STANFORD TECHNOLOGY ANALYTICS AND GENOMICS IN SLEEP

Manual of Procedures (MOP)

for

STAGES – Stanford Technology, Analytics, and Genomics in Sleep

Version Number: 002

08/09/2018

Summary of Changes

Number	Date	Affected Chapter(s)	Summary of Revisions Made:
1	08/09/2018	6.8, page 24	PHI updated to include email address
	08/09/2018	13.3.1, page 41	Addition of unrestricted sharing of blood samples to study assessments in exclusion criteria

Chapter/Appendix Version Tracker

Chapter Number / Appendix	Title	Current, Approved Version Number	Current, Approved Version Date

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1 List of abbreviation

AASM	American Academy of Sleep Medicine
AE	Adverse Event
AHI	Apnea Hypopnea Index
AR	Adverse reaction
CC	Clinical Center
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
Co-Inv	Co-Investigator
CRO	Contract Research Organization
CRF	Case Report Form
dbGaP	Database of Genotypes and Phenotypes
DC	Data Center
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMR	Electronic Medical Record
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERA	Genetic Epidemiology Research on Adult Health and Aging (*GERA*) Cohort
GTCA	Genome Wide Complex Trait Analysis
GWAS	Genome Wide Association Study
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
eICF	electronic Informed Consent Form
ICSD-3	International Classification of Sleep Disorders, 3rd Edition
IEC	Independent Ethics Committee
iPSC	induced Pluripotent Stem Cells
IRB	Institutional Review Board
IWRS	Interactive Web Response System

LIMS	Laboratory Inventory Management System
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NDA	National Institute of Mental Health (NIMH) Data Archive
NDA-GUID	NIMH Data Archive-Global Unique Identifier
NIH	National Institute of Health
NIMH	National Institute of Mental Health
NRGR	NIMH Repository and Genetics Resource
NSSR	National Sleep Research Resource
OHRP	The Office for Human Research Protections
OSA	Obstructive Sleep Apnea
OTC	Over the counter
PD	Project Director
PI	Principal Investigator
PLMI	Periodic Leg Movement Index
PSG	Polysomnography
QC	Quality Control
RLS	Restless Legs Syndrome
RUCDR	Rutgers University Cell and DNA Repository
SAE	Serious adverse event
SCCI	Stanford Center for Clinical Informatics
SCNR	Stanford Center for Narcolepsy Research
SCSSM	Stanford Center for Sleep Science and Medicine
SDR	Stanford Document Repository
SISS	Subject Information Summary Sheet
SMB	Stanford Medicine Box
SNP	Single Nucleotide Polymorphism
SOREM	Sleep onset REM period
SSDC	Stanford Sleep Disorder Clinic
STAGES	Stanford Technology Analytics and Genomics in Sleep
TST	Total Sleep Time

WSC Wisconsin Sleep Cohort

2 Introduction to the Manual of Procedures

2.1 Purpose

A Manual of Procedures (MOP) is a handbook that guides a study's conduct and operations. It supplements the study protocol by detailing a study's organization, operational data definitions, recruitment, screening, enrollment, procedures, data collection methods, data flow, (electronic) case report forms (eCRFs), and quality control procedures. The purpose of the MOP is to facilitate consistency in protocol implementation and data collection across participants and clinical sites. Procedures in the MOP should be followed with the same degree of vigor as those documented in the protocol. Use of the MOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participant safety and scientific integrity are closely monitored.

This MOP is to be used as a reference document for policies and procedures related to the study entitled STAGES – Stanford Technology, Analytics, and Genomics in Sleep.

All staff members participating in the conduct of this study at participating institutions should have ready access to the MOP and be familiar with its contents. The current version of the MOP and archived versions are posted to the STAGES Document Repository (SDR) on the Stanford Medicine Box (SMB), https://stanfordmedicine.app.box.com/v/STAGESDocumentRepository (see SDR directory).

3 Study Protocol

The STAGES study protocol was originally approved by the Stanford IRB on 07/11/2017. The current approved version is available through the SDR (see SDR directory).

3.1 Protocol Summary

Title:	**STAGES** – Stanford Technology Analytics and Genetics in Sleep
Summary:	The **STAGES** study is a prospective cross-sectional, multi-center study funded by the **Klarman Family Foundation (KFF)** to develop the critical infrastructure needed for sleep and sleep disorder research and will provide essential tools and data for future research projects. The study will collect the following information on 30,000 patients collected at 11 to 13 different sleep clinic sites (six collaborating institutions; one with five data collection sites and one with two to four data collection sites) over a recruitment period of ~43 months.

- On-line sleep/medical history questionnaire (the Alliance Sleep Questionnaire (ASQ),
- In-lab nocturnal Polysomnography data (one night PSG; includes Pre- and Post- Sleep Questionnaires)
- Computerized Neurocognitive Battery (UPenn CNB)
- Actigraphy over at least 2 weeks (includes sleep diary)
- 3-D Photo (uGo3D image)
- Genetics - Genome wide association data
- Stored biological samples (DNA, plasma, serum) for future biomarker research
- Electronic Medical Record manual extract

Objectives:

The STAGES study aims to create a database containing sleep related data on 30,000 sleep clinic patients (age 13 and over) including genetic and phenotypic data to obtain a better understanding of the genetic architecture of sleep, and to improve detection, treatment and prevention of sleep disorders. The study hopes to identify new diagnostic biomarkers for sleep disorders and obtain a molecular understanding of sleep regulation using genetic analysis. If one or more unique gene(s) or blood marker(s) could be identified, physicians would have a simple, minimally invasive test for aiding diagnosis of sleep disorders.

To maximize research potential, all tools and data will be made available to the research community via the National Institute of Mental Health (NIMH) Data Archive (NDA) and the database of Genotypes and Phenotypes (dbGaP).

Population:

The STAGES sample is not population-based, but composed of patients visiting sleep clinics across the USA and Canada. The sample is therefore not representative of a general population as it is enriched in sleep disorders. The study aims to recruit 30,000 subjects (age 13 and over).

Sites / Clinical Centers (CC):

Patients will be recruited from 11 to 13 different clinical centers (CC) across the USA and Canada (six institutions; one with five data collection sites and one with two data collection sites). Stanford University will act as both a CC and the data center (DC).

Study Duration:

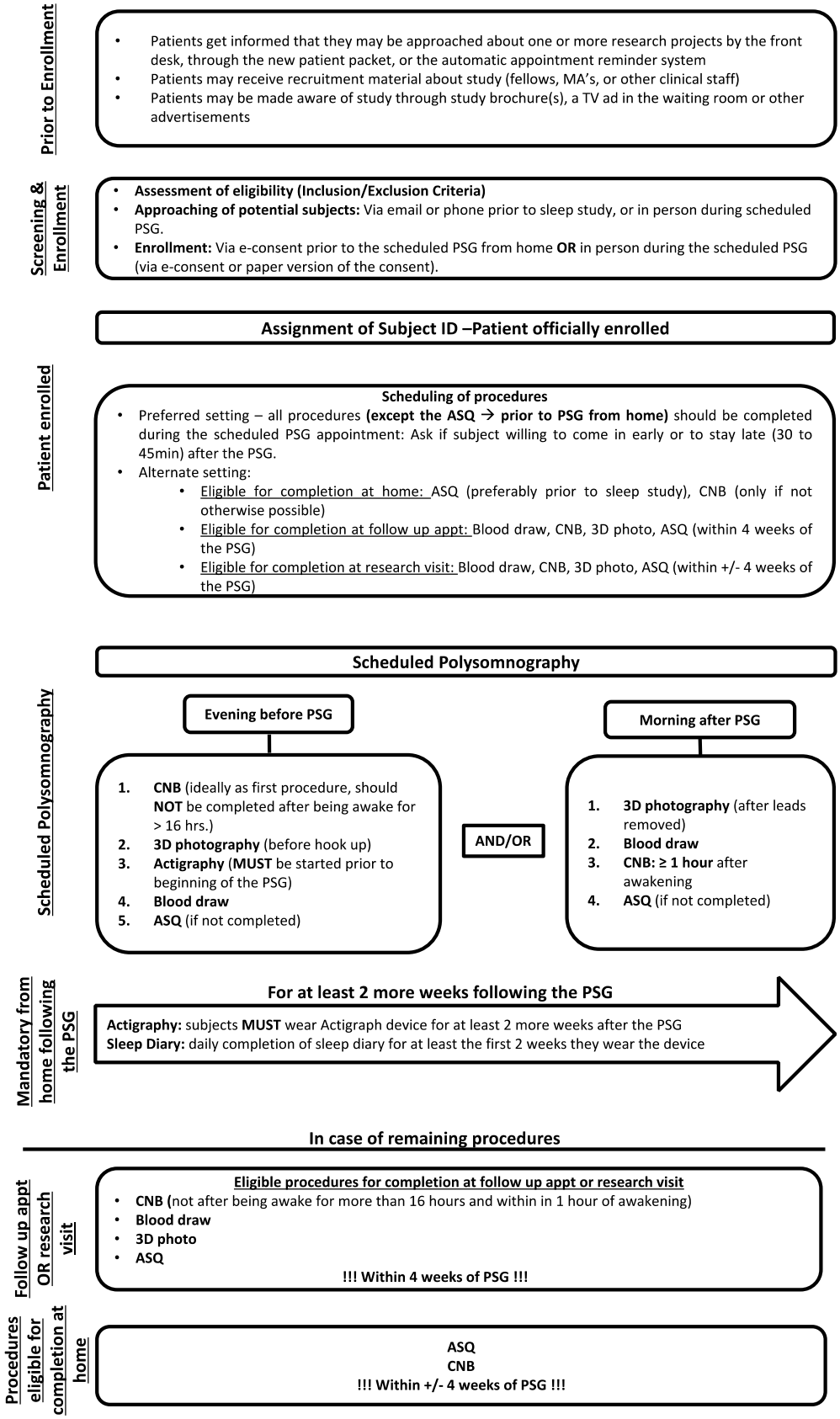
The estimated time from enrollment until completion of data analysis is 51 months.

