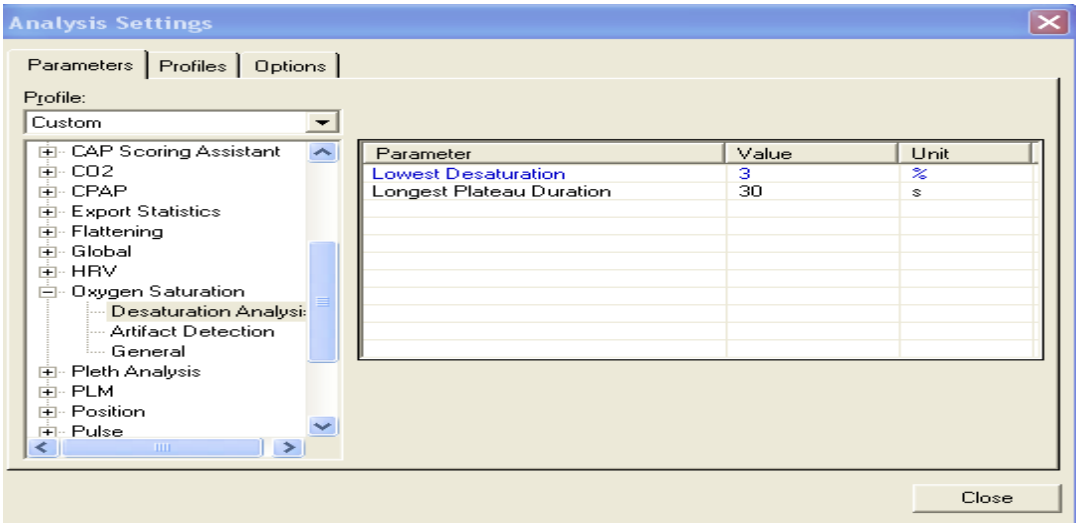
2. Import recording: From the main menu, select File, import, Recording.

3. The Browse for folder dialog is displayed. Browse for recording that should be imported and select the file. Then click OK. *A progress bar is displayed while the recording is copied in the Recording Manager.*

4. Open study and load scoring workspace.

5. Review signals, and set Analysis start (+) and Analysis stop (-).

6. Run Analysis: From the Main Menu select Analysis, Settings, Custom, and click OK.



Under the custom setting verify the lowest Desaturation value to be 3.

7. Run Analysis: From the Main Menu Select Respiratory Analysis. Select Nasal Flow (cannula) for Apnea and select Sum for Hypopnea.

If the cannula is unreliable, click on skip analysis. If the SUM is unreliable, either default to nasal flow or to a working reliable belt.

Additional Software Analysis

To derive additional analytical variables, studies are exported as edf files to Compumedics Profusion 3 software. Annotations are used to distinguish hypopneas that meet the two amplitude criteria described earlier. For primary analyses and participant feedback, the primary AHI (Apnea/Hypopnea Index) is defined as the total number of all respiratory events with ≥ 3% desaturation (AASM 2007 criteria). In addition, secondary analyses include the AHI calculated using various thresholds for corroborative desaturation (0% to 5%), indices of time in desaturation, and indices that combine SpO_2 desaturation events with changes in airflow and/or effort to derive a hierarchy of respiratory events.

7.5.8 Saving Scoring Template, Generating Reports and Archiving

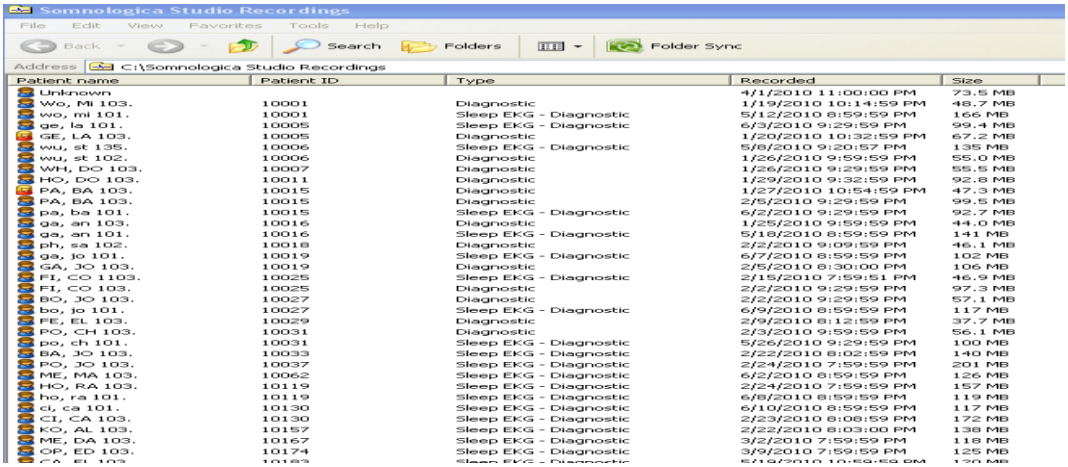
Any recording that has been reviewed, analyzed, and scored are saved as a workpad file. This is saved in the format FILENAME_SCORED.

