Title: A Single Arm, Open-Label, Multi-Center, and Comparative Study of the ANNE™ Sleep System versus Polysomnography to Diagnose Obstructive Sleep Apnea: ANNE Program for the Non-Invasive Evaluation of Apnea in Sleep (APNEAs)

Protocol Version: v1.1

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PROTOCOL SUMMARY

Protocol Title (Long Title)	A Single Arm, Open-Label, Multi-Center, and Comparative Study of the ANNE™ Sleep System versus Polysomnography to Diagnose Obstructive Sleep Apnea: ANNE Program for the Non-Invasive Evaluation of Apnea in Sleep (APNEAs)
Protocol Title (Short Title)	ANNE Program for the Non-Invasive Evaluation of Apnea in Sleep (APNEAs)
Protocol Number	TP-210216-01-A
Phase	Clinical Validation
Study Design	Single-Arm, Open Label, Multicenter, Comparative Study
Study Duration	Start: March 2021 End: December 2021
Setting	Multiple Centers: 1. Carle Foundation Hospital 2. Northwestern Memorial Hospital (NMH) 3. Northwestern Lake Forest Hospital 4. Northwestern Medical Group (NMG) 5. Central DuPage Hospital (CDH)
Sample Size	A total of approximately 214 subjects may be recruited to complete the study. All sites will aim to contribute an equal or similar number of subjects to contribute to the sample size.
Main Inclusion Criteria	● 22 years old or older ● Subjects with suspected OSA based on history and physical who qualify for, and have PSG or HST ordered, as determined by their regular healthcare provider ● Persons with a previous diagnosis of OSA ● Subjects with self-reported symptoms of OSA ● Willingness to give consent and comply with study procedures

Primary Objectives:	The main objective of this study is to evaluate the accuracy of the ANNE™ Sleep system to serve as a diagnostic aid for moderate to severe obstructive sleep apnea (OSA) in adults. Our primary hypothesis is that the ANNE™ Sleep system is non-inferior compared to polysomnography (PSG) for the diagnosis of moderate to severe OSA.
Investigational Product and Planned Use	ANNE™ Sleep System
Statistical Analysis	The apnea-hypopnea index (AHI) will be calculated in ranges of 15 – 30 apnea/hypopnea events per hour for moderate OSA and ≥30 apnea/hypopnea events per hour for severe OSA. The oxygen desaturation index (ODI), the hourly average number of desaturation episodes, will also be calculated. The accuracy (sum of the number of true positives and true negatives divided by the sum of the number of true positives, true negatives, false positives, and false negatives), sensitivity, specificity, positive predictive value, and negative predictive value of ANNE™ Sleep to detect moderate to severe obstructive sleep apnea will be compared to outputs from PSG.

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1. LIST OF ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AHI	Apnea-Hypopnea Index
CDH	Central DuPage Hospital
ECG	Electrocardiogram
EDF	European Data Format
EDW	Electronic Data Warehouse
EHR	Electronic Health Record
EMG	Electromyography
FAS	Full Analysis Set
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	Heart Rate
HST	Home Sleep Test
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization Good Clinical Practice
IRB	Institutional Review Board
MRN	Medical Record Number
NMG	Northwestern Medical Group
NMH	Northwestern Memorial Hospital
NPV	Negative Predictive Value
OSA	Obstructive Sleep Apnea
ODI	Oxygen Desaturation Index
PAP	Positive Airway Pressurewas
PAT	Peripheral Arterial Tonometry
PHI	Protected Health Information

PI	Principal Investigator
PPAS	Per Protocol Analysis Set
PPV	Positive Predictive Value
PSG	Polysomnography
PTT	Pulse Transit Time
RPSGT	Registered Polysomnography Technicians
RR	Respiratory Rate
SDB	Sleep Disordered Breathing
SL	Sleep Latency
SoC	System-on-Chip
TRT	Total Recording Time
TST	Total Sleep Time
WASO	Wake after sleep onset

2. OBJECTIVES

The main objective of this study is to evaluate the accuracy of the ANNE™ Sleep system to serve as a diagnostic aid for moderate to severe obstructive sleep apnea (OSA) in adults. Our primary hypothesis is that the ANNE™ Sleep system is non-inferior compared to polysomnography (PSG) for the diagnosis of moderate to severe OSA.

3. INTRODUCTION

Sleep disordered breathing (SDB) is an increasingly common disorder characterized by a pathological increase in upper airway resistance experienced during sleep that ranges from benign snoring to its most severe form of obstructive sleep apnea (OSA). OSA is characterized by recurrent episodes of cessation of breathing and physiological stress as a result of intermittent periods of hypoxemia, and arousals. Studies have demonstrated that OSA leads to profound sleep fragmentation, disturbance of the autonomic nervous system, insulin resistance, increased systemic inflammation, oxidative stress, and subsequent vascular endothelial dysfunction. These physiologic changes cause significant morbidity; OSA is an independent risk factor for wide ranging adverse health outcomes including cardiovascular disease (hypertension, stroke, myocardial infarction), metabolic disorders (insulin insensitivity, diabetes), neurological (dementia), motor vehicle accidents, and mood disorders.[1-5]

The ANNE™ Sleep system has been validated in multiple clinical studies including a pilot investigation of its performance against a Type III Home Sleep Apnea Test (HST). In controlled clinical testing scenarios (n=13) with breathe-down studies of gases with lower and lower amounts of oxygen to induce hypoxia, the system has validated heart rate, respiratory rate, and oxygen saturation (SpO_2) against gold-standard monitoring systems. The average root mean square error (A_{RMS}) is <1 heart beats per minute, 2.9% blood oxygenation, and 1.3 breaths per minute. The A_{RMS} in the pediatric population (>150 subjects) is <2.5 heart beats per minute, 2.9% blood oxygenation, and 1.9 breaths per minute. In a comparison study of ANNE™ Sleep vs HST in n=46 high-risk individuals, the sensitivity of 85% and specificity of 95% for the diagnosis of moderate to severe OSA was defined by an apnea-hypopnea index >15. The system is indicated for detection limits as follows:

- Heart rate: 0 to 300 beats per minute
- Respiratory rate: 0 to 60 breaths per minute
- Oxygen Saturation (SpO_2): 70 – 100%

In this context, this study is designed to evaluate the accuracy of the ANNE™ Sleep system to serve as a diagnostic aid for moderate to severe OSA.

4. STUDY ENDPOINTS

4.1 Primary Outcome Measures

The diagnosis of moderate to severe OSA by determining a patient's Apnea-Hypopnea Index (AHI) using the ANNE™ Sleep system compared to Polysomnography (PSG) over one (1) night worn concurrently.

4.2 Exploratory measures

The following subset of exploratory measures are intended to provide additional information. A full list is provided in section 11.5.

- Evaluation of the predictive value of the ANNE™ Sleep system to differentiate obstructive vs central apnea events using the system's onboard sensors
- Patient reported preferences between PSG and ANNE™ Sleep
- Patient reported survey results for the ANNE™ Sleep system

5. RECRUITMENT METHODS

5.1 Recruitment centers

Study subjects will be recruited in 4 centers if they self-report symptoms of OSA or are prescribed either a PSG or HST by their regular healthcare provider when OSA is suspected from one of the following study sites:

1) Carle Foundation Hospital
2) Northwestern Memorial Hospital (NMH)
3) Northwestern Lake Forest Hospital
4) Northwestern Medical Group (NMG)
5) Central DuPage Hospital (CDH)

5.2 Recruitment procedures

All recruiting processes will follow this protocol and meet the inclusion and exclusion criteria. Recruitment will occur in via two main strategies. The first will be community based and clinic based advertisements via social media ads, and physical fliers. The second will be center based recruitment via Electronic Health Records (EHRs).

5.2.1 Screening potential patients

A study coordinator may flag orders for PSG or HST studies via screening of EHRs. An algorithm will be set up based on the eligibility criteria of the trial to identify potential patients who have met enrollment criteria to establish a roster of potential subjects to be recruited. Study subjects who have a previous diagnosis of OSA or self-reported OSA symptoms may be enrolled in the study.

For all Northwestern Hospitals, additional methods of identifying participants will be through the Electronic Data Warehouse (EDW) and through the use of study flyers and recruitment materials. The EDW at Northwestern is updated daily. An algorithm can be set up based on the eligibility criteria of the trial to identify potential participants that have met enrollment criteria. Data gathered

in the EDW request will include Name, contact information (address, email and/or phone), Date of Birth, MRN, hospitalization date(s), and if applicable, date that a HST or PSG is ordered. The EDW request may exclude people based on the exclusion criteria. The use of the EDW will be used exclusively for recruitment purposes and no data from the warehouse will be added to the study data set for research analysis. The use of study flyers or advertisements will also be shared with potential study subjects who will be given contact information to follow up with the study team. For Carle Foundation Hospital, the site may utilize MyCarle, a patient database, to locate and contact potential participants using the approved scripts (**Appendix A & B**).