Subject Participation Duration:

We estimate that each participant will spend approximately 1.0 – 2.5 hours completing questionnaires, neurocognitive testing, photography, and blood sampling. In addition, participants are asked to wear an Actigraph device for at least 2 weeks at home. The

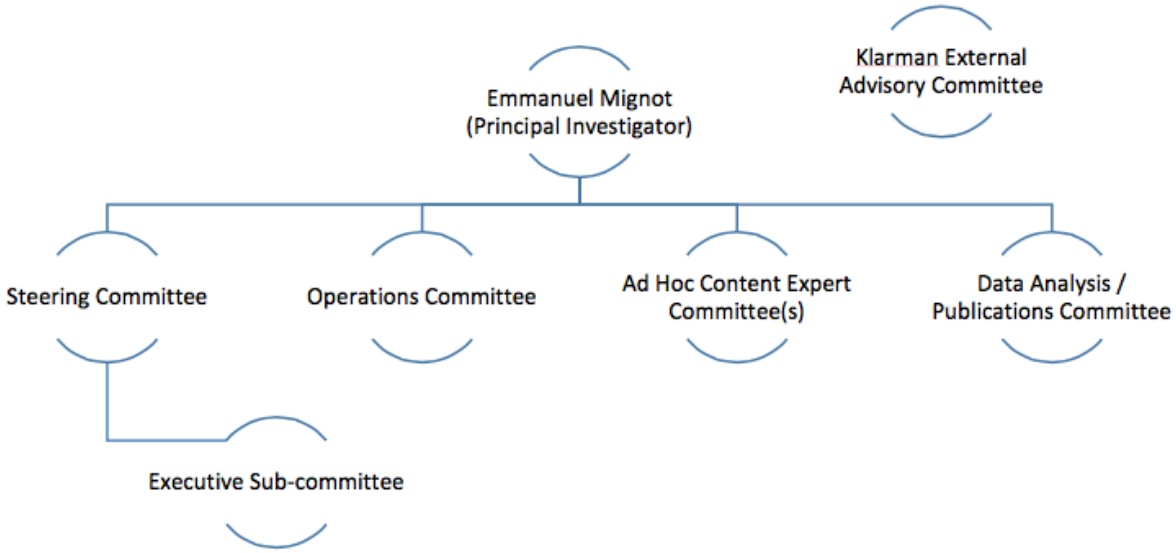
	PSG will be conducted as part of standard of care and is therefore not included in the overall hours of the subject's active participation.
Estimated Time to Complete Enrollment:	Enrollment will begin month 11 of the study and end month 54. The estimated time from enrollment of the first subject to enrollment of the last subject is approximately 43 months.

3.2 Schematic of Study Design



4 Study Organization and Responsibilities

4.1 Organizational Chart



4.2 Administrative Structure

The administrative structure of the study includes:

Principal Investigator: Dr. Emmanuel Mignot, MD, PhD

Co-Investigator: Dr. Clete Kushida, MD, PhD

Six clinical centers (CCs):

- Stanford University (Stanford, CA)
- Mayo Clinic (Rochester, MN)
- MedSleep (Canada, 5 collection sites)
- St. Luke's Hospital (Chesterfield, MO)
- Geisinger Health (Pennsylvania, PA; 2 to 4 collection sites)
- BoganSleep (Columbia, SC)

Six Advisory Committees (see section 4.5):

- Steering Committee
- Executive Committee
- Operations Committee
- Data Analysis and Publications Committee
- Ad Hoc Domain/Content Expert Committee
- Klarman External Advisory Committee
- Data Center

4.3 Key Roles

Dr. Emmanuel Mignot, **MD, PhD** is the Principal Investigator (PI) of the study. He is responsible for the management and integrity of the design, conduct, and reporting of the research project and for managing, monitoring, and ensuring the integrity of any collaborative relationships. Dr. Mignot is the chair of the Steering Committee, Executive Sub-committee, Ad Hoc Content Expert Committees, and Data Analysis / Publications Committee to ensure quality data are collected, useful sleep analytic tools are developed and data are shared with the scientific community.

Clete Kushida, MD, PhD is both a Co-Investigator (Co-Inv.) and Site Director (SD) for the study. He will be responsible for working with the sites to ensure that they successfully meet the project milestones and complete all deliverables and he will run the Stanford Clinical Center.

Eileen Leary, MS, RPSGT is the Project Director (PD). She is responsible for managing the study at the strategic level to ensure that the project progresses on time and on budget. She will chair the Operations Committee, coordinate the development of the data management portal, oversee the site coordinators and provide high-level oversight for data collection, and manage the databases and servers for convenient and secure data storage and sharing.

4.4 Clinical Centers and Contact Information

4.4.1 Stanford Center for Sleep Sciences and Medicine

- Lead PI: Emmanuel Mignot, MD, PhD
- Co-Inv.: Clete Kushida, MD, PhD
- Project Director: Eileen Leary, MS, RPSGT
- Site Coordinator: Rebekka Seeger, MD

4.4.2 Data Collection Sites

Please see SDR > STAGES Key Contact Info for list of STAGES Site Contact Information

4.5 Committees

4.5.1 Steering Committee

The Steering Committee is the main administrating and governing body of the study. It supervises the study and makes decisions regarding the protocol. The committee is chaired by the PI and is comprised of the site directors from each clinical center and the project director. For problems or decisions not resolved easily within Steering Committee, one of the other committees will be consulted.

<u>Responsibilities of the Steering Committee include but are not limited to:</u>

- Responsibility for the general design and conduct of the study
- Review of data collection practices and procedures
- Changes in study procedures as appropriate

- Approval of protocol amendments prior to submitting the amendment to the IRB
- Appointments to and disbanding of study implementation subcommittees
- Allocation of resources based on priorities of competing study demands
- Review of study progress and implementation of necessary steps to ensure the achievement of study goals
- Review and implementation of recommendations from those responsible for safety monitoring
- Review and response to other general advice and/or recommendations (e.g., from the NIH, etc.)

Please see Operational Plan (SDR > STAGES Operational Plan) for a list of the Steering Committee Members.

4.5.2 Executive Sub-Committee

The Executive Sub-committee handles the day-to-day protocol decisions, which are relayed to the other committees when appropriate. The group is comprised of Emmanuel Mignot, Clete Kushida, Eileen Leary, and Rebekka Seeger.

4.5.3 Operations Committee

The Operations Committee oversees implementation of the protocol at the sites including training of all staff, development of standard operating procedures (SOPs), and quality assurance/control of data. The group is comprised of the clinical coordinators (CCs) from each of the five clinical centers and is chaired by the PD.

4.5.4 Data Analysis and Publication and Presentation Committees

The Data Analysis and Publications Committees are comprised of individuals who have extensive expertise in the areas of genetic analysis, machine learning and technology, and sleep and circadian phenotypes. They include key analytic personnel from the study and external contributors who have expressed interest in analyzing these data. The committees are chaired by the PI and charged with creating a data analysis plan for each domain and organizing initial analyses and publications.

Please see Operational Plan (SDR > STAGES Operational Plan) for a list of the Data Analysis and Publications Committee Members.

4.5.5 Ad Hoc Domain/Content Expert Committee(s)

The Ad Hoc Domain/Content Expert Committee(s) will be assembled as needed to make suggestions regarding specific data types or questions/issues that arise. The committee(s) will be chaired by the PI or his designee.

Please see Operational Plan (SDR > STAGES Operational Plan) for a list of the Ad Hoc Domain/Content Expert Committee(s) Members.

4.5.6 Klarman External Scientific Advisory Committee (SAC)

The Klarman External Scientific Advisory Committee (SAC) is comprised of members elected by the Klarman Family Foundation to oversee the project and ensure the scientific integrity of the study.

Please see Operational Plan (SDR > STAGES Operational Plan) for a list of the Klarman External Scientific Advisory Committee (SAC) Members.

4.5.7 Data Center

The Data Center has been established at Stanford and is comprised of members of the executive sub-committee and key consultants. The data center is responsible for the overall direction of the study and to oversee the collection of quality data and process the data for distribution according to the resource sharing plan.

Responsibilities of the DC include but are not limited to:

- Preparation of the essential study documents, including the protocol, protocol amendments, MOP, and data collection forms
- Organizing conference calls, meetings, training sessions, and site audits
- IRB assistance and oversight: maintaining records of IRB submissions, approvals and expiration dates for all study sites; providing guidance or review on IRB forms, tracking of annual review
- Ensuring compliance with protocols and procedures
- Ensuring subject safety and compliance with Institutional Review Boards (IRBs)
- Developing mechanisms to ensure a smooth transfer of data between the sites and the DC
- Monitoring of data collection and submission of data from all sites
- Review of study progress and implementation of necessary steps to ensure the achievement of study goals
- Monitoring of monthly progress reports to the Prometheus data platform
- Monitoring and reporting of unanticipated problems
- Monitoring federal regulatory compliance, fiscal and personnel management and development of conflict-of-interest policies
- Working with the key investigators to assume the leadership role in maintaining the scientific integrity, cooperation, and morale among the sites

5 Administrative

5.1 Protocol Amendment Procedures

Approval from the DC must be obtained for all major protocol amendments and amendments to the ICF (e.g., changes more substantive than updating personnel). Each site's local IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the study. Each CC's Principal Investigator must send a copy of the approval letter from the IRB to the Data Center. The DC will then coordinate the distribution to

the Klarman Family Foundation and/or designee. Any amendment to the protocol will be adhered to by all study staff and will apply to all subjects.

5.2 Version Control of the Manual of Procedures

The MOP is a dynamic document that will be updated throughout the conduct of a study to reflect any protocol or consent amendments as well as the refinement of the Case Report Forms (CRFs) and study procedures. As sections/chapters are revised, the MOP version information and date on the cover page and Table of Contents will be updated; the Summary of Changes table on the cover page will list the chapters that have changed and will include a general summary of those changes. Further, each page of the MOP will contain the version number and date. As pages are revised, an updated version number and associated date will replace the original page(s) in the MOP.

