PROTOCOL SUMMARY

Title	Minimizing Overnight Vital Signs to Improve Sleep in Hospitalized Children
Protocol ID #	1052853
Protocol Issue Date	March 25, 2024
IRB Approval Date	June 27, 2024
Amendment Date(s)	November 15, 2024; February 13, 2025
Location of Research	Primary Children's Hospital, 100 Mario Capecchi Dr., Salt Lake City, UT
Principal Investigator	Leandra Bitterfeld, RN, MSN, PhD(c), Research Nurse Coordinator, Primary Children's Hospital
Co-Principal Investigator, if applicable	Not applicable
Sub-Investigators	Brianna Peterson Waldron, RN, BSN Julianne Mathias, RN, BSN, CPN
Internal Collaborators	Jody Osteyee, DNP, APRN, CPNP-PC, EBP-C Scott Short, MD Frank Cipriano, MD
External Collaborators	Not applicable
Sponsor	Intermountain Foundation at Primary Children's Hospital
Contract Research Organization (CRO) (if applicable)	Not applicable
Study Team	
PROTOCOL SUMMARY	
Purpose of Study	To understand the effect of forgone overnight vital signs on sleep quality and duration among children hospitalized in medical-surgical units, compared with children who receive standard of care vital signs.
Design	Non-randomized controlled study
Study Duration	March 2024-March 2025
Number of Subjects	160

Description of Subject Population	Patients hospitalized on a pediatric medical-surgical floor who are eligible for reduced overnight vital signs monitoring, as described below.
Eligibility Criteria	Inclusion criteria: - Hospitalized at Primary Children's Hospital on units 3SE, 3NE, 3NW - Age 1-18 years - PEWS score ≤ 1 at 2000 - A parent/home caregiver present to consent to study - Patient and home caregiver speak English or Spanish. - Deemed appropriate for forgone overnight vital signs by care team (attending MD/Advanced Practice Provider and bedside RN). Exclusion Criteria - Pre-existing diagnosis of hypertension, kidney disease, pulmonary hypertension, chronic lung disease, congenital heart disease causing cardiopulmonary compromise, obstructive sleep apnea, seizure disorder, neuromuscular disability. - Patients requiring O2 monitoring at home. - The following medications in the previous 24 hours: opioids, intravenous immunoglobulin, intravenous magnesium, continuous albuterol, benzodiazapines, other sedating medications beyond home regimen. - Anaphylaxis within 24 hours - Within the first 24 hours post-operative period - Requiring oxygen above baseline - Fever in the last 24 hours. - Sepsis alert in the last 72 hours.
Screening and/or Recruitment Location	Medical-surgical units (3SE, 3NE, 3NW) at Primary Children's Hospital
Brief Description of Study Procedures	Patients will be screened at Primary Children's Hospital. Patients who are deemed eligible to forgo overnight vital signs will be considered for study. After written informed consent (parental permission/assent) is obtained, subjects who meet eligibility criteria will be allocated 1:1 to 2 treatment arms in sequential order: Group 1: standard of care vital signs monitoring and Group 2: no overnight vital signs at 0000 and 0400. The study period is approximately 24 hours, including one night of sleep. All participants will wear an actigraphy watch for one night and complete a sleep diary and sleep disruption survey after the study night.
Primary Endpoint	The primary endpoint is total sleep time, as measured by actigraphy.
Secondary Endpoints	- Nocturnal wake frequency, nocturnal wake duration (actigraphy) - Self-reported total sleep time (sleep diary)

	- Self-reported overnight disruptions (sleep diary) - Self-reported restfulness upon waking (sleep diary) - Self-reported sleep disturbances (sleep disturbance survey)
Analysis Population(s)	Intent-to-treat
Benefits	The direct benefit to the research participants is that they may experience improved sleep related to forgoing overnight vital signs monitoring. Furthermore, the information gleaned from this study may inform policies and practices that inform sleep for hospitalized children in the future.
Risks	This study presents no more than minimal risk. Risks associated with wearing the actigraphy watch include potential minor discomfort. The risk associated with forgoing vital signs administration is an unnoticed decline in clinical status. This risk will be mitigated by q. 4 hour PEWS score monitoring by the bedside nurse. This risk will be further mitigated by allowing for as needed vital signs administration if anyone in the clinical team is concerned about the participant's clinical status.
Authors	N/A

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DEFINITIONS

- Q4: every 4 hours
- Q12: Every 12 hours
- Q4 vital signs: measurement of blood pressure (BP), heart rate (HR), respiratory rate (RR), oxygen saturation level (SpO2), and temperature.
- Routine vital signs: measurement of blood pressure q12 hours and measurement of HR, RR, SpO2 and temperature every 4 hours.
- Standard of care vital signs: Q4 or routine vital signs as ordered by the care team prior to study enrollment.
- PEWS: Pediatric Early Warning Sign

1.0 INTRODUCTION

1.1 Background and Rationale

Adequate sleep is vital for healing and optimal functioning, and sleep deprivation negatively impacts the body's breathing, circulation, immune system function, endocrine function, and metabolism (American Academy of Nursing [AAN], 2015). A lack of sleep is also associated with diminished cognitive and emotional functioning (Vriend et al., 2015), an increase in self-reported pain, altered pain threshold (Schrimpf et al., 2015), and depressive symptoms (Hillman, 2021). Hospitalized children are at high risk for disturbed sleep and its physiological effects given the high-sensory and unfamiliar nature of hospitals.

