# ANNE Vital Sign System Remote Sleep Assessment

# Remote sleep assessment in adults at risk for dementia using the ANNE Vital Sign System

## Protocol Number: *Sunnybrook Research Institute REB 5366*

## Version Number: 2.2 dated August 05, 2022

| | |
|---|---|
| **Principal Investigator:** | Dr. Andrew Lim |
| **Regulatory Sponsor:** | Sunnybrook Research Institute |
| **Funding Agency:** | Centre for Aging and Brain Health Innovation;<br>Canadian Consortium on Neurodegeneration in Aging |
| **Investigational Product:** | Advanced NeoNatal Epidermal (ANNE$^{TM}$) Vital Sign System |

## PROTOCOL SIGNATURE PAGE

I have read this protocol in its entirety and its appendices. I agree to comply with the requirements of the study protocol and procedures for data recording/reporting and acknowledge my responsibility for the well-being of each research participant, and to ensure that all persons involved in study activities are adequately informed about the protocol, the investigational product, and their trial-related duties. The signature below constitutes the agreement to conduct this study in accordance with the REB approved protocol, GCP and applicable regulatory requirements, including confidentiality, ethical guidelines and regulations regarding the conduct of research in humans.

Qualified Investigator:

Name:
*(Print)* _____

Title & Institution:
*(Print)* _____

Signature: _____

Date of signature:
*(yyyy-mmm-dd)* _____

# TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

The following abbreviations describe terms, documents and study personnel used in the conduct of this study protocol.

| | |
|---|---|
| AD | Alzheimer's Disease |
| AE | Adverse Event/Adverse Experience |
| AHI | Apnea Hypopnea Index |
| ANNE | Advanced NeoNatal Epidermal |
| BMI | Body Mass Index |
| CAPCR | Coordinated Approval Process for Clinical Research |
| CCNA | Canadian Consortium for Neurodegeneration in Aging |
| CCTS | Centre for Clinical Trial Support |
| CRF | Case Report Form |
| CT | Computed Tomography |
| CTU | Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia |
| DCF | Data Clarification FOrms |
| DSMB | Data and Safety Monitoring Board |
| DSPC | Data Sharing and Publications Committee |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| GCP | Good Clinical Practice |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICMJE | International Committee of Medication Journal Editors |
| IP | Investigational Product |
| ITA | Investigational Testing Authorization |
| LORIS | Longitudinal Online Research and Imaging System120 |
| MCI | Mild Cognitive Impairment |
| MoCA | Montreal Cognitive Assessment |
| MRI | Magnetic Resonance Imaging |
| NIH | National Institutes of Health |
| ODI | Oxygen Desaturation Index |

| | |
|---|---|
| pCRF | Paper Case Report Form |
| PHI | Personal Health Information |
| PI | Principal Investigator |
| PM | Product Monograph |
| QI | Qualified Investigator |
| RCT | Randomized Controlled Trial |
| REB | Research Ethics Board |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SC | Steering Committee |
| SFTP | Secure File Transfer Protocol |
| SOP | Standard Operating Procedure |
| SRI | Sunnybrook Research Institute |
| SUADR | Serious and Unexpected Adverse Drug Reaction |
| TMF | Trial Master File |

## PROTOCOL SUMMARY

| | |
|---|---|
| **Protocol Title (Short Title)** | Remote sleep assessment in adults at risk for dementia using the ANNE Vital Sign System |
| **Protocol Number** | 5366 |
| **Phase** | Initial Phase |
| **Study Design** | Prospective cohort study |
| **Study Duration** | 3 years |
| **Setting** | Home-based assessment of sleep apnea. |
| **Sample Size** | 750 |
| **Main Inclusion Criteria** | Enrolled participants in the Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia (CTU) and affiliated trials. All participants will be individuals ages 60-85 classified as **Not Dementia** according to Canadian Consortium for Neurodegeneration in Aging (CCNA) criteria and classified as being at increased risk of dementia. |
| **Primary Outcome(s):** | The primary objective of this study is to test the hypothesis that sleep apnea is associated with accelerated cognitive decline in older adults at risk for dementia |
| **Secondary Outcome(s):** | Sex-stratification will be used in analyses as appropriate. Qualitative feedback forms will be used to collect information about participant ease of use and experience with the ANNE Vital Sign System. |
| **Investigational Product and Planned Use** | The Advanced NeoNatal Epidermal (ANNE) Vital Sign System is a wireless remote monitoring system intended for use by researchers and healthcare professionals for continuous collection of physiological data in home and professional healthcare settings. The ANNE Vital Sign System integrates simultaneous synchronized ambulatory measurement of electrocardiography, photoplethysmography with derived pulse oximetry, pulse arrival time with derived beat-to-beat blood pressure, triaxial accelerometry, respiratory rate, and temperature, which would enable accurate measurement of sleep apnea. The ANNE Vital Sign System is non-invasive, flexible, easy to use, comfortable, and skin safe.<br><br>All individuals enrolled in CTU and affiliated trials will be eligible to complete the ANNE Vital Sign System sleep assessment unless excluded by an additional set of exclusion criteria specific to the ANNE Vital Sign System.<br><br>Recruiting sites for CTU and affiliated trials will refer potential participants to Sunnybrook Research Institute (SRI) to obtain |

| | |
|---|---|
| | informed consent and then prepare shipment of ANNE Vital Sign System and instructions to participant. After study device and associated materials are shipped to and received by the participant, study staff will instruct the participant on the proper application and use of the ANNE Vital Sign System over remote video-conference according to manufacturer recommendations. Participants will wear the sensors for 24 hours and this procedure will be completed at the Baseline visit and repeated at the Month 12 visit. |
| **Statistical Analysis:** | Cardiopulmonary data – .shrd file type – from the ANNE Vital Sign System will be downloaded locally by Sunnybrook Research Institute (SRI) who will convert to .edf file type, and manually annotate to extract information on sleep apnea. SRI will then upload de-identified, processed data to the Longitudinal Online Research and Imaging System120 (LORIS). All uploads and downloads will be by Secure File Transfer Protocol (SFTP). We will quantify the apnea hypopnea index (AHI), oxygen desaturation index (ODI), hypoxemia burden, and time with oxygen saturation below 90% (O2<90). Participants will be considered to have sleep apnea if their AHI is greater than or equal to 15. We will relate presence of sleep apnea to 1-year change in cognition measured using the Montreal Cognitive Assessment (MoCA), collected as part of CTU and affiliated trials. Sex-stratification will be used in analyses as appropriate. |

# 1 KEY ROLES AND CONTACT INFORMATION

| | |
|---|---|
| **Regulatory Sponsor:** | Sunnybrook Research Institute (SRI)<br>2075 Bayview Avenue<br>Toronto, ON Canada M4N 3M5 |
| **Principal Investigator:** | Dr. Andrew Lim<br>Associate Professor, Division of Neurology<br>Sunnybrook Health Sciences Centre<br>University of Toronto<br>2075 Bayview Ave – Room M1-600<br>Toronto, ON M4N 3M5<br>416-480-6100 x2461 (phone)<br>416-480-6092 (fax)<br>andrew.lim@sunnybrook.ca |
| **Co-Principal Investigator:** | Dr. Mark Boulos<br>Staff Neurologist, Division of Neurology<br>Sunnybrook Health Sciences Centre<br>University of Toronto<br>2075 Bayview Ave – Room A4-42<br>Toronto, ON M4N 3M5<br>416-480-4473 (phone)<br>416-480-5753 (fax)<br>Mark.boulos@sunnybrook.ca |
| **Academic Research Organization:** | Centre for Clinical Trial Support, SRI<br>2075 Bayview Avenue<br>Toronto, ON Canada M4N 3M5 |
| **DSMB/Medical Expert/Monitor:** | N/A |

# 2 INTRODUCTION

This study document is the protocol for research involving human participants. This study is to be conducted according to Canadian and international standards, and in compliance with the protocol, World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements and research policies.