As the study progresses, the Data Center (DC) at Stanford will be responsible for documenting any recommended and approved changes to the MOP. The DC will incorporate all of the approved changes and will update the MOP periodically. When the revisions are final, the MOP will be posted to the Stanford Medicine Box (SDR > Manual of Procedures) or otherwise made available to all study personnel. All clinical sites will be notified that the MOP has been updated via a numbered memo (see section 5.4), which will also summarize the changes that were made. Additionally, study coordinators will be reminded of the MOP update during the regularly scheduled monthly teleconference.

The author of an updated MOP section will ensure that all necessary changes are captured in the update and that the updated document is distributed.

The Data Center at Stanford is responsible for document control of the MOP on the Stanford Medicine Box and for filing updates in a timely manner. The DC will post updated MOP sections on the Stanford Medicine Box within 2 business days of receipt.

The site principal investigator (site PI) or designee is responsible for on-site document control of the MOP and for filing updates in a timely manner.

If sites decide to maintain paper copies of the MOP, they will be filed in the Essential Documents binder, the study coordinator will print and store the updated materials in the binder. Outdated materials will be removed from the binder and filed in another location clearly marked “obsolete.”

5.3 Communication Plan

The Data Center at Stanford conducts all aspects of administrative guidance, oversight, and support. Communication, both method and frequency between the entities of the DC, the clinical centers, the operations committee, and the steering committee are scheduled as follows:

- Routine conference calls with the operations committee are scheduled on a monthly basis to discuss potential concerns at the sites, to discuss progress and amendments, and to build an esprit de corps.
- Regular conference calls with the Steering Committee are occurring on a monthly basis. Communications are documented by the Data Center and distributed to the sites.

Additionally, all stakeholders may contact the DC staff directly via email or telephone.

5.4 Numbered Memo

The objective of numbered memos is to document and communicate important study information to all investigative sites in a consistent manner. The numbering of the memos is intended to facilitate reference to the memos, as well as tracking and archiving of the memos.

Responsibilities

- The Data Center may identify issues that require across-site communication/clarification above and beyond discussion during an Operations Committee or Steering Committee meeting.
- The Data Center will identify an author and reviewer(s) for the memo.
- The PI or designee is responsible for approving the memo. (Approval may be communicated via email from the PI or by signature on a version of the memo itself.)
- The facilitators of the Steering Committee and Operations Committee meetings are responsible for including a discussion of each new numbered memo on the agenda for the corresponding meeting.
- The Data Center will be responsible for the email distribution of the numbered memos.
- The Site Correspondence Manager or designee will be responsible for the email distribution of the numbered memos.
- The Data Center will store the numbered memo tracking spreadsheet and all numbered memos under "Numbered Memos" on the SDR.
- All Site PIs and Site Coordinators are responsible for reviewing each numbered memo. In addition, all other individuals identified in the "TO" or "CC" lines of the memo are responsible for reading the memo (i.e., regulatory coordinator, lab techs, etc.).
- Study Coordinators will ensure that all relevant site staff members are aware of the memo and that all numbered memos are stored in the site's Essential Documents binder if appropriate.

5.4.1 Procedures

If a study issue or new information is of enough complexity and importance to require a numbered memo, then the Data Center will identify an author and the reviewers for the memo. Examples of items that may trigger the generation of a numbered memo are 1) establishing a new method for the conversion and export of the Polysomnography (PSG) file or 2) addition of new data element.

The Site Correspondence Manager will track all aspects of the generation, review, approval, and distribution of the numbered memos.

5.4.2 Creating, Reviewing, and Approving a New Numbered Memo

Structure of Memo: Memos will be numbered consecutively, starting with #0001. The numbered memo will include a standard memo heading with TO, CC, RE, and the date of issuance. It will also contain a "Site Action Required" section in the header. This section is designed to communicate whether the memo requires some action on the part of the site or whether it is being provided for informational purposes only. The body of the memo will provide the details of the information.

The author will identify the required time frame for completion of the numbered memo and will be responsible for managing the production, review, and approval process. The author is responsible for confirming that he/she is using the appropriate number for the memo.

All memos must be approved prior to electronic distribution to the sites. It is not necessary to distribute the signed version of the memo to the sites.

5.4.3 Distributing a New Numbered Memo

An electronic version of each numbered memo will be emailed to the study coordinator(s), site PIs, and other relevant study personnel. (Note: It is not necessary to email the signed version of the memo.)

Each memo will also be posted to the Stanford Medicine Box (SDR > Numbered Memos).

5.4.4 Reading and Archiving Numbered Memos

The site PIs and study coordinators will read each numbered memo. All numbered memos will be available and archived on the Stanford Medicine Box (SDR > Numbered Memos).

5.4.5 Amending Information in a Numbered Memo

If it becomes necessary to correct a numbered memo, a new memo will be distributed with the same memo number and will include a _Corrected_Date designation (e.g., Memorandum #0005_Corrected_20JULY2018).

The nature of the corrections will be identified in the header of the memo.

If a study decision changes the guidance in a previous numbered memo, a new numbered memo will be issued and will refer to the numbered memo being superseded. This status of the previous numbered memo will be highlighted on the SDR as well.

5.5 Conflict of Interest (COI) and Financial Disclosure Policies

Conflict of Interest (COI) on the part of the investigators may compromise the well-being of research subjects, may lead to bias in the conduct of research trials, and may undermine trust in the results.

We follow the Stanford regulations on disclosing financial interests of the STAGES study investigators (Stanford Conflict of Interest and Financial Disclosure Policies). The STAGES study investigators have to disclose any personal financial interest defined as income, honoraria or other payment for services (such as payment for consulting), equity such as stock, stock options or other ownership interests, and royalties. This includes financial interests of the investigators' spouses or domestic partners and dependent children or the relationship with a for-profit company that either directly supports the study or that conducts research which is related to the study.

All personal financial interests related to the STAGES study must be reported, regardless of the dollar amount. While most disclosures of financial interests will probably be deemed not significant conflict of interests, financial interests above certain thresholds will automatically be

deemed significant conflicts of interest and will require closer scrutiny and possible elimination, mitigation, and/or management. The thresholds are as follows:

A. These interests are over $10,000 in monetary value.

B. (1) These interests involve the ownership or promise of stock or stock options over $10,000 or 0.5% of the total value of the company, in a **publicly traded** company.

(2) These interests involve the ownership or promise of stock or stock options of any amount in a **privately-held** or start-up company.

C. An individual serves in a consulting or other fiduciary role for a financially interested company, whether or not remuneration is received.

All reported financial interests will be reviewed by the DC and the Stanford Conflict of Interest Review Program (COIRP) to determine if a significant conflict of interest exists. Conflicts of interest with direct negative impact on the study would be referred to the Stanford Conflict of Interest Committee in order to determine what steps might be needed to eliminate, mitigate or manage the conflict. Please see the Stanford Medicine Website for more details on Eliminating, Mitigating, or Managing Conflicts of Interest.

Investigators of ancillary studies are also subject to the above-outlined Conflict of Interest and Financial Disclosure Policies.

6 Regulatory

6.1 Protection of Human Subjects

The study will conform to ICH GCP Guidelines when appropriate.

6.2 Regulatory Approval

The planned regulatory pathway for this study is through the submission and approval process to regulatory and local ethics committee(s). No other regulatory approvals will be required.

A site may not start recruiting until all required local approvals have been obtained.

6.3 Institutional Review Board (IRB) Approval

Each Site Principal Investigator is responsible for obtaining IRB approval for the protocol, sponsor-approved (electronic) informed consent form ((e)ICF), recruitment materials and all participant materials. Approval of both the protocol and the consent form must be obtained before any participant is enrolled at a center.

Each Site Principal Investigator is also responsible for:

- Obtaining approval by the IRB for any amendment to the protocol before the changes are implemented in the study
- Providing the IRB with any required information before or during the Study
- Submitting progress reports to the IRB, as required, during the conduct of the Study requesting re-review and approval of the Study, as needed; providing copies of all IRB re-

approvals and relevant communication to the DC. The DC will then coordinate the distribution to the Klarman Family Foundation and/or designee.

- Notifying the IRB of all serious and unanticipated AEs that occurred at the site.

6.4 (Electronic) Informed Consent / Assent Process

The Principal Investigator and Sponsor must agree upon the format and content of the ICF, and a copy of the IRB approved ICF will be forwarded to the Sponsor.

Before conducting any study related activities, written, IRB-approved ICF and privacy protection release form must be obtained from each patient.

6.4.1 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Participants will be given the opportunity to ask study staff about the content of the study, and their surrogates or think about it prior to agreeing to participate.

CCs may use paper and/or electronic versions of the informed consent form. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The participant will sign the (electronic) informed consent document prior to any study-related assessments or procedures. They may withdraw consent at any time throughout the course of the study.

A copy of the informed consent document will be made available to participants for their records. For example, if enrolled via e-consent, a clean copy of the consent will be sent via email; if enrolled in person using the paper version, participants will receive a copy of the signed consent. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

6.4.2 Re-Consenting for Protocol Changes of Safety Updates

If a consent document is revised due to changes in study procedures, subjects who were enrolled prior to the change, but are affected by the change, will be informed of the changes and will sign the amended consent document per local IRB requirmeents. If a consent document is revised due to changes in the risks or safety of the study, all active participants must sign the revised consent.

6.4.3 Informed Consent Form Template and Informed Consent Checklist

A copy of the most recent approved version of Stanford's ICF and ICF checklist will be available on the STAGES Medicine Box (SDR > IRB Templates > STAGES IRB Templates March 2018).

6.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the Principal Investigator of this study. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The Data Center (DC) has been working closely with the Privacy Office to negotiate the security concerns involved with building a multi-site research data repository. Each subject will be assigned a unique STAGES Subject ID via the Prometheus Data Platform. Participant names will not be used on any STAGES data analysis files; only ID numbers will be used whenever possible on paper forms, PSG data files, all data files created from the paper forms, and all other data files of each required data element. Paper files will be maintained in locked files or rooms. Computerized data will be stored on password-protected computers and on secured servers at the Data Center. Additionally, all data will be associated with an NIMH Data Archive (NDA) Global Unique Identifier to allow researchers to share data specific to a study participant without exposing personal health information (PHI) and to make it possible to match participants across research data repositories.

