Comparison of **S**leep Apnea **A**ssessment **S**trategies to Maximize TBI Rehabilitation Participation and Outcome **(C-SAS)**

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Title: **C**omparison of **S**leep Apnea **A**ssessment **S**trategies to Maximize TBI Rehabilitation Participation and Outcome **(C-SAS)**

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STUDY SUMMARY

Title	Comparison of Sleep Apnea Assessment Strategies to Maximize TBI Rehabilitation Participation and Outcome (C-SAS)
Methodology	Prospective, diagnostic clinical trial
Study Duration	Study recruitment was initiated on 05/2017 and completion of all participants in the protocol occurred on 02/2019.
Study Centers	Potential participants were consecutive patients enrolled in the TBI Model Systems (TBIMS) at six sites (Tampa, FL [James A. Haley Veterans Hospital]; Seattle, WA [University of Washington]; Dallas, TX [Baylor Scott & White Rehabilitation]; Columbus, OH [Ohio State University]; Denver, CO [Craig Hospital]; and Philadelphia, PA [Moss Rehabilitation Institute]).
Objectives	Aim 1: For individuals with TBI, determine comparative effectiveness of AASM endorsed patient-reported screening tools and objective actigraphy to identify those at high risk of sleep apnea as diagnosed through Level 1 Diagnostic Polysomnography. Aim 2: Determine the diagnostic accuracy (non-inferiority of Level 3 portable diagnostic testing in determining presence of sleep apnea in patients with acute TBI patients in the rehabilitation setting.
Number of Subjects	Aim 1: 248 Aim 2: 214
Diagnosis and Main Inclusion Criteria	**Inclusion Criteria:** *Damage to brain tissue caused by an external mechanical force *Alteration of consciousness > 24 hours, or loss of consciousness > 30 minutes, or Glasgow Coma Scale (GCS) score in the Emergency Department of 3-12, or intracranial abnormalities on imaging regardless of GCS *Admission to inpatient rehabilitation *Minimum age 16 years at civilian sites and 18 years at the VA site *Consent to participate by person with brain injury (if able), family member or legally authorized representative into the TBI Model System lifetime study. This criterion was relaxed in Study Month 11.

	Exclusion Criteria: *Habitual sleep duration > 2 hours/night for two (2) consecutive nights not being established prior to PSG *Presence of a physical deformity precluding sensitivity of PSG instrumentation (i.e. full body cast, PSG that could not be removed prior to PSG) *Medical instability as determined by the treating physician (i.e. agitation, acute illness) *Infeasibility of tracheostomy placement with decannulation or overnight capping during rehabilitation
Study Product	Aim1: Subjects will complete paper and pencil screening tests (STOPBang, Berlin, MAPI), actigraphy, and Level 1 Diagnostic Polysomnography. Aim 2: Subjects recruited will undergo simultaneous administration of Level 1 Diagnostic Polysomnography and Level 3 Portable Diagnostic tests.
Statistical Methodology	Aim 1: Area under the curve (AUC) of screening tools predicting sleep apnea status and severity. Aim2: Non-inferiority of Level 3 portable diagnostic tests to the criterion standard, Level 1 Polysomnography.

Purpose:
The primary objective is to identify the comparative effectiveness of existing screening and diagnostic tools for sleep apnea to promote earlier detection (thus treatment) during inpatient rehabilitation for moderate to severe traumatic brain injury (TBI).

Background:
Given that sleep is critical for neural repair and disordered sleep may play a role in slowing functional recovery and prolonging rehabilitation, early detection of sleep apnea is critical (Stakeholder Input). The Agency for Healthcare Research and Quality's (AHRQ) Comparative Effectiveness Review highlighted insufficient comparative effectiveness evidence for sleep apnea diagnostic and screening tools. This is a prospective, observational cohort study conducted on inpatient rehabilitation units at six Traumatic Brain Injury (TBI) TBI Model System sites. The diagnostic utility of existing sleep studies is needed to inform clinical management during acute recovery from TBI.

Goals of the Study:
(Aim 1: Screening) For individuals with TBI, determine comparative effectiveness of the American Academy of Sleep Medicine (AASM) endorsed screening tools and objective actigraphy (ACG) to identify those at high risk of sleep apnea as diagnosed through Level 1 polysomnography (PSG) which is the criterion standard. (Aim 2: Diagnosis). Determine the diagnostic accuracy (non-inferiority) of portable diagnostic testing (more accessible test) relative to Level 1 PSG (laboratory-quality study; criterion standard, less accessible test) in determining presence of sleep apnea in patients with acute TBI during inpatient rehabilitation hospitalization.

