Comparison 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.

Statistical and Power Considerations

Data Quality & Management. During its' 25-year tenure, the TBIMS has developed extensive quality control procedures to minimize missing data (quarterly missing data reports, data entry filters/feedback), minimize attrition (follow-up strategy standards with monitored adherence) and enhance data capture (periodic on-site audits) which will be part of the infrastructure utilized in this study assuring robust capture of needed covariates and outcomes. Study sites collaborating on sleep research meet monthly via teleconference to review procedural issues and review quarterly reports as part of the TBIMS Sleep Special Interest Group. Existing bi-annual meetings in Washington DC will be utilized to discuss data collection, quality, analyses, and dissemination activities throughout this grant cycle. A mandatory 2-day training will occur with site PI and PSG technician in Tampa, Florida to standardize assessment protocols. Study teams will meet weekly in the first three months to monitor progress with IRB activities and hiring of new personnel. Biweekly telephone calls will occur the following three months and transition to monthly calls to discuss study progress. (Data Management). The database will be developed by the TBIMS National Data and Statistical Center at Craig Hospital which has the existing infrastructure and IRB-approved clearances to accept both civilian and VA data for the TBIMS program. Only registered TBIMS users will be assigned a password to access the database for online data entry. Once data collection is complete, study information will be entered into a password protected database accessible via secured-internet connection. Study databases will be automatically linked to existing TBIMS databases with demographic, injury severity, and rehabilitation outcome data collected as part of the TBIMS infrastructure. All data will be de-identified to protect the privacy of participants. Each subject will retain the original TBIMS ID number to allow for merging of the data between the C-SAS and TBIMS data elements. Project investigators will audit data entry prior to final submission as part of routine TBIMS study procedures. To facilitate scoring and interpretation of the PSG studies, the PSG data from all sites will be transferred from the National Data Center to the Tampa VA for scoring and clinical interpretation by a board-certified sleep medicine physician within 7 days of study completion. The database sits behind a Cisco ASA 5520 firewall on a separate Microsoft SQL 2005 Server and will utilize whole database encryption technology using NetLib Encryptionizer (FIPS 140.2 compliant). All local information security practices will be implemented. Due to HIPAA and Institutional Review Board (IRB) guidelines, any personal identifying information transmitted from the participant to the research office needs to remain private and confidential. Data analysis will be performed under the direction of Dr. Jessica Ketchum (Senior Statistician) with assistance from the National Data and Statistical Center. (Missing data): To ensure data quality and minimize missing data several levels of data checks will be implemented. First, when data collectors enter data into the web based data entry program they will be notified which fields have been skipped. In general all fields, with the exception of some text fields, will have valid codes associated with them, so no true blank variables should exist in the database. Furthermore, when appropriate, skip patterns will exist for some variables, which can automatically populate variables that would then be considered "not applicable". The data entry program will also not allow an entry that isn't considered valid mostly through the use of drop down controls in which only valid answers are presented. Second, while data is being entered there will be a process for a data collector to run various data checks like logical errors (e.g. injury date occurring before birth date) or data inconsistencies (e. g. currently working, but hours of work past week = 0) can be programmed into the system to alert the data collector of variables that need attention. Above and beyond the notifications of errors and missingness that occurs while a data collector is entering data, all authorized people of the study can run real time reports that reflect not only missingness by variable, but missingness by person. Reasons for missingness have been

established in the TBIMS database and will be applied for this study (i.e., unknown, not applicable) and generated in missing data reports for discussion. As the primary hypotheses require complete data from each subject (STOPBang, ACG, Level 1 PSG, and Level 3 PSG) all efforts will be made to minimize missing data from these key variables. For example, a patient may need to repeat PSG if it was not adequately captured. Any reasons for missing data will be recorded for each patient for a global sensitivity analyses to examine the effect of missingness on the conclusions of the hypotheses tests. Missing data reports will be reviewed on a quarterly basis by staff at the NDSC as well as coordinators at each site. This study will be a multi-site, prospective observational study investigating the comparative effectiveness of sleep apnea screening (Aim 1) and diagnostic (Aim 2) measures. A total of 258 subjects will be recruited to allow for attrition and meet study goals. Initial analyses will be undertaken to inspect data for errors, inconsistencies, and incomplete information. This will include examining the distribution of the data (frequency tables, histograms, box-plots). Data anomalies that cannot be resolved will be examined by study staff for clarification and possible correction. During the verification process, we will correct any inaccuracies in data entry and track the changes in the data accordingly. Incomplete entries will also be rectified if the missing information is available. However, missing data are inevitable in any study. Given the novelty of this area, imputation methods for missing data will not be applied. Efforts to minimize missing data impacting analyses include 1) close monitoring of missing data in real time (missing data reports reviewed biweekly) and 2) repeat testing given the captive nature of the audience during inpatient rehabilitation. Serial attempt to capture data will be tracked and analyzed across key demographic and injury severity variables. We will also examine consent rates and attrition from time of consent to completion of diagnostic tests and illustrated with the use of the STARD diagram. Participants who drop-out vs. those who complete the study will be compared on the key demographic and injury severity variables (e.g., sex, race, severity measures) to determine if there are group differences. If differences are present, interpretations of all study results will be made in light of these differences. Data analysis will begin with a review of descriptive statistics for all major variables and all major subgroupings of variables in the data set.