All external vendors contributing to the STAGES study underwent a thorough Data Risk Assessment Process by the Stanford Security and Privacy Offices to ensure they meet best practice guidelines for data security during transmission, storage, and backup.

6.6 NIH Data Sharing Policy for Genome-Wide Association Studies

We will comply with the NIH GDS Policy and the funding agency's existing policies on sharing data on sleep genetics to include secondary analysis of data resulting from a genome wide association study through the repository. Submission of data to the NIH GWAS repository will be consistent with the permissions and limitations delineated on the study consent signed by study participants.

6.7 Future Use of Stored Specimens and Other Identifiable Data

All data and biological samples collected under the STAGES project will be made publicly available for analysis by any interested researcher, providing a request is submitted to the National Institutes of Health (NIH) and approved. All resources will be shared with sufficient metadata to allow them to be discovered, interpreted, and used by others, and in accordance with recognized data standards, where these exist, in a way that maximizes opportunity for data linkage and interoperability. We will share phenotypic data (such as questionnaire data and clinical information) associated with the collected samples by depositing these data at both the NIMH Data Archive (NDA) and Database of Genotypes and Phenotypes (dbGaP), which are NIH-funded repositories. Genotype data will be shared by depositing these data at dbGaP. Additional data documentation and de-identified data will be deposited for sharing along with phenotypic data, which includes demographics, family history, and diagnosis, consistent with applicable laws and regulations. Biological samples will be stored at RUCDR, the federal biorepository for the NIH, and surplus samples will be stored at Stanford. All biological samples will be stored in barcoded aliquot tubes that will be registered through a Laboratory Inventory Management System to maintain chain of custody.

The STAGES ICF will be NIH compatible to allow for deposition of phenotype/genotype data into an accessible NIH data warehouse such that genotype (and in the future full sequence) data can be shared. Subjects will be consented broadly such that both clinical data and genomic data may be shared with qualified investigators who are studying diseases in other domains (not just in sleep). Consent forms will allow for the future use of the STAGES samples for whole genome

sequencing and other unspecified genetic analyses. Subjects who decline to have their data and their tissues to be studied now or saved for future study will not be enrolled into the study.

6.8 Health Insurance Portability and Accountability Act (HIPAA) Authorization

The HIPAA authorization form for this study may be a separate document from the informed consent, and must be reviewed by all study participants in addition to reviewing and signing the consent form. The format of the HIPAA authorization is established by each local IRB, not all IRBs require participants to sign the form.

We will collect the following personal identifiable health information (PHI):

- Name
- Email address
- Telephone
- Address
- Medical Record Number
- Date of Birth
- Dates of Service
- 3D image

All PHI will be stored in secure, password protected databases that have gone through security review. PHI will be stored at Prometheus Research and an on premise server located behind the Stanford firewall and maintained by Stanford's IRT Research Technology group. The server is accessed by staff using two step authentication.

To minimize the privacy risk to all participants, names of subjects and other PHI will only be available to critical staff members such as the PI, the Protocol Director, clinical coordinator and other staff receiving data or samples containing PHI. Participant names will be coded in all research arenas not protected by computer passwords or shielded by locks. Lab and other research personnel performing data analysis receive an extracted data set that does not include PHI.

Any data disclosed will be associated with an NIMH Data Archive(NDA) Global Unique Identifier (GUID, a unique identifier assigned based on the participant's legal name, date of birth, sex, and city of birth).

All members of the STAGES study who will handle PHI received HIPAA training to ensure the confidentiality and accuracy. Each of the participating sites will further monitor the conduct of their staffs to guarantee HIPAA compliance.

6.9 Essential Documents

Essential documents are those documents that individually and collectively permit evaluation of both the conduct of a clinical trial and the quality of the data produced.

6.9.1 Non-subject, study-specific documents provided by the Data Center

All non-subject specific essential documents provided by the data center will be available on the Stanford Medicine Box. The documents include, but are not limited to:

- Study protocol and all protocol amendments
- Informed Consent and Informed Consent Checklist
- Study communication (numbered memos)
- Manual of Procedures
- SOPs for each data element
- Study brochures and workflows

Please see STAGES Document Repository Index for a detailed description of the location of each document on the Stanford Medicine Box.

6.9.2 Non-subject, site-specific documents

A folder will be created for each site to allow storage of site-specific documents. This folder can only be accessed by the respective site PI, coordinator and designated staff, and the DC at Stanford.

Sites will file paper versions of non-subject, site-specific essential documents in the STAGES specific Essential Documents binder, if applicable. The site-specific documents include, but are not limited to:

- All versions of IRB approved consent documents
- IRB documentation, approvals, and correspondence
- Financial disclosure forms
- Documentation of clinical research and study training
- Protocol deviations
- Documentation of clinical site monitoring visits
- Delegation of responsibilities log

6.9.3 Subject-specific documents (Central Handling via Prometheus Data Platform)

Whenever possible, subject-specific documents should be completed electronically via the Prometheus Data Platform. However, all paper versions of subject-specific documents such as CRFs, ICFs, questionnaires completed by the participant, etc. will ultimately be either uploaded or keyed into the appropriate form on the Prometheus Data Platform. Additionally, paper versions of the subject-specific documents will be filed in the subject-specific essential documents binder, if appropriate.

- Completed case report forms
- Data correction forms
- Signed consent documents
- Questionnaires completed by the participant
- Screening and enrollment log
- Serious Adverse Events (SAEs)/Unanticipated Problems
- Protocol Violation
- Specimen Tracking Log

6.10 Document Maintenance

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

7 Assessment of Safety

7.1 Risk-Benefit Assessment

7.1.1 Risks

The project will take every step necessary to avoid subjecting participants to any unnecessary physical risk. The physical risks inherent to this study are minimal as the only source of potential physical harm is the blood draw. Physical harm will be minimized by (1) having certified phlebotomists, registered nurses (RNs), or physicians draw blood for this study, and (2) by the use of blood collection kits with sterile needles, blood collection tubes, bandages, and alcohol swabs to minimize the risk of infection.

The other risk relates to confidentiality, so every reasonable effort will be made to minimize the privacy risk to all participants. Participant names will be coded in all research arenas not protected by several layers of computer passwords or shielded by multiple locks. Those codes, in turn, are protected under additional passwords. The study data center has been working closely with the Stanford University Privacy office to negotiate the security concerns involved with building a multi-site research data repository.

7.1.2 Benefits

Although the participation in the STAGES study may not be directly beneficial to each subject, the information gathered from this study will likely help countless others who are either currently treated for sleep disorders or those who have undiagnosed and untreated sleep disorders.

7.2 Specification of Safety Parameters

Since the study procedures are not greater than minimal risk, few adverse events (AEs) and serious adverse events (SAE) are expected. In this context, any events/information typically covered as part of standard clinical care are not considered related to research. PSG and ASQ content (at sites that established ASQ as part of standard of care) related to sleep evaluation can be considered standard of care. Other important events such as depression or anxiety are directly handled by an ASQ disclaimer.

However, if any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including AEs, and SAEs), these will be reported according to local IRB policy.

7.3 Unanticipated Problems

7.3.1 Definition Unanticipated Problems

Unanticipated problems are reportable events that include any incident, experience, or outcome, and require reporting to the IRB.

An unanticipated problem is an event that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3.2 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.3.3 Collection Procedures for Unanticipated Problems

This is not an intervention study and the majority of subjects are completing the proctored part of their participation at the sleep clinic sites within a 24-hour period. Participants will then continue wearing their actigraph devices in an un-proctored setting at home for two more weeks following their overnight sleep study.

Participants who may return to the sleep center for a research visit will be queried about whether there were any adverse events since their last appointment.

We will include the following information when reporting an adverse event:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

7.3.4 Reporting Procedures

To satisfy the requirement for prompt reporting, unanticipated problems will be reported according each site's local IRB timeline. The study encourages the following general guidelines:

- Any suicide of a participant should be reported promptly to the Principal Investigator and IRB, regardless of relatedness.
- Unanticipated problems that are serious adverse events should be reported to the Principal Investigator, ideally within 24 hours of becoming aware of the event and to the local IRB within 3 business days.
- Unanticipated problems that are not serious adverse events should be entered into the Prometheus data platform ideally within 1 week of collection to allow timely review by the data center. Additionally, events should be reported at annual IRB renewal or before if appropriate.

7.4 Protocol Deviations

Protocol Deviations are accidental or unintentional changes to, or non-compliance with the research protocol that does not increase the risk or decrease benefit or; does not have a significant effect on the subject's rights, safety or welfare; and/or the integrity of the data.

Examples of Protocol Deviations include, but are not limited to:

- Consistent failure of sleep clinic sites to collect all required data elements
- Consistent failure of sleep clinic sites to upload required data
- Consistent submission of data that fails quality control tests

As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All deviations will be tracked in a Protocol Deviation Form on the Prometheus Data Platform.

Protocol Deviations are communicated to the DC at Stanford via email.

The report should include:

- Date of Protocol Deviation
- Description of Protocol Deviation
- Subject ID of subject involved (if applicable)
- Corrective Action
- Date site PI notified

7.5 Protocol Violations

Protocol Violations are reportable events that are accidental or unintentional changes to or non-compliance with the IRB approved protocol without prior sponsor and IRB approval. Violations generally increase risk or decrease benefit, affect the subject's rights, safety, or welfare, or the integrity of the data. Examples of Protocol Violations include, but are not limited to:

- Inadequate or delinquent informed consent
- Inclusion/Exclusion criteria not met
- Unreported Serious Adverse Events

All Protocol Violations will be entered into a Protocol Violation Form on the Prometheus Data Platform and reported to the IRB according to local IRB timelines.