Duration of the Study:
The study completed enrollment and met recruitment goals within a 19-month period. Participants completed study activities upon completion of diagnostic testing.

Product Description and Intended Use:
Sleep Apnea Screening Tools (comparators)
STOPBANG (OSA Screening Comparator). The STOPBANG is comprised of eight (8) items that refer to Snoring, Tiredness, Observed breathing pauses during sleep, treatment for high blood Pressure, elevated Body mass index, older Age, wide Neck circumference, and male Gender. An affirmative response to 2 items indicates low risk, 3-4 items intermediate risk, 5-8 items high risk.

Berlin (OSA Screening Comparator). The Berlin Questionnaire is a 10-item measure that evaluates risk factors for sleep apnea into three (3) categories (snoring severity, excessive daytime sleepiness and history of high blood pressure or obesity). Positivity in two or more of these categories is associated with a high likelihood of clinically-relevant sleep apnea.

Multivariate Apnea Prediction Index (MAPI; OSA Screening Comparator). The questionnaire consists of three breathing-related questions and utilizes information on demographics (sex, weight, height, age), from which a probability of having sleep apnea (0-100%) can be calculated.

Actigraphy (ACG; Comparator). A wrist-worn accelerometer (Actiwatch Spectrum, Philips/Respironics, Bend, OR) was used to document sleep metrics during the trial. Activity data informing sleep statistics were recorded in 15-second intervals.

Diagnostic Comparators

Level 1 Polysomnography (gold standard method) is the criterion standard for diagnosing sleep apnea with overnight monitoring conducted routinely in a sleep laboratory with a registered polysomnography technician in attendance to assure quality of the study through monitoring of data collection using computer interfaces. All sites utilized a uniform system which for this trial was the Philips Alice 6 LDx Diagnostic Sleep System with results scored in and generated by the Philips Sleepware G3 version 3.8.1 software. The Alice has the capability for up to 55 channels of information collected during overnight monitoring to diagnose sleep disorders including 19 EEG (electroencephalography) inputs, 5 dedicated EMG (electromyography) channels, 3 Chin EMG inputs, EOG (ocular) channels and 7 ECG (heart) channels. Additional features include measurement of thermal flow, snoring, body position, actimeter inputs, light sensors, pulse oximetry, chest and abdominal effort with 8 AUC inputs, and video and audio integration. Many devices are available on the market. Clinician stakeholders on the study (with no conflicts of interest) recommended the system chosen for study purposes.

Portable Sleep Studies (comparator for non-inferiority) are also known as home sleep apnea tests (HSATs in the sleep medicine field). The portable sleep study device used in this trial was the Nox T-3 Monitor [Nox Medical Inc., Reykjavik, Iceland] and Noxturnal version 4.4.2 software. This device used a total of four channels for assessment of sleep apnea including chest and abdominal effort (2), thermal flow (1), and pulse oximetry (1) along with audio recording of snoring. It does not utilize electroencephalography data to determine sleep states which is included in the scoring of sleep apnea using the criterion standard test, Level 1 PSG. Technicians do not monitor the quality of the study information being collected overnight. Many devices are available on the market. Clinician stakeholders on the study (with no conflicts of interest) recommended the system chosen for study purposes.

Product Acquisition:

The screening tests are in the public domain thus no cost to the participant or study institutions. The diagnostic tests, supplies, and software were purchased using grant funding for study purposes.

Potential Benefits and Risks to the Participants

Protections Against Risk Implemented at Start of Trial: To minimize the risk of uncomfortable questions on assessments, participants are instructed during the informed consent process that they can decline to answer any question or discontinue participation at any point in the study. Participants will be informed in the consent form that they do not have to discuss any topics and engage in any procedures that they do not wish to during the assessment periods. In addition, participants are informed during the consent process they are free to stop an assessment at any time. Participants are also informed before each assessment period that they may refuse to answer any questions or procedures that make them feel uncomfortable. Any discomfort from wearing the sleep monitoring equipment (ACG or PSG), either physical or emotional, should be readily resolved with adjustments and repositioning. Continuous monitoring by a registered sleep technician during the PSG study will provide the participant with physical assistance for adjusting the equipment and with reassurance for the duration of the study. Any skins problems related to wearing the equipment, should be readily treated with skin lotion and repositioning the device. If the sleep assessment procedures are determined to be too physically or emotionally uncomfortable for the participant by either clinical or research staff, he/she may be administratively withdrawn from the study. All changes in the participant's medical status during an assessment will be communicated to clinical staff for follow up. Should the participant appear to become medically distressed during the course of an assessment, research staff will immediately contact the participant's clinical staff and study investigators for follow up. If research personnel discover new medical or emotional concerns during study assessments, the research staff member will promptly report this information to clinical staff and to study investigators for follow up. If, during the course of