5.2.2 Assess eligibility of subjects for the study

Potential subjects will be further screened for eligibility per the inclusion/exclusion criteria. A study coordinator will contact potential subjects either in person or by phone and provide an overview of the study using an approved phone script (**Appendix A**), email (**Appendix B**), or patient recruitment flyer (**Appendix C)**. The screening questionnaire will be asked during phone interviews and or email. An additional tool for screening study subjects will be completed with the use of the STOP-BANG questionnaire and Epworth Sleepiness Scale (**Appendix D**) and screening questions which may be done over the phone, in-person, or using a link to an electronic survey.

5.2.3 Informed Consent Form (ICF)

If a subject is deemed eligible, the study coordinator will explain that if they consent they will wear the ANNE Sleep during an attended PSG study for one (1) night. The coordinator will also inform subjects that they will be asked to complete the Sleep Diary log (**Appendix E**) during the morning following data collection and a patient survey at the end of the study (**Appendix F**).

If subjects are interested in participating in the study, the subject will sign the IRB approved Informed Consent Form (ICF) (**Appendix G**). Subjects may provide an electronic signature via REDCap, a secure web application for building and managing online data capture for research studies. Study subjects may also be asked to be photographed in-person at the time of their PSG study to demonstrate and document the location of the ANNE™ Sleep sensors.

5.2.4 Subject Screening/Enrollment Log

When a signed consent form is completed, the coordinator will obtain the subject's medical history from the EHR and information including name, date of birth, address, telephone number, email, demographics, age, and sex. Each consented subject will be assigned a unique subject number. Subject numbers will not be reassigned or reused for any reason. Only their assigned subject number will identify subjects. The investigator must maintain a list of potential subjects and enrolled subjects using the Subject Screening/Enrollment Log.

5.3 Recruitment monitoring

Recruitment for all sites will be monitored carefully with weekly meetings between study coordinators and study investigators. Barriers to recruitment will be identified and addressed to ensure recruitment remains on track.

6.0 INCLUSION AND EXCLUSION CRITERIA

Eligible participants will be screened using electronic medical records from their respective study sites. Eligible participants may also be screened over the phone. No special populations will be targeted for the enrollment in this study. Additional patient referrals will be made by the physicians who are participating as investigators on this study. The referring physicians of patients to the study will make an assessment if a potential study subject is capable of providing informed consent and will not refer patients unlikely to understand what is being asked of them. All potential subjects will be evaluated by research staff in order to match them to the inclusion and exclusion criteria that has been established.

6.1 Inclusion Criteria

1) ≥22 years old.
2) Subjects with suspected OSA based on history and physical who qualify for, and have either a PSG or HSAT ordered, as determined by their regular provider. Subjects with self-reported symptoms of OSA based on the STOP-Bang questionnaire indicating affirmative answers to any of the following: snoring, daytime fatigue/sleepiness/tiredness, partners who have observed the subject stopping breathing or choking/gasping during sleep. Persons with a previous diagnosis of OSA are also eligible.
3) Willingness to give written consent and comply with study procedures

6.2 Exclusion Criteria

1) An unstable medical condition, acute or chronic, that in the opinion of the investigator puts the subject at health risks related to this trial or interferes with the clinical trial and data collection based on the opinion of the investigator, this includes but is not limited to:
    A. Significant cardiorespiratory disease: patients that are oxygen dependent, previous hospitalization for cardiorespiratory issues
    B. Respiratory muscle weakness due to a neuromuscular condition
    C. Awake hypoventilation or suspicion of sleep related hypoventilation
    D. Chronic opioid medication use
    E. History of stroke
    F. History of severe insomnia
2) Inability to understand instructions
3) Has an active skin abnormality that precludes assessment
4) Has a history of dementia
5) Patients with implanted pacemakers or defibrillators
6) Subject is pregnant, nursing or planning a pregnancy over the expected course of the study

7. STUDY INVESTIGATIONAL DEVICE

ANNE™ Sleep system

Sibel's ANNE™ Sleep system includes two skin-mounted, bio-integrated sensors to record vital signs, a wireless charger, a wireless charger adaptor, single-use chest adhesives, single-use over the sensor adhesives, single-use finger adhesives, and a mobile device with a mobile software application that enables data recording for download for further analysis.

Heart rate (HR), respiratory rate (RR), actigraphy, and skin temperature are recorded from the ANNE™ Chest sensor. Blood oxygenation (SpO_2), peripheral arterial tonometry (PAT), and skin temperature are recorded from the ANNE™ Limb sensor. PAT is indicative of vasoconstriction, which can serve as a proxy for respiratory disturbances and accepted by the American Academy of Sleep Medicine for use as part of home sleep testing. The ANNE™ Sleep system also calculates pulse transit time (PTT), a measure of time for a pulse generated from the heart to travel to the peripheral limb. It is used as a surrogate marker of respiratory effort, apnea, and hypopnea events.

The first sensor (chest unit) located on the chest contains a 3-axis gyroscope and 3-axis accelerometer, Bluetooth Low Energy System-on-Chip (SoC), a Lithium-Polymer battery, power management component, an analog front-end component, passive electrodes for electrocardiogram (ECG) and electromyography (EMG), bio-impedance feature for RR, and a temperature sensing unit.

The second sensor (limb unit) located on the finger of a patient contains Bluetooth Low Energy SoC, a Lithium-Polymer battery, power management solution, low-power microcontroller, an analog front-end component, pulse oximeter (SpO2), and a temperature-measuring unit.

The chest sensor is placed on the body via a single-use chest adhesive as well as an optional over the sensor adhesive. Both adhesives will be removed and discarded after one use. The limb sensor is held in place by a single-use finger adhesive, which is removed and discarded after one use, then replaced with a new finger adhesive.

	Chest Unit	Limb Unit
Multi-Use		

Figure 1. The ANNE™ Sleep consists of 2 sensors, a chest unit worn on the thorax and a limb unit that wraps around a finger.

8. PREPARATION OF ANNE™ SLEEP SYSTEM

8.1 Standard study supply kit

The study sponsor will ship ANNE™ Sleep system (study supply kit) to the study centers.

Study supply kit list
• Cardboard mailer box

- Wearable study sensors
- Study devices (Tablet(s) or smart phone(s) with sensor application pre-loaded).
- Wireless charger(s), charger adaptors
- Device accessories; chest adhesives, over the sensor adhesives, finger adhesives
- Printed instructions or other study materials

The research coordinator from the sponsor will document tracking records of each device. All adhesives are single use with new ones provided to each new subject.

8.2 Study Kit Cleaning

Study sensors are reusable after completion of study procedures and data collection. Used study kit containers will be wiped on the outside using Sani-Cloth before handling and placed in a fume hood labeled “Contaminated Study Kits”.

The below table lists materials and PPE for sanitation.

Table 1. (Part 1: Sanitation procedure for wearable study devices and device accessories)

Materials and PPE	Study supply kit list
● 70% ETOH ● Super Sani-Cloth Germicidal Wipe* ● Disposable paper towel ● Nitrile Gloves ● Lab coat ● Face mask*	● Cardboard mailer box. ● Wearable study sensors ● Study devices (Tablet(s) or smart phone(s) with sensor application). ● Wireless charger(s), charger cords, bricks ● Device accessories; adhesives for both sensors ● Printed instructions or study other study materials

*Super Sani-Cloth is an EPA registered hospital-grade disinfectant to accommodate the many situations and hard non-porous environmental surfaces found in healthcare settings. This wipe kills bacteria, viruses and yeast.

*Face masks are to be used only if social distancing cannot be maintained.

The detailed sanitation instructions for the study kit are attached as **APPENDIX G.**

The study sponsor should perform an inspection of each device and ensure cleaning procedures should be conducted before shipping and after receiving the return shipment per guidance from the Center for Disease Control[8].

9. STUDY PROCEDURES

9.1 Pre-study

The study coordinator will schedule a conversation, via phone or in person, with the potential study subjects.

To minimize the risk of loss of privacy and enhance confidentiality, the subject may have the option to discuss with the study coordinator over the phone or by a Zoom teleconference from the subject's personal device. If Zoom communication is selected a unique meeting number and password known only to the subject will be provided. The study coordinator will monitor the number of attendees in the meeting and restrict meetings to IRB approved researchers on this study, the study subject, and additional people at the subject's discretion. Researchers will host the Zoom sessions and will utilize the waiting room feature to ensure that only the appropriate participants are included on the call.

The study coordinator will cover following topics associated with the study:

(1) The qualified subject will be asked to schedule a PSG study to operate concurrently with the ANNE™ Sleep system for one supervised night at the sleep center with the assistance of a study coordinator as needed. The target time frame will be to complete the sleep night within 2 weeks of enrollment and confirm when they will be completing the PSG night.

(2) Advise subjects to avoid alcohol and sleep medication use such as antihistamine (OTC) or prescribed medicines for sleep support on the testing night. Any use of these substances on the night of monitoring sleep will be asked to be recorded in the diary.

(3) Discuss with the subjects regarding the completion of the Demographic, Medical History and Sleep Survey (**Appendix I**) sleep diary (**Appendix E**) and usability survey (**Appendix F**). The sleep diary and usability survey should be available to complete via an email link through REDCap or printed out forms.