## 2.1 Background

Over 500,000 Canadians are currently living with dementia and this is predicted to reach one million in the next two decades. With no effective cures, there is an urgent need to identify and treat causal risk factors. Sleep and circadian rhythm disruption, including sleep deprivation, sleep fragmentation, sleep apnea, and abnormal circadian rhythms, are common. In model organisms, they accelerate development of dementia-associated neuropathologies and accumulating evidence suggests that in older adults they may be associated with a greater risk of dementia and dementia-related structural brain changes.

Sleep apnea is characterized by recurrent episodes of absent (apneas) or reduced (hypopneas) airflow in sleep, accompanied by hypercarbia and hypoxemia, and terminated by arousal and resumption of normal breathing. Sleep apnea is common in adults with Alzheimer's Disease (AD) and other dementias. The prevalence of moderate sleep apnea (apnea hypopnea index (AHI) $\geq$ 15) in patients with mild AD is estimated at 68% and may be higher in moderate to severe AD. Moreover, a recent meta-analysis suggested that patients with AD have a five-fold increased odds of presenting with sleep apnea than adults with normal cognition.

The overall goal of this study is to test the hypothesis that sleep apnea is associated with accelerated cognitive decline in older adults at risk for dementia. We will measure sleep apnea and its cardiovascular consequences at baseline and 12 months later and relate this to cognitive function at the same time points. To achieve this, we will study participants enrolled in the Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia (CTU) and affiliated trials. The CTU is a Canada-wide study of older adults at risk for dementia, being undertaken by the Canadian Consortium on Neurodegeneration that will begin recruitment in May 2022. It, and affiliated trials, are anticipated to recruit 750 participants from May 2022-April 2024.

In clinical practice, sleep apnea is diagnosed using inpatient polysomnography. However, this is not feasible for many older adults. To overcome this barrier, we will utilize an investigational vital signs monitor – the Advanced NeoNatal Epidermal (ANNE) Vital Sign System (Sibel Inc., Evanston, IL, USA).

The ANNE Vital Sign System is a wireless remote monitoring system consisting of two flexible, soft, and skin-mounted electronic devices for use by researchers and healthcare professionals for continuous collection of physiological data in home and professional healthcare settings. The ANNE Vital Sign System integrates simultaneous synchronized ambulatory measurement of electrocardiography, photoplethysmography with derived pulse oximetry, pulse arrival time with derived beat-to-beat blood pressure, triaxial accelerometry, respiratory rate, and temperature, which would enable accurate measurement of sleep apnea. Indeed, in compelling in-laboratory

preliminary data, we show the capacity for the ANNE Vital Sign System to detect and characterize sleep apnea in older patients. The ANNE Vital Sign System is non-invasive, flexible, easy to use, comfortable, and skin safe.

A separate 8-site Canadian in-lab study of the ANNE Vital Sign System is already underway, with participants undergoing diagnostic polysomnography per usual care or in the context of existing research projects approved by an institutional ethics board. ANNE Vital Sign System has an approved Investigational Testing Authorization (ITA) for this in-lab study (ITA application number 319430, approved December 11, 2020).

CTU recruiting sites will refer potential participants to Sunnybrook Research Institute (SRI) to obtain informed consent and then prepare shipment of ANNE Vital Sign System and instructions to participant. After study equipment and materials are shipped to and received by the participant, study staff will instruct the participant on the proper application and use of the ANNE Vital Sign System over remote video-conference. Specifically, study staff will instruct the participant to attach the two sensors of the ANNE Vital Sign System according to manufacturer recommendations. Participants will wear the sensors for 24 hours before removing it themselves at home and shipping back to Sunnybrook Research Institute. This procedure will be completed at two time points: Baseline and 12 months later.

There are minimal known risks associated with the use of the ANNE Vital Sign System. This device is not intended to be used with defibrillation, magnetic resonance imaging (MRI), x-ray or computed tomography (CT), none of which apply to this protocol or CTU or affiliated trials. The ANNE Vital Sign System will not be used on individuals with known nickel allergies or implantable cardiac devices, and will only be used if there are no signs that the silicone shell or any other device components are damaged after shipment to the participant. Participants will be instructed on how to remove the device during the instructional video-conference in the event that the participant experiences excessive heat or discomfort from the device. An adverse event will be documented as per Section 8 of this protocol.

## 2.2 Preclinical Data

Electrical safety: As per the investigator's brochure or product monograph, the ANNE Vital Sign System sensors provides the full level of safety regarding electrical short, overheat and overcurrent during both charging and normal operation. In the electrical design aspect, the safety is offered by using two-level of battery protection through two different battery management IC (Bq25120 and Bq2970, Texas Instruments). Bq25120 is the power management IC in the sensor that basically controls the power delivery from the battery to each sensor component. The safety aspect from Bq25120 is from the charging phase. The charging profile is based on JEITA (industry’s charging standard) standard to comply with safety charging profile that minimizes heat generating during charging. In addition, the NTC (thermistor) connected next to battery checks the temperature of battery during charging at the same time, which defines 40 °C (104 °F) as the peak temperature and terminates charging if the temperature rises above this point. In addition, the safety timer set for 3 hours automatically terminates any current drain from the battery to avoid overcharging event that might create overheating. Bq2970 provides the safety feature for normal operation. It protects the battery from overcurrent and high discharge conditions, where it automatically terminates the connection to the battery if such events are observed. It also detects short-circuit condition and does the same termination event to prevent overheating of the battery.

The ANNE Vital Sign System sensors and wireless charger were evaluated for electrical safety and electromagnetic compatibility by an accredited independent laboratory (UL LLC, Northbrook IL) and found to be in compliance with applicable electrical safety requirements for IEC 60601-1 Edition 3.1 (2012) and with all EMC requirements specified in IEC 60601-1-2 (2014).

Thermal safety: With a high-fidelity thermal camera, we have evaluated the heat generation of the sensors after 24 hours of continuous operation. Negligible heat (<0.2 C) is produced by the sensor suggesting safe thermal load dissipation.