the study, the patient is discovered to have sleep apnea or another sleep disorder, this information will be communicated to the participant's clinical staff for follow up.

All unanticipated problems and adverse events will be tracked by research staff and promptly reported to the study investigators and IRBs for appropriate resolution. An unanticipated problem is defined as any incident, experience, or outcome that is unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents; possibly related to participation in the research; and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Unanticipated problems will be promptly reported immediately to the site investigator and to the local IRB, as well as to the study Principal Investigators. An Unanticipated Problem Report form will be completed and returned to all regulatory institutions as soon as possible.

An adverse event (AE) is any unfavorable and unintended sign, symptom or disease temporally associated with a study procedure regardless of whether it is considered related to the procedure. A serious adverse event (SAE) is any untoward medical occurrence that 1) results in death, 2) is life-threatening, 3) requires inpatient hospitalization or prolongation of existing hospitalization, or 4) results in persistent or significant disability/incapacity. AEs may be graded as mild (no limitation of usual activities), moderate (some limitation) or severe (inability to carry out usual activities) and attributed according to the relationship to the study procedures as not related, possibly related, or related. A clinical event form will be completed in the case of any and all reported adverse events associated with the treatment procedures. Copies of these forms will be sent to the Principal Investigators. The original will be placed in the participant's study folder. The purpose of this procedure is to make certain all possible adverse events are examined to determine the proper action, if any, that needs to be taken. Mild and moderate AEs will be tracked and reported quarterly to the Principal Investigator. SAEs will be reported immediately to the site principal investigator and to the local IRB. An Adverse Event Report form will be completed and returned to all regulatory institutions as soon as possible. To protect confidentiality of data, all data will be maintained in a secure database on secure servers. Within the database and on all data collection forms, numbers will be used in place of names or other direct identifiers. Any hard copies of data collection forms and tools are kept in locked file cabinets. Only research staff members assigned to the project will have access to documents and computer databases. All investigators and research staff involved in the project will have completed online training in protection of human subjects. Research staff will not disclose the identity of a participant or any information regarding participation to anyone beyond legal parties who are privy to this information.

Methods

Study Design: Prospective diagnostic clinical trial of comparative effectiveness of screening and diagnostic tools for sleep apnea.

Study population and selection criteria: Potential participants were consecutive patients enrolled in the TBI Model Systems (TBIMS) at six sites (Tampa FL, Seattle WA, Dallas TX, Columbus OH, Denver CO, and Philadelphia, PA) described earlier and over 19 months. Study inclusion/exclusion criteria for the TBI Model Systems and this trial are described in Table 1.63 The requirement of TBIMS enrollment at time of consent for the clinical trial was relaxed at study-month 11 to allow for earlier enrollment during rehabilitation but the clinical criteria remained unchanged.

Recruitment Methods: All participating sites received institutional review board approval for conduct of the study. Consecutive admissions were screened for eligibility. Participants who passed the first level of

screening (or their proxies) were consented and further screened for final eligibility including 1) ≥ 2 hours sleep/night based on actigraphy placement or nursing logs/report, and 2) medical stability (including no emergent medical issues precluding overnight PSG and minimal to no post-traumatic agitation, as assessed by the Agitated Behavior Scale). Once determined eligible, an overnight PSG study was conducted by a registered polysomnographic technician (RPSGT) in the participant's own bed. Within 72 hours of the PSG, questionnaire-based sleep apnea screening measures were completed with the participant and/or best source available using established TBIMS procedures by local staff blinded to PSG results. Sleep-related information during hospitalization was collected from the medical staff (snoring status, daytime sleepiness) or medical record (weight, height). The patient-reported outcome was the primary source of data. When data were missing due to the participant's inability to respond or with unknown responses, it was imputed using best source data if available otherwise was considered missing data.