1. To save the workpad Click on the “save” icon and rename.

2. To generate a report from the Main Menu select Reports, nuMOM2b Embletta sleep reports. **The report template used for the nuMOM2b study has been customized. If any issues arise with report generating contact EMBLA tech support.**

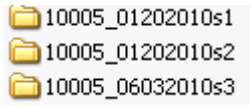
3. Save the report with the study ID as a doc file and then resave as a txt file.

4. To archive the study, locate the RemLogic studio recording folder on your local drive. It should resemble the window below.

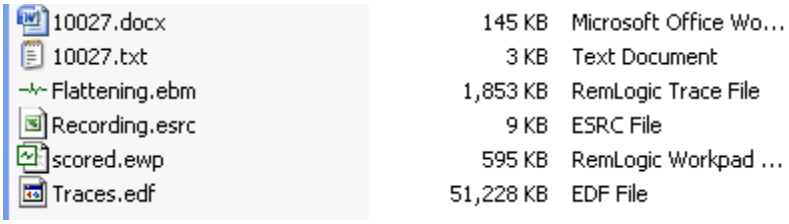


5. Select the study that needs to be archived. Copy and paste it into the directory.

6. The study once pasted into the directory has a long string of letters and numbers. Rename the file to reflect the study ID and the date the study was recorded.



7. The folder should contain the following files:



7.5.9 Reporting

Study data are transmitted to the Sleep Reading Center and a report is generated and provided to the Data Coordinating and Analysis Center (DCAC) for the parent study. Questionnaire and scored sleep data are managed centrally by the DCAC, which develops a database of the sleep measures that is linked by the study ID to pregnancy outcome measures and other data from nuMoM2b. AHI, oximetry statistics and sleep time are reported.

7.6 Providing Data to the DCAC

Data are provided to the DCAC via an FTP server on a regular basis, from weekly to monthly, depending on the amount of data received.

7.7 Data Security and Confidentiality

Data confidentiality and security are applied at all levels of data acquisition, transfer and storage at all of the clinical sites, as well as at the SRC and DCAC. Password controlled access to

clinical site, SRC, and DCAC computers is the initial level of security. All data transmitted to the DCAC and SRC are encrypted. All data transmitted to the DCAC and SRC are stripped of personal identifiers (other than date of study) using only a study specific number (the nuMoM2b Study ID) for identification purposes. The SRC servers are exclusively managed by study personnel.

All SRC systems are secured behind the Partners firewall and follow Partners Healthcare Information Security policies for authenticated, minimum access. All systems are patched, monitored and scanned routinely for vulnerabilities and intrusions by the systems administrator and PHS Information Security. Data are encrypted, where applicable, in compliance with state and federal government standards, regulations, and in accordance with Partners Security and Privacy policies. All configuration changes that could affect accessibility or security are approved by management.

The SRC virtual services and databases are backed up nightly via the enterprise backup system, IBM Tivoli Storage Management, and storage tapes that are maintained off site are encrypted. All systems administrative personnel and support staff have completed the NIH training program in Computer Security and have additionally completed their certification in the Collaborative IRB Training Initiative (CITI) program.

Additional information about data security at the sites and the DCAC is provided in Sections E and J.4 of the nuMoM2b study protocol.

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8. QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Introduction

The nuMoM2b study has implemented a number of procedures to assure the quality of the study. These include establishing qualifications for staff; training in ethics, maternal visit procedures, ultrasounds, and keying; certification of staff; establishing quality control and quality assurance procedures for various aspects of the study; on-site monitoring by local coordinators; interactions among the coordinators and between site staff and Data Coordinating and Analysis Center (DCAC) staff; and, possibly, quality assurance visits to the clinical sites. Many of these are described in the Manual of Operations for the main study.

The remainder of this chapter describes quality control and quality assurance procedures specific to the Sleep Breathing Substudy.

8.2 Site Sleep Breathing Staff Training, Certification, and Quality Assurance

8.2.1 Central Training

All staff working on the Sleep Breathing Substudy who use the Embletta Gold system or its resulting data in any way must be trained in Substudy procedures and certified by the Sleep Reading Center.

Sleep Breathing Substudy training requires the site staff member to become familiar with the purpose of the nuMOM2b Sleep Breathing Substudy, the purpose of sleep breathing monitoring and relevance to the overall study goals; how to use the sleep monitor hardware and software; how to transmit data to the SRC; how to maintain relevant study documents; interpret unit-generated quality control checks; routine maintenance checks and other unit troubleshooting methods; and how to act on identified Urgent Sleep Alerts.

Every site and subsite must have at least one (1) clinical staff member or study coordinator who is responsible for overseeing the sleep breathing assessment data collection at central training. This staff member is the first at each site to certify for sleep collection and then becomes responsible for training and oversight of any additional staff seeking certification as technicians for sleep breathing assessment data collection at the site

Clinical site staff who attend central training and have received documentation of their certification from the Sleep Reading Center may train others locally. This local training includes the content of presentations during central training, a review of study documents, administration of the practical exam, and distribution and collection of the written examination. Each staff member seeking certification needs to submit a high quality study and associated paperwork to the Sleep Reading Center. Staff, whether trained centrally or locally, must complete the entire certification process and receive written documentation of certification from the Sleep Reading Center before performing duties related to Sleep Breathing Substudy assessments at the site. A checklist for on-site training is provided to ensure that staff members who did not attend central training have the same basic understanding of collecting data for the Sleep Breathing Substudy as those who attended central training. This checklist must be signed by the trainee and the certified staff member conducting the training and submitted to the Sleep Reading Center as part of the certification process.