7.6 Incidental Findings

This study is neither designed nor intended to detect health problems, and doctors or other specialists will not routinely analyze the results of this study. Any events/information typically covered as part of clinical care are not considered related to research. In this context, PSG and ASQ content related to sleep evaluation can be considered standard of care. Other important events such as depression or anxiety are directly handled by an ASQ disclaimer. We also do not expect to unveil incidental findings from the GWAS because of the nature of the data obtained, which are common polymorphisms and not reportable strong disease mutations. Should we decide later to extend the genetic testing (e. g. whole genome sequencing), the plan will be revised.

Nonetheless, it is possible that during the review of the results, we may uncover incidental findings or data that may have potential safety, health, or reproductive importance for the subject. In case of its occurrence, the Site Principal Investigator (or his/her designee) will then be responsible for contacting the subjects if they agreed in the (e)ICF to be contacted in the event information is identified that may significantly impact their (or their family's) health.

The discovery of an incidental finding may cause psychological stress for the subject. If the subject's medical doctor will do further tests, those results will then become part of the subject's medical record, which may affect the subject's current and future health or life insurance. The costs for any care needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be the subject's responsibility (financial assistance programs may be available through the treating facility).

8 Early Termination/Withdrawal

8.1 Subject Withdrawal

Subjects are free to withdraw from participation in the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

8.2 Early Termination of a Participant

The Protocol Director may terminate a study subject's participation in the study if:

- The Protocol Director decides that continuing the participation could be harmful to the subject.
- Any medical condition, event or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The TST of the subject's diagnostic PSG is less than 2 hours.
- The study is cancelled.
- Other administrative reasons.
- The subject is unacceptably rude or aggressive with the staff.
- Unanticipated circumstances.

8.3 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform the IRB and will provide the reason(s) for suspension or termination.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

9 Data Management and Data Quality Control

Data integrity and study credibility depend on factors such as ensuring adherence to the protocol, protecting the rights and safety of study participants, obtaining informed consent prior to conducting any study related procedures, and using quality control measures to establish and maintain high standards for data quality.

The Data Center (DC) has been working closely with the Stanford Privacy office to negotiate the security concerns involved with building a multi-site research data repository and with the team of Prometheus Research to establish a strong data platform.

9.1 Prometheus Data Platform

To satisfy the needs of the STAGES study for a versatile platform, we chose to work with a company called Prometheus Research. Their platform, RexStudy (*'Rex' stands for Research Exchange),* allows not only subject-, recruitment-, and data-management, but also supports data analysis and facilitates the sharing and repurpose of scientific data. The platform, 'RexStudy' supports the following activities and capabilities:

Study Management

- Protocol creation and management for individual studies
- Participant recruitment and management
- Patient scheduling
- Data Entry
- Instrument and sensor data collection
- Subject (e)consent acquisition and tracking
- Patient data collection (via forms [EMR], instruments [SISS], and outside databases)

Data Management

- Cloud VM managed data hosting
- Provisioning
- Quality checks
- Upload and download scripts
- Error reporting

Data Analysis

- Patient matching mechanism for joining the disparate data sources by a common element (e.g. Study ID, Token).
- Sophisticated query tool within RexStudy to allow for simple to complex queries across all datasets within the Study instance (SISS data, EMR data, ASQ data, CNB data, and external data files [actigraph, polysomnogram, 3-D photo])
- Export function for further analysis using third-party software such as R or Julia
- Export formats - HTML, JSON, XML, CSV, TSV, SPSS

Granular Privileging

- Support for multiple user classes and multiple sleep centers
- Configurable control over each class and what they are able to view/write/delete

9.2 Data Entry

9.2.1 Site Preparation

Each site user will be trained on the Prometheus Data Platform system prior to being granted permission to work in the production version of the system. Study staff will receive training on the User Acceptance Testing Environment on creating new subjects, electronic Case Report Forms, the dashboard, and reports and queries.

Sites are responsible for entering complete, reliable and accurate study data into the Consortium's clinical data management system as determined by the DC.

9.2.2 Data Entry Completion Guidelines

To streamline and standardize the data entry process, Data Entry Completion Guidelines for each of the eCRFs can be found uploaded to the SDR, see section 11.5 below.

Data entry to the eCRF should ideally be completed within 14 calendar days of the scheduled visit. Corrected data should be entered within 14 calendar days after a site has been notified of a discrepancy.

Sites are responsible for entering complete, reliable and accurate study data into the Consortium's clinical data management system as determined by the DC. The DC at Stanford will provide report templates to allow sites to correct potential issues with data entry and/or transmission in real time.

9.3 Ongoing Quality Control Through the Data Platform

The Prometheus data platform will perform ongoing quality control throughout the study with built-in routines to ensure data integrity. Sites will a) perform quarterly quality checks using a control checklist and report/query templates provided by the DC and b) submit these quality reports for review to the DC. In addition, sites may also use these report templates to correct potential issues with data entry and/or transmission in real time.

Once the data/file passes the QC checks, it is catalogued, de-identified when needed, and stored on the Prometheus and/or study server. Data will be QC'ed more thoroughly by domain experts for that data type on an ongoing basis to identify potential issues or problems with the data.

9.4 Data Transmission

The DC, the team of Prometheus research, and domain experts of each type of data element have been working closely to establish a secure data transmission protocol for each of the required data elements to the Prometheus data platform. Data will be transmitted either through custom built APIs or secure FTP.

9.5 Stanford Medicine Box

All general, non-subject-specific essential documents will be stored and be accessible through the Stanford Medicine Box. The Stanford Medicine Box is a Personal Health Information (PHI) compliant document management system. It allows document sharing and collaboration with Box users within and external to Stanford Medicine. Stanford Medicine Box can only be accessed from a verifiably encrypted and password-protected computer or mobile device. The DC at Stanford is responsible for the management and maintenance of this central storage hub.

10 Data Collection Contingency Plans

10.1 Missing Data

Collection of ASQ, clinical summary/EMR extract data, PSG file, CNB data, and blood sample will be mandatory and CCs will not receive payment unless these elements are submitted. However, we recognize that some data elements may be refused by subjects due to privacy concerns (3-D craniofacial picture, sound recording during PSG) or have poor compliance (Actigraphy).

10.2 Poor Quality Data

All data will be submitted to the central Prometheus data platform which will process and log the incoming data. Monthly Data Reports will be available for the Executive Sub-committee, site PI, and Clinical Coordinator listing participants with incomplete data sets and details on which elements are missing to reduce the possibility of an ongoing data quality issue at any one site.

10.3 Technological Issues Impacting Data

For this project, we are reliant on several vendors for tests and equipment (i.e. University of Pennsylvania for CNB, Huami for Actigraphy). Contracts are written with contingencies to mitigate the following potential issues:

- Failure to Deliver Data in Timely Fashion
- Hardware or Ongoing Technical Issues
- Changes in Technology

11 Data Collection and Study Forms

11.1 Overview

The DC at Stanford will provide electronic versions of all data collection- and study forms, which will be available through the Prometheus Data Platform.

To ensure consistency throughout the collection process and to minimize errors caused by a paper transcription step, all forms should ideally be completed directly into the electronic case report form (eCRF).

However, paper forms can be used for data collection when the eCRF is not possible. They can either be printed directly from Prometheus or a paper version of the electronic form can be created locally as long as they contain the same information as the eCRF. Ultimately, all paper forms need to be keyed into the corresponding form on the Prometheus Data Platform. Paper forms should be retained for review during site audits.

In some instances, staff might need documentation from a clinical form (e.g., Pre- and Post-Sleep Questionnaire, or a hospital report for an SAE). In this case, a copy of the record from the institution should be requested. It is also recommended that those copies be added to the subject's binder.

11.2 Electronic Case Report Forms (eCRFs) as Source Documents

As already mentioned above, whenever possible, eCRFs should be used as first-line data collection instruments, making the eCRF the source document. ECRFs on the Prometheus data platform record the name of the study staff completing the form or generating the data, the date and time of data entry or generation, and, if applicable, the subject ID of the subject for which the data was collected. These data element identifiers will allow for later examination of data quality by authorized parties.

Depending on the nature of the respective eCRF, it can either be completed by staff or assigned for completion by the participant through the Patient Portal of the Prometheus Data Platform.

For confidentiality reasons, only the subject laptop should be used for forms to be completed in the lab by the participant.

11.2.1 Data Quality Checks in the eCRFs

Wherever possible, we will use electronic prompts and data quality checks in the eCRF to minimize errors and omissions during data entry. Prompts are designed to alert the data entry person to missing data, inconsistencies, inadmissible values (e. g., date out of range), and to request additional data where appropriate (e. g., prompting data entry person to complete an SAE form triggered by an Unanticipated Problem Report Form).

Data originators will also have the ability to enter comments about issues associated with the data.

11.2.2 Modifications and Corrections to eCRFs

Only delegated clinical study staff can perform modifications or corrections to eCRF data. Modified and/or corrected data elements will have data element identifiers that reflect the date, originator and reason for the change, and will retain data from the previous entry.

A field will be provided allowing originators to describe the reason for the change (e.g., transcription error).

Detailed instructions on how to modify or correct an eCRF will be available through the SDR (SDR > SOPs Data Elements > eCRFs).

11.3 Paper CRFs as Source Documents

If necessary, paper CRFs can be used for data collection, making the paper form the source document. Only blue or black ink should be used on source documents. Corrections should be made with a single line through the entry and the change initialed and dated. Original entries should remain legible (i.e., they should never be erased or covered with correction fluid to obscure the original entry). Late entries (e.g., laboratory results on the Eligibility Checklist) should be initialed and dated at the time entered.

All source documents should be filled out completely by the examining personnel or the study coordinator.

Source documents need to be stored in the appropriate essential document binder and must be maintained following the same guidelines as outlined above, section 6. The same applies for source documents of subjects who are screened, but not enrolled.

Ultimately, all information collected on paper forms need to be uploaded or keyed into the appropriate form on the Prometheus Data Platform, see section 10.4 below.

11.4 Transcription of Data From Paper or Electronic Sources to the eCRF

Data elements can be transcribed into the eCRF from paper or electronic source documents. The authorized person transcribing the data from the source documents is regarded as the data originator. For these data elements, the electronic or paper documents from which the data elements are transcribed are the source.