Overnight vital signs are typically done every four hours on pediatric acute care units, despite limited evidence supporting the efficacy of this practice (Mann, 2019). Additionally, vital signs are often ordered and collected without considering the patient's clinical status or the potential impact that they may have on sleep. This practice is in direct contradiction to guidance from the American Academy of Nursing's Choosing Wisely Campaign that states: "Don't wake the patient for routine care unless the patient's condition or care specifically requires it" (AAN, 2015).

This team's previously published scoping review (Bitterfeld et al., 2023) found that vital sign checks and nursing cares are the most frequent cause of nighttime awakenings among hospitalized children (Crawford et al., 2019; Herbert et al., 2014; Meltzer et al., 2012; Stremler et al., 2021).Additionally, only one study included sleep duration as an outcome of reducing vital signs. They found that sleep duration increased by 82.4 minutes for children older than 24 months ($p < 0.001$) when forgoing nonessential blood pressures overnight, and there was no significant difference in sleep duration among children less than 24 months old (Cook et al., 2020). Three quality improvement projects (Cook et al., 2020; Lee et al., 2021; Lin et al., 2022) experienced no escalations of care (PICU transfer or rapid response team calls) or code blue events among children where overnight vital signs were reduced.

1.2 Previous Work

The PI and sub-Is of this study recently published a scoping review of the effect of reduced overnight vital signs on sleep among hospitalized children. The PI is a nurse and PhD candidate with extensive research experience. The sub-Is are both nurses who completed the Intermountain Evidence-based Practice (EBP) course and are involved in additional research and quality improvement (QI) projects.

2.0 STUDY OBJECTIVES/PURPOSE OF THE STUDY

Understand the effect of forgone overnight vital signs on sleep quality and duration among children hospitalized in medical-surgical units, compared with children who receive standard of care vital signs.

2.1 Hypothesis/Research Questions

Children who do not have vital signs taken overnight, defined as no vital signs measured at 0000 and 0400, will experience significantly greater sleep quality and longer periods of uninterrupted sleep, when compared with children who experience standard of care vital signs monitoring, defined as vital signs taken every 4 hours.

3.0 STUDY DESIGN

This is a non-randomized controlled study to evaluate the effect of forgoing overnight vital signs on sleep quality and duration. Patients will be screened at a single center. Subjects will be sequentially recruited, first into the control cohort, and then into the experimental cohort.

3.1 Study Duration

The study will last for approximately 12 months (a target of up to 8 months to recruit the required subjects and 4 months for study closure and analysis). The approximate target start and stop dates for the study are March 2024 and March 2025, respectively.

2.2 Number of Subjects

Approximately 160 patients will be enrolled/consented into the study (1:1 ratio; see section 4.3 for details).
The expected drop-out rate for this study is 20%. Hence, it is expected that 160 patients will be enrolled to meet the target of 128 subjects who will complete the trial (see section 8.2 for sample size calculation).

2.3 Screening and Selection of Subjects

Patients hospitalized on a medical-surgical unit at Primary Children's Hospital will be screened for this study. The Principal Investigator, Sub-Investigator and/or the designated Clinical Research Coordinator will review the patient's history and medical records and discuss eligibility with the attending medical provider or Advanced Practice Provider. Data gathered is used to evaluate the patient in relation to the inclusion and exclusion criteria listed below. It may be necessary to exclude subjects based on this assessment.

A patient-screening log will be maintained throughout the study. The log will record all subjects considered for enrollment in the trial and indicate whether they were enrolled or not enrolled. In the case of non-enrollment, an explanation will be provided on the log as to the reason for their exclusion.

2.3.1 Inclusion Criteria

Iris section 5.1
Inclusion criteria:

- Hospitalized at Primary Children's Hospital on units 3SE, 3NE, 3NW
- Age 1-18 years
- PEWS score ≤ 1 at 2000
- A parent/legal guardian present and willing to consent to study
- Patient and home caregiver speak English or Spanish.
- Deemed appropriate for forgone overnight vital signs by daytime care team (attending MD and bedside RN).

Exclusion Criteria
Iris section 5.1

- Pre-existing diagnosis of hypertension, kidney disease, pulmonary hypertension, chronic lung disease, congenital heart disease causing cardiopulmonary compromise, obstructive sleep apnea, seizure disorder, neuromuscular disability, unless explicitly approved and acknowledged by attending physician_.
- Patients requiring O2 monitoring (pulse oximetry) at home.

- The following medications in the previous 24 hours: intravenous immunoglobulin, intravenous magnesium, continuous albuterol,
- The following medications in the previous 12 hours: opioids, benzodiazapines, other sedating medications beyond home regimen. Children on clonidine alone need not be excluded.

