Title: Implementation of digital vital sign monitoring to decrease sleep interruption and enhance recovery in Phase II of the **PRO**moting **S**leep, **P**atient **E**ngagement and **R**ecovery (PROSPER) project

Study Co-Chairs: Vijaya Gottumukkala, Diwakar Balachandran & Eileen Hacker

Collaborators: Anaeze C. Offodile II, Juliann Truver, Samuel Swanson, Josiah Halm, Kodwo Dickson, George Chang, Michael White, Mary Welch, Daniel Mullen, Nicole Vaughan-Adams, Darrell Puckett, Kristofer Jennings, Delmy Vesho

Important Note: This protocol contains a parent trial (main study) and a substudy component.

PROSPER (Parent Trial)

1.0 Objectives

1.1 Primary Objective: Investigate the impact of our sleep enhancement intervention, which entails a wearable digital vital sign monitoring device, on variation in the quality of life of acute care cancer patients

1.2 Secondary Objectives:

a. Assess the impact of our sleep enhancement intervention on acute care utilization e.g. length of stay, 30-day readmissions
b. Assess the implementation and feasibility of wearable digital vital signs capture in an inpatient oncologic setting using validated instruments such as system usability scale (SUS) and Weiner implementation outcomes (AIM, FIM, IAM).
c. Assess the impact, via validated survey instruments, of our sleep enhancement intervention on patient mood, patient activation and satisfaction with inpatient stay experience.

2.0 Background/Rationale

Post hospitalization syndrome refers to a generalized increased risk for a range of adverse health related events following an acute hospitalization.[1] The mechanism is thought to be driven by allostatic and physiologic stress acquired during the hospitalization.[2] Sleep disruptions, deconditioning from acute illness, loss of personal autonomy, pain, and disruption of normal circadian rhythms are prominent examples.[2] Numerous reports have documented the prevalence and risk of these perturbations. The clinical impact of post-hospitalization syndrome is also being increasingly recognized. This includes but is not limited to immune dysfunction, coagulopathy, impaired physical coordination and poor wound healing.[3–5] According to estimates, up to 20% of Medicare beneficiaries (approx. 2.6 million seniors) are readmitted within 30 days for reasons unrelated to the diagnosis that prompted the index admission.[6] As a result, post-hospitalization syndrome has become the impetus for numerous quality improvement (QI) initiatives that promote successful recovery. A prominent example involves a multi-level QI project implemented at Ochsner clinic that bundled reduced nighttime noise, passive vital monitoring, delayed morning phlebotomy and use of red-enriched lighting after sunset.[2] This program was associated with reduced length of stay (LOS), improved readmission rates and enhanced sleep quality across a sample of 3425 consecutive medical-surgical patients.[2] However, it is unclear whether and to what extent these findings are generalizable to a population of acute care cancer patients. Phase I of the PROSPER protocol involved the use of various standard of care methods to minimize sleep interruptions during the hours or 10pm to 6am including, noise monitoring and reduction strategies, minimizing bedtime medication administration, delayed early morning phlebotomy, and use of red-light instead of white light when provider-patient interactions were necessary. These interventions were bundled into a “clustered care approach” along with eliminating nocturnal vital sign check when possible. Clustered care has been shown to improve sleep quality, improve

patient satisfaction and clinical outcomes. One concern with clustered care regarding avoiding intermittent nocturnal vital sign checks is that these sleep interruptions are justified by the need to anticipate and prevent clinical deterioration. In this proposal we aim to use an FDA-approved digital vital sign motioning device (ViSi Mobile, Sotera Wireless, San Diego CA) to replace manual nurse bedtime vital sign check allowing for vital sign evaluation at the clinically appropriate cadence without compromising sleep quality.

This FDA approved digital wearable technology that continuously monitors vital signs has previously been demonstrated in peer-reviewed studies to improve outcome measures such as decreased need to call rapid response teams, ICU transfer, length of stay, and 30-day mortality. To our knowledge, the effects of substituting digital motoring for manual nocturnal vital sign checks, and the effects of reducing / eliminating sleep interruptions on sleep quality and quantity in an acute oncologic setting has not been previously reported. **Our aim is to investigate the impact of the Phase II of our "PROSPER" bundle with the addition of digital passive vital sign monitoring to replace routine nocturnal vital sign checks on sleep hygiene (quantity and quality), clinical outcomes (LOS, readmission) and patient-centered outcomes (patient experience and satisfaction) in an acute oncologic patient population.**

Hypothesis

We hypothesize that the implementation of our wearable technology intervention will result in a reduced LOS, lower 30-day readmission rates, and improved patient recovery (sleep quality and quantity), and enhanced subjective measures of patient engagement (PAM-13), satisfaction (HCAHPS) and well-being (EQ-5D-5L).

3.0 Research Plan

3.1 Study Population

This study will include consented consecutive patients who are admitted to the medical-surgical floor at MD Anderson Cancer Center (Texas Medical Center location only) for the conditions and/or surgical procedures outlined below.

3.2 Inclusion Criteria

Adult patients (> 18 years of age), English-speaking, able to complete consent and survey materials. Patients must be admitted to the hospital for at least 3 nights. Patients using pharmacological sleeping aides will be included in the study, as this will help us understand if the intervention also helps patients with pre-exisitng sleep disturbances.