11.5 List of Data Collection and Study Forms

11.5.1 Subject Information Summary Sheet (SISS)

The first form to be completed after the informed consent has been obtained is the Subject Information Summary Sheet (SISS). This form contains key information about the subject enrolled as well as information needed to create the NIMH Data Archive-Global Unique identifier (NDA-GUID) (i.e. name [legal first, middle, and last name], email address, date of birth, city/municipality of birth, gender, ethnicity, and race).

The SISS can be completed by authorized study staff or can be assigned for completion by the participant through the patient portal.

A copy of the SISS along with instructions on its completion can be found on the SDR (SDR > SOPs Data Elements > SISS).

11.5.2 Blood Collection Form

After each blood draw, study staff will document specifics about the blood collection (e. g., full draw vs. partial draw, barcode of collection kit and tubes, date and time of blood collection, etc.) on the Blood Collection Form on the Prometheus Data Platform. In order to minimize transcription errors, the barcode of the collection kit and tubes will be captured using a barcode scanner that is connected to the coordinator laptop.

A copy of the Blood Collection Form along with instructions on its completion will be uploaded to the SDR (SDR > SOPs Data Elements > Blood Collection).

11.5.3 Actigraphy Collection Form

The Actigraphy Collection Form is completed after pairing the Arc device to the subject's smart phone. The form collects information about the login information used (original vs. alternative login), make and model of the smartphone the Arc device was paired to (e. g., iPhone X), date and time of pairing, key information from the device set-up (including the number of days the date was changed [date jiggle setting]), and any issues encountered during the pairing process. The form can be amended to include any issues reported by the subject during their data collection at home.

A copy of the Actigraphy Collection Form is uploaded to the SDR along with instructions on its completion (SDR > SOPs Data Elements > Actigraphy).

11.5.4 PSG Upload Form

Before transferring the scored and de-identified PSGs to the DC, study staff needs to complete the "PSG Upload Form" through the Prometheus data platform. This form tracks the subject ID, date and type of study, and whether the study met the 2 hours Total Sleep Time (TST of diagnostic study) Inclusion Criteria. The form content along with the subject's scored PSG should then be saved to the STAGES PSG folder on local computer with guaranteed internet access 24 hours a day, 7 days a week awaiting de-identification and conversion to European Data Format (EDF) by an automated process through an external application downloaded to the local server.

The most recent version of the PSG upload form including instructions on its completion will be uploaded to the SDR (SDR > SOPs Data Elements > PSG).

11.5.5 Pre and Post Sleep Questionnaires

In addition to their PSG, participants will complete a STAGES specific Pre- and Post- Sleep Questionnaire during their sleep study appointment. The Pre Sleep Questionnaire reviews physical complaints, caffeine and alcohol intake, medications, and the sleep schedule and the composition of the participant's last meal prior to the sleep study. The Post Sleep Questionnaire assesses details about the night of the sleep study.

The STAGES Pre- and Post- Sleep Questionnaires are available through the Prometheus Data Platform and may be assigned for completion by the participant through the Patient Portal. Sites may also expand their local forms to collect the additional STAGES related questions to be keyed into the eCRF afterwards.

Copies of the Pre and Post Sleep Questionnaires are uploaded to the SDR along with instructions on its completion (SDR > SOPs Data Elements > PSG).

11.5.6 Electronic Medical Record (EMR) manual extract

Approximately 6 months after enrollment, qualified study staff or clinicians will obtain crucial diagnostic information from the medical record of each subject. The EMR Form captures information about the reason for the sleep study, the final physician diagnose(s), medications/treatments used the night of and/or initiated after the sleep study, and recent lab results, etc. All data will be keyed into the EMR-form on the Prometheus data platform.

A copy of the EMR Form is uploaded to the SDR along with instructions on its completion (SDR > SOPs Data Elements > EMR).

11.5.7 Unanticipated Problem Report Form

The Unanticipated Problem Report Form is available through the Prometheus Data Platform. The Form collects the date and a general description of the event, and study staff will be guided through a number of questions that determine whether or not the event qualifies as an Unanticipated Problem (UP). If so, study staff will be reminded to report the UP to the IRB and will be prompted with another set of criteria that determine whether the UP also meets the criteria for a serious adverse event (SAE). In case the criteria for an SAE are met, study staff will be referred to the SAE Report Form.

Study staff should adhere to the following timeline to satisfy the requirement for prompt reporting of unanticipated problems (see also section 7):

- Any suicide of a participant should be reported immediately to the Principal Investigator and IRB, regardless of relatedness.
- Unanticipated problems that are serious adverse events should be reported to the Principal Investigator, ideally within 24 hours of becoming aware of the event and to the local IRB within 3 business days.
- Unanticipated problems that are not serious adverse events should be entered into the Prometheus data platform ideally within 1 week of collection to allow timely review by

the data center. Additionally, events should be reported at annual IRB renewal or before if appropriate.

A copy of the Unanticipated Problem Report Form is uploaded to the SDR along with instructions on its completion (SDR > Regulatory > Unanticipated Problem).

11.5.8 Serious Adverse Event Report Form

The Serious Adverse Event Report Form collects a detailed description about the SAE itself and its relatedness to research, the seriousness criteria and outcome, and about the subject involved in the SAE. Qualified study staff will complete this form through the Prometheus Data Platform ideally within 24 hours of becoming aware of the event in addition to reporting it to the local site PI and the DC at Stanford.

A copy of the SAE Report Form will be available on the SDR along with instructions on its completion (SDR > Regulatory > Unanticipated Problem).

11.5.9 Protocol Violation Form

The Protocol Violation Form on the Prometheus data platform includes a definition of Protocol Violations and guides study staff through the different steps necessary to correctly report the event. The Protocol Violation Form should be completed within 3 business days of the occurrence of the violation.

A copy of the Protocol Violation Form is available on the SDR (SDR > Regulatory > Protocol Violation Form).

11.5.10 Subject Withdrawal and Termination Log

The Subject Withdrawal and Termination Log documents the date and the reason for the subject's withdrawal or termination.

A copy of the Subject Withdrawal and Termination Log along with instructions on its completion can be found on the SDR (SDR > Regulatory > Subject Withdrawal and Termination Log).

11.5.11 Problem Report Form

In case study staff experience unexpected problems during the data collection process, they should report and document these issues on the Problem Report Form on the Prometheus Data Platform. The form collects a description about the issue encountered, its date and time, information about its outcome, if a subject was involved in the event, and in relation to which of the data elements the problem occurred. Study staff also have the opportunity to enter notes, such as suggestions for improvements in the comments box.

12 SITE PREPARATION

The Data Center has the responsibility to ensure that mechanisms and procedures are in place to protect the safety of subjects. Therefore, prior to subject accrual or enrollment the following elements of site preparation will be reviewed and approved by the Data Center:

- IRB-approved clinical research protocol identified by version number and date
- Documentation of IRB approval, including OHRP FWA number, IRB registration number, and IRB name
- IRB-approved consent document that is used to document informed consent, identified by version number, date, or both
- Plans for managing unanticipated problems
- Procedures for assessing and reporting unanticipated problems
- Plans for data and safety monitoring, and for monitoring of the study site and laboratory
- Documentation that the institution and all study staff responsible for the design or conduct of the research have received training in the protection of human subjects
- Supplies for study conduct, including CRFs, specimen collection materials, and shipping materials
- Site initiation visit and study-specific training
- Contract and other agreements

12.1 Facilities Requirements

12.1.1 Clinical Research Area

Depending on the sites' specific workflow, first personal contact to the subjects will either occur during their regular clinical appointment or during their regular scheduled overnight PSG. In both scenarios, screening and consenting will occur in closed office spaces or private rooms of the sleep clinic sites to ensure privacy. Collection of all other data elements will be carried out in either exam rooms or private rooms.

Computerized data will be stored on encrypted, password-protected computers and on secure servers on the Prometheus Data Platform and the Data Center. Confidential subject identifying information (e. g. signed (e)ICF, SISS, etc.) and the codebook of the subject ID will be held in strict confidence by the PI in compliance with federal regulations or other applicable laws or ICH and GCP Guidelines and only qualified and authorized study personnel will have access to confidential subject identifying information and to the codebook. Paper versions of study documents will be stored in locked files or rooms.

12.1.2 Laboratory Services and Handling of Samples

Blood will be collected using pre-assembled kits comprised of collection instructions, requisition form, and pre-barcoded vacutainer tubes. The blood will be drawn by certified phlebotomists, physicians, or registered nurses (RNs) either directly at the sleep clinic in private rooms, in the sleep clinic's laboratory, or subjects may be sent to another affiliated laboratory.

After the blood collection, kits will be stored at room temperature at the facility's research laboratory or another dedicated specimen collection area until they are ready to be shipped to Stanford for central processing.

See section 13.5.6 below for a detailed description of the Blood Collection and Shipping.

12.1.3 Courier Services

Blood samples will be shipped via FedEx priority overnight. Each participating site will be assisted in creating a STAGES specific FedEx shipment profile to avoid errors in routing, billing, and tracking. The shipment profile includes the shipping address, the billing information, and the email address of the Stanford Biobank in the notification section for tracking purposes.

Records of shipments will be maintained centrally through the Stanford FedEx account.

The routing guide will be available through the SDR (SDR > SOPs Data Elements > Blood Collection).

12.2 Staff Training

12.2.1 Human Subjects Protection Training

Completion of human subject training and good clinical practice training is required for all key personnel working on the STAGES study. Key personnel includes all individuals who will be involved in the design or conduct of the STAGES study, the Principal Investigator(s), and those individuals identified as key personnel at collaborating sites.