Data collection and reporting: Demographic and pre-injury medical histories, and medical record abstraction were conducted by trained research assistants following the TBIMS protocol. Within 72 hours of the PSG, questionnaire-based sleep apnea screening measures were completed with the participant and/or best source available using established TBIMS procedures by local staff blinded to PSG results. Sleep-related information during hospitalization was collected from the medical staff (snoring status, daytime sleepiness) or medical record (weight, height). The patient-reported outcome was the primary source of data. When data were missing due to the participant's inability to respond or with unknown responses, it was imputed using best source data if available otherwise was considered missing data. Participants underwent simultaneous administration of Level 1 PSG (Philips Alice 6 LDx Diagnostic Sleep System with Philips Sleepware G3 version 3.8.1 software) and portable sleep study (i.e., HSAT using the Nox T-3 Monitor [Nox Medical Inc., Reykjavik, Iceland] and Noxturnal version 4.4.2 software. Fully attended Level 1 PSG was conducted in accordance with the American Academy of Sleep Medicine recommended procedures.49 Staff were instructed to allow participants their normal sleep period.

The lead center (James A. Haley Veterans' Hospital, Tampa, FL) served as a centralized scoring center for all sleep studies. All Level 1 PSG studies were masked and scored within seven business days of PSG completion with results subsequently databased and entered by research assistants. The Level 3 portable sleep studies were masked and scored in batches of 50+ studies approximately 3-6 months after completion and scoring of Level 1 PSG to assure blinding of portable study scoring from the Level 1 PSG results. All portable sleep studies were edited by the RPSGT; the automated software results were not used in analyses. Editing entailed setting start/stop recording times based on assessment of embedded actigraphy (reduction in movement) in the portable device and elimination of data during periods of absent valid waveforms for oximetric plethysmographic data, nasal pressure transducer data, and effort signal data.

Outcomes

The psychometric properties of screenings tools for sleep apnea endorsed by the AASM are now available for persons with moderate to severe TBI undergoing inpatient rehabilitation.

Nakase-Richardson R, Schwartz DJ, Drasher-Phillips L, Ketchum JM, Calero K, Dahdah MN, Monden KR, Bell K, Magalang U, Hoffman J, Whyte J, Bogner J, Zeitzer J. Comparative effectiveness of sleep apnea screening instruments during inpatient rehabilitation following moderate to severe TBI. *Archives Phys Med Rehabil.* 2020;101:283-96. doi: 10.1016/j.apmr.2019.09.019. PMID:31705855

The comparative effectiveness (non-inferiority) of portable diagnostic testing relative to the criterion standard in persons with moderate to severe TBI undergoing inpatient rehabilitation is now available. See below:

> Nakase-Richardson R, Schwartz D, Ketchum J, Drasher-Phillips L, Dahdah M, Monden K, Bell K, Hoffman J, Whyte J, Bogner J, Calero K, Magalang U. Comparison of diagnostic sleep studies in moderate to severe traumatic brain injury neurorehabilitation admissions. *Chest*. 2020;pii: S0012-3692(20)30863-1. doi: 10.1016/j.chest.2020.03.083. [Epub ahead of print]. PMID: 32387522

Adverse Reactions

None reported.

Reasons for withdrawal or termination

No subjects were terminated from the study. No participant completely withdrew from the study. However, some study procedures were refused as described in corresponding publications for each aim.

Premature termination or suspension of the study

Not applicable.

Methods and Study Schedule

Baseline Screening Visit: All participating sites received institutional review board approval for conduct of the study. Consecutive admissions were screened for eligibility. Participants who passed the first level of screening (or their proxies) were consented and further screened for final eligibility including 1) ≥ 2 hours sleep/night based on actigraphy placement or nursing logs/report, and 2) medical stability (including no emergent medical issues precluding overnight PSG and minimal to no post-traumatic agitation, as assessed by the Agitated Behavior Scale). Once determined eligible, an overnight PSG study was conducted by a registered polysomnographic technician (RPSGT) in the participant's own bed. Within 72 hours of the PSG, questionnaire-based sleep apnea screening measures were completed with the participant and/or best source available using established TBIMS procedures by local staff blinded to PSG results. Sleep-related information during hospitalization was collected from the medical staff (snoring status, daytime sleepiness) or medical record (weight, height). The patient-reported outcome was the primary source of data. When data were missing due to the participant's inability to respond or with unknown responses, it was imputed using best source data if available otherwise was considered missing data.