3.3 Exclusion Criteria

Vulnerable populations (pregnancy, incarcerated, history of delirium, suicidal ideation, ischemic stroke with measurable neurologic deficit, cerebral palsy, seizures).Patients concurrently enrolled in contact isolation with SARS-CoV2 will be excluded. Lastly, hospice or hospice-bound patients will also be excluded. Any patient can remove themselves from the study at any point.

Table 1: Study participants

Participating Surgical Services	Participating Medical Services
Colorectal Surgery	Hospitalist service

3.4 Study Design

This is a pragmatic, quasi-experimental study wherein patients admitted for any of the aforementioned conditions will be allocated into treatment (ViSi mobile plus PROSPER) and control (PROSPER only) based on non-critical care bed availability on a floor unit. Specifically, for patients on colorectal service admitted to P10 floor, one side ("unit A") will be designated as an intervention arm while the other ("unit B") will serve as a control arm. For patients admitted to Hospitalist Medicine service; patients on " unit G21" will be designated as the intervention arm, and patients admitted to "unit G22" as the control arm. Our pseudorandomization scheme is based on the naturally occurring random variation in bed assignment by availability across both the intervention and control units on a given floor, or floors at the time of patient enrollment. Since bed designation is made by hospital admissions based on availability, it is independent of the care delivery processes across the study floors / units. Our approach is intended to reduce the

burden on frontline staff, i.e., changing existing workflows to randomize patients and track allocation in a database. It also serves to reinforce the embedded intent of our QI work.[7] Participants, family members and clinicians will not be blinded to the intervention, and given our pragmatic design, we will not attempt to control patients' communication or information-seeking behaviors beyond the pseudo-randomization described above. The intervention wing will employ the following initiatives to improve the sleep quality, level of engagement, and overall care journey of patients.

1. Passive digital monitoring of vital signs – Blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature – will be wirelessly and passively collected using a U.S. Food and Drug Administration-approved wireless technology, which is worn on the wrist and chest (ViSiMobile, Sotera, San Diego, Calif), and recorded data will be sent directly to the electronic medical record (Epic Systems Corporation, Verona,Wis) at protocolized set intervals. Abnormal vitals will trigger a nursing alert via text message or page. If an in-person assessment is warranted, handheld red-spectrum lighting will be used by nursing staff as an alternative to the standard overhead white lighting.[2]

An intervention checklist will be created to ensure consistent adherence and documentation. Monthly feedback sessions will be held with the respective care teams to solicit frontline feedback with respect to implementation issues. Patients in the control arm will receive routine care per hospital routine.

3.5 Recruitment

Potential participants admitted to participating floors in the study will be identified in the EMR. Research coordinators will approach patients to participate in the study within 1-2 days of admission. The recruitment process will be documented and attested by the Investigators and their delegates.

3.6 Informed Consent

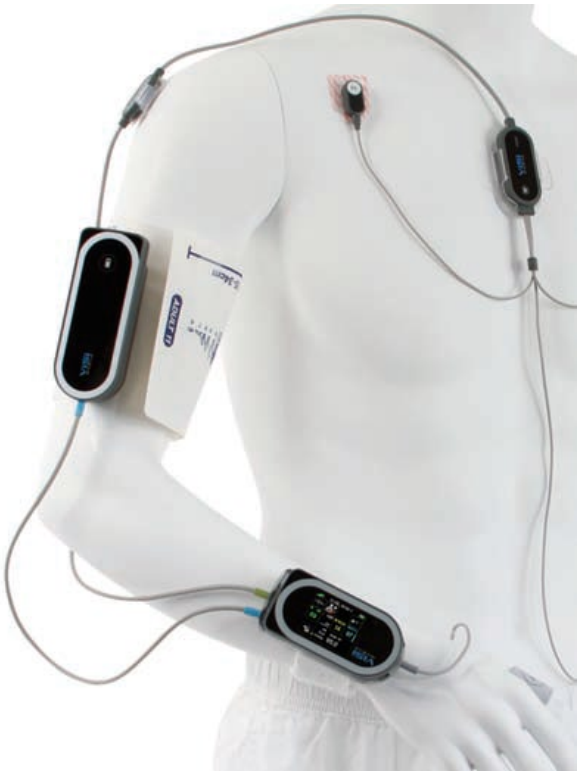
Informed Consent from eligible patients will be obtained following the Clinical Research Informed Consent SOP 4.0.

3.7 Patient Allocation to study groups

There is generally one patient per room and patient assignment to a room is largely driven by unit census (i.e., bed availability) as well as other clinical factors: e.g., need for an isolation room, nursing availability. All of these factors vary independently of the preferences of the patient or research team, reducing the risk for systematic bias. The unit of randomization is by pod on a floor. Research coordinators as part of the "on-boarding process" will also provide culturally competent instructions and in-person teaching for device use.

3.8 Data collection

This will entail a blend of Epic medical record abstraction and primary data collection using validated surveys. Example of variables to be exstracted from the medical record include patient demographics (e.g., age, sex, race), primary diagnosis (cancer type), body mass index (BMI), timing of AM phlebotomy, comorbid conditions (used to compute Charlson co-morbidity index), length of stay, and 30-day readmission. To reduce survey burden for patients and ensure parity in scope of responses across the 2 groups, the majority of questionnaires will be distributed at two time points - at admission and within 24 hours of the date of discharge. All validated surveys will be administered via the hospital-owned iPad device, via text message or email, or recorded manually. A password-protected database will be used to collate the clinical and outcomes data collected. Lastly, all patients will receive a phone call 24 hours after discharge to ensure all questions are answered and follow-up care has been arranged.