12.2.2 Protocol Training

Study staff will receive training on all aspects of the protocol, aspects include but are not limited to:

- Study Objectives
- Inclusion/Exclusion Criteria
- Screening and Enrollment
- Procedure Scheduling
- Data Elements
- Assessment of Safety
- Early Termination / Withdrawal
- Protocol Deviations/Violations

12.2.3 Clinical Operations

Study staff will receive training in the following areas of clinical operations:

- Communication
- Clinical Research Associate (CRA) Functions and Expectations for Sites
- Manual of Procedures
- Standard Operating Procedures for each Data Element
- Investigator Responsibilities
- Good Clinical Practice (GCP)
- Essential Document Collection and Storage
- IRB Reporting Requirements
- Informed Consent Procedures
- Query Process
- Sample Handling

12.3 Equipment and Supplies

A complete list detailing all required study equipment and supplies will be available through the SDR on the Stanford Medicine Box. In case of any changes, sites will be notified and an updated version of this list will posted to the SDR (SDR > Equipment).

13 Protocol Implementation

13.1 Example Study Schedule

Given the design of the study, the clinical centers have the flexibility to inform and enroll patients, and to administer the required study procedures in a way that best fits their local workflow.

An example study flow is uploaded to the SDR (SDR > Study Protocol > Study Protocol March).

13.2 First contact of patient with study/research

Depending on the CCs' clinic schedule/organization, patients may be made aware of the STAGES study through mechanisms such as brochures, pamphlets, and flyers, as well as through TV advertisements in the waiting room, and on the sleep clinics web sites prior to their scheduled PSG.

13.3 Screening

Since the patient population of this study will primarily consist of patients scheduled for a PSG, screening procedures will be incredibly minimal. Before contacting potential subjects, study staff will ensure that the potential subject is scheduled for a PSG and meets the Inclusion/Exclusion criteria.

Of note, while recruitment will be based on the above parameters, we will record each participant's age, gender, and ethnicity.

13.3.1 Inclusion and Exclusion Criteria

Inclusion Criteria:

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Age 13 and over
- Undergo an in-lab sleep study for diagnosis of a sleep disorder such as obstructive sleep apnea, restless legs syndrome, insomnia, or other less common sleep disorders, or receiving follow up care that requires a PSG be collected meeting the following criteria:
    - Full diagnostic PSG with a minimum of 2 hours TST (studies with TST < 2h require approval from the Data Center), OR
    - A split-night study with a minimum of 2 hours TST diagnostic data (studies with TST < 2h diagnostic data require approval from the Data Center)

Exclusion Criteria:

An individual who meets any of the following criteria will be excluded from participation in this study:

- Unable to read and/or understand English.
- Unable or unwilling to complete all required study assessments.
    - Including unrestricted sharing of blood samples
- Undergoing a PSG conducted exclusively for treatment purposes. Examples of excluded studies are full-night PAP titration, oral appliance evaluation, evaluation for other OSA treatment.
- Does not have a smartphone to pair with actigraph device.
- Presence of:
    - Acutely unstable medical condition
    - Acutely unstable behavioral or psychiatric disorder (including active suicidal ideation)
    - Any medical condition or surgical history that could affect the safety of the subject or interfere with study assessments, safety, or the ability of the subject to complete the evaluation per the judgment of the site principal investigator.

The Inclusion/Exclusion criteria checklist is posted to the SDR (SDR > SOPs Data Elements > Screening and Enrollment).

13.4 Enrollment

13.4.1 Overview of different enrollment scenarios

Once identified as a potential subject, patients will ideally be asked to participate in the study via email or phone prior to their PSG/consultation appointment to allow for the completion of all required study procedures during their PSG appointment without interfering with their clinical care.

Alternately, patients may also be invited to participate in the study in-person on the evening of their scheduled PSG or during their consultation appointment.

During this pre-enrollment conversation patients will receive detailed information about the study and will have the opportunity to ask questions. Study staff will then check the I/E criteria again, and if the prospective participant is found to be eligible and agrees to participate, he/she will be enrolled in the study either via e-consent through the Prometheus Data Platform or using the paper version of the consent.

13.4.2 Enrollment via e-consent

Enrollment of patients via e-consent through the Prometheus Data Platform can occur either prior to the patient's PSG/consultation appointment from home or in an in-person setting at the clinic.

In both scenarios, the e-consent process starts with an email invitation sent to the potential subject that includes basic information about the study and a site-specific link to a patient portal registration page of the Prometheus Data Platform. Patients can register for the patient portal using their name and email address. Once the registration process has been completed and the account confirmed, patients will be assigned a "site-specific, pre-enrollment ID" (RexID, different from the final STAGES ID). Patients can now log onto the patient portal, where they can find the site-specific e-consent form waiting for them in the task list as well as a clean copy for download.

Using branching logic, the Prometheus Data Platform assigns each patient the applicable e-consent form (e. g., assent vs. adult version, etc.) based on the patient's date of birth.

The e-consenting process furthermore ensures that only patients that provided all required signatures and checkmarks will be enrolled into the study.

Detailed instructions on the enrollment via e-consent are uploaded to SDR (SDR > Enrollment > E-Consent).

13.4.2.1 Assignment of STAGES ID using the e-consent process

Once the e-consent form was completed correctly, patients are officially enrolled into the study. Subjects will then automatically be a) assigned a STAGES study ID on the Prometheus Data Platform (RexStudy application) and b) assigned the SISS for completion through the patient portal of the platform.

13.4.3 Enrollment via paper consent

If necessary, patients can also be enrolled into the study using the paper version of the informed consent form. To ensure the use of the most recent approved version of the consent, study staff should always print the consent form directly from their site's e-protocol.

Once the patient has completed the ICF, study staff will a) confirm that the consent form contains all required signatures and checkmarks, b) also sign the form as the person obtaining the consent, and c) provide subjects with a signed and dated copy of the ICF.

Ultimately, all paper consent forms need to be a) uploaded to the Prometheus Data Platform, and b) transcribed into the e-consent form of the respective participant.

Please see the SDR for instructions on the transcription of paper ICFs into the e-ICF (SDR > Enrollment > Paper Consent).

13.4.3.1 Assignment of STAGES ID using the paper consent

After completion of the ICF, study staff will manually enter the patient information into the Prometheus Data Platform by creating a "New Subject". Once this process is completed, subjects will automatically be a) assigned their STAGES ID, b) sent an email with a link to the patient portal, and c) assigned the SISS for completion through the Patient Portal.

Please see the SDR for detailed instructions on the manual creation of subjects on the Prometheus Data Platform (SDR > Enrollment > Manual Creation of Subjects).

13.5 Study Procedures

13.5.1 Alliance Sleep Questionnaire (ASQ)

13.5.1.1 Purpose

The ASQ is a comprehensive, on-line questionnaire comprised of validated measures and novel questions used to collect subjective data related to an individual's sleep/medical history and current symptoms. It was designed by 5 top tier sleep centers to standardize clinical and research data collection and provides a Summary Report. It uses complex branching logic to lead users through a comprehensive set of questions covering topics relevant to sleep including: current sleep symptoms, medical history, current medications, previous treatments for sleep disorders, sleep habits/schedule, daytime fatigue, as well as symptoms of all sleep disorders, including insomnia, obstructive sleep apnea (OSA), restless legs syndrome (RLS), narcolepsy and other disorders.

A demo of the survey can be accessed at https://oursleep.stanford.edu/demo. Enter any user credentials, and then hit "Create User" button from the Login Unsuccessful screen. Surveys from this URL are automatically coded as test data, so answers can be modified to explore the different branching available in the survey.

13.5.1.2 Administration Guidelines

The preferred time for the completion of the ASQ is from home prior to the subject's scheduled PSG. Alternately, subjects can also complete the ASQ the evening before or the morning after the PSG at the clinic, from home after the PSG, or at the follow-up/research visit (ideally within +/- 4 weeks of the PSG). The estimated time subjects will need to complete the ASQ is between 30 and 45 min.

Study staff will email subjects a site-specific link to the ASQ, where subjects can login by using their name and date of birth. A customized URL is used to identify the site and silo the data. Through an administrative site, staff can then view aggregate data for their site only.

Once a survey has been submitted, it will be locked and subjects are not able to view or modify their responses. If the survey is left incomplete, the survey will be locked after 25 days of inactivity.

Study staff can identify subjects with missing or incomplete surveys through the dashboard of the Prometheus data platform or through customized queries.

Please see the SDR for detailed administration guidelines (SDR > SOPs Data Elements > ASQ).

13.5.2 Polysomnography

13.5.2.1 Purpose

Polysomnography (PSG) is an objective method of assessing sleep and sleep disorders such as sleep-related breathing disorders, insomnia, periodic limb movement in sleep (PLMS), restless legs syndrome (RLS), or other less common sleep disorders. PSG is a multi-parametric test that includes the measurement of: brain activity, cardiac activity, breathing (respiratory airflow and respiratory effort indicators - measurement of thoracic and abdominal movements), ocular activity, muscle activity, and oxygen levels (Practice Parameters of the American Academy of Sleep Medicine (AASM) 2003; Kushida et al, 2005 (Sleep)).

13.5.2.2 Administration and Transfer Guidelines

All PSG's will be conducted as part of standard of care according to the clinic protocol of each site, and using the sampling rates/filters recommended by the data center.

Once the PSG is scored, study staff will transfer the PSG to a site-specific "STAGES PSG" folder on a local device (with guaranteed internet access for 24 hours a day, 7 days a week) along with an export of the subject's PSG upload form, where it awaits de-identification, conversion to EDF, and transfer to the study's server by an automated process through an external application.

The PSG also includes the administration of the Pre- and Post- Sleep Questionnaires. Study staff may assign them for completion by the participant through the data platform's patient portal or staff may use a paper version of the questionnaires.

Please see the SDR for detailed administration and transfer guidelines (SDR > SOPs Data Elements > PSG).