Final Study Visit: Fully attended Level 1 PSG was conducted in accordance with the American Academy of Sleep Medicine recommended procedures[1]. The RPSGT also conducted a physical examination of the participants and rated agitation. Staff were instructed to allow participants to sleep their normal habitual sleep period with a minimum of two hours of sleep needed for adequate study. The lead center (James A. Haley Veterans' Hospital, Tampa, FL) served as a centralized scoring center for all sleep studies. All de-identified studies were scored by one of two certified RPSGT (CD, LW) and interpreted by a board-certified sleep medicine physician (DS, KC). All staff that scored and interpreted studies were blinded to other sleep assessments.

Sample Size Justification

Power Analyses from Research Plan:

(Aim 1) To test the hypothesis for Aim 1, a paired-sample diagnostic analysis (estimated sensitivities/specificities) for each screening measure relative to the criterion standard, Level 1 PSG) was

performed using the same sample of patients. Prevalence of sleep apnea (as determined by Level 1 PSG) was conservatively estimated to be 30% using investigators' published reports of 37-39% prevalence in acute rehabilitation TBI samples.36-37 A two-sided McNemar's test, assuming a significance level of α = 0.05, will have at least 80% power to detect a difference in sensitivities of 20% between screening measures for a sample size of 237. The power of the test will increase if the prevalence is higher than 30% (e.g., a prevalence of 35% would yield 87% power with 237 subjects and only require 203 subjects for 80% power). Furthermore, a sample size of 237 will have at least 80% power to detect a difference of 20% in sensitivities between screening measures in detecting sleep apnea.

(Aim 2) To test the non-inferiority hypothesis of the portable device for diagnosing sleep apnea, the non-inferiority of SE and SP (relative to SEH = 0.9 and SPH = 0.6, each within Δ = 0.1) were jointly tested at the significance level of α=0.05 by estimating the cross-product of two one-sided 1-α* confidence intervals;96 SEH and SPH were selected a priori and were considered sufficiently large to obviate the need Level 1 PSG. For the purposes of the clinical trial, the study was powered to demonstrate non-inferiority of Level 3 sleep studies relative to fixed values of sensitivity (SE) and specificity (SP).97 Minimum sample sizes of 83 and 153 patients achieved at least 80% power to detect non-inferiority of SE to 90% and SP to 60% with a non-inferiority limit of Δ = 0.1, using one-sided exact tests each at a 5% level of significance. In total, 214 subjects were available for analysis which yields 83.9% and 98.8% power, respectively, when testing the non-inferiority of SE and SP each at a 2.53% level of significance and maintaining a 5% level of significance when testing SE and SP jointly.[2]

Loss to follow-up:
See sample flow diagrams for each aim in corresponding publications.

Statistical Analysis Plan

Primary Endpoint: (Aim 1) Receiver Operating Characteristic Area Under the Curve
To determine the predictive utility of the screening tools for diagnosing mild (AHI ≥ 5), moderate (AHI ≥ 15), and severe (AHI ≥ 30) sleep apnea, receiver-operating characteristics (ROC) curve analyses were performed. A ROC curve plots the true positive rate (sensitivity) against the false positive rate (1 – specificity) for all possible cut-off scores of the screening tools. The area under the ROC curve (ROC AUC) and corresponding 95% confidence interval (CI) were estimated to provide a measure of overall discrimination for each screening tool. Standard diagnostic measures including sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV), and false negative rate (FNR) were calculated across varying cut-off scores for each screening tool. The Youden index, commonly used to determine the optimal cut-off score where equal weight is given to sensitivity and specificity (defined as "sensitivity + specificity – 1" was also calculated).88-91 For MAPI probability, cut-off scores of 0.1 to 0.9 in increments of 0.1 were summarized along with the optimal cut-off score. For the Berlin, participants were either low risk (0 or 1 category positive) or high risk (≥2 categories positive), so there is only one possible cut-off score. For Actigraphy, since less sleep is thought to be associated with worse sleep outcomes (such as sleep apnea), 12 hours minus the total sleep time was examined at 60- minute cut points from 3 to 10 hours. The ROC AUCs were compared among the four screening tools using a χ^2 test. Median with interquartile range (IQR) are provided.