The digital device is worn on the wrist, like a watch, and provides continuous vital sign monitoring using a three-lead system that included electrocardiography (ECG), pulse oximetry, continuous noninvasive blood pressure, mean arterial pressure, temperature, respiratory rate, heart rate, and pulse rate. Patients will be able to view their vital signs on the wrist-worn device's display screen.
Pre-programmed alarm parameters for abnormal vital signs will be established by the research team in close collaboration with the clinical and nursing leadership of each participating service (Table 1).[2] Nurses will be alerted to abnormal vital signs via secure machine to nurse messaging via a Sotera app on the iPhone device that is carried by each nurse. This workflow is consistent with published literature.[2] Continuous monitoring data from all patients wearing the ViSi Mobile monitor will be recorded directly into the electronic medical record at intervals determined by the clinical team. (EPIC, Epic Systems, Verona WI) and will also be temporarily stored in an on-premise server. The ViSi Mobile data will be periodically accessed and downloaded into a virtual private cloud operated by Sotera Wireless on Amazon Web Services. This data does not include protected healthcare information and is deidentified. It includes all vital signs, device data, user interactions, and full waveform data, including high frequency ECG, PPG, and accelerometer data. This information will be attributed to a unique patient via time stamp and the ViSi Mobile device ID of the wrist monitor. The device ID must be recorded for all consenting patients in the EMR. Sotera Wireless research staff will access the cloud data and apply signal processing and machine learning algorithms to quantify metrics and events from the continuous monitoring data during sleep. MD Anderson staff will annotate events, collect patient reported outcome responses (Table 2 and 3). Also, in addition to vitals and alarms the MD Anderson EMR will be configured to record VISI Mobile Device ID for each patient placed on continuous monitoring. The device ID will allow patient data in the Sotera cloud server to be linked to patient data in the EMR by MD Anderson staff. Sotera will have access to designated MD Anderson research staff and clinicians to collaborate on the development of novel metrics, graphic reports, and explore how patient care would benefit from clinically meaningful alerts triggered by the new information. Access to MD Anderson research staff & clinicians will include a minimum of 4 hours of clinical collaboration and consultation on a quarterly (3-month) basis throughout the duration of the proposal. MD Anderson staff will have the ability to correlate this new information with EQ-5D scores, PAM-13 scores, HADS scores, Richard Campbell Questionnaire responses, and implementation outcome surveys.

3.9 Outcomes

Patient-Centered Outcomes (Primary): The present study will be powered to the EQ-5D measure at discharge, our primary outcome, which allows us to discern variations in self-reported quality-of-life over the course of the inpatient care episode that is attributable to our intervention (Table 2)

Table 2: Patient Reported Outcomes

Primary Outcome	**Instrument**	**Duration**	**Analysis level**	**Assessment Calendar**
Quality of Life	EQ-5D-5L	2-5 min	Patient	Admit, discharge +/- 1 day
Secondary Outcome	**Instrument**	**Duration**	**Analysis level**	**Assessment Calendar**
Patient Engagement	PAM-13	3 min	Patient	Admit, discharge +/- 1 day
Patient Mood	Hospital Anxiety & Depression Survey (HADS)	2-5 min	Patient	Admit, discharge +/- 1 day

Patient Satisfaction	1. HCAHPS 2. Net Promoter Score	7 mins 2 mins	Floor unit Patient	4x a year (rolling) Discharge +/- 1 day
Sleep Perception	Richard Campbell Sleep Questionnaire (Daily)	1 min	Patient	Admit, discharge +/- 1 day

PAM: Patient Activation Measure; EQ-5D-5L: EuroQol – 5 dimension – 5 level; HADS: Hospital Anxiety and Depression Scale; HCAHPS – Hospital Consumer Assessment of Healthcare Providers and Systems

Additional Outcomes:

a. *Acute care utilization:* Median length of stay (LOS) in hours, all-cause Emergency Room (ER) visit, and hospital readmission within 30 days postoperatively

b. *Implementation and feasibility outcomes:* We will also perform psychometric assessments, from the perspective of patient and nursing stakeholders, of the implementation process and perceived effectiveness associated with our passive vital sign monitoring intervention. Three 5-item validated implementation metrics of Acceptability (AIM), Appropriateness (IAM), Feasibility (FIM) will be used to monitor and evaluate the adoption of our passive vital signs monitoring intervention.[8] We will also leverage the system usability scale (SUS) to examine the usability and ergonomics of the passive vital sign monitoring platform (Table 3).[9]

Table 3: Implementation Outcomes

Outcome	Instrument	Duration	Analysis level	Assessment Calendar
Intervention usability	System Usability Scale	5 mins	Patient, Nurse	Admit, discharge +/- 1 day
Intervention acceptance	Acceptability of Intervention measure (AIM)	3 min	Patient, Nurse	Admit, discharge +/- 1 day
Intervention feasibility	Feasibility of Intervention Measure (FIM)	2-5 min	Patient, Nurse	Admit, discharge +/- 1 day
Intervention appropriateness	Intervention Appropriateness Measure (IAM)	2-5 min	Provider, Nurse	Admit, discharge +/- 1 day

c. *Secondary patient-reported outcomes:* Validated surveys that capture patient mood (HADS), engagement with care (PAM), and satisfaction with inpatient stay (HCAHPS, Net promoter score), outlined in Table 2 as well, will also be administered to intervention and control patients according through a pre-specified schedule.