Any subject's questions or concerns associated with the study will also be addressed. **9.2 Study procedures**

The following summarizes the procedure subjects will go through during the PSG/ANNE™ Sleep night. At least 24 hours prior to the subject's PSG/ANNE™ Sleep study, the study coordinator will contact the participant by phone to confirm their scheduled appointment. Once confirmed, the study coordinator will meet the subject at their respective sleep health centers on the night of the PSG/ANNE™ Sleep study.

9.2.1 PSG procedures

The subject should expect the following PSG procedures to be conducted by a sleep technician following established AASM practice parameters for PSG.

1) Subjects will follow all typical PSG procedures and wear all appropriate PSG equipment as instructed by their sleep technician.

2) Set up PSG
    a) Electrodes placed on the scalp, outer edges of the eyes, and chin to record brain, heart and muscle activity, cannula for airflow, and eye movement; elastic belt around the chest and abdomen to monitor breathing; a sensor on the index finger to check oxygen levels in blood and heart rate.
    b) Subjects will also be videotaped while they sleep to review any changes observed during the PSG study.

3) The data collection for PSG procedures
    The data collection during the study night will be handled by the sleep technician. After a full night of data collection, the data will be stored in a secure and private database designated in the respective sleep laboratories.

9.2.2 ANNE™ Sleep procedures

After PSG equipment is applied, the ANNE™ Sleep will be applied on the subject by the principal investigators (PIs) or study coordinators.

1) The PI or study coordinator will ensure the ANNE™ Sleep sensors are functional and collecting data properly. The study coordinator will provide instructions for use of the ANNE™ Sleep system to the sleep technician as well.

2) Place sensors on subjects

    The subject should expect the following ANNE™ Sleep procedures to be conducted by the PI or study coordinator:

    a) Using IPA alcohol wipes, the areas on the skin where the sensors will be placed will be wiped down thoroughly to remove any dirt, oils, etc. IPA alcohol wipes will be used to clean the surface of the sensors before placement. If necessary, the chest may be shaved to provide better adhesion and comfort of the sensor.
    b) A single use adhesive will be applied to the chest sensor and placed on the subject's chest at the suprasternal notch (see Figure 2). When the chest sensor is placed, an over the sensor adhesive will be applied around the sensor as well to enhance the adhesion of the sensor to the subject. The limb sensor will be attached to the subject's finger using a single-use adhesive (see Figure 2).

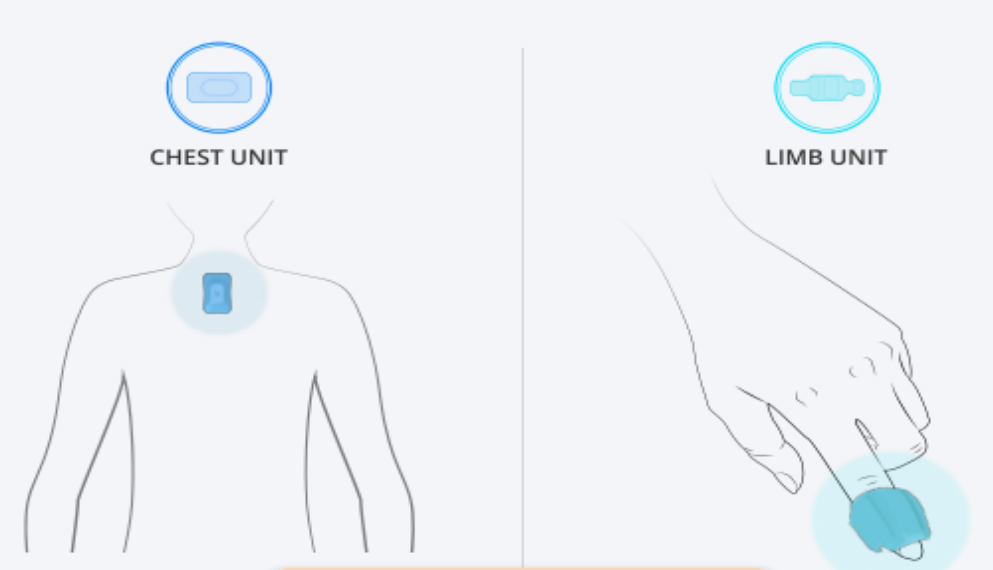

Figure 2. Placement of the ANNE™ chest and limb sensors

3) Photographs of the ANNE™ Sleep sensors on the subjects will be obtained in-person at the time of the PSG study to demonstrate and document the location of the ANNE™ Sleep sensors. Photographs will be taken by research personnel with a research-dedicated mobile phone. Photographs will not include the patients face or identifying features. All photographs will be stored on a secure server maintained by the study team and will be labeled with a unique subject study number.

4) Set up a mobile device with an ANNE Sleep application

   a) The ANNE™ Chest and ANNE™ Limb sensors are paired with the ANNE Sleep mobile application by following the instructions on mobile device
   b) After checking that the sensors are placed correctly and the signal quality is adequate, subjects will then proceed to sleep.

5) Data collection and storage

   a) After a full night of data collection, data will be collected through the ANNE Sleep application by downloading the data from the sensor through Bluetooth.
   b) The data will be uploaded automatically to ANNE™ Hub, a secure data repository from the application, and will be associated with the subject ID.
   c) The data will be stored in an EDF data format for further analysis.

9.2.3 Completion of PSG/ANNE Sleep Study

(1) After completing data collection, subjects will complete their sleep diary (**Appendix D**) and be given surveys (**Appendix E**) to complete in print material or by email link via REDCap.

(2) Once the surveys are complete, the study coordinator will let the subject know that their participation is complete. A compensation gift card will then be mailed to the subject's home address or given to them in-person.

(3) After completing the PSG/ANNE™ Sleep study night, the study coordinator will have a phone call with the subject or discuss in person to confirm testing was successful and address any issues if needed.

After review of sleep technician's report, study coordinator will send out risk letter to subject if applicable. Study physician will review study and/or follow-up with subject's physician regarding critical values as medically necessary.

9.2.4 Checklist for scheduled events

The study coordinator should review the schedule of events, summarized below:

	Initial Visit Day: Screening/ Enrollment	PSG/ANNE™ Sleep night	End of Study*
Eligibility	X		
Consent	X		
Demographics, Medical Hx and Sleep Survey	X		
ANNE™ Sleep		X	
PSG		X	
Photos of ANNE™ Sleep on Subject		X	
Sleep Diary			X
Phone follow-up (which may occur up to 1 week after the study)			X
Usability Survey			X
Adverse Events		X	X

* Immediately following the PSG test night

10. SCORING

10.1 PSG Scoring

The data from PSG will be reviewed and scored for sleep staging and respiratory events by 3 registered polysomnography technicians (RPSGT) who are blinded to the experimental condition, the scoring of the ANNE™ sleep system, and represent scorers in clinical practice in AASM accredited sleep disorder centers. In order to minimize interscorer variability, the technicians will have >85% concordance and to ensure quality and reproducibility, a board certified sleep medicine physician who is blinded to the experimental condition will review all raw PSG data If AHI determined from PSG do not meet the 85% concordance between three RPSGTs, a board-certified sleep medicine physician will provide the final determination of the AHI.

Scoring of PSG data will follow guidelines established by the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events (v2.6)[6]. Sleep scoring includes the following variables: clock time (hr:min) of lights off and lights on; total recording time (TRT= duration in minutes from lights off to lights on); total sleep time (TST= time in minutes spent in sleep stages N1 + N2 + N3 + REM); sleep latency (SL= time in minutes from lights off to the first epoch of any sleep stage); REM latency (time in minutes from lights off to the first epoch of REM sleep); wake after sleep onset (WASO= duration in minutes of TRT minus TST minus SL); sleep efficiency (SE= TST/TRT*100%); time in minutes in each sleep stage (N1, N2, N3 and REM sleep); percentage of time spent in each sleep stage (time in minute in each stage/TST *100%). Arousal events are quantified as total number of arousals and as arousal index (AI= number of arousals x 60/TST). The scoring of respiratory events to evaluate for sleep disordered breathing will also follow AASM scoring rules. The thermistor will be used for scoring apneas, and the pressure transducer and pulse oximetry will be used for scoring hypopneas. Chest and abdominal belts will be used to determine apnea type.

The apnea-hypopnea index (AHI) will be calculated in ranges of 15–30 apnea/hypopnea events per hour for moderate OSA and ≥30 apnea/hypopnea events per hour for severe OSA. The oxygen desaturation index (ODI), the hourly average number of desaturation episodes, will also be calculated based on similar criteria.

An apnea event is defined when BOTH of the following criteria are met:

- There is a drop in the peak signal excursion by ≥90% of pre-event baseline using an oronasal thermal sensor (diagnostic study), PAP device flow (titration study) or an alternative apnea sensor (diagnostic study).
- The duration of the ≥90% drop in sensor signal is ≥10 seconds

Hypopnea is defined when ALL of the following criteria are met:

- The peak signal excursions drop by ≥30% of pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative hypopnea sensor (diagnostic study).
- The duration of the ≥30% drop in signal excursion is ≥10 seconds.
- There is a ≥4% oxygen desaturation from pre-event baseline.