Adhesive safety: The chest adhesive is a silicone gel adhesive (Polymer Science, PS-1835 Silicone/Acrylic Roll) with conductive tape (Flexcon Omni-wave) and open cell foam (McMaster-Carr, Antistatic Super-Cushioning Foam PN 87035K62). The limb adhesive is a medical foam tape adhesive (3M 9780, Single Sided Blue Polyvinyl Chloride). Both adhesives comply with the requirements of ISO 10993-5 and ISO 10993-10.

Mechanical Testing: The sensor is designed to endure multiple mechanical deformation. We have evaluated and validated the sensor's robustness by 540 cycles of bending (radius at 2.5 cm), 180 cycles of tension (elongation by 15% in horizontal direction), 90 cycles of torsion (60 degrees), and 90 cycles of drop (at 1 meter above the ceramic ground) tests.

Electrical Reliability: The sensor's electrical reliability has been evaluated by 50 cycles of discharging and recharging event. The conditions for full-discharge and charge are confirmed by the calibrated multimeter at 2.9V and 4.2V, respectively. In addition, the sensor's over discharge protection has been validated for 90 days that the battery is not discharged further below to 2.9V.

## 2.3 Clinical Data to Date

The ANNE Vital Sign System has been shown to correlate well with gold-standard clinical sensors for the measurement of skin temperature, electrocardiogram (ECG), pulse oximetry, and blood pressure both in neonates and in adults.

In a validation cohort of n=13 adults, we achieve average root mean square differences of 0.93 beats per minute for heart rate, 1.5% blood oxygenation, and 1.3 breaths per minute compared to Philips Intellivue MP50 – a gold-standard FDA-cleared monitoring system. No adverse events were seen.

The ANNE Vital Sign System has been shown to correlate well with gold-standard SpO2 measurements and obstructive sleep apnea measurements, as below.

Sibel Health validated the accuracy of SpO2 measurements compared to blood gas analysis in n=12 healthy subjects over the range of 70-100% oxygen saturation according to Section 201.12.1 of ISO 80601-2-61 and Pulse Oximeters - Premarket Notification Submissions [510(k)s]: Guidance for Industry and Food and Drug Administration Staff, Issued March 2013. Enrolled subjects had skin tones varying from Fitzpatrick 2-5, with two subjects having darker skin pigmentation (Fitzpatrick 5). The average root mean square error (ARMS) was 2.31%, meeting the requirements of the above-mentioned standard.

Performance as a diagnostic aid for moderate to severe obstructive sleep apnea (OSA) in adults was evaluated compared to the gold standard, polysomnography (PSG), in a single-arm, open-label, multi-center clinical study with n=225 subjects that was conducted in the United States. Subjects were representative of the intended target population, including individuals 22 years of age or older who are suspected of having OSA. Subjects were 44% male and 56% female. Subjects were 73% white, 12% Black or African American, 9% Asian, 0.4% American Indian or Alaska Native, and 4% multi-racial. The results of the study indicate sufficient accuracy as an aid to the diagnosis of moderate to severe OSA, with a sensitivity and specificity of 90% and 98%, respectively, for the identification of moderate sleep apnea defined as an apnea hypopnea index of 15. Additionally, skin tolerance was assessed following removal of the chest sensor for n=184 patients. No evidence of increased breakdown or skin dryness was reported. No adverse events were reported during the study.

This performance exceeds that required for new physiological devices by the FDA. The following consensus standards and bench testing were used to evaluate safety and effectiveness:

- Electrical safety and electromagnetic compatibility testing according to ANSI/AAMI ES60601-1:2005/(R)2012 and IEC 60601-1-2:2014 standards. Electrical safety testing in the home healthcare environment per IEC 60601-1-11:2015.
- Safety and Performance testing of pulse oximeter per ISO 80601-2-61:2017.
- Biocompatibility testing according to ISO 10993-1:2018, ISO 10993-5:2009, and ISO 10993-10:2010 for new patient contacting materials.
- Wireless coexistence testing according to ANSI IEEE C63.27-2017.
- Software verification and validation testing according to IEC 62304:2015 and the FDA guidance document, Content of Premarket Submissions for Software Contained in Medical Devices.
- Shelf life testing of the adhesive to demonstrate safe and effective performance over the intended device life cycle.
- Bench testing to demonstrate the mechanical durability of the sensors.
- Usability testing in accordance with the FDA guidance document, Applying Human Factors and Usability Engineering to Medical Devices
- Performance testing of heart rate, body position, PAT, pulse rate, perfusion index, snore, total sleep time, and chest movement parameters.
- Performance testing to demonstrate the precision and repeatability of the system over multiple nights of sleep.
- Cybersecurity evaluation according to the requirements of the FDA draft guidance document, Content of Premarket Submissions for Management of Cybersecurity in Medical Devices
- Assessment of Software of Unknown Provenance per the FDA guidance document, Off-The-Shelf Software Use in Medical Devices

## 2.4 Potential Risks/Benefits and Rationale

The ANNE Vital Sign System has been tested and evaluated in >60 adults of a diverse demographic background in various clinical contexts. No adverse events were seen. No significant adverse skin events have been observed thus far in any of these subjects. To note,

adverse skin events are distinct from skin reactions. Skin reactions are defined by only transient erythema (redness) that dissipates within 1 hour of adhesive removal.

This study carries minimal risk and any adverse effects (e.g. skin irritation) are expected to be minor and subside in appropriate time. In the unlikely event of a significant adverse event or emergency, the study principal investigator will be available by telephone to advise and arrange the involvement of hospital acute care services (e.g. the ER) if deemed necessary. Further, if the principal investigator is not available for any reason, the co-principal investigator will assume this role.

# 3 STUDY OBJECTIVES

## 3.1 Primary Objective

The primary objective of this study is to test the hypothesis that sleep apnea is associated with accelerated cognitive decline in older adults at risk for dementia. We will measure sleep apnea at baseline and 12 months later and relate this to cognitive function at the same time points.

## 3.2 Secondary Objective(s)

Sex-stratification will be used in analyses as appropriate. Qualitative feedback forms (Appendix 1) will be used to collect information about participant ease of use and experience with the ANNE Vital Sign System.

# 4 STUDY DESIGN

## 4.1 General Design

The Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia (CTU) is a Canada-wide study of older adults at risk for dementia, undertaken by the Canadian Consortium on Neurodegeneration that will begin recruitment in May 2022 and is anticipated to recruit 750 participants from May 2022-April 2024. The main goal of the CTU study is to serve as a shared platform to support studies of technologies and interventions to prevent dementia. These sub-studies are able to share CTU resources for recruitment and outcome ascertainment.