- Anaphylaxis within 24 hours
- Within the first 24 hours post-operative period
- Requiring oxygen above baseline
- Fever in the last 24 hours.
- Sepsis alert in the last 72 hours.

3.0 STUDY PROCEDURES

This study will be conducted in accordance with the ICH Good Clinical Practice guidelines (E6), the Code of Federal Regulations (CFR), and the Declaration of Helsinki (see Appendix D). Study-specific procedures and tests are described in the sections below.

3.1 Informed Consent

Iris section 8.0

Patients and children that meet eligibility criteria and agree to participate will be considered for the study. Written informed consent using a form that is approved by the Intermountain Healthcare Institutional Review Board (IRB) will be obtained prior to study inclusion, signed by the subject or his/her legally authorized representative, in accordance with applicable regulations. The LAR can be a family member, health care agent or legal guardian as defined by the State of Utah.

Parental permission will be required of all subjects who are under 18 years of age. In addition to parental permission, subjects who are between 7 and 17 years of age will be asked to provide assent, and an IRB-approved assent document will be used to document the subject's agreement to participate in this study. In determining whether subjects are capable of assenting, the consenter shall take into account the age, maturity and psychological state of the participant involved. Assent will be obtained from all children that are deemed capable of providing assent by the investigator. If the potentially eligible participant is deemed incapable of providing assent due to a cognitive impairment, the research may proceed with permission of the parent(s) alone. If the participant gains capacity to provide assent during the course of the study, they will be reapproached to obtain assent. The Principal Investigator or an appropriately delegated member of the study team under his/her supervision, will administer the parental permission and assent process.

If these subjects turn 18 years old while participating in this study, they will be asked to re-confirm their agreement to continue their participation by signing a new informed consent form. If the participant is unable to give consent, surrogate consent will be obtained from the participant's legally authorized representative, in accordance with applicable regulations. This authorized representative can be a family member, health care agent or legal guardian, as defined by the State of Utah. A prospective enrollee's capacity to provide informed consent for research participation will be determined by the Principal Investigator and/or his/her delegate, in collaboration with the participant's inpatient attending physician.

The informed consent process will be conducted at an Intermountain Healthcare facility. The Principal Investigator or an appropriately delegated member of the study team (e.g. the Clinical Research Coordinator) under his/her supervision, will administer the informed consent process.

Following assessment of qualification for study participation as per inclusion/exclusion criteria, eligible patients will be presented with protocol information and will be invited to participate in this project. Patients and parents will be provided as much time as they need to consider participation, ask questions, and obtain satisfactory answers to their questions. Patients and parents will be asked to provide written consent by signing the informed consent document. Unless otherwise indicated, consent will be obtained only after the Principal Investigator and/or his/her delegate has/have reviewed and approved the inclusion and exclusion criteria.

3.2 Methods

Patients will be screened for eligibility per inclusion and exclusion criteria (See Sections 3.3.1 and 3.3.2 respectively) and consented as described in Section 4.1.

The following information (history) will be obtained from each subject at study onset:

- Age, gender, height, weight
- Location of hospitalization (unit)
- Medical history
- Admitting diagnosis

The following tests/interventions will be conducted:

- Sleep duration recording via actigraphy watch.
- Daily sleep diary completion.
- Sleep disturbance survey completion.

3.3 Study Treatments

After verifying study eligibility and a written informed consent has been obtained, subjects will receive either standard of care vital signs monitoring or forgone overnight vital signs monitoring in a 1:1 ratio, as indicated in the Treatment Arm/Intervention Table below. Patients will be allocated to these groups sequentially, meaning the first 64 enrolled children will receive standard of care vital signs monitoring and the next 64 children will receive no overnight vital signs monitoring.

Treatment/Intervention Arm	Intervention
Intervention	Children in the intervention group will not have vital signs taken at 0000 and 0400. Bedside nurses will be asked to monitor a PEWS score every four hours to assess patient's clinical status and ensure safety. If a patient has a change in clinical status at any point during the study period, such that PEWS>1, or if a nurse/provider has a concern about a patient's clinical status, vital signs may be taken as the nurse/provider feel is most appropriate.

Control	Standard of care vital signs and PEWS monitoring (ie – no change from current orders). This monitoring may include routine vital signs or Q4 vital signs

3.4 Study Visits/Study Evaluations

The study period will be one approximately 24-hour period. The study period will be mid-day on day 0 to mid-day on day 1. See time and event schedule below.

After obtaining informed consent, subjects will be fitted with an actigraphy watch and instructed on survey completion. This visit must be conducted prior to the child's bedtime (Day 0). After fitting the actigraphy watch, subjects will wear the watch for the entire duration of the study period, which will be ~24 hours. At the completion of the study period (Day 1), Children /caregivers will complete a sleep diary and the PROMIS 8-item Pediatric Sleep Disturbance short form.