(Aim 2) Sensitivity and Specificity Jointly Tested: To test the non-inferiority hypothesis of the portable device for diagnosing sleep apnea, the non-inferiority of SE and SP (relative to SEH = 0.9 and SPH = 0.6, each within Δ = 0.1) were jointly tested at the significance level of α=0.05 by estimating the cross-product of two one-sided 1-α* confidence intervals;[e3] SEH and SPH were selected a priori and were considered sufficiently large to obviate the need Level 1 PSG.

Using individual significance levels of αSE = αSP = α*=0.0253 ensures that the overall significance region of the joint test of both SE and SP simultaneously remains no greater than α=0.05. If the lower confidence limits (LCL) from both 1-α* = 94.9% confidence intervals are strictly above 0.8 for SE and 0.5 for SP, then a claim of non-inferiority of the portable diagnostic test would be established. Analyses were conducted for each AHI cutoff score (Total AHI ≥ 5, ≥ 15, and ≥ 30) for the overall sample and by subgroups. The non-inferiority thresholds were chosen based on a prior systematic review showing estimates of SEs and SP for AHI ≥5 were 0.96 (95% CI = 0.90, 0.98) and 0.76 (95% CI = 0.63, 0.85), respectively, across varying OSA prevalence rates.[2] Based on the lower bounds of these 95% confidence intervals (rounded to the nearest 10th), 90% SE and 60% SP with a delta of 0.1 were selected for declaration of non-inferiority.

1. Shayeb EM, Topfer LA, Stafinski T, Pawluk L, Menon D. Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disorders breathing: a systematic review and meta-analysis. *CMAJ*. 2014;186(1):E25-51. doi:10.1503/cmaj.130952
2. Shayeb EM, Topfer LA, Stafinski T, Pawluk L, Menon D. Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disorders breathing: a systematic review and meta-analysis. *CMAJ*. 2014;186(1):E25-51. doi:10.1503/cmaj.130952
3. Pepe MS. *The statistical evaluation of medical tests for classification and prediction*. 2003; Oxford University Press, New York.

Assessment of Safety

Potential adverse events were monitored by local study teams under oversight by local institutional review boards. Potential risks associated with this type of observational sleep research are minimal. The sleep assessment procedures employed in this study are commonly used in clinical sleep evaluations. Risk of physical harm or injury is unlikely given non-invasive nature of ACG and PSG. The Actiwatches® (ACG) wrist bands could be physically or emotionally distracting. The multiple monitoring devices required for (PSG) may be uncomfortable either physically or emotionally. The placement of breathing bands could result in contact dermatitis. Some of the questions asked during the assessment periods might be deemed personal or sensitive and make the participant feel uncomfortable. There was the risk that the study assessments will discover a medical condition previously unknown to the participant such as the diagnosis of sleep apnea or another sleep disorder. There was also a chance that a participant could experience medical distress or a medical emergency unrelated to the study during the course of an assessment. There was a remote chance that an outside party may discover a participant's identity and participation in the study. No risk to study personnel was anticipated.

Pregnancy

If a female participant was pregnant during the trial, no alteration of study procedures was indicated.

Data Safety Monitoring

A data safety monitoring board was not required.

Data Monitoring

The PI and Site PIs were responsible for study conduct and compliance with the overall protocol, good clinical practice (GCP), applicable regulatory requirements, and that the data recorded were valid. To achieve this objective, the study team continuously monitored the enrollment and completion of participants in the trial on a weekly basis using live-reports and bi-weekly, multi-center meetings.

Data Handling and Record Keeping

Procedures for the current study were carefully documented in a Manual of Procedures, and adherence to the procedures will be regularly monitored by the lead site. Standard procedures as recommended by the American Association of Sleep Technologists were followed for performing the PSGs, with the exception that the studies will be conducted on the rehabilitation units rather the in a sleep lab. Likewise, standard procedures for administering the screening measures and other instruments were also followed.

Institutional Review Board

All sites received Institutional Review Board approval to conduct the study.

Consent Process

Summary of Existing Currently Funded TBIMS Study Procedures. Eligibility is determined in consecutive admissions to inpatient brain injury rehabilitation by TBIMS staff already in place at each site. (Consent) TBIMS procedures in place commonly identify eligible candidates prior to admission with consent obtained during rehabilitation. TBIMS procedures in place at each site track subject eligibility and reason for exclusion into the TBIMS. These data are submitted quarterly to the TBIMS National Data Center for quality control purposes and subject tracking to meet data quality standards and input into Standards for Reports of Diagnostic Accuracy (STARD) diagrams. Consent and eligibility were tracked for this project using the same procedures already in place.