Participants in CTU and affiliated studies will be invited to participate in the ANNE Vital Sign System sub-study. CTU recruiting sites will refer potential participants to Sunnybrook Research Institute (SRI) to obtain informed consent and then prepare shipment of ANNE Vital Sign System and instructions to participant. The informed consent process will be conducted according to sections 7.1 and 13.3 of this protocol. After study equipment and materials are shipped to and received by the participant, study staff will instruct the participant on the proper application and use of the ANNE Vital Sign System over remote video-conference. Specifically, study staff will instruct the participant to affix the ANNE Vital Sign System chest sensor to the participant's chest using electrode paste, the ANNE chest adhesive, and Tegaderm or similar. Study staff may ask participants to shave a 3"x2" section of their chest, but participants will be informed this is optional. Next, study staff will instruct the participant to affix the ANNE Vital Sign System finger sensor to the participant's non-dominant index finger using the ANNE limb adhesive. Participants will wear the sensors for 24 hours before removing it themselves at home and shipping back to Sunnybrook Research Institute using a pre-paid, pre-addressed package. This procedure will be completed at the Baseline visit and repeated 12 months later.

Cardiopulmonary data – .shrd file type – from the ANNE Vital Sign System will be downloaded via Bluetooth locally to an iOS tablet, then converted to .edf file type, and manually annotated to extract information on sleep apnea. SRI will then upload de-identified processed data and summary measures to the Longitudinal Online Research and Imaging System120 (LORIS) using the media uploaded functionality. All uploads and downloads will be by Secure File Transfer Protocol (SFTP).

LORIS is a web-based database solution for neuroimaging and other research data that is physically located at McGill University in Montreal. It will store data that has been processed to remove any direct identifiers of an individual study participant. Study subjects will be assigned a unique coded study identification number (LORIS Project Study Centre ID (PSCID)) that will be used to store their data. Local study sites will be responsible for storing all participant identifying information (name, contact, e-mail address) in secured encrypted databases and to maintain the master file that links the participant to their unique LORIS PSCID.

Study data may be sent to and received from investigators at other academic institutions for the research purposes explained in this protocol. Additionally, some study data may be shared with the device manufacturers to facilitate analyses in support of the academic aims above. Any study data about participants that is sent outside of the participating institution will have a code and will not contain name or address, or any information that directly identifies participants. All data transfer will be achieved through secured FTP, secure VPN or an encrypted hard drive.

## 4.2 Primary Outcomes/Endpoint(s)

We will quantify the apnea hypopnea index (AHI), oxygen desaturation index (ODI), hypoxemia burden, and time with oxygen saturation below 90% (O2<90). A participant will be considered to have sleep apnea if their AHI is greater than or equal to 15. In addition, we will quantify 24-hour resting heart rate, and average heart rate, which are important physiological consequences of sleep apnea.

As part of their participation in CTU, participants will undergo a Montreal Cognitive Assessment (MoCA) at baseline and after 12 months. We will relate the presence of sleep apnea to change in MoCA scores between baseline and 12 months using t-tests. We will then use mediation analyses to test if any observed associations are mediated by effects of sleep apnea on average and daytime resting heart rate.

## 4.3 Secondary Outcomes/Endpoint(s)

Sex stratification will be used in analyses as appropriate.

# 5 PARTICIPANT SELECTION AND WITHDRAWAL

All individuals enrolled in CTU and affiliated studies will be eligible to complete the ANNE Vital Sign System sleep assessment unless excluded by an additional set of exclusion criteria specific to the ANNE Vital Sign System. CTU recruitment is aiming to recruit 50% women to allow for later stratification of analyses to assess for sex differences.

## 5.1 Inclusion Criteria

The only inclusion criteria for this study is that participants must have consented and enrolled into a CTU affiliated study. There are no additional inclusion criteria. Individuals from CTU affiliated studies will be asked to confirm their enrollment in a CTU affiliated study as part of the informed consent process for this study.

For reference, inclusion criteria of CTU affiliated studies from which we will recruit may include, but are not limited to, the following list:

1. Ages 60-85

2. Sufficient proficiency in English or French

3. Technical ability to participate in remote assessments

4. Meets criteria for **No Dementia** and one of the following (according to CCNA Criteria):
    a. Cognitively Unimpaired
    b. Cognitively Unimpaired plus Subjective Cognitive Impairment
    c. Mild Cognitive Impairment (MCI)

5. **AND** Classified as being at **increased risk** of dementia based on **at least one of the following**:
    a. First-degree family history of dementia
    b. Self-Reported or documented current and/or history at midlife (45-60 years) of the following risk factors:
        i. Hypertension
        ii. Hypercholesterolemia
        iii. Body Mass Index > 30 kg/$m^2$
        iv. Physical Inactivity
        v. Insomnia
        vi. Vascular-metabolic risk

## 5.2 Exclusion Criteria

The exclusion criteria for this study are:

1. Known nickel allergy
2. Known cardiac implantable device
3. Known arrhythmias

4. Otherwise unable to use the sensors; for example, finger amputations

For reference, exclusion criteria of CTU affiliated studies from which we will recruit may include, but are not limited to, the following list:

1. Participants who, in the opinion of the investigator, are not able to complete trial procedures remotely or adhere to the schedule of study assessments.
2. Individuals where English or French is not sufficiently proficient for remote clinical assessment.
3. Individuals who do not have the technical ability. Technical ability is defined as having computer and internet access; ability to send and receive emails; ability to participate in remote assessments.
4. Individuals who have a clinical diagnosis of Dementia
5. Clinical Dementia Rating (CDR; telephone/video-conference administration) Score of $\geq$1 or having a diagnosis of dementia based on DSM-IV criteria
6. Total Score on the Montreal Cognitive Assessment (MoCA; video-conference administration) <13

## 5.3 Participant Recruitment

We anticipate recruiting 750 participants from CTU studies that meet the above criteria. We anticipate none of the CTU participants will be excluded from the ANNE Vital Sign System assessment based on the exclusions in section 5.2.

## 5.4 Participant Withdrawal and Discontinuation of IP

### *5.4.1 Reasons for Withdrawal/Discontinuation of IP*

Participants can choose to end their participation in this research (called withdrawal) at any time without having to provide a reason. If participants choose to withdraw from the study, they are encouraged to contact the study doctor or study staff.

Information that was recorded before participant withdrew will be used by the researchers for the purposes of the study, but no information will be collected after withdraw of participant permission. If participant would like information that was recorded before they withdrew not to be used by the researchers, they may submit a verbal or written request to the study staff and their data will not be used.

The study doctor may stop their participation in the study early, and without their consent, for reasons such as:

- Participant is unable to complete all required study procedures
- The study doctor no longer feels this is the best option for the participant

- The Sponsor decides to stop the study
- The Regulatory Authority/ies (for example, Health Canada) or research ethics board withdraw permission for this study to continue

If participant is removed from this study, the study doctor will discuss the reasons with them.

### *5.4.2 Data Collection and Follow-up for Withdrawn Participants*

Participants withdrawing from the study should be contacted by the study research team for follow up assessment or to follow up with any unresolved adverse events. Once withdrawn from the study, no further study procedures or evaluations should be performed, or additional study data collected. However, every effort should be made to obtain permission to document the reason for withdrawal and to collect participant outcomes, such as survival data up to the protocol-described end of participant follow up period, where possible. Any data collected prior to the withdrawal of consent may be retained and used by the sponsor and may be used in analysis towards the aims of this study. Participants will be required to return all study devices and associated equipment and materials at the time of withdrawal.