Time and Events Schedule

	Day 0	Night 1	Day 1	Night 2	Day 2
Informed consent signed	X				
Inclusion/exclusion criteria	X				
History	X				
Actigraphy	X	X	X		
Sleep Diary			X		
Sleep Disruption Survey (age≥5)			X		
Discontinue actigraphy			X		
Safety events	X	X	X	X	X

3.5 Clinical Tests and Procedures

A description of the clinical tools and surveys are outlined below:

Appendix	Tool	Concept Measured	Brief Description	Reliability and validity	Score Range	Completion instructions
A-1	PEWS score	Clinical status	Reproducible assessment of clinical status	Associated with lower risk of mortality and unplanned code events (Chong et al., 2022).	0-11, lower is greater clinical stability	Bedside nurse q. 4 hrs

A-2	Basic Mini Motionlogger actigraph watch	Total sleep time, nocturnal wake frequency, nocturnal wake duration according to Meltzer, Montgomery-Downs et al. (2012)	An actigraphy watch that has been validated in children as young as three years old.	Sensitivity=0.89 and specificity=0.73 when compared to polysomnography. Underestimated sleep efficacy by ~4.4%. (Meltzer, Walsh et al., 2012).	N/A	Apply watch prior to 2000 on day 0. Wear continuously until after awakening on day 1.
A-3	Sleep Diary	Self-reported sleep duration and interruptions	A sleep diary modified from the National Sleep Foundation (Carney et al., 2012) to accommodate study period and only capture information of interest.	The sleep diary was developed in collaboration with insomnia experts and potential users. Our modifications are similar to those made by the Children's Hospital of Orange County sleep diary.	NA	Complete by children≥8 yo, parents for children <8 years old (Mazza et al., 2020).
A-4	PROMIS 8-item Pediatric Sleep Disturbance short form	Sleep disturbances/ sleep quality	A validated measure of self-reported sleep disturbances.	Cronbach's α=0.91, adequate structural validity. Concurrent validity with general health, chronic health conditions, use of other medications for sleep (Forrest et al., 2018). Also validated in children with neurodevelopmental disorders (Meltzer et al., 2020).	8-40, higher scores indicating worse sleep/ fewer disturbances. Scores can be convered to T scores	Complete by children≥8 yo, parents for children <8 years old

See Time and Events Schedule table above for specific tests and procedures to be obtained at each visit, as follows:

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3.5.1 Pre-Intervention Tests and Procedures

None

3.5.2 Intra-Intervention Tests and Procedures

During the study period the following tests and procedures will be done:

- Actigraphy watch sleep monitoring
- Sleep diary
- PROMIS 8-item Pediatric Sleep Disturbance short form survey

3.5.3 Post-Intervention Tests and Procedures

Immediately after completion of the study period, no further tests and procedures will be done. The clinical status of the patient will be monitored for 24 hours after study completion to monitor for any potential safety events, as described in section 5.1.

3.5.4 Follow-Up Evaluations

There are no follow-up evaluations.

3.6 Risks

Iris section 7.8

This study presents no more than minimal risk. Risks associated with wearing the actigraphy watch include potential minor discomfort. The risk associated with forgoing vital signs administration is an unnoticed decline in clinical status. This risk will be mitigated by q. 4 hour PEWS score monitoring by the bedside nurse. The PEWS score is used to identify patients at risk for clinical deterioration and has been validated as a predictor of ICU transfer (Agulnik, et al., 2017). PEWS scores are routinely documented once per shift and Intermountain policies indicate that a PEWS score of 0-2 indicates no additional assessment or intervention is needed. This risk will be further mitigated by allowing for as needed vital signs administration if anyone in the clinical team is concerned about the participant's clinical status.

3.7 Benefits

Iris section 7.10

The direct benefit to the research participants is that they may experience improved sleep related to forgoing overnight vital signs monitoring. Furthermore, the information gleaned from this study may inform policies and practices that improve sleep for hospitalized children in the future.

4.0 CONCOMITANT MEDICAL THERAPY

N/A

5.0 MONITORING AND SAFETY REPORTING

5.1 Monitoring

Iris section 7.12

Safety Events

Safety events of concern include any unnoticed, clinically significant change in clinical status, measured as an unplanned transfer to the PICU/CICU, rapid response activation, code sepsis alert, or code blue event.

Safety Monitoring and Reporting

All safety-related data for this study will be collected on standardized Case Report Forms. The PI will be notified of any safety-related events within 12 hours of the occurrence. If a safety event occurs, enrollment will be paused while the PI and consulting physicians debrief the event and identify underlying causes. Appropriate changes will be made to the protocol if needed. Enrollment will resume once any necessary changes are made and amendments approved by the IRB.

6.0 END OF STUDY CONSIDERATIONS

6.1 Study Completion

A participating subject will be considered as having completed the study if the subject has met the following:

- Completed the treatment/intervention course described in this protocol.
- Has complied with all the procedures as required by the study.

6.2 Voluntary Withdrawal of Consent

Subjects shall have the ability to withdraw consent for study participation and/or the use of their clinical information at any time, without penalty or loss of benefit to which the subject is otherwise entitled, by contacting the Principal Investigator or a designated member of his research team, preferably in writing and addressed to the Principal Investigator at the address indicated on the cover page of this protocol.

