STU#: STU00212891

PROTOCOL TITLE: The association between Sleep, Heart Rate Variability, and Anxiety following brain injury.

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VERSION DATE:
Version 1

STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	
IND / IDE / HDE #	
Indicate Special Population(s)	☐Children ☐ Children who are wards of the state ☒ Adults Unable to Consent ☒ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	
Funding Source	
Indicate the type of consent to be obtained	☒Written ☐Verbal/Waiver of Documentation of Informed Consent ☐Waiver of HIPAA Authorization ☐Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐Yes ☐ No
DSMB / DMC / IDMC	☐Yes ☐No

OBJECTIVES:

Aim: To investigate the association between heart rate variability, anxiety and sleep in the Brain Injury population using biosensors.

Hypothesis: We predict that decreased heart rate variability and poor sleep quality will be significantly correlated with higher self-reported anxiety following BI.

BACKGROUND:

1.1 Anxiety is a common problem after Brain Injury (BI). Anxiety has been associated with interference in rehabilitation following BI and worse functional outcomes. Dysregulation of mood, including anxiety are common following TBI[1]. This is a result of the primary neuropathology, as well as secondary factors such as sleep disturbances and memory of the inciting trauma. Depression and anxiety after a TBI are associated with poorer cognitive, social, and functional outcomes.[4]

1.2 The hospital anxiety and depression scale (HADS), is a self-reported scale used to measure symptoms of depression and anxiety within the past one week. Patients rate the frequency of these symptoms on a 4-point Likert-type scale. It has been validated in both medical and general populations, the HADS consists of 14 items total and is divided into the Anxiety subscale (HADS-A) and Depression subscale (HADS-D). The HADS has strong internal validity in the TBI population with good concurrent and discriminant validity with other self-report scales.[4] In addition, the depression anxiety stress scales (DASS-21) is a self-report scale assessing levels of depression, anxiety, and stress over the previous week. Items are rated on a 4-point Likert-type scale, with higher scores reflecting higher levels of depression, anxiety, or stress. The measure displays good-to-excellent reliability and validity.[5] The association between sleep and anxiety, as assessed by the HADS and DASS-21, has not been studied in an inpatient TBI population.

1.3 Sleep Disorders are also common following BI. Many of the impairments demonstrated by individuals following BI may be exacerbated by sleep disorders[2]. Current assessment of sleep in inpatient BI patients is subjective, often obtained from patient self-reports or based on gross observation by a staff member. The inpatient BI population is frequently in an amnestic state –

[1] Mallya, S., Ornstein, T.J, et. al. 2015. *The Manifestation of Anxiety Disorders after Traumatic Brain Injury: A Review. J Neurotrauma*. 2015 Apr 1;32(7):411-21. doi: 10.1089/neu.2014.3504. Epub 2015 Jan 23.

4 Driskell, L.D., Starosta, A.J., Brenner, L.A. 2016. *Clinical Utility and Measurement Characteristics of the Hospital Anxiety and Depression Scale for Individuals With Traumatic Brain Injury*. Rehabil Psycho 2016 Feb;61(1):112-3. doi: 10.1037/rep0000079.
5 Lovibond, SH, Lovibond PF. 1995. *Manual for the Depression Anxiety Stress Scales (DASS)*, 2nd. Ed. edn. Sydney: Psychology Foundation; 1995.
6 Betthauser, LM, Bahraini, N, Krengel, MH, Brenner, L.A. 2012. *Self-Report Measures to Identify Post Traumatic Stress Disorder and/or Mild Traumatic Brain Injury and Associated Symptoms in Military Veterans of Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF).* Neuropsychol Rev (2012) 22:35–53. DOI 10.1007/s11065-012-9191-4
7 Klein, E., Caspi, Y., Gil, S. 2003. *The Relation Between Memory of the Traumatic Event and PTSD: Evidence From Studies of Traumatic Brain Injury*. Can J Psychiatry. 2003 Feb;48(1):28-33. doi: 10.1177/070674370304800106.
[1]Orff, H., Ayalon, L. and Drummond, S. (2009). Traumatic brain injury and sleep disturbance: a review of current research. *The Journal of Head Trauma Rehabilitation* 24, 155.

referred to as post-traumatic amnesia. Therefore, these patients have difficulty with accurately reporting their recollection of duration and quality of sleep. The use of activity monitors, such as the ANNE sensors or BiostampRC patch, may be a more accurate way of measuring quality of sleep in patients with BI.