# 6 INTERVENTIONS

## 6.1 Investigational Product

The ANNE Vital Sign System was originally created for the purposes of providing real-time vital signs monitoring in the paediatric intensive care unit. The ANNE Vital Sign System consists of two water-resistant sensors, each encapsulated with a biocompatible silicone material. The ANNE Chest has two exposed gold-plated electrodes, but there are no external wires extending from the Sensor. The Sensor measures biosignals including electrocardiogram (ECG), acceleration, and temperature to measure vital signs such as heart rate, respiratory rate, body temperature, and skin temperature. The ANNE Limb is fully enclosed by the silicone encapsulation and measures photoplethysmogram for pulse rate, SpO2, body temperature, and skin temperature measurements

### *6.1.1 Acquisition, Formulation and Packaging*

#### **6.1.1.1** Acquisition and Formulation

53 ANNE Vital Sign System sensor sets will be shipped directly to Sunnybrook Research Institute from the manufacturer (Sibel Inc., Evanston, IL).

#### **6.1.1.2** Packaging

ANNE Vital Sign System sensor sets will be shipped as a bulk order with all units individually boxed.

### *6.1.2 Receiving, Storage, Dispensing and Return*

#### **6.1.2.1** Receipt of Investigational Product

Upon receipt of the investigational product and/or study supplies, an inventory must be performed and a receipt log filled out and signed by the research team member accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable product in a given shipment will be documented in the study files. The site must notify the study sponsor of any damaged or unusable product that was supplied to the site.

#### **6.1.2.2** Storage and Stability

The sensors may be stored at room temperature.

#### **6.1.2.3** Dispensing of Investigational Product

The investigational product will be reconciled by the research team at regular intervals, in addition to reconciliations performed during monitoring. Reconciliation will include verification of

investigational product kit/device assignment, inventory and recording of any damage or markings on the investigational product.

#### **6.1.2.4** Return and/or Destruction of Investigational Product

At the completion of the study, there will be a final reconciliation of investigational product shipped, used, returned, and remaining. This reconciliation will be documented. Any discrepancies noted will be investigated, resolved, and documented prior to return of the devices to the manufacturer.

# 7 STUDY SCHEDULE AND PROCEDURES

## 7.1 Screening

At the time of their enrollment in CTU and affiliated studies at participating recruitment sites, individuals will be invited to indicate interest in participating in the ANNE Vital Sign System assessment. This will be done by secure video conference. If interested, participant contact information (name, telephone number, email address) and study ID will be sent by encrypted email to study staff at SRI. Study staff at SRI will confirm that there are no exclusions from the ANNE Vital Sign System assessment based on exclusion criteria specific to the ANNE Vital Sign System. Eligible participants will be asked to complete a separate informed consent process specific to the ANNE Vital Sign System study. For participants enrolled at French-speaking sites, a study team member from that site may assist SRI with participant communications.

For the purposes of this study, the consent process will be completed remotely. A site team member will email a copy of the consent form to the participant and schedule a phone/video call with the participant where they will walk through the key elements of consent with the participant and allow time for questions. If a participant is unable to receive the consent form, they will be mailed a hard copy. After walking through the key elements of consent and the participant has been given time and opportunity to consider participation and ask questions, they will be asked their willingness to participate. If agreeable, study staff and witness will sign and date two copies of the consent form, to be included in the shipment of study device and materials. For those who indicate a desire to participate, study staff will collect mailing information (name, address). Study staff will explain the mailing procedures and tell the participant to expect a package in the mail with tracking information emailed to them. This package will include two hard copies of the consent form, already signed by study staff and witness.

A second scheduled phone/video call with the participant will be conducted after the participant has received the package. During this call, key elements of the consent form will be reviewed again and participants will have additional opportunity to ask questions. If agreeable, participants will then sign both copies of the consent form, retain one for their records, and return the other in the return package with the device after completion of their measurements.

The method of obtaining and documenting the informed consent and the contents of the consent must comply with ICH-GCP and all applicable regulatory requirement(s).

It will be made clear to each potential participant or substitute-decision maker, that informed consent may be withdrawn at any time without needing to give a reason and that such withdrawal will not compromise the relationship between the participant and the Investigator nor the participant’s future treatment.

The ICF must be in a language fully comprehensible to the prospective participants and ample opportunity must be given to inquire about the details of the study.

The ICF will include consent to access stored data for future analyses.

## 7.2 Baseline/Enrollment

Participants who are confirmed eligible and enrolled in CTU, are not excluded based on exclusion criteria specific to the ANNE Vital Sign System, and have completed the informed consent process will be provided instruction for use via video-conference with a member of the study team.

Study device will be sent to the participant via pre-paid package and tracked by a member of the study team.

As soon as possible after the study device and materials are received by the participant, study staff will instruct the participant on the proper application and use of the ANNE Vital Sign System via remote video-conference. Specifically, study staff will instruct the participant to affix the ANNE Vital Sign System chest sensor to the participant's chest using electrode paste, ANNE chest adhesive and Tegaderm or similar. Study staff may ask participants to shave a 3"x2" section of their chest, but participants will be informed this is optional. Next, study staff will instruct the participant to affix the ANNE Vital Sign System finger sensor to the participant's non-dominant index finger using the ANNE limb adhesive. Participants will wear the sensors for 24 hours before removing it themselves at home. Within 24 hours of removing the device, participants will be asked to fill out the Feedback Survey of Device Experience (Appendix 1), noted as optional. Finally, participants will be asked to return the device and feedback form by shipping back to SRI using a pre-paid, pre-addressed package. A new device and feedback form will be shipped to participants for their 12 month visit.

## 7.3 Study visits/Follow up

Baseline procedures will be repeated 12 months later. Participants at either time point with an AHI of $\geq$15 as determined by our quantification will be called via telephone by study staff to be a) notified that they have a high probability of having sleep apnea and if accompanied by severe sleepiness should refrain from driving, b) encouraged to contact their family physician for clinical evaluation where an official diagnosis of sleep apnea may or may not be made, and c) asked to notify study staff if they obtain treatment, unless treatment is obtained after their month 12 visit. Participants will be reminded that data collected as part of this study are for research purposes only and may not constitute a diagnosis of sleep apnea.

## 7.4 Protocol Deviations

It is the responsibility of the investigator to ensure that only investigative procedures, as outlined in this protocol are performed on study participants; the occurrence of deviations from the protocol or standard operating procedures (SOP) are limited; and compliance with the regulations is maintained. Planned deviations from the protocol must not be implemented without prior agreement from the sponsor and approval from the local REB, as required, unless to eliminate an immediate hazard to a participant.

Planned or unplanned deviations may occur on the part of the participant, the investigator, or study research team. In resolution to a deviation, corrective/preventative actions are to be

developed and implemented in a timely manner. Protocol deviations will be documented and reported as required and assessed where necessary during analysis.

# 8 ASSESSMENT OF SAFETY

The safety of research participants is foremost and should always be considered throughout the conduct of research.