d. *Sleep interruption and relationship to patient outcomes:* Sleep interruptions between the control and intervention arms will be collected electronically from the hospital Electronic Medical Record

3.10 Statistical Analysis Plan

Means with standard deviations, frequencies and percentages will be used to convey descriptive statistics. Standard tests of association (chi-squared, t-tests) will be used for comparing characteristics between the control and intervention arm. Inverse probability weighting using propensity scores modeled from baseline covariates and instrumental variable analysis will be the quasi-experimental approach used to minimize any confounding bias from our pseudorandomization process. We will model most outcomes with weighted multivariate generalized mixed effects regression models, focusing primarily on estimate the average treatment effect. The effect of unit will be modeled using a random intercept term. Care utilization outcomes will be compared using standard time-to-event models and log-rank testing. Final analyses will be performed when all data has been entered, cleaned, and locked.

All analyses will be based on an intent-to-treat framework. For missing covariate values, a multiple imputation approach will be used. Outcomes will be assumed to be missing at random; a sensitivity analysis will be conducted to assess the robustness of significant findings to different magnitudes of missing data mechanisms.

3.11 Sample size justification

Preliminary calculations, based on an estimated conservative change of 10% from baselines scores in QOL, as measured by the EQ-5D instrument total score (with a baseline of mean of 13 units and standard deviation of 5 units). We expect to detect a significant change with at least 80% power using 250 patients per treatment arm. To account for increased estimation variance due to propensity score-based reweighting (and a small rate of drop-out after enrollment), we plan to enroll 350 patients per treatment arm to ensure a reasonable expectation of significance.

4.0 Sub-Study

This pilot sub-study is intended to compliment the parent trial by generating objective measures of sleep quality (sleep time, sleep latency, efficiency, awakenings after sleep onset) and leveraging additional patient-reported outcome measures (i.e. PROMIS) in this smaller population of consented patients. The present sub-study is nested within the parent trial, i.e. eligible patients for the parent trial will be eligible for the sub-study.

4.1 Hypothesis

a. *Primary Hypothesis*: Participants assigned to PROSPER with digital vital sign monitoring will trend toward improved objective sleep parameters compared to participants assigned to PROSPER without digital vital sign monitoring.

b. *Secondary Hypothesis:* Participants assigned to PROSPER with digital vital sign monitoring will trend toward fewer sleep disturbances and reduced fatigue compared to participants assigned to PROSPER without digital vital sign monitoring.

4.2 Objectives

a. *Primary Objective:* Determine the preliminary effects of the PROmoting Sleep, Patient Engagement and Recovery (PROSPER) intervention with digital vital sign monitoring (experimental group) compared to PROSPER without digital vital sign monitoring (control group) on objective sleep parameters (total sleep time, sleep latency [minutes until sleep onset], sleep efficiency, frequency and duration of awakenings after sleep onset [WASO], and number of awakenings).

b. *Secondary Objective:* Determine the preliminary effects of the PROSPER intervention with digital vital sign monitoring (experimental group) compared to PROSPER without digital vital sign monitoring (control group) on patient reported symptom outcomes (real-time fatigue, fatigue [PROMIS] and sleep disturbance [PROMIS]).

4.3 Research Plan

a. *Study Population:* In order to participate in the sub-study, participants must be enrolled in the PROSPER trial. We plan to enroll 100 participants from the parent trial in this pilot study, 50 participants from each arm of the parent trial. The inclusion and exclusion criteria for the sub-study are the same as the parent trial.

b. *Inclusion criteria:* Adult patients (> 18 years of age), English-speaking and able to complete consent and survey materials are eligible to participate. Potential participants must be admitted to the hospital for an anticipated minimum of 3 nights.

c. *Exclusion criteria:* Vulnerable populations (pregnant, incarcerated, history of delirium, suicidal ideation, ischemic stroke with measurable neurologic deficit, cerebral palsy, seizures), primary brain tumor/metastases patients) are not eligible. Patients concurrently enrolled in contact isolation with SARS-CoV2 will be excluded. Lastly, hospice or hospice-bound patients will also be excluded. Any patient can remove themselves from the study at any point.

4.4 Study Methods

a. *Study design:* The pilot sub-study will be integrated into the parent trial. This pilot study leverages a two-group, pre-post test design to conduct preliminary tests for differences between the experimental arm (PROSPER intervention with digital vital sign monitoring) and the control arm (PROSPER intervention without digital vital sign monitoring) on objective sleep parameters and patient reported sleep disturbances and fatigue.

b. *Recruitment:* Once participants are enrolled in the parent trial, they will be evaluated for inclusion in the pilot sub-study based on the availability of the device that measures objective sleep parameters (Actiwatch Spectrum Pro®). Thirty wrist actigraphy devices (Actiwatch Spectrum Pro®) are available for use at any given time. Fifty participants from the patient care units designated as the intervention arm for the parent trial will be enrolled as treatment patients in the substudy; fifty participants from the patient care units designated as the control arm will be enrolled as control patients in the substudy. Participants will be consecutively enrolled in the sub-study as they are enrolled in the parent study although enrollment may pause if wrist actigraphy devices are not available.