In the case a subject enrolled in this study decides to withdraw from the research, or an Investigator decides to terminate a subject's participation, study investigators must follow accepted standard practices regarding the management of collected data about these subjects, as follows:

- Investigators must document in the research record each instance of a subject's withdrawal, including the reasons for the withdrawal, if known.
- Previously collected information that has been gathered, and all material from the subject's identifiable samples that they have at the time of the subject's withdrawal from the study will remain in the study to maintain the integrity of the research, in accordance with current FDA regulations.
- The investigator(s) may ask the subject whether he/she will agree to continued follow-up and further collection of clinical information following his/her withdrawal.
- If the subject withdraws and does not consent to continued follow-up and collection of clinical information, the investigator(s) will discontinue access to the subject's medical record or other confidential records, for purposes related to the study.
- Following the subject's withdrawal from the study, the Study Team will no longer contact the subject nor have access to his/her medical records for research purposes (unless specific informed consent has been obtained as described above).

In the event of study withdrawal is a participant receiving the forgone vital signs intervention, the subject will receive standard of care vital signs monitoring

6.3 Early Termination

The study sponsor or Principal Investigator of the study may decide to suspend or terminate a study for various reasons, including but not limited to the occurrence of an unanticipated problem, evidence of noncompliance or serious and/or continuing noncompliance. If this occurs, the Principal Investigator will notify the IRB in writing within three days of the suspension/termination. This communication will include a description of what steps have or will be taken to protect the welfare of currently enrolled participants, and what corrective actions, if applicable, will be taken to address the root cause for the suspension/termination.

The IRB has the authority to suspend the approval of research when it is suspected or determined that the following has/have occurred: an unanticipated problem associated with unexpected serious harm to research participants, the research is not being conducted in accordance with the IRB requirements with possible risk of harm to research participants, and/or serious or continuing noncompliance has taken place.

After a suspension of an IRB approval, the IRB has the authority to terminate the research if the event(s) prompting the suspension of research approval cannot be corrected in a way that serves the best interests of the research participants. The IRB may also terminate a research study if the noncompliance with the IRB requirements is serious and/or continuing and the proposed corrective action plan is not sufficient to alleviate or rectify the noncompliance. The termination of research involves all research activities (enrollment, treatment and/or intervention, follow-up, and data analysis).

6.4 Lost to Follow-Up Subjects

Because this is a single encounter study, with no periods of time between research-related interactions, retention of participating subjects until study completion will not be a challenge. There will be no need to recontact subjects.

6.5 Disposition of Investigational Product

N/A

6.6 Records Retention

The Principal Investigator and his/her designated research staff are responsible for maintaining accurate, complete, and current records relating to the conduct of the investigation, in accordance with ICH Good Clinical Practice guidelines (E6) and the Code of Federal Regulations (CFR) (refer to ICH GCP 8.1 to 8.4 for a list of essential documents for retention).

In addition, the Principal Investigator and his/her designated research staff are responsible for retaining any additional documents as required by Intermountain Health, in accordance with departmental and/or institutional records retention policy.

If there is inadequate records storage space at any Intermountain facility, all or part of the clinical study records can be sent to an Intermountain-approved archival storage facility that has a current executed service contract with Intermountain. As appropriate, the study sponsor and other stakeholders will be notified.

If the Principal Investigator transfers custody of all or part of the clinical study records to another person or entity, the IRB must be notified within 10 working days after the transfer occurs. In addition, and as appropriate, the study sponsor and other stakeholders will be notified.

7.0 DATA MANAGEMENT AND STATISTICAL ANALYSIS

7.1 Data Collection

Iris section 11.0

All required data for this study will be collected on standardized Case Report Forms (CRFs) in RedCap, to be created by the Principal Investigator, Clinical Research Coordinator (CRC) or a designated member of the study team. A duly-assigned CRC will perform primary data collection drawn from review of source-documents (hospital charts) and from on-going study procedures.

Data will be gathered in several ways.

EHR Data elements: data from the electronic health record will be collected on Day 0-1 and entered into RedCap by a CRC. The elements collected and their definition are described below.

Element	Day collected	Definition/Notes
Age	0	Years, gathered from DOB
Sex	0	Male/Female
Race	0	As listed in EHR
Ethnicity	0	As listed in EHR
Height	0	At admission, cm
Weight	0	At admission, kg
Medical History	0	All conditions listed in the "Past Medical History" section of the admission H&P note.
Admitting diagnosis	0	Primary reason, collected from admission H&P
Hospital unit	0	Location during study, 3SE, 3NE or 3NW
Vital signs measurements	0-1	HR, RR, BP, temp, SpO2
PEWS scores	0-1	
Safety events – code blue, rapid response, unplanned transfer	0-1	Gathered from event or transfer notes. Type of event, date, time.

Sleep diary and survey: Participants will complete the sleep diary and survey as described above in a paper form. The CRC will transcribe the paper responses into the RedCap CRF.

Actigraphy: Actigraphy records will be uploaded onto a secure Intermountain computer. Variables of interest will be transcribed into the RedCap CRF.