## 8.1 Definitions

### *8.1.1 Adverse Events*

An adverse event (AE) means any untoward medical occurrence in a participant from the time of first contact with the ANNE Vital Sign System to 7 days following removal of the ANNE Vital Sign System at both Baseline and at Month 12. Participants will be advised during the informed consent process that it is their responsibility to report any adverse events to study staff up to seven (7) days following removal of the ANNE Vital Sign System sensors. Participants will be given the contact information of two CPSO-licensed physicians serving as qualified investigator and co-investigator. In the unlikely event that a participant experiences a possible adverse event, the qualified investigator or co-investigator will 1) advise the patient to seek care with their local health care provider, 2) liaise with the local health care provider, with the consent of the participant, to support the provision of necessary health care; and 3) collect information on, record, and report as necessary to the REB and Health Canada details of the possible adverse event.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

### *8.1.2 Serious Adverse Events*

A serious adverse event (SAE) or reaction is any untoward occurrence that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or in significant disability/incapacity,
- Is a congenital abnormality or a birth defect.

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

### *8.1.3 Unexpected Adverse Event*

An unexpected adverse event is any AE that is not identified in nature, severity or frequency in the current Investigator’s Brochure or Product Monograph.

## 8.2 Assessment of an Adverse Event

### *8.2.1 Relationship (Causality/Relatedness)*

The causality assessment is the determination, according to the investigator's clinical judgment, of the existence of a reasonable possibility that the investigational device caused or contributed to an adverse event.

If the investigator or delegated sub-investigator is unsure about whether or not the investigational device caused or is related to the event, then the event will be handled as "related" to the investigational device for reporting purposes of the trial. If the causality assessment is "unknown but not related" to the investigational device, this should be clearly documented in the source documents.

### *8.2.2 Expectedness*

Events are classified as unforeseen or unexpected if the nature, severity or frequency is not consistent with the risk information set out in the Product Monograph (PM) or label.

### *8.2.3 Seriousness*

Events are classified as serious if associated with effects threatening the life or physiological functions of a participant. Refer to the definition for "Serious Adverse Events" in section 8.1.2.

### *8.2.4 Severity*

The term "severe" is often used to describe the intensity (severity) of a specific event (e.g. mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. The terms "serious" and "severe" are not synonymous. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

## 8.3 Adverse Event Recording

All AEs both non-serious and either temporally and causally related to study procedures (i.e., a new event or an exacerbation of a pre-existing condition) that occur from the time of first contact with the ANNE Vital Sign System to 7 days following removal of the ANNE Vital Sign System at both Baseline and at Month 12 will be recorded as an AR in LORIS.

The following are not considered AEs and therefore do not require recording:

- Pre-existing diseases or conditions identified and recorded at screening/baseline unless, at the discretion of the investigator, the disease or condition worsens in severity or frequency

- At the discretion of the investigator, events considered likely manifestations of the underlying disease or that commonly occur in the study population independent of exposure to the investigational device

- Elective medical or surgical procedures.

Details of the event must include the dates of onset and resolution, severity, relationship to study procedures, seriousness, whether the event caused the participant to withdraw from the study, and outcome.

**Severity:** Severity should be graded and recorded according to the table below.

| Severity | Definition |
|---|---|
| Mild | Awareness of event but easily tolerated |
| Moderate | Discomfort enough to cause interference with usual activity |
| Severe | Inability to carry out usual activity, incapacitating, requires medical intervention |

**Relationship:** The relationship of the AE to study procedures will be determined by the Investigator, and assessed using the following definitions:

| Relationship | Description |
|---|---|
| Not Related | There is no evidence of a causal relationship and a causal relationship cannot be reasonably attributed to the study procedures. The event is clearly due to non-study causes. |
| Unlikely Related | A poor temporal relationship exists between the event onset and study procedures. The event could easily be explained by the participant's clinical state, intercurrent illness, or concomitant therapies. |
| Possibly Related | A relationship between event onset and study procedures cannot be ruled out with certainty and the event may be related. There is some evidence to suggest a causal relationship but the influence of other factors may have contributed to the event, such as the participant's clinical condition or concomitant treatment. |
| Probably Related | The event is likely related to study participation. There is evidence to suggest a causal relationship, such as reasonable temporal sequence from procedure. The influence of other factors is unlikely. |
| Definitely Related | The event is clearly related to study participation. There is clear evidence to suggest a causal relationship. The influence of other factors can be ruled out. |

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment.

## 8.4 Reporting of SAEs and Unanticipated Events

### *8.4.1 Investigator reporting: Notifying the REB*

Serious adverse events and unanticipated events should be recorded and reported to the REB in accordance with local reporting requirements and timelines.

### *8.4.2 Investigator reporting: Notifying the Sponsor*

The investigator is responsible for reporting serious adverse events to the sponsor in accordance with applicable regulations and reporting requirements and timelines.

Reporting should include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. The minimum information required includes at least one identifiable participant, one identifiable reporter, one serious reaction, and one suspect product.

### *8.4.3 Investigator Reporting of SUADRs: Notifying Health Canada*

In the event of an incident related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use that leads to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur, the qualified investigator of this study will report the incident to Health Canada. The qualified investigator will report the incident and the circumstances surrounding it to the Minister and to the manufacturer or importer of the device within 72 hours after it comes to the attention of the qualified investigator.

### *8.4.4 Manufacturer or Importer Reporting of SUADRs: Notifying Health Canada*

The manufacturer of the investigational device is required to report medical device incidents to Health Canada. A preliminary report will be submitted to the Minister within 10 days after the manufacturer becomes aware of an incident, if the incident has led to the death or a serious deterioration in the state of health of a patient, user or other person, or within 30 days after the manufacturer becomes aware of an incident, if the incident has not led to the death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur. The preliminary report will include:

(a) the name of the device and its identifier, including the identifier of any medical device that is part of a system, test kit, medical device group, medical device family or medical device group family;

(b) the manufacturer, the name and address of that manufacturer and of any known importer, and the name, title and telephone and facsimile numbers of a representative of the manufacturer to contact for any information concerning the incident;

(c) the date on which the incident came to the attention of the manufacturer;

(d) the details known in respect of the incident, including the date on which the incident occurred and the consequences for the patient, user or other person;

(e) the name, address and telephone number, if known, of the person who reported the incident to the manufacturer;

(f) the identity of any other medical devices or accessories involved in the incident, if known;

(g) the manufacturer's preliminary comments with respect to the incident;

(h) the course of action, including an investigation, that the manufacturer proposes to follow in respect of the incident and a timetable for carrying out any proposed action and for submitting a final report; and

(i) a statement indicating whether a previous report has been made to the Minister with respect to the device and, if so, the date of the report.

After the preliminary report is made, a final report shall be submitted to the Minister, containing the following:

(a) a description of the incident, including the number of persons who have experienced a serious deterioration in the state of their health or who have died;

(b) a detailed explanation of the cause of the incident and a justification for the actions taken in respect of the incident; and

(c) any actions taken as a result of the investigation, which may include

(i) increased post-market surveillance of the device,

(ii) corrective and preventive action respecting the design and manufacture of the device, and

(iii) recall of the device.