AHI will be calculated manually by its standard formula—AHI = apneas + hypopneas * 60/TST).:

$$\frac{\textbf{\textit{Total Number of Apnea Events}} + \textbf{\textit{Total Number of Hypopnea Events}}}{\textbf{\textit{Total Number of Minutes Asleep}}} \times \mathbf{60}$$

10.2 ANNE™ Sleep Scoring

The data from ANNE™ will be reviewed and scored for respiratory events by 3 registered polysomnography technicians (RPSGT) who are blinded to the scoring of the PSG, and represent scorers in clinical practice in AASM accredited sleep disorder centers. An average will be taken of the three scores. In order to minimize interscorer variability, the technicians will have >85% concordance and to ensure quality and reproducibility, a board certified sleep medicine physician who is blinded to the experimental condition will review all raw PSG data. If AHI determined from ANNE™ Sleep exhibits greater than 20% difference between three RPSGTs, a board-certified sleep medicine physician will provide the final determination of the AHI.

Scoring of ANNE™ Sleep data will follow guidelines established by the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events (v2.6)[6]. Sleep scoring includes the following variables: total recording time (TRT= duration in minutes from sensor activation to sensor disconnection). The scoring of respiratory events to evaluate for sleep disordered breathing will also follow AASM scoring rules.

The ANNE™ Sleep will be scored similarly with the system's onboard sensors as an alternative hypopnea and apnea sensor via PAT. The definition of mild, moderate, or severe obstructive sleep apnea is based on AHI.

- AHI < 5: Normal
- AHI ≥ 5 – <15: Mild
- AHI ≥15 – <30: Moderate
- AHI ≥ 30: Severe

The AHI calculated from ANNE™ Sleep will be considered an estimation of AHI, coined as Sibel-AHI.

An apnea event is defined as:

- A drop in peak signal excursion by ≥ 90% of pre-event baseline for ≥ 10 seconds using an oronasal thermal signal, PAP device flow, or an alternative apnea sensor.
- No requirement for a desaturation or an arousal

Hypopnea will be defined by:

- The peak signal excursions drop by ≥30% of pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative hypopnea sensor (diagnostic study)
- The duration of the ≥30% drop in signal excursion is ≥10 seconds
- There is a ≥4% oxygen desaturation from pre-event baseline and/or the event is associated with an arousal

The scoring of respiratory events to evaluate for sleep disordered breathing will also follow AASM scoring rules. Apnea-hypopnea index will be used to determine the presence and severity of sleep apnea (AHI= apneas + hypopneas *60/TRT).

The accuracy (sum of the number of true positives and true negatives divided by the sum of the number of true positives, true negatives, false positives, and false negatives), sensitivity,

specificity, positive predictive value, and negative predictive value of the ANNE™ Sleep to detect moderate to severe obstructive sleep apnea will be compared to outputs from PSG.

11. STATISTICAL ANALYSIS

11.1 Determination of Sample Size

The sample size determination is based on the primary endpoint of determining the ANNE™ Sleep system's diagnostic test characteristics (sensitivity and specificity) when compared to the gold standard, PSG for AHI. The calculations are based on parameters derived from a pilot program conducted in a similar patient population of subjects (n=46) who self-reported symptoms of OSA based on the STOP-BANG questionnaire. In this program, an overall prevalence of moderate to severe sleep apnea was 58%. We assume that the patient population from which this current study will be recruited will have a similar burden of moderate to severe OSA. We assume the prevalence to be 50% given that broader community outreach may reduce the total prevalence of moderate to severe OSA in our final cohort. For the primary objective, we will compare the sensitivity, specificity, positive predictive value, and negative predictive value of ANNE™ Sleep against the gold standard of diagnosis, the PSG for the diagnosis of moderate to severe OSA.

11.2 Power Calculation

Power Calculation Assumptions for Primary Endpoint of Sensitivity:

- Prevalence of moderate to severe OSA in the population = 50%
- H0: sensitivity of 80%
- HA: sensitivity of 90%

A total of approximately 214 subjects may be recruited to complete the study. A minimum sample size of 164 subjects will be required to achieve a minimum power of 80% (actual power = 80.6%) in order to detect a change in the percentage value of sensitivity greater than or equal to 0.80, based on a target significance level of 0.05.

Power Calculation Assumptions for Primary Endpoint of Specificity:

- Prevalence of moderate to severe OSA = 50%
- H0: specificity of 80%
- HA: specificity of 90%

A minimum sample size of 164 subjects will be required to achieve a minimum power of 80% (actual power = 80.6%) in order to detect a change in the percentage value of specificity greater than or equal to 0.80, based on a target significance level of 0.05. Assuming a PSG and/or ANNE™ Sleep failure rate of 10% of study subjects, the target sample size is 181.259 E.. Erie, Lavin,

The power analysis was conducted in the statistical software PASS v15.0.11 following established statistical references.[9-12]

11.3 Disposition of Subjects

Disposition status of the enrolled patients (Full Analysis Set) will be summarized using frequencies and percentages. Frequency and percentage of FAS patients with full follow-up will be reported, as well as patients with early withdrawal from the study, and the related reasons.

The following disposition status for subjects will be summarized overall and by group:

1) Number and percentage of subjects in each FAS and per protocol analysis set (PPAS) analysis population
2) Number and percentage of subjects who completed the study/withdrew from the study (and reasons for premature discontinuations)

Analysis Sets

Two analysis sets will be created for study purpose:

Full Analysis Set (FAS). FAS includes all enrolled subjects (those who signed the informed consent and who satisfied the eligibility criteria). FAS will be used for subjects' disposition, population description, and for Safety analysis.

The PPAS is a subset of the FAS, restricted to subjects who adhere to the protocol and complete the PSG sleep night and ANNE sleep night concurrently without technical failures. The PPAS will be used for the performance analyses. The PPAS will serve as the primary analysis for the performance endpoints. If the FAS population is different from the PPAS population, then the analyses will be repeated for the FAS population.

11.4 General Methodology

Continuous variables will be summarized using tables of descriptive statistics: number of patients with recorded observations, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized using counts and percentages. Descriptive statistics will be presented by diagnosis and clinical center. Diagnostic outcomes will be tabulated and compared for ANNE™ Sleep vs PSG.

11.5 Exploratory measurements for research purposes

Additional statistical analyses will be performed to compare outputs of AHI between the different systems. Specifically, these analyses include:

1) Evaluation of the predictive value of the ANNE™ Sleep system to differentiate obstructive vs central apnea events using the system's onboard sensors
2) Linear regression to establish correlation between AHI determined by ANNE™ Sleep vs PSG on the same night
3) Bland-Altman plots will be created to establish bias and 95% confidence intervals of agreement between AHI determined by ANNE™ Sleep and PSG.
4) Summary statistics of the sensitivity, specificity and accuracy of the classification of the severity of OSA (normal, mild, moderate, and severe OSA) determined by AHI between PSG vs ANNE™ Sleep.

5) Accuracy analysis between AHI determined by ANNE™ Sleep vs AHI determined by PSG on the same night.
6) Descriptive analysis of patients' characteristics and assessments (e.g. sleep diary) before and after study procedures. Patient characteristics include age, gender, ethnicity, race, height, weight, baseline vital signs, relevant medical and surgical co-morbidities will be abstracted from the medical record or by direct survey of the participants. (**Appendix I**)
7) Descriptive and comparative analysis of safety parameters related to between ANNE™ Sleep and PSG.

Parameters ascribed to the safety of patients will be summarized by diagnosis and clinical center. All available data from patients who fail to complete this study will be included in all safety summaries. Accuracy analysis will be run to provide % of agreement (overall, positive and negative agreement) between both procedures, p-value and 95% confidence interval. Correlation analysis (between two quantitative parameters) will be run: Pearson coefficient, p-value and 95% confidence interval will be calculated.

For other analyses:

- Continuous variables will be summarized using descriptive statistics, specifically the mean, standard deviation, median, minimum and maximum. Comparison of continuous parameters between two groups will be performed using T-test or Wilcoxon Mann-Whitney U test, or Wilcoxon signed rank test (non-parametric) for paired data, as appropriate.
- Categorical variables will be summarized using frequencies and percentages, and compared between two groups using Chi-Square or Fisher exact test, or Mac Nemar Chi-square test for paired data, as appropriate.
- Subject disposition and follow-up, as well as demographic and baseline characteristics of patients, or to any questionnaire will be described for each clinical center in the follow up phone call within 1 week of completing the study.

11.6 Data Analysis Presentation

All data analysis will be performed by HealthCore Inc. Statistical programming and analyses will be performed using SAS Version 9.4 or higher. Raw data (i.e., minimum and maximum values presented for range in continuous variables) will be reported out to the precision with which it was collected. Means will be reported to 1 decimal place more than the raw data. SD will be reported to 1 decimal place more than the mean. Percentages will be reported to 1 decimal place. Trailing zeros will be presented to maintain a consistent level of precision, e.g. 2.0 rather than 2. All p-values will be rounded to 3 decimal places. If a rounded p-value is 0.000 (i.e., the actual p-value is less than 0.0005), then the p- value will be presented as 'p< 0.001.'

The listings, specifically adverse events and major protocol deviations, will be ordered by site, subject and visit as applicable, unless otherwise stated.