This manual of operations details procedures, equipment use, quality assurance procedures, and data management. Staff members from the SRC are available to clinical site staff to answer questions and assist in troubleshooting related specifically to the Sleep Breathing Substudy assessments and equipment. Staff from the DCAC are available to answer more general questions related to how the Sleep Breathing Substudy integrates into nuMoM2b.

8.2.2 Certification

Certification requirements include:

- completion of a written exam;
- completion of a practical exam, that includes observation by a Sleep Reading Center approved investigator or staff member or a centrally trained and certified clinical site staff member to evaluate the ability of the trainee to initialize and download the studies and to clearly explain the use of the portable sleep monitoring device; and
- documentation of a successful transmission of a high quality study and associated paperwork to the SRC.

Staff are required to demonstrate proficiency in using the sleep monitor for collection and transmitting data by submitting one (1) acceptable night time recording on a volunteer. This serves both as part of the staff certification and as practical experience in using the equipment in the study environment. Certification studies also allow for verification that sensors and equipment are functioning properly before being used on a study participant. To be considered acceptable for certification the sleep recording must:

- have good quality signal on each channel (i.e., all sensors must work and be relatively free from artifact) for at least 4 hours of monitoring time;
- include proper naming of the study recording (including the Study ID-Visit #-Date of Demonstration, Staff ID, and Unit ID);
- include a completed Sleep Breathing Substudy Evaluation Visit 1 or Visit 3 form (E1A or E3A); and
- be successfully downloaded and transmitted to the SRC.

Once all steps are complete, Sleep Reading Center staff certify those staff demonstrating proficiency in Sleep Breathing Substudy procedures

8.2.3 Maintaining Certification

After initial certification, sleep certification can be maintained by performing successful data collection and transmission of a minimum of one (1) study per month. Signal and study codes, specific to each technician and unit will be summarized and reported on a monthly basis to the NuMoM2b Steering Committee and relevant subcommittees allowing individual technicians who do not meet pre-defined levels of performance to be identified. If needed, the SRC plans to lead periodic Sleep Quality Control calls for the purposes of facilitating dissemination of information regarding problem identification as well as developing solutions (e.g., optimizing presentation of equipment to pregnant women). A practice maintenance study is defined as successful data

collection (at least 2 hours in length of scorable/reliable oximetry and one respiratory channel) and transmission on a non-participant volunteer.

8.2.4 Quality Assurance

Each Embletta Gold must have at least one successful study completed on a volunteer before it is used to obtain data from a participant. For all studies, visual inspection of the data at the time of download is performed by clinical site staff, who complete a Sleep Study Evaluation Visit 1 or Visit 3 Form prior to transmitting the study to the Sleep Reading Center. If problems are identified, the clinical site staff attempt to troubleshoot, contacting the Sleep Reading Center for guidance if needed. In addition, all files are inspected by Sleep Reading Center staff prior to scoring. As described elsewhere in this manual, each study received at the Sleep Reading Center is assigned quality codes. The Sleep Reading Center contacts sites if consecutive studies demonstrate poor quality or if any one study shows evidence of faulty technique or malfunctioning equipment or needs to be repeated. Signal and study quality codes, specific to each technician and monitor are summarized and reported on a monthly basis to the DCAC to share with the Steering Committee and the Sleep Breathing Committee. Individual technicians who do not meet pre-defined levels of performance are identified in these reports. If needed, the Sleep Reading Center leads Sleep Breathing Substudy Quality Control calls for the purposes of facilitating dissemination of information regarding problem identification as well as developing solutions (e.g., optimizing presentation of equipment to Spanish speaking families).

8.3 Quality Control of Sleep Scoring

The Sleep Reading Center includes a senior Chief Polysomnologist and 9 dedicated certified research polysomnologists. Each staff member undergoes training and certification for each study to which they are assigned. Training and certification includes providing evidence of scoring agreement within 5% for respiratory event identification in a test set of 20 studies. Scorers participate in weekly quality control exercises, which include rescoring of difficult epochs individually identified and scoring of randomly identified studies (50 epoch exercises). Scoring results are discussed as a group and any differences are adjudicated by consensus. Bi-annually, scorers participate in a formal re-evaluation of scoring, which includes rescoring 20 or more studies and calculating inter- and intra-scorer reliability. Evidence of scorer drift or inter-scorer variability is addressed by review, retraining, and recertification if needed. For nuMoM2b Sleep Breathing Substudy, the plan is to dedicate two full time scorers, supervised by the Chief Polysomnologist, to the substudy. However, if work load demands, a third scorer can be trained and certified for this substudy.