1.4 No study to date has evaluated the association between anxiety and sleep quality after BI. In other populations, sleep deprivation results in an increase in self-reported feelings of depressed mood, anger, frustration, tension, and anxiety[3]. Manifestation of such behaviors has the potential to impede the patient's recovery by interfering with participation in therapies while participating in inpatient rehabilitation. Properly regulating the patient's sleep-wake cycle is one way such behaviors can be minimized as much as possible. In addition, early identification and treatment of anxiety and post-traumatic stress disorder (PTSD) may improve functional recovery for these patients.

1.5 Similar to self-reports of sleep, BI patients may have difficulty expressing their subjective experience of anxiety to clinicians. Reduced heart rate variability has been demonstrated to correlate with symptoms of anxiety in the general population.[8,4] Using biosensors, such as ANNE sensors or BiostampRC patch, the ECG component may be used to calculate heart rate variability in TBI patients. Heart rate variability is a physiologic measure that has been used to indirectly estimate function of the cardiac autonomic nervous system. It is comprised of various frequencies that are influenced by circadian rhythm, core body temperature, sympathetic and parasympathetic activity.[9] Heart rate variability and anxiety has been studied in the mild TBI population, however it has not yet been assessed in the moderate and severe BI population using validated scales such as HADS and DASS-21.[10]

STUDY ENDPOINTS:
This study will enroll up to 100 subjects who have had a TBI. Data collection will end after enough subjects have enrolled for adequate analysis of the data.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):
2.1 ANNE™sensor system: A research grade noninvasive sensor system measuring Vital signs monitoring system for sleep worn on the chest and finger, providing respiratory,

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[3] Orton, D. and Gruzelier, J. (1989). Adverse changes in mood and cognitive performance of house officers after night duty. *British Medical Journal* 298, 6665.
[8] Chalmers, JA, Heathers, JAJ, Abbott, MJ, Kemp, AH, Quintana, DS. 2016. *Worry Is Associated With Robust Reductions in Heart Rate Variability: A Transdiagnostic Study of Anxiety Psychopathology*. BMC Psychol. 2016 Jun 3;4(1):32. doi: 10.1186/s40359-016-0138-z.
[9] Stauss, H. 2003. *Heart rate variability and circadian rhythm*. American Journal of Regul Integr Comp Physiol 285:R927-R931, 2003; 10.1152/ajpregu.00452.2003.
[10] Liao, K-H, Sung, C-W, Chu, S-F, et al. 2016. *Reduced Power Spectra of Heart Rate Variability Are Correlated With Anxiety in Patients With Mild Traumatic Brain Injury*. Psychiatry Res 2016 Sep 30;243:349-56. doi: 10.1016/j.psychres.2016.07.001. Epub 2016 Jul 1.

Photoplethysmograph (SpO_2), Temperature (+/- 0.1 ºC), Continuous Blood Pressure from Pulse Arrival Time (PAT) and Pulse Transit Time (PTT) and sleep quality.

2.2 ActiGraphy: Participants will be asked to wear the Actiwatch for 7 consecutive days in conjunction with the sleep and wake diary described below. They will be given the Actiwatch to wear at the time of clinical examination. Participants will also be required to wear Actigraph during in-clinic sleep visit. Actigraphy is established as a valid and objective method of assessing sleep-wake parameters in natural settings[3]. In addition, the actigraphy data can be used to determine the duration and timing of naps, the phase of the rest/activity cycle, amplitude of the rest/activity rhythm and activity levels during the day and sleep period. Of particular interest is the timing and stability of the sleep and wake (rest/activity) rhythm in this older adult population because of the age related changes in circadian timing. It is designed for long-term monitoring of gross motor activity in humans and has an accelerometer capable of sensing motion with a minimal resultant force of 0.01 x g^3. Actigraphy has been used on a variety of population, including older adults. Study Participants are instructed to wear an actigraph around the clock (except when bathing) for 7 consecutive days, on the nondominant wrist. We set the recording parameters as follow: epoch length, 0.5 minutes, and threshold automatic sensitivity (the algorithm automatically scores an epoch as sleep if the total activity value is equal to or less than the threshold sensitivity value calculated from the mean score in the active period multiplied by K [constant=0.888) and divided by epoch length.

2.3 Biostamp Npoint: Small flexible sensor that contours to the skin. This sensor will be used to measure additional physical activity and heart rate.