Protocol Deviation

Protocol deviations occur when noncompliance with the clinical trial or GCP requirements. No protocol deviations occurred during the trial.

Laws and Regulation

The clinical study was completed in compliance with all national laws and regulations of the United States. The trial was registered on www.clinicaltrials.gov.

Publication and Data Sharing Policy

In accordance with Standard Operating Procedures in place for each TBI Model System and implemented by the TBIMS National Data Center (Infrastructure leveraged for this project), C-SAS unique data elements will be archived at the lead study site (Tampa VA) and made available for future analyses and dissemination following TBIMS established procedures. Both internal and external investigators will be able to request the data following completion of a Notification Form and Data Use Agreement that was developed by the TBIMS National Data Center. Syllabus and protocol materials will be made available online similar to other data elements collected in the TBI Model Systems (https://www.tbindsc.org/Syllabus.aspx). The Internal and External Notifications for Data Use and Data Use Agreement Policies will remain a method for ongoing continued access for both funded TBI Model System investigators (Internal Requests) and other scientists (External Requests). Finally, all manuscripts describing the study's procedures and protocols will be submitted to PubMed Central to maximize data sharing.

Study Personnel and Roles by Site

Name	Title	Responsibilities
James A. Haley Veterans Hospital		
Risa Nakase-Richardson, PhD	Principal Investigator	All study-related activities
Leah Drasher-Phillips, MPH	Multisite Project Manger	Multi-site coordination, fiscal management, regulatory,

Name	Title	Responsibilities
		technology acquisition, communication, meeting planning, and execution.
Danielle O'Connor, MPH, MA; Lauren McGlynn, BA; Deveney Ching, MA, CRC, CBIS; Emily Noyes, MA	Research Assistants	Enrollment; data collection, entry, and auditing; sleep study scheduling
Daniel Schwartz, MD	Co-Investigator and Sleep Medicine Physician	Review scored Level 1 and HSATs and provided clinical reports
Karel Calero, MD	Sleep Medicine Physician	Review scored Level 1 and HSATs and provided clinical reports
Lancie Wharton, RPSGT	Registered Polysomnographic Technician	Attend and score Level 1 and HST sleep studies; scored Level 1 and HSATs
Carlos Diaz-Sein, RPSGT	Registered Polysomnographic Technician	Score Level 1 and HSATs
Mary Muscolino, RPSGT; Kenneth Parker, RPSGT; Laura Naughton, RPSGT, Marc Copeland RPSGT	Registered Polysomnographic Technicians	Conducted Level 1 and HST sleep studies
North Texas TBI Model System		
Marie Dahdah, PhD	Site Principal Investigator	All study-related activities
Kathleen Bell, MD	Co-Investigator	All study-related activities
Amber Merfeld, MPH-PAPH and Lacy McDonald	Research Assistants	Enrollment, data collection and entry, sleep study scheduling, regulatory
Jessica Behrs, RPSGT; Michael Elliot, RPSGT	Registered Polysomnographic Technicians	Conducted Level 1 and HST sleep studies
Craig Hospital		
Don Gerber, PsyD and Kimberly Monden, PhD	Site Principal Investigator	All study-related activities
Cynthia Harrison-Felix, PhD	Data Coordinating Center PI	All study-related activities
Jessica Ketchum, PhD	Biostatistician	Consult on study design, methodology, implementation; conduct statistical analyses, collaborate on dissemination activities, provide final dataset and data dictionary
Jody Newman, MA, CCC	Site Coordinator	Enrollment, regulatory
Angie Philippus, BA	Data Collector	Data collection, entry, and quality checks