Every precaution will be taken to protect the privacy of research subjects and the confidentiality of their personal information. The Principal Investigator, Intermountain Regulatory Specialists and Clinical Research Coordinator will maintain all patients' information supplied by the clinical investigators in accordance with Health Insurance Portability and Accountability Act of 1996 (HIPAA) and Intermountain Healthcare's guidelines for compliance and privacy. For example, the patient files will be secured at Primary Children's Hospital, using alphanumeric codes to identify each subject (sequential number + first letter of first, middle and last names: 001 ABC).

7.2 Sample Size Calculation

To detect a moderate effect size (Cohen's d=0.50) difference between the intervention and comparison group with adequate power (β=.80) and a significance criterion of α=.05, a sample size of 128 (64 in each group) is needed. We will aim to enroll 80 children in each group to allow for participant attrition due to unexpected change in clinical status, dropout, or incomplete outcome data.

Considering that prior studies demonstrated an in-hospital total sleep time of m(SD)=412(73.3) by actigraphy (Meltzer, Walsh et al., 2012), an effect size of d=0.5 equates to an increase in sleep of approximately 37 minutes (Becker, 2000).

7.3 Evaluation Endpoints

7.3.1 Primary Endpoint

The primary endpoint is total sleep time, as measured by actigraphy.

7.3.2 Secondary Endpoints

The secondary endpoints are as follow:

- Nocturnal wake frequency, nocturnal wake duration (actigraphy)
- Self-reported total sleep time (sleep diary)
- Self-reported overnight disruptions (sleep diary)
- Self-reported restfulness upon waking (sleep diary)
- Self-reported sleep disturbances (sleep disturbance survey)

7.4 Statistical Analysis

7.4.1 Populations for Analysis

All children with at least one night of complete actigraphy data will be included.

7.4.2 Statistical Methods

Independent samples T tests and Chi square tests will be used to compare continuous and nominal data, respectively, between the case and control group. If continuous data do not meet the assumptions needed for a T test, namely normal distribution, a Mann-Whitney U test will be used instead.

8.0 DISSEMINATION OF RESULTS

8.1 Release of Information to Participants

Whenever possible within the limits of the study, effort will be made to keep study participants informed of significant study results. This will mainly be a 1:1 discussion between the subject and Principal Investigator, as appropriate. All other results will be considered for research only and will not be shared with the individual subject directly.

Other methods of informing participants may also include web announcements or press releases. IRB approval will be obtained prior to use of any method for study progress information dissemination to participants.

8.2 Public Release of Information

Methods of disseminating study results and/or study progress to the public may include web announcements or press releases/newsletters. IRB approval will be obtained prior to use of any method for information dissemination to the public.

Requests for interviews, comments, or press conferences with the study investigators will be honored to more fully describe the results or explain the implications of the results, following consultation with the Intermountain public relations team. Any direct request to the investigators will be sent to the public relations team first, before the investigator responds to the media request.

8.3 Data-Sharing with Collaborators

Iris section 10.5

- The results of this study will be shared with the University of Utah as per the clinical research agreement and as defined in the informed consent document. The physicians in this study team are employed by the University of Utah and sharing data is necessary for ensuring safety of the participants and study monitoring.

The CRF will be fully deidentified. The study team will assign each participant an identifier as described in section 7.1. A separate record will be maintained that links the study identifier to the patients identifying information. All study data will be maintained on a secure Intermountain server, and the CRF will be maintained on a secure electronic data capture platform (RedCap). Information will be shared either via login to the study RedCap or encrypted email. Data may be reidentified if needed to evaluate safety events.

All shared data will be de-identified as per the Privacy Rule of the NIH (National Institutes of Health, 2007) and in accordance with Intermountain policies.

8.4 Publications

The results of this study may be published as a paper, abstract or poster, or may be presented orally at a conference or symposium. Any publication resulting from this study will comply with the guidelines recommended by the International Council of Medical Journal Editors (i.e., *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, 2013*).

9.0 FINANCIAL CONSIDERATIONS

9.1 Funding Source

Iris section 13.1

This study is funded by The Intermountain Foundation at Primary Children's Hospital

The tests and procedures listed below are considered non-standard of care and will be paid for by the study budget. All other tests, procedures, and study visits are either conducted by study personnel (e.g. questionnaire administration, etc.) or charged to the patient as routine, standard of care activities. The budget, contract and financial agreements will be available in a separate document.

Non-standard of care tests and procedures covered by the study budget are as follows:

- Actigraphy watch sleep measurement
- Survey administration

9.2 Compensation

Iris section 7.4

Subjects will not receive any monetary or other forms of compensation for participating in this research study.

Likewise, the investigators and their research staff will not receive any monetary or other forms of direct compensation for conducting this research study. Payment is made directly to Intermountain Healthcare to cover the costs of study conduct.

9.3 Disclosure of Conflicts of Information

Iris section 13.3

The Principal Investigator, Sub-Investigators and protocol authors declare that they have no conflicts of interest relevant to this study.

10.0 REFERENCES

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11.0 APPENDICES

Appendices A to D are standard appendices to be attached to all protocols for clinical studies to be conducted at Intermountain CVR. Standard statements are suggested below. As appropriate, changes can be made to fit the needs of the clinical study.