PROCEDURES INVOLVED:

Following admission to the inpatient brain injury service, patients will be screened in order to determine whether or not they meet all of the inclusion or any of the exclusion criteria as outlined above. If a subject is deemed to be a candidate for the research protocol, they will be approached in order to obtain informed consent for the study. Wearable Biosensors and the ActiGraph will be placed on the subject's non-dominant wrist. If the non-dominant wrist has motor impairment due to brain injury, then the ActiGraph will be placed on the dominant wrist. If both arms have motor weakness due to the brain injury, then the ActiGraph will be placed on the least affected extremity. The ANNE^{TM}sensor system set will be placed on the patient's chest and finger. Sleep data will be obtained for seven consecutive nights. For anxiety, we will have a daytime, 5-10 minute epoch to measure heart rate variability, using ANNE ECG and skin temperature sensors, or manual temperature. We will measure overnight sleep, not during the day, with ANNE sensor accelerometer and ECG. Sleep log data will be extracted from the medical record.

Each subject will be randomly assigned a coded identifier. A list of the subjects' names and respective coded identifiers will be stored in a secure location on one of the co-investigator's encrypted and password protected computers at the Shirley Ryan AbilityLab. The data collected will be associated with the coded identifiers on a Microsoft Excel spreadsheet on one of the co-investigator's encrypted and password protected computer at the Shirley Ryan AbilityLab. Data will consist of sleep and heart rate variability data from the wearable biosensors, and sleep logs by nursing staff, self-reported sleep quality, anxiety and PTSD scales. The scales, HAD, DASS-21 and PCL-S, will be obtained on five separate occasions.

The subject will be monitored to ensure they are not experiencing an allergic reaction/skin irritation from the wearable biosensor system. If this is the case, the treating physician will be notified and they will determine whether or not the patient should continue with the study.

Sleep log data will be extracted from the Cerner electronic medical record of each patient and recorded in a Microsoft Excel spreadsheet with associated coded identifier. Data will be stored on one of the co-investigator's password protected and encrypted computer at the Shirley Ryan AbilityLab.

Data recorded will include: sleep data as measured by sleep logs, ActiGraph, ANNE^{TM}sensor system; scores of the HAD, DASS-21 and PCL-S on five separate occasions. No long-term follow-up data will be collected. Post-hoc analyses will be performed on biometric data collected by the ANNE^{TM}sensor system – including heart rate, temperature and movement.

Questionnaires

1. *Karolinska Sleep and wake diaries:* Participants will be asked to maintain daily sleep logs for 7 consecutive days and to note bedtime, wake-up time, total sleep time, sleep latency, wake after sleep onset, naps, any unusual events during the day or night, any hot flashes per day (if female), and rating of overall sleep quality. The sleep diary will provide more detailed information of sleep quality.

2. *The Pittsburgh Sleep Quality Index (PSQI):* This self-rated 21 item questionnaire assesses individual sleep habits (bedtime, morning rising time, sleep-onset latency, and night sleep duration), insomnia, and hypnotic use over a 1-month time interval. The PSQI has internal consistency and a reliability coefficient (Cronbach's alpha) of 0.83 for its seven components. The PSQI has been widely applied in a variety of clinical settings and epidemiological studies in many countries, because of its satisfactory

3. *The Berlin Questionnaire:* These questions were designed to identify adult patients who are likely to have sleep apnea. It asks about snoring behavior, wake time sleepiness or fatigue, and the presence of obesity or hypertension.

4. *Post-traumatic Stress Disorder Checklist:* To evaluate for symptoms of PTSD in our BI population, we will use the Post-traumatic Stress Disorder Checklist (PCL) which assesses self-reported PTSD symptoms within the past 1 month that correspond with the DSM-IV criteria and the Davidson Trauma Scale (DTS). These scales have been researched and validated for use in civilian and veteran populations.[6] The PCL-S, "S" for specific, is a 17-item self-report measure covering the 17 DSM-IV symptoms of PTSD that specifies date and event of trauma.
5. *The Hospital Anxiety and Depression Scale (HADS):* It is a self-reported scale used to measure symptoms of depression and anxiety within the past one week. Patients rate the frequency of these symptoms on a 4-point Likert-type scale. It has been validated in both medical and general populations, the HADS consists of 14 items total and is divided into the Anxiety subscale (HADS-A) and Depression subscale (HADS-D). The HADS has strong internal validity in the TBI population with good concurrent and discriminant validity with other self-report scales.[4]
6. *The Depression Anxiety Stress Scale (DASS-21):* It is a self-report scale assessing levels of depression, anxiety, and stress over the previous week. Items are rated on a 4-point