Name	Title	Responsibilities
David Mellick, PhD	Data Coordinating Center Manager	Developed, implemented and maintained study web-based data management system
William Williams, MS	Data Coordinating Center Database Developer	Supported and provided web programming for study web-based data management system
Emily Almeida, MS	Data Analyst	Data analyses
	Registered Polysomnographic Technicians	Conducted Level 1 and HST sleep studies
Albert Einstein Healthcare Network/Moss Rehabilitation Hospital		
John Whyte, MD, PhD and Thomas Watanabe, MD	Site Principal Investigators	All study-related activities
Kelly Bognar, Rachel Raucci and Julie Wilson	Research Assistants	Enrollment, data collection and entry, sleep study scheduling, regulatory
	Registered Polysomnographic Technicians	Conducted Level 1 and HST sleep studies
University of Washington		
Jeanne Hoffman, PhD	Site Principal Investigator	All study-related activities
Jesse Fann, MD	Co-Investigator	Collaborated on decision making, participated on local and multi-site calls
Leslie Kempthorne, BS	Research Manager	Regulatory
Erica Wasmund	Research Study Coordinator	Enrollment, data collection and entry, sleep study scheduling
	Registered Polysomnographic Technicians	Conducted Level 1 and HST sleep studies
Ohio State University		
Jennifer Bogner, PhD	Site Principal Investigator	All study-related activities
Ulysses Magalang, MD	Co-Investigator	All study-related activities
Randa Mireb	Data Manager	Data entry and quality checks
Dominic Sauer and Jacob Goodfleisch	Project Managers	Regulatory, Data collection, and sleep study scheduling
Elizabeth Windisch	Recruitment Specialist	Enrollment
	Registered Polysomnographic Technicians	Conducted Level 1 and HST sleep studies
North Florida/South Georgia Veterans' Hospital		
Mo Modarres, PhD	Co-Investigator	study development, implementation, analysis, and dissemination

Name	Title	Responsibilities
Palo Alto VA Healthcare System & Stanford University		
Jamie Zeitzer, PhD	Co-Investigator	experimental design and the analysis of all actigraphy data and dissemination
University of South Florida		
Ambuj Kumar, MD and Athanasios Tsalatsanis, PhD	Statisticians	Data analyses and dissemination
Tea Reljic, MPH	Statistical Data Analyst	Data analyses and dissemination
Stakeholders		
Jill Coulter	Caregiver of TBI Survivor	Co-Chair Stakeholder Advisory Board Meetings, provide feedback on study materials, and dissemination
Jill Massengale, ARNP, DNP	Associate Chief of Nursing Research, James A. Haley Veterans' Hospital	Co-Chair Stakeholder Advisory Board Meetings, provide feedback on study materials, and dissemination
Mark Aloia, PhD	Associate Professor of Medicine, National Jewish Health Center, Denver; Senior Director of Global Clinical Research, Philips Healthcare	Facilitate translation of findings to industry
Joseph "Pepper" Coulter	Veteran and TBI Survivor	Study development, implementation, and dissemination
Col. Geoffrey Grammer, MD and Scott Livingtson, PhD, PT, ATC, SCS	Defense and Veterans Brain Injury Center	Participate in Stakeholder Advisory Board Meetings, provide feedback on study materials, and dissemination
Sidney Hinds, MD	Former DVBIC National Director, Program Coordinator for Brain Health Research for the DoD Blast Injury Research Program Coordinating Office	Participate in Stakeholder Advisory Board Meetings, provide feedback on study materials, and dissemination
Kathryn Keiffer, SLP	Speech Language Pathologist, James A. Haley Veterans' Hospital	Participate in Stakeholder Advisory Board Meetings, provide feedback on study materials, and dissemination
Kerri Martin, OTR/L	Occupational Therapist, James A. Haley Veterans' Hospital	Participate in Stakeholder Advisory Board Meetings, provide feedback on study materials, and dissemination

Name	Title	Responsibilities
Christina Montemayor-Wong, RN	Nurse, Brain Injury, James A. Haley Veterans' Hospital	Participate in Stakeholder Advisory Board Meetings, provide feedback on study materials, and dissemination
Linda Picon, MCD, CCC-SLP	VA Senior Consultant, TBI Liaison to the Defense Centers of Excellence for PH and TBI	Participate in Stakeholder Advisory Board Meetings, provide feedback on study materials, and dissemination
Amy Pieragowski, OTR/L, CBIS	Occupational Therapist, James A. Haley Veterans' Hospital	Participate in Stakeholder Advisory Board Meetings, provide feedback on study materials, and dissemination
Joel Scholten, MD	National Director, Physical Medicine and Rehabilitation, Veterans Health Administration	Participate in Stakeholder Advisory Board Meetings, provide feedback on study materials, and dissemination
Steven Scott, DO	Chief, Physical Medicine and Rehabilitation, James A. Haley Veterans' Hospital	Participate in Stakeholder Advisory Board Meetings, provide feedback on study materials, and dissemination