c. *Instrumentation:* Objective sleep parameters will be assessed with the Actiwatch Spectrum Pro® during the course of hospitalization, consistent with the parent trial. Patient-reported sleep disturbances will be measured with the PROMIS Sleep Disturbance Adult Short Form. Patient-reported fatigue will be measured in real-time with a one-time global fatigue intensity rating over the course of the hospitalization and the PROMIS Fatigue Adult Short Form. The PROMIS instruments will be completed upon enrollment and discharge +/- 1 day, consistent with the parent trial.

d. *Sleep:* The Actiwatch Spectrum Pro® (Phillips Respironics, Bend, OR) will be used to objectively assess sleep parameters. Sleep parameters will be computed using Actiware® software (V. 6.0). Data are stored in one-minute epochs. The software scores each epoch as wake or sleep. The software assigns rest, sleep, or active intervals based on activity counts. The default software settings will be used for the analysis as recommended by the manufacturer. Using an automated process, the software determines sleep start by searching for the first 10 minutes during which no more than one epoch is scored as "wake." The sleep parameters produced include total sleep time, sleep latency (minutes until sleep onset), sleep efficiency, frequency and duration of awakenings after sleep onset (WASO), and number of awakenings. Sleep variables will be scored for each 24-hour period, and averages over the course of hospitalization will be computed for nighttime sleep alone and nighttime sleep plus daytime naps. Wrist actigraphy is highly correlated with polysomnography, the gold standard for assessing sleep.[1] Compared to polysomnography, wrist actigraphy is highly accurate (86%) and sensitive (96%) for detecting sleep.[2] It has been successfully used to assess sleep and sleep disturbances across a wide range of populations, including people with cancer.[3-5] Subjective sleep disturbances will be measured using the PROMIS Sleep Disturbance Adult Short Form described in detail below.[6]

e. *Fatigue:* Fatigue will be measured with a one-item fatigue intensity scale, using computerized ecological momentary assessment (real-time assessment) and the Fatigue Adult Short Form (PROMIS instrument).[7] The Actiwatch Spectrum Pro® (Phillips Respironics, Bend, OR) contains a subjective event marker on the face of the activity monitor. This subjective event marker will be used as a real-time, single-item, global, self-report scale to measure real-time fatigue intensity. The fatigue intensity scores range from 0 (no fatigue) to 10 (worst). This rating of fatigue is particularly attractive for use in fatigued people due to ease of use and ability to capture repeated real-time measurements of fatigue throughout the day. While numeric intensity ratings do not provide information regarding the multidimensional nature of fatigue, this type of scale is suggested for use as a fatigue-screening device in clinical situations.[8-12] A computerized ecological momentary assessment approach to collecting the real-time fatigue data was chosen to allow for improved documentation of compliance, avoid the problems with recall inaccuracies, and improve compliance.[13] Data entered into the subjective event marker are stored in the onboard memory of the wrist actigraphy device.

We successfully used this computerized methodology with people with cancer, such as hematopoietic cell transplantation patients.[14-16] Fatigue will also be measured using the PROMIS Fatigue Adult Short Form.[7] The Adult Short Forms of the PROMIS instruments, including fatigue, are described together and in detail below.

f. *Sleep Disturbance and Fatigue PROMIS Instruments:* In concert with the NIH's move to utilize common data elements for research related to symptom science, PROMIS instruments will be used to assess patient-reported symptoms. We will use the Adult Short Forms for fatigue[7] and sleep disturbances.[6] These instruments are reliable, valid, and precise.[17,18] Computerized versions will be used. The PROMIS instruments use a 5-point Likert scale and employ 7-day recall. Higher scores indicate higher levels of fatigue and sleep disturbances. Scores on all instruments are standardized (M = 50, SD = 10) and normed to a reference (U.S.) population; thus, enabling normative comparisons and providing an interpretative context for scores.

Table. Variables and Measurement

Variable	Measure
Fatigue	Patient-Reported Real-Time Assessments over course of hospitalization (Actiwatch Spectrum Pro) • 1-item fatigue intensity scale using the subjective event marker of the Actiwatch Spectrum Pro
	Patient-Reported Questionnaires • PROMIS Fatigue Adult Short Form
Sleep Disturbances	Patient-Reported Questionnaires • PROMIS Sleep Disturbance Adult Short Form
	Objective Real-Time Assessment averaged over the time of hospitalization (Actiwatch Spectrum Pro) • Total Sleep Time • Sleep Latency (minutes until sleep onset) • Sleep Efficiency • Frequency and Duration of Awakenings after sleep onset (WASO) • Number of Awakenings

4.4 Data Collection

Upon enrollment to the pilot sub-study, the wrist actigraph will be placed on the non-dominant wrist. The research staff will review real-time fatigue intensity rating procedures and instruct participants to leave the device in place for the duration of the hospitalization. Participants will be directed to carry on with normal activities. They will be asked to rate the intensity of fatigue at that moment in time on a 0 (no fatigue) to 10 (worst fatigue) scale five times during each day (upon awakening, 10:00 am, 2:00 pm, 6:00 pm, and at bedtime). An audible and vibratory alarm on the wrist actigraph will sound at preset times (10:00 am, 2:00 pm, and 6:00 pm) to remind participants to complete the real-time fatigue assessment. They will enter the rating directly into the subjective event marker of the wrist actigraph. Because of the expected time variability associated with awakening and going to bed, it will not be possible to program the Actiwatch Spectrum Pro® to alarm at these times. Participants will complete the PROMIS Sleep Disturbance and Fatigue questionnaires upon enrollment and hospital discharge +/- 1 day, in keeping with the parent trial data collection periods.