Likert-type scale, with higher scores reflecting higher levels of depression, anxiety, or stress. The measure displays good-to-excellent reliability and validity.[5]

DATA AND SPECIMEN BANKING

Subjects will be assigned confidential codes for data collection. Code assignment will be kept separate from data information; subject code will be kept in a secure room under lock and key. No personal information will be stored with their data. Any data, photos or video will be stored for 7 years and stored on a secure, password protected computer at Shirley Ryan AbilityLab.

The data stored includes all information pertaining to the performance based outcomes measures and evaluations.

In the event this study will be published, data may be released to report the outcomes of this study. No released data will include identifiable information.

SHARING RESULTS WITH PARTICIPANTS

Results will be shared with participants if they request the information, but only after data analysis is complete. Results will only be shared among qualified research staff within Shirley Ryan AbilityLab and/or other Northwestern research labs. If the participant is interested in seeing the data collected, he/she will be given a summary of analyzed data. Research staff will explain and interpret the observations

INCLUSION AND EXCLUSION CRITERIA

Every patient admitted to the Shirley Ryan AbilityLab for rehabilitation following brain injury will be screened for the inclusion and exclusion criteria in order to assess their candidacy to participate in the study

Inclusion criteria:

- Subject must have had a brain injury
- Subject must be at least 18 years of age at the time of the injury
- The injury must have occurred in the past 6 months
- Subject must be medically stable – as determined by their ability to participate in acute inpatient rehabilitation

Exclusion criteria:

- Current use of beta blockers
- History of sensitivity or previous skin reactions to skin adhesives
- Non-English speaking
- Pregnant women
- Prisoners

This study will not exclude members of the following special populations: adults unable to consent.

This study will exclude individuals who are not yet adults, pregnant women, and prisoners.

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VULNERABLE POPULATIONS

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"CHECKLIST: Cognitively Impaired Adults (HRP-417)"

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Local	cognitive impaired adults	40 patients	15 patients
Study-wide	cognitive impaired adults	40 patients	15 patients
Total:	cognitive impaired adults	40	15

RECRUITMENT METHODS

Subjects will be approached for enrollment into the study following admission to the Shirley Ryan AbilityLab. A co-investigator will explain the purpose of the research to the subject (and medical proxy if applicable) and obtain informed consent for participation in the study.

The source of subjects is admission to the Shirley Ryan AbilityLab for rehabilitation following brain injury.

Admissions to the brain injury service will be assessed to determine if they meet all of the inclusion criteria or any of the exclusion criteria as outlined above.

No advertisements will be used for recruitment

Subjects will not be paid for their participation in the study

WITHDRAWAL OF PARTICIPANTS

Subjects will be withdrawn from the study in the event of a medical event or complication (i.e. hospitalization) that may alter the inclusion/exclusion criteria or which limits the patient from safely completing the remainder of the study, or at the discretion of the PI.

Subjects can voluntarily discontinue the study at any time. The participant will then be requested to notify the Principal Investigator, Dr. David Ripley, in writing or call at 312-238-4745, if assistance is needed in this process. Information collected prior to the study discontinuation by a participant may still be used by the research team.

The researchers reserve the right to discontinue study participation for any individual or for the study as a whole at their discretion.

RISKS TO PARTICIPANTS

a. Participation will be voluntary and participants may terminate participation at any time. The alternative to this study is to not participate.

b. Skin irritation where the wearable sensor monitors or electrodes are attached. This risk will be reduced by minimized by excluding people who have a known allergy and discontinued use if skin irritation occurs.

c. Potential risk of breach of confidentiality. There is potential risk of breach of privacy and confidentiality of which will be minimized by having computer based data records identifiable only by a participant number. Names will not be stored with the participant data. Identifying information will be stored separately in a password protected file that will be linked to a participant number.

POTENTIAL BENEFITS TO PARTICIPANTS

There is no direct benefit for the subject. However this information will be used to develop better sleeping surfaces/conditions.