11.6.1 Center Pooling

Descriptive statistics will be presented by diagnosis and clinical center. Parameters ascribed to the safety of patients will be summarized by diagnosis and clinical center.

11.6.2 Handling of Missing Data and Dropouts

Missing data will not be imputed and excluded from calculations. A summary of missing data will be provided according to the number of subjects, the time points where the data are missing and the clinical center. For each clinical center, number and percent of subjects with no missing data will be presented in tabular form. All final variables will undergo assessments of missingness to ensure that there is no systematic pattern of missing data.

11.6.3 Major Protocol Deviations

Major protocol deviations will be summarized by type (e.g. informed consent, inclusion or exclusion criteria error, unreported serious adverse events (SAEs), treatment violation, study visit not per protocol, other). In addition, any patient-specific protocol deviations will be listed for each subject. Each individual site will record protocol deviations.

11.6.4 Adjustments for Multiple Comparisons

No adjustment will be made.

11.6.5 Demographics and Baseline Characteristics

Patients' characteristics and other baseline data will be summarized (see section 11.3 General Methodology).

11.6.6 Primary Endpoint

Analysis of the primary endpoint will evaluate the accuracy of the ANNE™ Sleep system as a diagnostic aid of moderate to severe OSA via AHI derived from both systems based on the gold standard, PSG. Sensitivity is defined as the number of true positives divided by the sum of the number of true positives and the number of false negatives. Specificity is defined as the number of true negatives divided by the sum of the number of true negatives and the number of false positives. Positive predictive value (PPV) is defined as the proportion of people with a test result who actually have the disease: the number of true positives divided by the sum of the number of true positives and the number of false positives. Negative predictive value (NPV) is defined as the proportion of those with a negative test result who do not have the disease: the number of true negatives divided by the sum of the number of true negatives and the number of false negatives. Evaluation of the ANNE™ Sleep System as a diagnostic tool for moderate to severe OSA will be assessed based on the following criteria:

- A goal of sensitivity and specificity of greater than 80% in diagnosing moderate or severe OSA in comparison with the ANNE™ Sleep against PSG.
- PPV and NPV will be calculated along with 95% confidence intervals.

	PSG: AHI ≥15	PSG: AHI <15
ANNE Sleep: AHI ≥15	True Positive	False Positive
ANNE Sleep: AHI <15	False Negative	True Negative

11.6.7 Safety Evaluation

Adverse events should be assessed in terms of their seriousness, duration, intensity, and relationship to the study and use of the study device. All anticipated and unanticipated adverse events will be collected. Subjects will be able to contact the investigator at any time during the study if they note any change in their medical condition. The outcome of each adverse event will be observed and documented. Safety analysis, including adverse events and device deficiencies' incidence and description will be run on FAS only.

12. COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Subjects will receive $150 in gift cards for their time and effort. Compensation will be given to participants directly or mailed to the participant's home within 3 weeks after study completion (which includes participating in a PSG and wearing ANNE™ Sleep for one night and completing the diary and usability survey).

The cost of the PSG will be covered by the research study unless ordered as Standard of Care and approved by the study subjects' insurance provider. Participants will not be informed of the results of this research.

13. WITHDRAWAL OF PARTICIPANTS

Participants may end their participation at any time during the study. The study investigators may choose to withdraw a study subject if he or she is unable to use the devices or complete the survey and diary. The study investigators may withdraw a patient if they develop skin sensitivity or have a medical complication that precludes wearing of the sensors on the suprasternal notch.

If a subject is withdrawn from the study, they will be asked to return the study kit that is given to them at the start of the study. Unless specifically requested in writing, researchers will maintain and use data from patients that end their participation early.

14. RISKS TO PARTICIPANTS

Risk category: minimal

Potential risk: There is a risk of skin irritation or allergic reaction to the ANNE™ Sleep sensors. The devices will be placed on skin epidermis without conductive gel, thereby minimizing the risk of any skin irritation or allergic reaction. In addition, there will be no skin preparation except the use of a sterile alcohol pad (provided) to gently exfoliate the dead skin cells or dirt on epidermis. The adhesives have passed both biocompatibility, skin sensitization and cytotoxicity testing.

There is a risk of Protected Health Information (PHI) disclosure. Subject data will be de-identified and stored securely to prevent PHI disclosure.

Any adverse events during the PSG will be addressed by the sleep technicians in accordance with the sleep lab's standard procedure for handling adverse events. Any unique risks associated with the investigational sensors (as above) will be addressed by the study investigator and inform the sleep technicians of these risks prior to the PSG. The sleep technicians will be instructed to contact the study investigator if any skin irritation or allergic reactions occur. If significant, the study will be terminated and usual medical care will be provided.

Protection against risks: there is a high probability OSA subjects will be closely monitored by sleep technicians during their sleep study to avoid adverse events. The ANNE™ Sleep sensors will be removed if associated with significant discomfort or rash.

SURVEY/DIARY**:** Some questions may make subjects uncomfortable or upset. Subjects do not have to answer these questions if they do not want to.

15. ADVERSE EVENTS

The PI will determine whether adverse events are related to the study or unrelated to the study. The length of the study will be 1 night determined by the completion of the PSG night with the sensor concurrently. All serious adverse events – even if not deemed to be study-related – will be reported to the IRB. This includes a participant's death, life-threatening condition, hospitalization, or disability. All study-related adverse events determined by the PI as serious will be recorded and reported to the IRB and the sponsor within 1 business day. Serious study-related adverse events are defined as adverse skin effects that warrant prescription medical therapy, skin tears leading to bleeding or an open wound, or skin burns. Study-related adverse events will be recorded on the adverse event form. If participation is discontinued, the timing of this will be recorded. Adverse events or protocol deviations that will be reported include, but are not limited to the following:

- Skin related irritation or injury related to application or removal of the sensor.
- Any evidence of discomfort during device use will be recorded by observation and by interview of the subject.
- Human subjects research conducted without IRB approval.
- Research personnel do not obtain written consent or assent for a study when the IRB has determined that consent or assent is required. While no harm occurred, failure to obtain consent/assent is a violation of the research participant's rights.
- Enrollment of participants before IRB approval has occurred and/or after IRB approval has lapsed.
- Continued treatment of participants after IRB approval has lapsed without first obtaining permission from the IRB.
- PI enrolls a participant that does not meet all of the inclusion/exclusion criteria. The criteria that were not met puts the participant at risk of harm.
- Enrollment of children, prisoners, pregnant women and fetuses, without prior IRB approval.
- Use of an unapproved consent form.

- Use of unauthorized study personnel to conduct study procedures, obtain informed consent, or have access to identifiable participant information.
- Assessment for any inclusion/exclusion criterion was not done prior to beginning if study procedures. The criteria that were not evaluated prior to study procedures puts the participant at risk of harm.
- A procedure, treatment, or visit specified in the protocol is conducted outside of the required time frame and has clinical consequence; poses risk of harm to the subject or others; and/or is thought to be impactful to the scientific integrity of the study.

16. POTENTIAL BENEFITS TO PARTICIPANTS

There is no expected benefit for individuals participating in the OSA study. If a result is concerning, the subject will be notified via risk letter and/or study physician will follow-up with subject's physician if deemed medically necessary.

17. DATA MANAGEMENT AND PARTICIPANT CONFIDENTIALITY

Subject identifiable medical information obtained as a result of this study is considered confidential and disclosure to third parties other than the PI and the co-investigators is prohibited. All reports and communications relating to subjects in this study will refer to each subject only by their study identification number. Data generated as a result of this study are available for inspection on request by Food and Drug Administration or other government regulatory agency auditors, Sibel business partners specifically HealthCore, Inc. and the Institutional Review Board (IRB).

Subject identity will be protected through use of a coded list of identifiers which will be maintained separately from the data set. Source documents, questionnaires, and CRFs are kept in a secured area (in a locked cabinet in a locked room) and all electronic data is password protected so that only authorized personnel can have access. Photographs may be taken of the sensor on the suprasternal notch and finger for scientific and publication purposes only. Photographs and videos will be labeled only by subject identification number. All photos will be taken by research personnel with a research-dedicated phone and will be stored on a password protected server accessed by a password protected computer. Only authorized research personnel listed on the IRB protocol will have direct access to this data set, although there may be collaborative exchange of de-identified data with other research institutions for assistance in the analysis of raw data. De-identified sleep study raw data will be uploaded to a secure cloud-based platform, Sharefile, for use by Sibel study personnel.

Data stored and used for future research will be de-identified. Data will not be used for future research outside of the scope of this study.

17.1 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The Investigator and local site study personnel will be trained on case report form (CRF) completion and data entry into the REDCap system. The investigator is responsible for all entries in the CRF for completeness, accuracy and clarity. The investigator or designee should complete the CRF as soon as possible after the information is collected. The investigator is responsible to endorse all the information recorded in the CRF and will provide formal approval of the final submitted data.

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

17.2 CONSENT PROCESS (ALL PARTICIPANTS)

To protect participant confidentiality, we will conduct all research-related discussions and informed consent procedures in a private room. If a private room is not available, a designated area far enough away from other patients such that they cannot hear the conversation will be used. We will obtain written informed consent from the participant in English, using the IRB-approved consent form, prior to conducting any study procedure.