4.5 Statistical Analysis

Prior to analysis of the specific aims, we will clean the data, check internal consistency of scales using Crombach's alpha coefficient, and check distributions using both descriptive statistics and graphical displays.

a. Primary Objective

For each variable, differences between PROSPER with digital vital sign monitoring (the experimental group) and PROSPER without digital vital sign monitoring (the control group) will be calculated and reported with 95% two-sided confidence intervals. Further exploratory analysis with ANCOVA models will incorporate covariates of baseline measures and length of stay to assess the relative efficiency gain of each covariate, as well as potential for confounding.

Based on previous work by the investigators[15], the confidence interval for the difference between groups should have expected lengths of no more than 54 (total sleep time, min), 12 (sleep latency, min), 5 (sleep efficiency, %), 17 (frequency and duration of awakenings after sleep onset, min), and 5 (number of awakenings).

b. Secondary Objective

Descriptive data will be computed for the real-time fatigue scores, PROMIS Fatigue, and PROMIS Sleep disturbance. Preliminary analysis will be conducted using a two-sided independent samples *t*-tests comparing PROSPER with digital vital sign monitoring (experimental group) compared to PROSPER without digital vital sign monitoring (control group) over the course of the hospitalization.

5.0 Risks/Benefits

The parent study poses minimal risks to patient's well-being in light of the fact that they will still be receiving standard of care per hospital routine that is augmented by novel technologies (i.e., passive vital signs monitoring). Although not anticipated, there may also be a minimal risk of emotional distress in patients when answering questions about depression and anxiety (HADS scale). However, study participation is completely voluntary, and participants may opt to skip any/all questions in the survey that they do not feel comfortable answering. Finally, we believe that any possible risks will be counterbalanced by potential benefits to study participants such as new insights, potential to help others, feelings of well-being and an opportunity to discuss their inpatient care journey.

This pilot sub-study is a minimal risk study. The risk of wearing the wrist actigraph device is minimal but may include skin irritation from the wristband. The risks associated with wearing a wrist actigraph are the same as wearing a wristwatch. In all of our studies that measured physical activity and sleep with wrist actigraphy, only one subject complained of skin irritation from the wristband. The skin irritation was minimal, did not require treatment, and was rectified using a different wristband. The subject continued in the study. No other subjects complained of skin irritation. There is minimal risk associated with self-reported assessments (fatigue and sleep disturbances). Providing these data may cause subjects some emotional discomfort. In our previous studies using these measures, no subjects reported emotional discomfort and/or distress.

6.0 Data Confidentiality Plan

The study team is committed to protecting patient confidentiality at all times and in all circumstances. No patient identifying information will be used in the publication of findings and all information extracted from the medical record will be entered onto coded data sheets which will be maintained on Excel spreadsheets stored in approved locations and accessible by MDACC employees. Electronic data will be strictly stored only on password protected institutional computers and/or electronic databases behind the MD Anderson firewall and accessible only to the PI and collaborators. If needed, hard copies of the coded study will be stored in a locked cabinet in the principal investigator's or study manager's office. Only the PI and the collaborators will be participating in the collection and analysis of data. No patient identifying information will be used in presentation or publication of this material. Upon study termination, all data, questionnaires and remaining identifiers will be banked indefinitely in REDCap for future use only in IRB-approved research. The technology vendor (Sotera Wireless) will have no access to patient confidential information (name, medical history, demographics, treatment history). All the vital sign data captured on the ViSi mobile passive monitoring device are captured and transmitted in an anonymized fashion.

7.0 Data Protection

A contractual agreement will be reached between Sotera and MD Anderson regard data usage and will be subject to approval by MD Anderson legal counsel to specify the following: Unless necessary to use the Products or Professional Services, Hospital agrees to not submit to Company: (i) any personally identifiable information; (ii) any protected health information regulated by the U.S. Health Insurance Portability and Accountability Act ("HIPAA") or any similar federal, state, or local laws, rules, or regulations; or (iii) any information subject to regulation or protection under the Gramm-Leach-Bliley Act. Hospital acknowledges that any submission to Company contrary to the foregoing statement is at Hospital's own risk. In performing any Professional Services, Company may receive from Hospital patient healthcare, billing, or other confidential patient information ("Patient Information"). Hospital will identify to Company in writing all such information when Hospital provides such information to Company and Company will use Patient Information so identified by Hospital only as necessary to provide the Professional Services to Hospital. Company will treat Patient Information consistently with all applicable laws and regulations and in accordance with the Business Associate Agreement entered by the Parties concurrently with this Addendum or immediately prior to Company performing any Service. Hospital represents and certifies that Hospital has received appropriate consents to provide such Patient Information to Company. Hospital agrees to not interrogate, or extract data from any Company product without written consent from Company