DATA MANAGEMENT AND CONFIDENTIALITY

All personal information (names, addresses, email or phone numbers, etc.) gathered for this study that can identify participants will be kept secure to protect their privacy and will never be shared at any time with any person or entity. Data collected during the study and shared with others will reference participants only by an alphanumeric code. The “master list” linking personal information to the alphanumeric code will not be shared, and will be kept by the study PI in a secure location. De-identified information gathered from participants will be used by the Sponsor of this study.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

Participants will be notified if any new information concerning the safety of the study device becomes available which may affect their decision to remain in the study. Participants will however be asked to perform all activities under the supervision of a trained research staff member.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Every possible precaution will be taken to protect the privacy interests of subjects. To begin with participation in this is completely voluntary. Trained research personnel will explain the purpose of the study and intended use of subject’s personal health information and precautions taken to keep the study information and data confidential.

COMPENSATION FOR RESEARCH-RELATED INJURY

If the subject gets an injury or illness as a result of study, the subject is required to promptly notify the PI of the study about the illness or injury. The hospital [Researchers, Shirley Ryan AbilityLab, Northwestern University and all affiliated clinical sites] will not pay for medical care required because of a bad outcome resulting from participation in this research study. However,

this does not keep a subject from seeking to be paid back for care required because of a bad outcome.

ECONOMIC BURDEN TO PARTICIPANTS
Subjects will not be compensated for their participation in the study.

CONSENT PROCESS
Informed consent will take place at the Shirley Ryan AbilityLab with authorized study personnel.

Trained research personnel will guide the participant or authorized guardian through consenting process. Participant or authorized guardian will be given detailed explanation of the purpose, time line, commitment, procedures, data handling and privacy and confidentiality of information pertaining to the study.

Before recruitment and enrollment onto this study, the participant or authorized guardian will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements as approved by the Northwestern University Institutional Review Board. Once this essential information has been provided to the participant or authorized guardian and the investigator is assured that the participant or authorized guardian understands the implications of participating in the study, the participant or authorized guardian will be asked to give consent to participate in the study by signing an IRB approved consent form. Subjects will be consented with a new consent form if changes are made to the protocol.

Prior to a participation in the trial, the written informed consent form must be signed and personally dated by the participant or authorized guardian and by the person who conducted the informed consent discussion. The consent process will take place at the Shirley Ryan AbilityLab.

Cognitively Impaired Adults
Cognitive impairments will be determined by the physician, family and if needed, a speech language pathologist or psychologist to determine fit for consenting for the study.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

Subjects records will be kept completely confidential: Every possible precaution will be taken to protect the privacy interests of subjects. Participation in this study is completely voluntary. Trained research personnel will explain the purpose of the study and intended use of a subject's medical information and the precautions taken to keep the study information and data confidential. Data will be collected and kept confidential and compliant with HIPAA standards.

Participants will be assigned an alphabetical or numerical study ID. Identifying data will be kept in locked cabinets and password protected servers completely separate from de-identified data. Research data will be de-identified and stored in locked cabinets in the lab accessible only by authorized research personnel. Electronic data will be de-identified and kept on secure, password protected servers at the Shirley Ryan Ability Lab. Only authorized research staff will be able to access any of the formerly mentioned data. De-identified data will be kept indefinitely.

Study documentation will be collected and stored and kept confidential and compliant with HIPAA requirements. Identifying data will be held for 7 years after the study is completed and published.

All personal information (names, addresses, email or phone numbers, etc.) gathered for this study that can identify participants will be kept secure to protect their privacy and will never be shared at any time with any person or entity. Data collected during the study and shared with others will reference participants only by an alphanumeric code. The “master list” linking personal information to the alphanumeric code will not be shared, and will be kept by the study PI in a secure location. All personal information linking participants to their data will be destroyed after 7 years following the completion of the study.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

Research will be conducted in the Shirley Ryan AbilityLab, a 1.2 million square foot Inpatient rehabilitation hospital affiliated with Northwestern University. The facility houses a full contingency of staff and resources for the conduction of translational research, including IT, biostatistical support, and clinical care resources. Dr. David Ripley, the Principal Investigator, is an Associate Professor in the Department of PM&R at Northwestern University, with 20 years’ experience caring for individuals and conducting clinical research in Brain Injury. Dr. Arun Jayaraman, the Co-Investigator, is Director of the Max Näder Center for Rehabilitation Technologies & Outcomes Research at the Shirley Ryan AbilityLab and is an Associate Professor of PM&R, Medical Social Science, PTHMS, at Northwestern University.