The researcher is advised not to delete any of the standard appendices in this protocol template. These appendices serve as an information source, as well as a reminder of what the Study Team must be aware of, during the study conduct. In the instance that an appendix is assessed as not necessary or not relevant (e.g., for data-only studies), enter "Not Applicable" under the specific appendix. Other appendices can be added, for efficiency or clarification purposes.

Examples of documents, tools, information, collection forms, etc. that can go into an appendix:

- *Investigator agreement document*
- *Flow charts for the randomization sequence or procedures that must be performed for every subject*
- *Instruction sheets for treatment regimen or special procedures*
- *Patient questionnaires*
- *Subject recruitment plan*
- *Statistical analysis plan*

Ideally, study-specific patient questionnaires/surveys can be developed as documents separate from the protocol. This will prevent inconsistencies when the protocol and/or questionnaire is/are revised independently.

APPENDIX A: STUDY TOOLS AND INVESTIGATIONAL PRODUCT INFORMATION

Appendix A-1 PEWS Score Tool

Components	0	1	2	3	Score
Behavior	Playing/ Appropriate	Sleeping	Irritable	Lethargic/ Confused OR Reduced response to pain	
Cardiovascular	Pink or Capillary refill 1–2 seconds	Pale or Capillary refill 3 seconds	Grey or Capillary refill 4 seconds OR Tachycardia of 20 above normal rate	Grey and mottled or capillary refill 5 seconds or above. OR Tachycardia of 30 above normal rate or bradycardia	
Respiratory	Within normal parameters, no retractions	> 10 above Normal Parameters, using accessory muscles OR 30+% FiO2 or 3+ liters/min.	• > 20 above normal parameters • Retractions. OR • 40+% FiO2 or 6+ liters/min.	• 5 below normal Parameters with retractions • Grunting. OR • 50% FiO2 or 8+ liters/min.	
Score 2 extra for ¼ hourly nebulizers or persistent vomiting following surgery					

Appendix A2

Micro Motionlogger® Watch

The Excellence of a Motionlogger®

- ✓ The highest agreement with PSG
- ✓ 2 Mb Non-Volatile Memory
- ✓ Multiple Modes of Operation
- ✓ Temperature Channel
- ✓ Ambient Light Channel
- ✓ Off-Wrist Detection
- ✓ Event Marking with Visual Feedback
- ✓ Status indicator
- ✓ 30 day runtime

No Interface Required (for IR enabled devices)

PLUS a Watch

- ✓ Rugged Plastic Case
- ✓ Water Resistant – 100M
- ✓ Date Display
- ✓ Time Display Adjust Feature
- ✓ Easy Battery Changing

Ambulatory Monitoring, Inc.

info@ambulatory-monitoring.com
www.ambulatory-monitoring.com

Sleep Scoring Details

The Sadeh (age>1 year) or Sadeh infant (age<1 year) algorithm using one minute epochs will be used to automatically score the data. For children that have more than one sleep period, based on sleep diary response, where the additionally periods are not automatically captured, they will be manually marked and then automatically scored.

The collected variables will be:

- Sleep minutes (total if>1 sleep period)
- Sleep efficacy (mean if >1 sleep period)
- Wake after sleep onset (total if>1 sleep period)
- Wake episodes (total if>1 sleep period)
- Mean wake episode (mean if >1 sleep period)
- Mean lux (mean if >1 sleep period)
- Mins > 20 lux (total if>1 sleep period)
- Sleep onset latency (mean if>1 sleep period)

Appendix A-3i Patient Version Sleep Diary

Study ID	_____
Date	__ /__ /__
I fell asleep at:	AM / PM
I woke up at:	AM / PM
I woke up during the night:	
# of times	
# of minutes (total)	
When I woke up for the day I felt:	
Rested	☐
Somewhat rested	☐
Tired	☐
Hours slept (to be completed by study staff)	

Appendix A-3ii. Parent Version Sleep Diary

Study ID	_____
Date	__ /__ /__
My child fell asleep at:	AM / PM
My child woke up at:	AM / PM
My child woke up during the night:	
# of times	
# of minutes (total)	
When my child woke up for the day they felt:	
Rested	☐
Somewhat rested	☐
Tired	☐
Hours slept (to be completed by study staff)	

Appendix A-4 Sleep Disturbance Survey

Pediatric Sleep Disturbance Survey

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

Last night…

	Never	Almost Never	Sometimes	Almost Always	Always
I had difficulty falling asleep	❑	❑	❑	❑	❑
I slept through the night	❑	❑	❑	❑	❑
I had a problem with my sleep	❑	❑	❑	❑	❑
I had trouble sleeping	❑	❑	❑	❑	❑
It took me a long time to fall asleep	❑	❑	❑	❑	❑
I worried about not being able to fall asleep	❑	❑	❑	❑	❑
I woke up at night and had trouble falling back to sleep	❑	❑	❑	❑	❑
I tossed and turned at night	❑	❑	❑	❑	❑