8.0 Parent trial References

1. Krumholz HM. Post-Hospital Syndrome — An Acquired, Transient Condition of Generalized Risk. *N Engl J Med*. 2013;368(2):100-102. doi:10.1056/NEJMp1212324
2. Milani R V., Bober RM, Lavie CJ, Wilt JK, Milani AR, White CJ. Reducing Hospital Toxicity: Impact on Patient Outcomes. *Am J Med*. Published online 2018. doi:10.1016/j.amjmed.2018.04.013
3. Hoyle NP, Seinkmane E, Putker M, et al. Circadian actin dynamics drive rhythmic fibroblast mobilization during wound healing. *Sci Transl Med*. Published online 2017. doi:10.1126/scitranslmed.aal2774
4. Curtis AM, Bellet MM, Sassone-Corsi P, O'Neill LAJ. Circadian Clock Proteins and Immunity. *Immunity*. Published online 2014. doi:10.1016/j.immuni.2014.02.002
5. Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB. A circadian gene expression atlas in mammals: Implications for biology and medicine. *Proc Natl Acad Sci U S A*. Published online 2014. doi:10.1073/pnas.1408886111
6. Jencks SF, Williams M V., Coleman EA. Rehospitalizations among patients in the medicare fee-for-service program. *N Engl J Med*. Published online 2009. doi:10.1056/NEJMsa0803563
7. Horwitz LI, Kuznetsova M, Jones SA. Creating a learning health system through rapid-cycle, randomized testing. *N Engl J Med*. Published online 2019. doi:10.1056/NEJMsb1900856
8. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, Boynton MH, Halko H. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci. 2017 Aug 29;12(1):108
9. Bangor, A, Kortum, P., Miller, J., An empirical evaluation of the system usability scale. International Journal of Human-Computer Interation. 2008;6(24):574-594.

Pilot Sub-Study References

1. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. *Sleep.* 2003;26(3):342-392.
2. Marino M, Li Y, Rueschman MN, et al. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. *Sleep.* 2013;36(11):1747-1755.
3. Hacker ED, Ferrans C, Verlen E, et al. Fatigue and physical activity in patients undergoing hematopoietic stem cell transplant. *Oncol Nurs Forum.* 2006;33(3):614-624.
4. Dean GE, Abu Sabbah E, Yingrengreung S, et al. Sleeping with the enemy: sleep and quality of life in patients with lung cancer. *Cancer Nurs.* 2015;38(1):60-70.
5. Hacker ED, Kapella MC, Park C, Ferrans CE, Larson JL. Sleep Patterns During Hospitalization Following Hematopoietic Stem Cell Transplantation. *Oncol Nurs Forum.* 2015;42(4):371-379.

6. Buysse DJ, Yu L, Moul DE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep.* 2010;33(6):781-792.
7. Garcia SF, Cella D, Clauser SB, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. *J Clin Oncol.* 2007;25(32):5106-5112.
8. Mock V. Fatigue management: Evidence and guidelines for practice. *Cancer.* 2001;92(S6):1699-1701.
9. Glaus A. Assessment of fatigue in cancer and non-cancer patients and in healthy individuals. *Support Care Cancer.* 1993;1:305-315.
10. Berger AM, Abernethy AP, Atkinson A, et al. Cancer-related fatigue. *J Natl Compr Canc Netw.* 2010;8(8):904-931.
11. Denlinger CS, Ligibel JA, Are M, et al. Survivorship: fatigue, version 1.2014. *J Natl Compr Canc Netw.* 2014;12(6):876-887.
12. National Comprehensive Cancer Network. Cancer-Related Fatigue (Version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf. Accessed September 24, 2019.
13. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient non-compliance with paper diaries. *BMJ.* 2002;324(7347):1193-1194.
14. Hacker ED, Ferrans CE. Ecological momentary assessment of fatigue in patients receiving intensive cancer therapy. *J Pain Symptom Manage.* 2007;33(3):267-275.
15. Hacker ED, Fink AM, Peters T, Park C, Fantuzzi G, Rondelli D. Persistent Fatigue in Hematopoietic Stem Cell Transplantation Survivors. *Cancer Nurs.* 2017;40(3):174-183.
16. Hacker ED, Kim I, Park C, Peters T. Real-time Fatigue and Free-Living Physical Activity in Hematopoietic Stem Cell Transplantation Cancer Survivors and Healthy Controls: A Preliminary Examination of the Temporal, Dynamic Relationship. *Cancer Nurs.* 2017;40(4):259-268.
17. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol.* 2010;63(11):1179-1194.
18. Rothrock NE, Hays RD, Spritzer K, Yount SE, Riley W, Cella D. Relative to the general US population, chronic diseases are associated with poorer health-related quality of life as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS). *J Clin Epidemiol.* 2010;63(11):1195-1204.

Appendix – Surveys

Patient Activation Measure

1.	I am the person who is responsible for taking care of my health.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
2.	Taking an active role in my own health care is the most important thing that affects my health.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
3.	I am confident I can help prevent or reduce problems associated with my health.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
4.	I know what each of my prescribed medications do.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
5.	I am confident that I can tell whether I need to go to the doctor or whether I can take care of a health problem myself.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
6.	I am confident that I can tell a doctor or nurse concerns I have even when he or she does not ask.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
7.	I am confident that I can carry out medical treatments I may need to do at home.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
8.	I understand my health problems and what causes them.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
9.	I know what treatments are available for my health problems.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
10.	I have been able to maintain lifestyle changes, like healthy eating or exercising.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
11.	I know how to prevent problems with my health.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
12.	I am confident I can work out solutions when new problems arise with my health.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
13.	I am confident that I can maintain lifestyle changes, like healthy eating and exercising, even during times of stress.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A

Richards-Campbell Sleep Questionnaire

You are now ready to begin to answer the questions. Place your "X" **anywhere** on the answer line that you feel **best** describes your sleep last night.