Data analysis plan specific to each aim. The analytic methods designed *a priori* for each hypothesis are detailed below. Reporting of findings will strictly adhere to the requirements of the STARD guidelines.

Aim 1 (Hypothesis 1.1): *Sensitivity and specificity of actigraphy will be superior compared to clinical prediction rules (i.e., STOP-Bang) for determining risk of sleep apnea as diagnosed by Level 1 polysomnography in TBI patients undergoing inpatient rehabilitation.* Justification of Assumptions/Power Estimate: To test hypothesis 1.1, a paired-sample diagnostic analysis will be performed as the estimated sensitivities/specificities for STOPBang and ACG (each versus the reference gold standard, Level 1 PSG) will be estimated using the same sample of patients. Prevalence of sleep apnea (as determined by Level 1 PSG) is conservatively estimated to be 30% using investigators' published reports of 37-39% prevalence in acute rehabilitation TBI samples.[1-2] A two-sided McNemar's test, assuming a significance level of $\alpha = 0.05$, will have at least 80% power to detect a difference in sensitivities of 20% between ACG and STOPBang if the total sample size is at least 237 patients. 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 actigraphy and STOP-Bang in detecting sleep apnea. Analytic Plan: The sensitivity (SE) and specificity (SP) of both STOPBang and ACG will be estimated using Level 1 PSG as the reference gold standard. As STOPBang and ACG are measured on an interval scale, and are not

dichotomous, pre-specified cut-points for each screening tool will be used to classify a subject as being at high risk for sleep apnea. We expect that STOPBang values > 5 and abnormal ACG total sleep time (< 5 hours with desaturation) will produce sufficiently high SEs with reasonable tradeoff in SP (noting that SE and SP are inversely related). Similarly, for Level 1 PSG, a diagnosis of sleep apnea will be made if AHI ≥ 5. Cross-tabulations of STOPBang and ACG screening for high risk of sleep apnea (positive/negative) versus Level 1 PSG diagnosis (positive/negative) will be constructed and estimates of diagnostic accuracy (i.e., sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy, ROC curves, AUC) will be estimated along with 95% confidence intervals. To address hypothesis 1.1, two-sided McNemar's tests will be used to compare the paired SEs and paired SPs between STOPBang and ACG assuming a significance level of $\alpha = 0.05$. All analyses will be performed using SAS v.9.4 (SAS Institute Inc., Cary, NC).