### *8.4.5 Events of Special Interest*

The regulatory sponsor is responsible for distributing blinded expedited reports of serious adverse events and unanticipated events to each investigator for submission to local Ethics Committees within 15 days of sponsor awareness.

## 8.5 Type and Duration of Follow-up for Adverse Events

AEs occurring as of the first contact of the investigational product and 7 days following removal of the investigational product will be collected. AEs recorded during this period will be followed through to resolution, or until the event is assessed as chronic or stable. If an AE remains unresolved at the conclusion of participation, the Investigator will make a clinical assessment to determine whether continued follow-up of the AE is warranted.

## 8.6 Reporting and Entry Timelines

Study investigators will report SAEs to the sponsor within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded and reported to the sponsor within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported to the sponsor within 72 hours of site awareness.

Adverse event information will be entered into the CRF in a timely manner and **no later than 15 days** from the time the investigator becomes aware of the event.

Serious adverse event information will be entered into the CRF in a timely manner/**within 72 hours** from the time the investigator becomes aware of the event.

# 9 SITE MONITORING, AUDITING AND INSPECTING

## 9.1 Site Monitoring Plan

Site monitoring is conducted to ensure the safety of human study participants and the protection of their rights and well-being. Monitoring also verifies that collected study data is accurate, complete and verifiable by source documentation and that the study is conducted in accordance with the protocol and operating procedures.

The majority of Clinical Monitoring in this study will be done remotely by comparing completed Case Report Form (CRF) data to de-identified source documentation which will be made available for Clinical Monitor review. If needed, each site may be visited by a Clinical Monitor during the study to verify data entry and regulatory documentation. On-site monitoring visits will be conducted according to the applicable ICH-GCP guidelines to ensure protocol adherence, quality of data, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. The Investigator will cooperate in the monitoring process by ensuring the availability of the CRFs, source documents and other necessary documents via remote source document upload during the course of the study, as well as at the time of any on-site monitoring visits. The Investigator will also ensure prompt attention to any matters brought to his/her attention by the Clinical Monitor.

Study data will be entered in the CRF by trained site study personnel. Data validation edit checks will be defined and implemented. Inconsistent and questionable data detected during the data entry or data validation process will be queried. Data clarification forms (DCFs) will be generated and any discrepancies will be resolved.

## 9.2 Auditing and Inspecting

The investigator will provide direct access to source data/documents for the purposes of study-related monitoring, audits, and inspections by the REB, the sponsor, and applicable regulatory bodies. The investigator will permit the review of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) and will ensure access to applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

# 10 STATISTICAL CONSIDERATIONS

## 10.1 Study Hypotheses

We hypothesize that participants with sleep apnea will have a greater 12-month change in their Montreal Cognitive Assessment scores than those without

## 10.2 Sample Size Considerations

We anticipate that ~30% of participants (i.e. 210 participants) will have sleep apnea. Based on this, we estimate 86% power to detect a ~0.5 point difference in 12-month change in MoCA between participants with and without sleep apnea. As it is possible that treatment of sleep apnea may be a potential source of noise regarding longitudinal cognitive outcomes, we will adjust for this statistically by collecting information on treatment and adjusting as a covariate.

## 10.3 Planned Interim Analyses

We do not plan any interim analyses.

## 10.4 Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse events that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

## 10.5 Final Analysis Plan

Cardiopulmonary data – .shrd file type – from the ANNE Vital Sign System will be downloaded locally by Sunnybrook Research Institute (SRI) who will convert to .edf file type, and manually annotate to extract information on sleep apnea. SRI will then upload processed data to the Longitudinal Online Research and Imaging System120 (LORIS). All uploads and downloads will be by Secure File Transfer Protocol (SFTP). We will quantify the apnea hypopnea index (AHI), oxygen desaturation index (ODI), hypoxemia burden, and time with oxygen saturation below 90% (O2<90). In addition, we will quantify 24-hour resting heart rate, and average heart rate, which are important physiological consequences of sleep apnea. Participants will be considered to have sleep apnea if their AHI is greater than or equal to 15. We will relate the presence of sleep apnea to change in MoCA scores between baseline and 12 months using t-tests. We will then use mediation analyses to test if any observed associations are mediated by effects of sleep apnea on average and daytime resting heart rate. Sex-stratification will be used in analyses as appropriate.

# 11 DATA HANDLING AND RECORD KEEPING

## 11.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Personal Health Information Protection Act of 2004 (PHIPA) and the Research Ethics Board. PHIPA outlines the rules for the collection, use and disclosure of personal health information. The Act requires each participant to consent to the collection, use and access of personal health information (PHI), unless consent is waived by the REB. Where consent is required, each participant must be informed of the following:

- What PHI will be collected during this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator may use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

## 11.2 Source Documents

Source data/documents are original documents, data and records in a clinical study that are necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to:

- worksheets
- hospital records
- medical records
- memorandum
- participants' diaries or evaluation checklists
- recorded data from automated instruments (i.e. ECGs)
- copies or transcriptions certified after verification as being accurate and complete
- entries entered directly into the printed CRF

## 11.3 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study personnel under the supervision of the investigator. All source documents should be reviewed as needed and used to ensure that data collected for the purposes of the study are accurate and complete. Study personnel, including data entry team members, should use source documents to complete case report forms (CRFs).

As part of the safety plan for this study, the investigator will review individual study participant records to ensure that appropriate mechanisms to protect the safety of study participants are being followed, that protocol requirements are being adhered to, and that data is accurate, complete, and secure. Participant records include, but are not limited to: consent forms, case report forms, and data forms. All study data will be collected by a member of the study research team and recorded in accordance with applicable procedures.

## 11.4 Data Capture

### *11.4.1 Case Report Forms*

The study case report form (CRF) is the primary data collection instrument for the study. Electronic/Paper case report forms (eCRFs/pCRFs) will be used to collect data for this study. CRFs are to be completed by data capture personnel and signed off by the investigator in a timely manner. Good documentation practices should be implemented according to standard operating procedures. All data requested on the CRF must be recorded and verifiable by source document.

## 11.5 Records Retention

*It is the responsibility of the REB, investigator and regulatory sponsor to retain study essential documents as per local regulatory requirements and GCP Guidelines.*

Study essential documents must be maintained in a secure and confidential manner for participating Canadian sites for a period of 25 years. For the purposes of this study, the start date of the retention period is the date of the final report of the trial. Exceptions may be made for sites which close prematurely, wherein the start date for the retention period will be the date of notification to Health Canada of the sites closure. Sites conducting this study outside of Canada must maintain study records for the required retention period as stipulated by local regulatory authorities. All study records are then to be destroyed according to local and national policy and requirements. It is the investigator's responsibility to request authorization for destruction at the completion of the retention period and/or for the sponsor to inform the investigator/institution when these documents may be destroyed.

## 11.6 Clinical Trial Registration

In accordance with Health Canada's Notice "Registration and Disclosure of Clinical Trial Information, November 30, 2007", the sponsor will be responsible for registering the study on Clinicaltrials.gov (*www.clinicaltrials.gov*), a publically available registry that conforms to international standards for registries.