1. My sleep last night was:

Deep Sleep	_____	Light Sleep

2. Last night, the first time I got to sleep, I:

Fell Asleep Almost Immediately	_____	Just Never Could Fall Asleep

3. Last night I was:

Awake Very Little	_____	Awake All Night Long

4. Last night, when I woke up or was awakened, I:

Got Back To Sleep Immediately	_____	Couldn't Get Back To Sleep

5. I would describe my sleep last night as:

A Good Night's Sleep	_____	A Bad Night's Sleep

Hospital Anxiety and Depression Scale (HADS)

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0

Worrying thoughts go through my mind:	**A**
A great deal of the time	3
A lot of the time	2
From time to time but not too often	1
Only occasionally	0

I look forward with enjoyment to things:	**D**
A much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	3
Hardly at all	2

I feel cheerful:	**D**
Not at all	3
Not often	2
Sometimes	1
Most of the time	0

I get sudden feelings of panic:	**A**
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0

I can sit at ease and feel relaxed:	**A**
Definitely	0
Usually	1
Not often	2
Not at all	3

I can enjoy a good book or radio or TV programme:	**D**
Often	0
Sometimes	1
Not often	2
Very seldom	3

Questions relating to anxiety are indicated by an 'A' while those relating to depression are shown by a 'D'. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'

	The System Usability Scale Standard Version	Strongly Disagree	1	2	3	4	Strongly Agree 5
1	I think that I would like to use this system frequently.		O	O	O	O	O
2	I found the system unnecessarily complex.		O	O	O	O	O
3	I thought the system was easy to use.		O	O	O	O	O
4	I think that I would need the support of a technical person to be able to use this system.		O	O	O	O	O
5	I found the various functions in this system were well integrated.		O	O	O	O	O
6	I thought there was too much inconsistency in this system.		O	O	O	O	O
7	I would imagine that most people would learn to use this system very quickly.		O	O	O	O	O
8	I found the system very awkward to use.		O	O	O	O	O
9	I felt very confident using the system.		O	O	O	O	O
10	I needed to learn a lot of things before I could get going with this system.		O	O	O	O	O

Additional File 3. Final version of the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM)

GENERAL INSTRUCTIONS: These measures could be used independently or together. The IAM items could be modified to specify a referent organization, situation, or population (e.g., my clients). Please check and report the psychometric properties with each use or modification.

Acceptability of Intervention Measure (AIM)

	Completely disagree	Disagree	Neither agree nor disagree	Agree	Completely agree
1. (INSERT INTERVENTION) meets my approval.	①	②	③	④	⑤
2. (INSERT INTERVENTION) is appealing to me.	①	②	③	④	⑤
3. I like (INSERT INTERVENTION).	①	②	③	④	⑤
4. I welcome (INSERT INTERVENTION).	①	②	③	④	⑤

Intervention Appropriateness Measure (IAM)

	Completely disagree	Disagree	Neither agree nor disagree	Agree	Completely agree
1. (INSERT INTERVENTION) seems fitting.	①	②	③	④	⑤
2. (INSERT INTERVENTION) seems suitable.	①	②	③	④	⑤
3. (INSERT INTERVENTION) seems applicable.	①	②	③	④	⑤
4. (INSERT INTERVENTION) seems like a good match.	①	②	③	④	⑤

Feasibility of Intervention Measure (FIM)

	Completely disagree	Disagree	Neither agree nor disagree	Agree	Completely agree
1. (INSERT INTERVENTION) seems implementable.	①	②	③	④	⑤
2. (INSERT INTERVENTION) seems possible.	①	②	③	④	⑤
3. (INSERT INTERVENTION) seems doable.	①	②	③	④	⑤
4. (INSERT INTERVENTION) seems easy to use.	①	②	③	④	⑤

Pragmatic Qualities:

- Readability tested by substituting "This EBP" for "Insert Intervention." Flesch reading ease score (and grade level) is 95.15 (5th grade) for AIM, 99.60 (5th grade) for IAM, and 94.17 (5th grade) for FIM.
- No specialized training is needed to administer, score, or interpret the measures.
- Cut-off scores for interpretation not yet available; however, higher scores indicate greater acceptability, appropriateness, or feasibility.
- Norms not yet available.
- Scales can be created for each measure by averaging responses. Scale values range from 1 to 5. No items need to be reverse coded. Good measurement practice: assess structural validity to confirm the unidimensionality of each measure and calculate alpha coefficient to ascertain reliability.
- There is no cost to use these measures.
- Time to complete: less than 5 minutes per measure.

Fatigue – Short Form 8a

Please respond to each question or statement by marking one box per row.

	During the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41	How run-down did you feel on average? ..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP35	How much were you bothered by your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP49	To what degree did your fatigue interfere with your physical functioning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
FATIMP3	How often did you have to push yourself to get things done because of your fatigue?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP16	How often did you have trouble finishing things because of your fatigue?..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Sleep Disturbance – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep108	My sleep was restless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep72	I tried hard to get to sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep67	I worried about not being able to fall asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep115	I was satisfied with my sleep.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1