The consent process will be completed either in person or remotely by using an electronic consent document and collection of an electronic signature with REDCap or other electronic signature service like Adobe. The study coordinator will review the Informed Consent in person, by phone or in Zoom during the remote informed consent discussion.

The study procedures, risks, and benefits will be discussed and the study team will answer all questions prior to obtaining consent. The person performing the Informed Consent process, will ask questions of the study subject to confirm understanding and comprehension of the study. All versions of the consent forms will be approved by the relevant ethics committees prior to study initiation.

Eligible participants who do not wish to participate in this study will continue to receive care according to local clinical standards.

17.3 PARTICIPANT CONFIDENTIALITY

Study sites must keep original source documents in secured locations with access limited to approved study personnel or team members. Electronic documents will be stored in secure, encrypted servers maintained by the study site.

17.4 ADDITIONAL PRIVACY NOTE

This study is funded by Sibel Health. Sibel Health has a research collaboration with Anthem and its subsidiary companies, a U.S. based health insurer. This additional data privacy notice contains information on the transfer of de-identified health information to and use by Sibel Health and Anthem Health for internal research purposes or regulatory filings for FDA clearance.

17.5 PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

The following PHI will be collected, and is also listed on the consent form for study enrollment:

- All information in a medical record
- Results of physical examinations
- Medical history
- Patient demographics
- Patient address, phone number and email address

Entry of any data into a study site clinical record during the duration of the research study is also PHI that may be collected and listed in the consent form. PHI from the above categories may be obtained from the respective study sites and affiliated entities listed as study locations.
Any research information shared with outside entities during the study will not contain the name, address, telephone or social security number or any other personal identifier unless disclosure of the identifier is necessary for review by such parties or is required by law or study site policy except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigator's office.

18. MULTI-SITE RESEARCH

Study participants from external (non-Northwestern affiliated sites) may recruit potential study subjects by in person solicitation at the approved site by approved research personnel or investigators on the study. Study investigators may review their active patients to see if they meet enrollment criteria and invite them to participate in the study in person.

External study sites may create local recruitment or marketing materials and must have those materials reviewed and approved by the IRB prior to use.

Communication and responsibilities of each site are outlined in document (HRP-830) which is shared with each external site investigator. All sites will have the most current version of the protocol, consent document, and HIPAA authorization provided to them by the Lead Study Team. The Lead Study Team and sponsor of this study are responsible for communicating all study up-dates, will provide training, and ensure the completion of study training logs for external sites.

All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy and communicated to the lead study site and sponsor.

Data will be stored and de-identified locally at each study site. Data sharing and storage will follow local site policy and procedures specified in section 17. Data Management and participant confidentiality section in this protocol. Each study team is responsible for their study site data, de-identification of data and storage of study data in physically or digitally secure methods approved at each site. Local data may be transported within the site by approved research team members.

19. PROTOCOL DEVIATIONS

Any deviation from this protocol will be reported within 5 business days to the responsible IRB.

20. NON-ENGLISH SPEAKING PARTICIPANTS

Non-English speaking participants may be enrolled if the study team acquires an official translation of the approved informed consent form or performs consent with a translator and completes the accompanying short form in the participant's native language.

The research team will only enroll non-English speaking participants if a member of the study team is a fluent or native speaker of their language and assigned to them specifically. This is to ensure that continued support, clear communication and study training is possible for all study participants.

21. GOOD CLINICAL PRACTICE

The current study will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH-GCP), and the applicable regulatory requirements. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s) in accordance with GCP.

22. INSTITUTIONAL REVIEW BOARD (IRB)

All relevant documents for this study will be submitted to an appropriate Institutional Review Board (IRB) for review. A signed and dated letter documenting IRB approval must be obtained prior to entering participants at the site. IRBs must be constituted and their authority delegated through the institution's normal process of governance according to applicable regulatory requirements for each participating site. Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and relevant participant materials by an appropriate IRB. For each participating site, the protocol and associated informed consent and relevant participant materials will be submitted for approval to the local IRB, as per site local regulatory policies and procedures. The study will not commence at any site until initial approval is obtained from the designated IRB and an approval to enroll notification is released to the site.

The investigators must obtain approval from the IRB for all protocol amendments and, when warranted, changes to the informed consent document and/or participant materials. Protocol and

informed consent form amendments can be made only with the prior approval from the PI. The investigator may not implement any protocol deviation except where necessary to eliminate an immediate hazard to study participants, or when change(s) involve only logistical or administrative aspects of the trial, i.e., change of monitor(s) or telephone number(s) (ICH 4.5.2). The investigator shall notify the IRB of deviations from the protocol or serious adverse events occurring at the site.

23. REFERENCES

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APPENDIX A - PHONE RECRUITMENT SCRIPT

Hello, my name is _____ and I am a part of the research team at <insert site>. We are currently working on a research study with your physician and care team who provided us with your information or you have reached out to us after seeing our flyers about the study. We are currently working on a study which uses a wireless, wearable device to remotely diagnose sleep related breathing disorders at home.
Are you interested in speaking with me for a few minutes about this?

No? Okay thank you for your time!
Yes? Continue: Before we begin, I'd like to confirm that you're 22 years old or older and have recently been prescribed a Polysomnography (PSG) test or Home Sleep Test by your doctor. Are you currently pregnant, nursing, or planning to become pregnant in the next 6 months? Also, do you have any skin disorders on your chest or hands? Do you have a history of dementia?

No? I'm sorry. It is required that you must fall under these inclusion criteria and exclusion criteria in order to participate in this study. Have a nice day!
Yes? Great. The study entails wearing a small, flexible, wireless device on your chest and a small, flexible, wireless device wrapped around your finger. You will wear the device over one night during an in lab Polysomnography sleep test coordinated by our team. You will also be asked to complete a dairy and a survey on the usability of the sensors. This study pays $150. If you are interested, we will schedule approximately 1 hour to discuss the study in greater detail, show you the device, and set you up as a study participant.

Does this sound like something you are interested in participating?

No? That's perfectly okay. Thank you again for your time and if you change your mind, please feel free to call back at (your phone number).
Yes? That's great!

Recruitment instructions:

Remote: I can share the informed consent document with you electronically and I am available to review with you over the phone. Is now an okay time to send that and discuss?

Yes? Great, please confirm that <contact information> is correct and the best place to share this with you.

No? Ok, please let me know the best <contact information> to use for sharing this with you and when is a good time to review together.

If leaving a voicemail message:
Hello, this is <name> calling from <study site>. I am following up on an email that was sent to you about a paid, 1 night sleep study. If you are interested in hearing more about this research

volunteer opportunity please contact me at <contact number, email> or reply to the email sent to you about this study. Thank you!

APPENDIX B - EMAIL RECRUITMENT SCRIPT

Subject: Recruiting Volunteers for paid Sleep Study

The following is a letter letting you know about a research volunteer opportunity with <insert site name>. If you do not wish to be contacted to learn more about this or other research opportunities please reply to this email and state that you do not wish to be contacted.

Hello,
I am writing to tell you about a research volunteer opportunity at <insert site name>. You are being contacted because you have been or currently are a patient at <insert site name> or you have reached out to us after seeing our flyers about the study.

Who is this study for?
This study is for adults who may have Obstructive Sleep Apnea (OSA) and a Polysomnography Test (PSG) ordered by their doctor.

What is the study about?
The purpose of this study is to test a small wearable sensor that can monitor and evaluate people's health, detect sleep related respiratory problems, and to see how well it can find OSA compared to other kinds of tests.

What will you do if you participate?
If you qualify and decide to participate, you will be asked to:

Complete informed consent where we talk about the study in detail and then review how to use the sensors. The sensors are wireless, small, and soft devices that sticks to the skin with an adhesive or wraps around the finger. It is worn on overnight.

Participation in this study will involve minimal to no cost to you, and you will be paid for participating in this study for 1 day. Your participation is completely voluntary. You can leave the study at any time, and it will not be held against you, nor will it have an effect on the medical care you receive here at <insert site>.

What should you do if you are interested in participating?
Please compete go to this survey to see if you are eligible:

- <insert survey link>

If you would like to learn more about this study, you can contact the research team:

- <insert contact information>

A study coordinator will call you in the next week to tell you more about the study and answer any questions you may have. If you do not wish to be contacted, please call or email the contacts above.

Sincerely,

<Insert contact information>

APPENDIX C – PATIENT RECRUITMENT FLYERS

Flyer 1

Flyer 2

Flyer 3 (Facebook or other localized social media)

We are seeking volunteers to participate in a paid research study evaluating the accuracy of novel wireless sensors to help detect obstructive sleep apnea (OSA).

Subjects will be compensated for their participation.

STU0021444: ANNE Program for the Non-Invasive Evaluation of Apnea in Sleep (APNEAs)

APPENDIX D - STOP-BANG QUESTIONNAIRE

Snoring: Do you snore? Loud enough to be heard through closed doors or loud enough to disturb your partner?

Yes	**No**

Tired: Do you often feel tired, fatigued or sleepy during the daytime?

Yes	**No**

Observed: Has anyone observed you stop breathing, choking or gasping while you were sleeping?