# 12 QUALITY CONTROL AND QUALITY ASSURANCE

As per ICH-GCP and local regulations, the sponsor is responsible for ensuring the implementation and maintenance of systems that support quality assurance and quality control.

The study must be conducted in compliance with the study protocol and all data collected must be accurate and verifiable by source document(s). For the purpose of monitoring and auditing by the Sponsor, and inspection by regulatory authorities, the site will provide direct access to all study related source data/documents. The sponsor will verify that the study is conducted and data has been collected, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

Access to secure and validated electronic systems used for the purposes of this study will be controlled by the sponsor. Access will only be granted to individual research team members upon review of training and qualification and authorization by delegation of the investigator.

Quality assurance and control measures will be implemented to ensure training for specific trial–related tasks beyond the usual scope of practice. Only procedures or interventions as outlined in section 6.1, are considered study specific procedures requiring additional training, and will be reviewed for documentation of training and/or qualification.

For the purposes of this study, “research device” is defined as device used solely for the purposes of this study and that are unrelated to the delivery of standard-of-care treatment or procedures. In accordance with this definition, performance verification and /or calibration documentation will only be maintained for the following pieces of research device:

- ANNE Vital Sign System

# 13 ETHICS CONSIDERATIONS

## 13.1 Ethical Standard

The investigator will ensure that this study is conducted in accordance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research, and codified in the Tri-Council Policy Statement and/or the ICH E6.

## 13.2 Research Ethics Board (REB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented in the study, unless to eliminate an immediate hazard.

## 13.3 Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. A consent form describing in detail the study procedures and risks will be reviewed with and given to each participant according to the procedures outlined here. Consent forms will be REB-approved. For the purposes of this study, the consent process will be completed remotely with the participant, with a substitute decision maker available if necessary. A site team member will email a copy of the consent form to the participant and schedule a phone/video call with the participant where they will walk through the key elements of consent with the participant and allow time for questions. If a participant is unable to receive the consent form, they will be mailed a hard copy. After walking through the key elements of consent, and after the participant has been given time and opportunity to consider participation and ask questions, they will be asked to indicate their desire to participate. If agreeable, study staff will sign and date two copies of the consent form, to be included in the shipment of study device and materials. For those who indicate a desire to participate, study staff will collect mailing information (name, address, telephone, email). Study staff will explain the mailing procedures and tell the participant to expect a package in the mail with tracking information emailed to them. This package will include two hard copies of the consent form, already signed by study staff.

A second scheduled phone/video call with the participant will be conducted after the participant has received the package. During this call, key elements of the consent form will be reviewed again and participants will have additional opportunity to ask questions. If agreeable, participants will then sign both copies of the consent form, retain one for their records, and include the other in the return package at the conclusion of their measurements.

A substitute-decision maker may sign on behalf of the participant. The method of obtaining and documenting the informed consent and the contents of the consent must comply with ICH-GCP and all applicable regulatory requirement(s).

It will be made clear to each potential participant or substitute-decision maker, that informed consent may be withdrawn at any time without needing to give a reason and that such withdrawal will not compromise the relationship between the participant and the Investigator nor the participant's future treatment.

The ICF must be in a language fully comprehensible to the prospective participants and ample opportunity must be given to inquire about the details of the study.

The ICF will include consent to access stored data for future analyses.

Prior to involvement in any study-related activities, consent must be obtained as above for each participant using the current REB approved informed consent from. It is the responsibility of the investigator to ensure that all advertisements and written information, including the informed consent form, disseminated to participants has been approved by the local REB prior to use. The ethics approved Informed Consent Form (ICF) and any other written information, must be provided to each participant as above, allowing ample time to ask and have answered any questions prior to making a decision regarding participation. Neither the investigator nor study staff should unduly influence or coerce a participant to participate in the study.

The consent process will be documented in the clinical or research record.

The original ICF, in its entirety, will be maintained by the site, and a complete record of consent provided to the participant as above. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The provision of consent is an ongoing process and should be maintained throughout the duration of the study.

## 14 PUBLICATION/DATA SHARING POLICY

In order to access the data generated in this study, researchers must agree to abide by the Data Sharing and Publications Committee (DSPC) policy, a document developed by members of the CTU Steering Committee (SC) and Co-PIs, available for download at www.ccna-ccnv.ca. The DSPC, a sub-committee of the CTU SC, establishes policies and procedures to implement sharing CTU data, as well as, policies for publications and citations involving the use of CTU data. The DSPC members list is available upon request. Access to and analyses of CTU-acquired data, stored in LORIS, may be granted to qualified persons 12 months (embargo period) after the principal paper(s) answering primary research questions is/are published. A list of CTU protected planned projects and publications to be undertaken by the CTU Co-PIs, co-investigators or SC members will be posted in the LORIS publication module. Any CCNA investigator who wishes to analyze and subsequently publish data related to a question already listed in the “Protected planned projects and publications” must receive approval to join the designated writing group for that project to avoid duplication of the aims and methods of another CTU publication or wait until the “embargo period” has passed. Requests for use of CTU datasets may be made on the LORIS publications module and via email to CCNA; Central Administration [ccna.admin@ladydavis.ca]. Investigators will only be granted access to data related to the project outlined in the data access request.

Prior to submission for publication or for presentation of any data or results obtained in this study, notification to the DSPC is required. Draft manuscripts, abstracts and presentations should be submitted to the DSPC for administrative review. This review will ensure that confidentiality is protected; that the publication is not a duplication of the aims and methods of another CTU publication; CCNA and of the contribution of investigators. The participating sites will retain the ownership of their data obtained in this study. No researcher shall include identifiable personal health information in any publication or presentation. Authorship of publications resulting from this study should accurately reflect the academic contribution of individuals to the design and implementation of the trial, analysis of the data and preparation of the manuscript. Funding of CTU and CCNA by CIHR and other funding partners must be acknowledged. All publications that arise from the use of CTU data will give acknowledgement, attribution, or co-authorship as appropriate in accordance with the International Committee of Medication Journal Editors (ICMJE) standards and any rules established by the DSPC.

## 15 APPENDIX 1: FEEDBACK SURVEY OF DEVICE EXPERIENCE

**Study Name/Protocol Number: [_____]** **Participant ID: [_____]**

**Device Serial Number:** [Serial Number] **Visit**: ☐Baseline ☐Month 12

You are being asked to answer the following questions regarding your experience with the ANNE Vital Sign System sensors used in this study. Take your time and provide as much detail as possible. Return completed survey to the study site according to Shipping Instruction Card.

| |
|---|
| 1. What was the most uncomfortable aspect of sleeping with the ANNE chest and finger sensors? |

| |
|---|
| 2. Do you have feedback/suggestions about ways we could make the ANNE more comfortable? |

| |
|---|
| 3. What was the most challenging aspect of setting up the ANNE sensors? |

| |
|---|
| 4. Do you have feedback/suggestions about ways we could make wearing the ANNE sensors easier? |

Participant Signature: _____ Date:_____ (yy/mm/dd)