(Aim 2: Hypothesis 2.1): *Level 3 portable polysomnography with greater consumer accessibility will be equivalent (non-inferior) to the less accessible Level 1 polysomnography in determining presence of sleep apnea in TBI patients undergoing inpatient rehabilitation*. Justification of Assumptions/Power Estimate: To test hypothesis 2.1, the sensitivity (SE) and specificity (SP) of Level 3 PSG (compared to Level 1 PSG, the reference gold standard) will each be estimated and compared to fixed hypothesized rates of SE and SP considered sufficiently large enough to potentially obviate the need for Level 1 PSG. Based on a review of the literature and consensus among the investigators in this study, SE and SP no worse (non-inferior) to 90% and 60%, respectively, are considered sufficiently large enough. To test for non-inferiority of the SE to 90% and the SP to 60%, a non-inferiority threshold of $\Delta = 0.1$ is assumed for both measures. A sample size of at least 83 patients is necessary to achieve a minimum of 80% power to test the non-inferiority of the SE to 90% (assuming $\Delta = 0.1$ and $\alpha = 0.05$). A sample size of at least 153 patients is necessary for a minimum of 80% power to test the non-inferiority of the SP to 60% (assuming $\Delta = 0.1$ and $\alpha = 0.05$). Thus, a total of 153 subjects is required to sufficiently power both non-inferiority hypotheses. Analytic Plan: To test hypothesis 2.1, the sensitivity (SE) and specificity (SP) of Level 3 PSG (compared to Level 1 PSG, the reference gold standard) will each be estimated and compared to fixed hypothesized rates of SE and SP of 90% and 60%, respectively, considered sufficiently large enough. Level 1 PSG (reference) diagnosis of sleep apnea will be made based on AHI ≥ 5. Level 3 PSG (test) diagnosis will be made based AHI ≥ 5. A cross-tabulation of Level 3 PSG (positive/negative) versus Level 1 PSG (positive/negative) will be constructed and standard measures of diagnostic accuracy will be estimated along with 95% confidence intervals (i.e., sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy). To test for non-inferiority of the SE to 90% and the SP to 60%, a non-inferiority threshold of 0.1 is assumed. If the lower bound on the 95% confidence interval for SE is strictly above 80% and the lower bound on the confidence interval for SP is strictly above 50% then non-inferiority of Level 3 PSG (compared to Level 3 PSG) can be established. All analyses will be performed using SAS v.9.4 (SAS Institute Inc., Cary, NC).

Exploratory Aim 1 (HTE analyses): While an analysis of heterogeneity of treatment effects does not apply to the current study design, an important question to answer is whether the diagnosis of sleep apnea can be impacted by the presence of post-traumatic amnesia (PTA). The confusion and behavioral dysregulation associated with PTA could potentially reduce the person's ability to tolerate the procedures. While the lead site has successfully obtained PSG with EEG with persons experiencing PTA, this was a single site study with a select subject population (veterans who primarily experienced blast-induced TBI). The current study will allow for an assessment of differences in diagnostic accuracy with persons who are currently experiencing PTA in comparison to those who have cleared PTA. PTA will be operationalized based on the criterion used by the TBIMS consortium (obtaining an Orientation Log or

Galveston Orientation Amnesia Test scores in target range or consistent, repeated demonstration of orientation in medical record review). Analytical Plan: To address exploratory aim 1 regarding the heterogeneity of the screening and diagnostic accuracy across relevant sub-groups, the methods detailed for the primary aims will be replicated for the subgroups of injury severity (GCS), cognitive status (PTA), motor confounds (spasticity and hemiparesis), and limb placement. As these are exploratory aims and the study is not powered to test for differences or non-inferiority within each sub-group, focus will be on comparing the effect size of proportions (Cohen's *h*) among the subgroups. Values for *h* of 0.2, 0.5, and 0.8 are typically considered to be small, medium, and large differences, respectively. All analyses will be performed using SAS v.9.4 (SAS Institute Inc., Cary, NC).

Exploratory Aim 2: Two new screening measures, MAPI and Berlin, have been used extensively as screening measures for sleep apnea in the general population, however little is known about their diagnostic capabilities in TBI patients undergoing inpatient rehabilitation. This study proposes to explore the diagnostic accuracy of these screening tools within this specific population. (ADD ANY OTHER DETAILS/JUSTIFICATION) Analytical Plan: Receiver operator curve (ROC) analyses will be conducted for MAPI and Berlin each. This will provide estimates of sensitivity and specificity for all possible cut-points on the MAPI and Berlin. Of particular interest is to identify sufficiently high sensitivity without compromising too much specificity (e.g., 90% SE and SP no smaller than 60%). All analyses will be performed using SAS v.9.4 (SAS Institute Inc., Cary, NC).

References

1. Webster JB, Bell KR, Hussey JD, Natale, TK, Lakshminarayan S. Sleep apnea in adults with traumatic brain injury: a preliminary investigation. *Arch Phys Med Rehabil*. 2001; 82:316-21.
2. Holcomb EM, Schwartz DJ, McCarthy M, Thomas B, Barnett SD, Nakase-Richardson R. Incidence, characterization, and predictors of sleep apnea in consecutive brain injury rehabilitation admissions. J Head Trauma Rehabil. 2016;31(2):82-100. doi:10.1097/HTR.0000000000000230.