Yes	**No**

Pressure: Are you being treated for high blood pressure?

Yes	**No**

Body Mass: What is your Body Mass Index (BMI)?

Height (in inches):

Weight (in pounds):

Less than 25		**Greater than 25**
Greater than 30		**Greater than 35**

Age: Are you older than 50?

Yes	No

Is your shirt collar 16 inches / 40 cm or larger?

Yes	No	Unknown

Gender: Are you male?

Yes	No

OSA - Low Risk: Yes to 0 - 2 questions

OSA - Intermediate Risk: Yes to 3 - 4 questions

OSA - High Risk: Yes to 5 - 8 questions

or Yes to 2 or more of 4 STOP questions + male gender

or Yes to 2 or more of 4 STOP questions + BMI > 35kg/m2

or Yes to 2 or more of 4 STOP questions + neck circumference 17 inches / 43cm in male or 16 inches / 41cm in female

Eligibility Screening questions:

Are you 22 or older?

Do you have significant cardiorespiratory disease including any of the following?

Chronic obstructive pulmonary disease (COPD)

Congestive Heart Failure

Atrial Fibrillation

Other (please describe)

Have you previously been hospitalized for cardiorespiratory issues?

-If yes, please describe.

Do you have an implanted pacemaker or defibrillator?

Do you use oxygen while sleeping?

Do you have respiratory muscle weakness due to neuromuscular condition?

Have you experienced awake hypoventilation or suspicion of sleep related hypoventilation (breathing at an abnormally slow rate)?

Have you used opioid medication for more than 3 months?

Have you ever had a stroke?

Do you have a history of severe insomnia?

Do you have a history of dementia?

Epworth Sleepiness Scale (ESS)Please rate how likely you are to doze or fall asleep in the following situations by selecting the response that best applies. If you have not done some of these activities recently, select what would most likely happen if you were in that situation.

Scale:

0: Never doze

1: Slight chance of dozing

2: Moderate chance of dozing

3: High chance of dozing

Activities:

Sitting and reading 0 1 2 3

Watching television 0 1 2 3

Sitting inactive in a public place (eg, a theater or a meeting) 0 1 2 3

As a passenger in a car for an hour without a break 0 1 2 3

Lying down to rest in the afternoon when circumstances permit 0 1 2 3

Sitting and talking to someone 0 1 2 3

Sitting quietly after a lunch without alcohol 0 1 2 3

In a car, while stopped for a few minutes in traffic 0 1 2 3

Follow up enrollment questions:

What is the best phone number to reach you at?

What is your preferred email address?

What is the best time to contact you? (Day(s), time(s))

Are you fully vaccinated for Covid-19?

(2 weeks after their second dose in a 2-dose series, such as the Pfizer or Moderna vaccines, or 2 weeks after a single-dose vaccine, such as Johnson & Johnson's Janssen vaccine)

- Please indicate your preferred participation site (one in-person visit required for this study): Northwestern Medicine Center for Circadian and Sleep Medicine (676 N Saint Clair St, Chicago, IL 60611)
- Northwestern Medicine Central DuPage Hospital Sleep Health Center (25 N. Winfield Road, Winfield, IL 60190)
- Northwestern Medicine Grayslake Outpatient Center (1475 E. Belvidere Road, Grayslake, IL 60030)

APPENDIX E - SLEEP DIARY

ID/NAME:

	SAMPLE	
Today's Date	2/25/2021	
1. What time did you get into bed?	10:15 p.m.	
2. What time did you try to go to sleep?	11:30 p.m.	
3. How long did it take you to fall asleep?	55 min.	
4. How many times did you wake up, not counting your final awakening?	6 times	
5. In total, how long did these awakenings last?	2 hours 5 min.	
6a. What time was your final awakening?	6:35 a.m.	
6b. After your final awakening, how long did you spend in bed trying to sleep?	45 min.	
6c. Did you wake up earlier than you planned?	☑ Yes ☐ No	☐ Yes ☐ No
6d. If yes, how much earlier	1 hour	
7. What time did you get out of bed for the day?	7:20 a.m.	
8. In total, how long did you sleep?	4 hours 10 min.	
9. How would you rate the quality of your sleep?	☐ Very poor ☑ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good
10. How rested or refreshed did you feel when you woke-up for the day?	☐ Not at all rested ☑ Slightly rested ☐ Somewhat rested ☐ Well-rested ☐ Very well-rested	☐ Not at all rested ☐ Slightly rested ☐ Somewhat rested ☐ Well-rested ☐ Very well-rested
11a. How many times did you nap or doze?	2 times	
11b. In total, how long did you nap or doze?	1 hour 10 min.	
12a. How many drinks containing alcohol did you have?	3	
12b. What time was your last drink?	9:20 p.m.	
13a. How many caffeinated drinks (coffee, tea, soda, energy drinks) did you	2 drinks	
13b. What time was your last drink?	3:00 p.m.	
14a. Did you take any over-the counter or prescription medication(s) to help you sleep?	☑ Yes ☐ No	☐ Yes ☐ No
14b. If yes, list medication(s), dose, and time taken.	**Medication(s):** Relaxo-Herb **Dose:** 50 mg **Time(s) taken:**	**Medication(s):** **Dose:** **Time(s) taken:**
15. Comments (if applicable)	I have a cold	

APPENDIX F – PATIENT SURVEYS

APNEAS ANNE Sleep Sensor Survey

Subject #: _____ **Date: ____/_____/_____**

Thank you for participating in wearing the ANNE Sleep system. This survey helps researchers better understand your experience with wearing sensors and helps develop and improve them for future patients. Please provide one answer to each of the following questions. You can skip any questions you do not know the answer to or do not want to answer.

1. Overall, PSG was comfortable for me to sleep with:

☐ Strongly Agree	☐ Agree	☐ Neither agree or disagree	☐ Disagree	☐ Strongly Disagree

2. Overall, ANNE Sleep sensors were comfortable for me to sleep with:

☐ Strongly Agree	☐ Agree	☐ Neither agree or disagree	☐ Disagree	☐ Strongly Disagree

3. How quickly you fell asleep comparing to typical nights for you

☐ Much Slower	☐ Slower	☐ About the same	☐ Faster	☐ Much Faster

4. The ANNE Sleep Sensors would be more comfortable to wired sensors used in a PSG (sleep test) in the hospital

☐ Strongly Agree	☐ Agree	☐ Neither agree or disagree	☐ Disagree	☐ Strongly Disagree

5. The **application** of the ANNE Sleep Sensors was easy and comfortable.

☐ Strongly Agree	☐ Agree	☐ Neither agree or disagree	☐ Disagree	☐ Strongly Disagree

6. The **removal** of the ANNE Sleep Sensors was easy and comfortable.

☐ Strongly Agree	☐ Agree	☐ Neither agree or disagree	☐ Disagree	☐ Strongly Disagree

7. Using wireless ANNE Sleep Sensors would be easy to do at home.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐ Strongly Disagree

8. Please describe how the **wireless Chest sensor** felt while sleeping.

☐ Very uncomfortable ☐ Uncomfortable ☐ No change ☐ Comfortable ☐ Very comfortable

9. Please describe how the **wireless Limb sensor** felt on your finger while sleeping.

☐ Very uncomfortable ☐ Uncomfortable ☐ No change ☐ Comfortable ☐ Very comfortable

10. Please indicate if you experienced the following while wearing the **wireless sensors**:

☐ Redness ☐ Irritation ☐ Both ☐ None

11. Having my sleep data collected at home and sent to my doctor would be more convenient for me.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐ Strongly Disagree

12. I could see myself using ANNE Sleep at home to monitor my breathing while I sleep.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐ Strongly Disagree

13. Please provide any other thoughts about the concerns or benefits of wireless monitoring:

APPENDIX G - INFORMED CONSENT FORM (ICF) <See separate document>

APPENDIX H - STUDY KIT CLEANING INSTRUCTION

Study sensors are reusable after completion of study procedures and data collection. Used study kit containers will be wiped on the outside using Sani-Cloth before handling and placed in a fume hood labeled “Contaminated Study Kits” in accordance with the study protocol.

The following procedures will be conducted by a research assistant from the study sites:

1. The researcher assistant is to wear appropriate PPE including lab coat, and nitrile gloves before handling any study supplies.
2. The fume hood labeled “Contaminated Study Kits” will have all surfaces cleaned and wiped down with Sani-Cloth and/or 70% EtOH solution.
3. The outside of study kit containers will be cleaned and wiped down with Sani-Cloth and/or 70% ETOH solution.
4. Once all used study kits are cleaned on the outside they may be opened, one at a time, to have contents cleaned. All study sensors, devices, chargers, cords and accessories will be wiped with Sani-Cloth and allowed 2 minutes to air dry on a cleaned surface.
5. Sensors will be closely examined for physical breaks, holes or tears in the silicone packaging. Any sensors that have physical damage will be sealed in separate plastic containers or plastic bags and labeled for return to the manufacturer.
6. Do not reuse towelette. Dispose of used Sani-Cloth in trash.
7. Individually wrapped, sealed adhesives may be cleaned in the same process.
8. Unsealed adhesives will be discarded along with any printed materials from the study kit.
9. Once all contents of the study kit have been removed from the container, inside of study kit containers will be cleaned and wiped down with Sani-Cloth and/or 70% EtOH solution. Allow to air dry for 2 minutes.
10. Return study kit contents to the study container.
11. The fume hood with Contaminated Study Kits will have all surfaces cleaned and wiped down with Sani-Cloth and/or 70% EtOH solution.
12. Cleaned study kits may be placed in the “Clean Kits” designated area for reuse.