Pediatric Sleep Disturbance Survey - Parent Version

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

Last night…

	Never	Almost Never	Sometimes	Almost Always	Always
My child had difficulty falling asleep	❑	❑	❑	❑	❑
My child slept through the night	❑	❑	❑	❑	❑
My child had a problem with my sleep	❑	❑	❑	❑	❑
My child had trouble sleeping	❑	❑	❑	❑	❑
It took my child a long time to fall asleep	❑	❑	❑	❑	❑
My child worried about not being able to fall asleep	❑	❑	❑	❑	❑
My child woke up at night and had trouble falling back to sleep	❑	❑	❑	❑	❑
My child tossed and turned at night	❑	❑	❑	❑	❑

PROMIS Sleep Disturbance Survey T-score conversion table

Sleep Disturbance Child-Report

Look-Up Table SF8		
Raw Score	T Score	T Score SE
8	36.6	5.6
9	42.1	3.8
10	44.8	3.4
11	46.8	3
12	48.5	2.8
13	50	2.6
14	51.3	2.5
15	52.5	2.5
16	53.7	2.4
17	54.9	2.4
18	56	2.4
19	57.1	2.5
20	58.2	2.5
21	59.3	2.5
22	60.3	2.5
23	61.4	2.5
24	62.4	2.5
25	63.5	2.5
26	64.5	2.5
27	65.6	2.5
28	66.6	2.4

Look-Up Table

SF8

Raw Score	T Score	T Score SE
29	67.6	2.4
30	68.7	2.4
31	69.7	2.4
32	70.7	2.4
33	71.8	2.5
34	72.9	2.5
35	74.1	2.6
36	75.4	2.7
37	76.8	2.9
38	78.5	3.1
39	80.3	3.3
40	82.7	3.5

Appendix B: Safety-Related Events

Safety-related events information, as defined by ICH Good Clinical Practice guidelines (E6) (ICH GCP E6), the Code of Federal Regulations (CFR), and Intermountain research policy, (standard operating procedures (SOPs), will be collected throughout the study and will be reported using the appropriate case report forms, in accordance with relevant regulations/guidelines and Intermountain policy.

Adverse Events

All adverse events related to the subject's participation in the research (serious and non-serious, anticipated and unanticipated) will be assessed and recorded by the Principal Investigator and/or his/her delegate (, *Sub*-Investigators, Clinical Research Coordinator, etc), as per reporting timelines set forth by the guidelines, policies and regulations mentioned above. The Principal Investigator or his/her delegate will follow all adverse events until they are adequately resolved or explained. The follow-up process and actions taken will be appropriately documented on the source documents and/or progress notes.

Serious Adverse Events and Death

The Principal Investigator or his/her delegate must decide whether a safety-related event meets the definition of a "serious" adverse event, guided by ICH GCP E6 and CFR definitions. Further, the Principal Investigator will collaborate with attending physicians and exercise their medical and scientific judgment in deciding whether important medical events, other than those defined by ICH GCP E6 and/or CFR, should be considered as serious adverse events.

Anticipated Adverse Events

Anticipated adverse events include: no anticipated adverse events.

Unanticipated Problems Involving Risks to Subjects or Others

Any event that meets all the following criteria is considered an Unanticipated Problem Involving Risk to Subjects or Others (UP). This includes both adverse events and other types of incidences, experiences and outcomes that occur during the conduct of a research study. These events generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions, to protect the safety, welfare, or rights of subjects or others:

- Unexpected – considering the research procedures described in the protocol, investigator's brochures and informed consent documents, and in consideration of the characteristics of the study population;
- Is related or possibly related to the subject's participation in the research; and
- Suggests that the research places subjects or others at greater risk of harm than was previously known or recognized.

The Principal Investigator must report UPs that are not adverse events to the IRB within 10 business days/14 calendar days.

APPENDIX C: OTHER OVERSIGHT

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will not be used for this study. The Principal Investigator and his research team will monitor subject safety in accordance with ICH GCP E6, CFR, Declaration of Helsinki, Intermountain policies, Intermountain CVR SOPs, and all applicable local regulations.

APPENDIX D: DECLARATION OF HELSINKI

WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

<u>Risks, Burdens and Benefits</u>

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in

the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

12.0 PROTOCOL SIGNATURE PAGE

PROTOCOL IDENTIFICATION

[Insert protocol identification number, title and applicable short title or acronym here]

PRINCIPAL INVESTIGATOR AGREEMENT

I agree to conduct this clinical trial/research study in accordance with the design and specific provisions of this protocol. Deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment and approval by the Institutional Review Board (IRB). I also agree to report all information or data in accordance with the protocol. I agree to report any serious adverse experiences as defined in the Safety Reporting section of this protocol to the Intermountain IRB, and in accordance with the IRB's reporting requirements. I also agree to handle all clinical supplies provided by the sponsor, and collect and handle all biological specimens, in accordance with the protocol.

_____	_____	_____
Principal Investigator (Printed Name)	Principal Investigator (Signature)	Date

If there are Co-Principal Investigators designated for this study, they must also affix their dated signatures below:

_____	_____	_____
Co-Principal Investigator (Printed Name)	Co-Principal Investigator (Signature)	Date

_____	_____	_____
Co-Principal Investigator (Printed Name)	Co-Principal Investigator (Signature)	Date