APPENDIX I – DEMOGRAPHIC, MEDICAL HISTORY AND SLEEP SURVEY

Field Label	Choices, Calculations, OR Slider Labels
In order to ensure that this research serves all people living in the U.S., we need to ask you how identify your ethnic and racial background. This information will remain confidential, and will not affect your participation in the study in any way. It will only be used for reporting general demographics or statistics. **The following questions are about your demographic background:**	
Gender	1, Male | 2, Female
Race:	1, American Indian or Alaska Native | 2, Asian | 3, Native Hawaiian or Pacific Islander | 4, Black or African American | 5, White | 6, More than once race | 7, Choose not to answer
Ethnicity:	1, Hispanic or Latino | 2, Non-Hispanic or Latino | 3, Choose not to answer
Highest Education Level completed:	1, Never attended school or only attended kindergarten | 2, Grades 1 through 8 (Elementary) | 3, Grades 9 through 11 (Some high school) | 4, Grade 12 or GED (High school graduate) | 5, College 1 year to 3 years (Some college or technical school) | 6, College 4 years of more (College graduate)
Current Marital Status:	1, Married | 2, Single | 3, Widowed | 4, Divorced/Seperated | 5, Domestic partner
Current Employment Status:	1, Employed | 2, Unemployed | 3, Retired | 4, Retired due to disability
The following questions are about your Health:	
Date of last medical exam:	
Primary Care Provider:	
Primary Care Provider Address:	
Primary Care Provider Phone Number:	
Sleep Provider:	
Location:	1, Northwestern Memorial Hospital (Downtown) | 2, Carle Hospital | 3, Northwestern Lake Forest Hospital | 4, Central DuPage Hospital (CDH) | 5,

	Northwestern Medical Group (NMG)
Height:	
Weight:	
Are you currently diagnosed or do you have a history of any cardiovascular disorders?	
Please select all that apply:	1, Hypertension (high blood pressure) | 2, Congenital heart disease (malformations of heart structure existing at birth) | 3, Arrhythmia (abnormal heart rhythm) | 4, Coronary artery disease (narrowing of the arteries) | 5, Deep vein thrombosis (blood clot in lower extremities) | 6, Pulmonary embolism (blood clot in the lungs) | 7, Heart attack | 8, Heart failure | 9, Cardiomyopathy (heart muscle disease) | 10, Other
If other, please explain:	
If you selected any of the above disorders, please include dates of diagnosis and current status (ongoing or resolved). If resolved, please include end date:	
Are you currently diagnosed or do you have a history of any pulmonary or respiratory system disorders?	
Please select all that apply:	1, Asthma | 2, Chronic Obstructive Pulmonary Disease (COPD) | 3, Chronic Bronchitis | 4, Lung Cancer | 5, Pneumonia | 6, Emphysema | 7, COVID-19 | 8, Plueral Effusion (collection of fluid between the lung and chest wall) | 10, Other
If other, please explain:	
If you selected any of the above disorders, please include dates of diagnosis and current status (ongoing or resolved). If resolved, please include end date:	
Are you currently diagnosed or do you have a history of any gastrointestinal (GI) disorders?	
Please select all that apply:	1, Acid reflux | 2, Heartburn | 3, GERD | 4, Crohn's disease | 5, Ulcerative colitis | 6, Irritable Bowel Syndrome (IBS) | 7, Peritonitis | 8, Fibrosis adn cirrhosis of liver | 9, Cholecystitis | 10, Other
If other, please explain:	
If you selected any of the above disorders, please include dates of diagnosis and current status (ongoing or resolved). If resolved, please include end date:	
Are you currently diagnosed or do you have a history of any endocrine system disorders?	
Please select all that apply:	1, Hyperthrodism | 2, Hypothyroidism | 3, Throtoxicosis | 4, Hypoparathyrodism | 5, Type I Diabetes | 6, Type II Diabetes | 7, Adrenal disorder | 8, Cushing's syndrome | 10, Other
If other, please explain:	
If you selected any of the above disorders, please include dates of diagnosis and current	

status (ongoing or resolved). If resolved, please include end date:	
Are you currently diagnosed or do you have a history of any neurological disorders?	
Please select all that apply:	1, Dementia | 2, Huntington's Disease | 3, Parkinson's Disease | 4, Alzheimer's Disease | 5, Bell's Palsy | 6, Cerebral Aneurysm | 7, Epilepsy or Seizures | 8, Fibromyalgia | 9, Amyotrophic Lateral Sclerosis (ALS) | 10, Other
If other, please explain:	
If you selected any of the above disorders, please include dates of diagnosis and current status (ongoing or resolved). If resolved, please include end date:	
Are you currently diagnosed or do you have a history of any sleep disorders?	
Please select all that apply:	1, Insomnia | 2, Restless Leg Syndrome | 3, Parasomnia | 4, Sleep Apnea (confirmed diagnosis) | 5, Narcolepsy | 10, Other
If other, please explain:	
If you selected any of the above disorders, please include dates of diagnosis and current status (ongoing or resolved). If resolved, please include end date:	
Are you currently diagnosed or do you have a history of any psychiatric or psychological disorders?	
Please select all that apply:	1, Bipolar disorders | 2, Depression | 3, Anxiety | 4, Post-traumatic stress disorder (PTSD) | 5, Schizophrenia | 6, Personality disorders | 10, Other
If other, please explain:	
If you selected any of the above disorders, please include dates of diagnosis and current status (ongoing or resolved). If resolved, please include end date:	
Are you currently diagnosed or do you have a history of any lymphatic or hematologic disorders?	
Please select all that apply:	1, Lymphedema | 2, Hodgkin's Lymphoma | 3, Non-Hodgkin's Lymphoma | 4, Anemia | 5, Sickle cell | 6, Leukemia | 10, Other
If other, please explain:	
If you selected any of the above disorders, please include dates of diagnosis and current status (ongoing or resolved). If resolved, please include end date:	
Are you currently diagnosed or do you have a history of any skin or dermatological disorders?	
Please select all that apply:	1, Acne | 2, Hives | 3, Rosacea | 4, Eczema | 5, Psoriasis | 6, Melanoma | 10, Other
If other, please explain:	

If you selected any of the above disorders, please include dates of diagnosis and current status (ongoing or resolved). If resolved, please include end date:	
Are you currently diagnosed or do you have a history of any musculoskeletal disorders?	
Please select all that apply:	1, Carpal tunnel | 2, Arthritis | 3, Osteoporosis | 4, Tension Neck Syndrome | 5, Tendonitis | 6, Broken bone | 7, Tendon or Ligament Sprain | 8, Torn Rotator Cuff | 9, Ruptured or Herniated Disc | 10, Other
If other, please explain:	
If you selected any of the above disorders, please include dates of diagnosis and current status (ongoing or resolved). If resolved, please include end date:	
Do you have a history of any allergies? This can include seasonal, skin, food, or drug/medicine allergies.	
Please list allergies here, including start dates and current status (ongoing or resolved). If resolved, please include end date:	
Do you have a history of any other medical illness?	
The following questions are about your sleep last night (before study visit).	
Please list all other medical illnesses here, including start dates and current status (ongoing or resolved). If resolved, please include end date:	
2. Did you wear CPAP Device last night?	
If yes, level of titration:	
3. What time did you go into bed? {time_in_bed}	
4. What time did you try to go to sleep? {time_sleep} {ampm}	
	1, AM | 2, PM
5. How long did it take you to fall asleep?	
6a. How many times did you wake up, not counting your final awakening?	
6b. In total, how long did these awakenings last?	
7a. What time was your final awakening?	
7b. After your final awakening, how long did you spend in bed trying to fall back asleep?	
7c. Did you wake up earlier than you planned?	
7d. If yes, how much earlier?	
8. What time did you get out of bed for the day? {time_up} {am_and_pm}	
9. In total, how long did you sleep?	
10. How would you rate the quality of your sleep?	1, Very poor | 2, Poor | 3, Fair | 4, Good | 5, Very good

11. How rested or refreshed did you feel when you woke up for the day?	1, Not at all rested | 2, Slightly rested | 3, Somewhat rested | 4, Well-rested | 5, Very well-rested
12a. How many times did you nap or doze?	
12b. In total, how long did you nap or doze?	
13a. How many drinks containing alcohol did you have?	
13b. What time was your last drink? {time_drink}{am_pm_2}	
14a. How many caffeinated drinks (coffee, tea, soda, energy drinks) did you have?	
14b. What time was your last drink? {time_coffee}{am_pm_3}	
15. Did you take any over-the-counter or prescription medication(s) to help you sleep?	
Type of medication:	
Dose:	
Time taken:	
Did you take any additional medications?	
Type of medication:	
Dose:	
Time taken:	
16. Comments, if applicable:	