13.5.3 Computerized Neurocognitive Battery – CNB

13.5.3.1 Purpose

The CNB is an on-line, self-administered test of neurocognitive function designed by the University of Pennsylvania. It is based on, and validated with functional neuroimaging (Gur, R., 2010 J. Neurosci. Meth.). The original CNB consists of 14 tests that tap major cognitive and affective neuroscience domains. In order to adequately cover the domains most impacted by sleep and sleep disorders, the STAGES study has developed a modified version of the CNB test battery. The test will take a total of 26 minutes (without instructions) and will include the following tasks:

- Vigilance Testing: Penn Psychomotor Vigilance Test (PPVT - 3 min)
- Working Memory: Short Letter-N-Back (SLNB2 - 7 min)
- Attention: Continuous Performance (SPCPTNL - 4 min)

- Facial Episodic Memory: Computerized Penn Face Memory Test (CPF - 3 min)
- Verbal Episodic Memory: Computerized Penn Word Memory Test (CPW – 3 min)
- Abstraction and mental flexibility: Penn Conditional Exclusion Test (PCET - 6 min)

13.5.3.2 Administration Guidelines

The CNB is available in both a proctored (in-lab) and un-proctored (off-site) format. In general, the CNB should **NOT** be completed within 1 hour of awakening and **NOT** after being awake for more than 16 hours (avoid completion after 09:30pm). Subjects will need approximately 30 to 40 min to complete the CNB. To ensure consistency throughout all different test scenarios and environments, the test will have narrated subject instructions for the proctored, as well as the un-proctored setting.

Ideally, the CNB should be completed the evening before the PSG at the clinic before the hook up procedure, or alternately, the morning after the PSG ≥ 1 hour of awakening.

If necessary, subjects can also do the CNB from home, before or after their sleep study. However, it is required that those subjects complete the Psychomotor-Vigilance-Test-(PVT) part of the battery in a proctored setting at the clinic in addition to doing it in the un-proctored setting at home.

The dashboard of the Prometheus Data Platform informs study staff about subjects with missing/incomplete test batteries. Study staff may also use customized queries to see missing datasets.

Please see the SDR for detailed administration guidelines for both the proctored setting as well as the un-proctored setting (SDR > SOPs Data Elements > CNB).

13.5.4 Actigraphy

13.5.4.1 Purpose

Actigraphy is a non-invasive method of monitoring human rest/activity cycles to assess sleep/wake patterns (Ancoli-Israel 2003, Morgenthaler 2007). A small watch-like band is worn on the non-dominant wrist and can be worn for several weeks at a time.

In addition to usual actigraphic sleep data (e.g. total sleep time, total time in bed, wakefulness after sleep onset, sleep efficiency, sleep latency, and sleep timing) advanced functional actigraphic analytics such as by principal component analysis can be applied to generate new information on sleep disorder phenotyping by actigraphy.

The Actigraph device used in this study is a Huami “Arc-style device” (https://us.amazfit.com/shop/arc?variant=792). It allows high degrees of agreement in minute-to-minute data scoring for sleep and wake periods estimated using the Cole-Kripke algorithm.

13.5.4.2 Administration Guidelines

Actigraphy data collection will begin the evening of the PSG, this is critical in order to correlate the rest/activity patterns of the Actigraph device with the findings of the PSG (sleep architecture,

potential sleep disorders, etc.). Additionally, each subject will be asked to wear the Arc Actigraph device at home for at least 2 more weeks. NOTE: Subjects are also welcome to provide more than 2 weeks of their Actigraph data.

Set-up of the Arc device will take approximately 5 to 10 minutes. Study staff will pair the device to the subject's smartphone through a specifically for this study developed sleep research app. The sleep research app allows modifying the date of the data collection to ensure that no PHI will be shared with the device company's server. Data will initially be stored on the device/watch itself. Subjects will be asked to open the app daily and to transmit the data through blue tooth low energy to the device manufacturer's server. From there, data will be sent to the Prometheus data platform on a regular basis.

Study staff can identify the number of days the Actigraphy data for a specific subject has been collected through the dashboard of the data platform and through customized queries.

Please see SDR for detailed administration guidelines (SDR > SOPs Data Elements > Actigraphy).

13.5.5 3-D photography

13.5.5.1 Purpose

3-D imaging from a number of modalities, such as magnetic resonance (MR), computed tomography (CT), and positron emission tomography (PET) is currently an evolving field. It is focused on increasing the information obtained from traditionally diagnostic methods, and has resulted in new approaches for diagnosis and treatment planning as well as the development of completely new diagnostic tests (Shukla, G. 2017; Stanford 3-D and Quantitative Imaging Lab). Similarly, a craniofacial 3-D image created by an iPad could provide an easy, non-invasive, and cost-effective diagnostic tool in the assessment of sleep apnea patients as we already know that craniofacial structure can be a risk factor. In order to evaluate the association between craniofacial features and the risk of sleep apnea, we will create a craniofacial 3-D image of each subject through a company called Ugo3D (http://ugo3d.com/).

13.5.5.2 Administration Guidelines

Preferably, the 3-D images should be taken during the PSG visit, but it can also be completed at any clinic appointment (ideally within +/- 4 weeks of the PSG). Study staff will take the 3D scans using a study iPad with an external sensor through a customized study app. Taking the 3D scans will take approximately 5 to 10min.

After scanning the subject, study staff will collect information about how tired the participants felt at the time the photos were taken and how tired they think they looked.

The images will be uploaded directly to Stanford's mignot-sleep server. The original images will NOT be part of the data set shared through the NIMH Data Archive (NDA), and dbGaP. Instead, we will only share key measurements and/or a wire-overlay version of the original images with the publicly accessible databases.

At a participant's request, study staff may send them the original files via email for their own personal use.

Study staff will be notified about the receipt of the 3D scan on the study's server through the data platform's dashboard.

Detailed administration guidelines can be found uploaded to the SDR (SDR > SOPs Data Elements > 3D image).

13.5.6 Genetics – Genome Wide Association Study (GWAS) and other future biomarker research

13.5.6.1 Purpose

Genome-wide association studies are a way for scientists to identify genes involved in human disease. This method searches the genome for small variations, called single nucleotide polymorphisms or SNPs that occur more frequently in people with a particular disease than in people without the disease. Each study can look at hundreds or thousands of SNPs at the same time. Researchers use data from this type of study to pinpoint genes that may contribute to a person's risk of developing a certain disease. Researchers hope that future genome-wide association studies will identify more SNPs associated with chronic diseases, as well as variations that affect a person's response to certain drugs and influence interactions between a person's genes and the environment (NIH, US National Library of Medicine).

13.5.6.2 Blood Collection Guidelines

Each subject is asked to provide a small blood sample for the Genome Wide Association Study (GWAS) or other future biomarker research. Preferred time of completion of the blood draw is during the scheduled PSG, either the evening before, or the morning after the PSG. Alternately, the blood can also be drawn during the follow up appointment or the research visit (ideally within +/- 4 weeks of the PSG). We estimate that subjects will spend approximately 5 to 15 min with providing a blood sample.

The blood will be drawn by either certified phlebotomists, registered nurses, or physicians using barcoded blood collection kits comprised of barcoded collection tubes (barcode linked to kit ID), collection and shipping instructions, requisition form, absorbent pad, and biohazard bag. After the blood draw, the person drawing the blood will complete the requisition form and hand the kit over to study staff (if not the same person). Study staff will then key the information from the requisition form into the Blood Collection Protocol on the Prometheus Data Platform and scan the barcode of the kit as well as the tubes into the appropriate fields on the form using a handheld barcode scanner.

Study staff will ship samples via FedEx overnight at room temperature along with a hardcopy of the requisition form. Each site will be assisted in creating a STAGES specific shipment profile to streamline the shipping process.

The maximum time from collection to arrival of the sample at Stanford should not exceed 48h. Possible times for shipping are shown in table 1 below:

Possible Times for Blood Collection						
Monday Morning - Yes	**Tuesday** Morning - Yes	**Wednesday** Morning - Yes	**Thursday** Morning - Yes	**Friday** Morning - Yes	**Saturday** Morning - No	**Sunday** Morning - No
Monday Evening - Yes	**Tuesday** Evening - Yes	**Wednesday** Evening - Yes	**Thursday** Evening - Yes	**Friday** Evening - No	**Saturday** Evening - No	**Sunday** Evening - Yes

Table 1. Possible Times for Blood Collection

Once received at Stanford, samples will be registered along with receipt date and time, sample-, kit-, and subject-ID, in Stanford's LIMS OpenSpecimen (Laboratory Inventory Management System).

Detailed Blood Collection, Shipping Instructions, and the Routing Guide can be found on the SDR (SDR > SOPs Data Elements > Blood Collection).

13.5.6.3 Stored biological samples for future biomarker research

The primary biobank for the study is Rutgers University Cell and DNA Repository (RUCDR). All biological samples will be stored at their facility in – 80 C° freezers and tracked through their LIMS software. Researchers will request access to the samples through the NIMH.

A secondary biobank will be established at the SCSSM. Samples will be stored in -80 C° freezers and tracked using a LIMS software.

14 Publication and Presentation Policy

14.1 General Overview Publication Policy

This document describes the policies and guidelines governing the publication of scientific results originating from the analysis of data and material derived from the Stanford Technology, Analytics and Genomics in Sleep (STAGES) dataset. It does not apply to presentations or abstracts that only describe the general design of the STAGES study using information that is available through the public domain, for example presentations or abstracts that intended to promote the study and describe the dataset.

The STAGES Publication Policy is designed to promote scientific integrity and to ensure that fair credit is given to the authors and to other individuals who have contributed to STAGES.

Since all resources generated by the STAGES study or in collaboration with the study will be made available to the widest potential audience with the least number of restrictions, we will distinguish between two distinct Publication Policies:

"Primary" Publications or Other Forms of Presentations

"Primary" publications or other forms of presentations are originating from staff involved in the development of the resource (section 3):

- Staff involved in the design of the STAGES study
- Staff involved in the development of methodological and analytical tools
- Staff involved in data collection

- Staff of external vendors

"Secondary" Publications or Other Forms of Presentations

"Secondary" publications or other forms of presentations are originating from the publicly available STAGES data/material (section 5):

- Researchers can request access to all STAGES related data/material uploaded to the NIMH Data Archive (NDA) and dbGaP through the NIH

We also wish to distinguish between abstracts for congress and publications, whether peer reviewed or posted on open-registries such as Bio-archives.

14.2 Publication and Presentation Committee

A Publication and Presentation Committee will supervise publications and abstracts originating from STAGES related data to ensure accuracy and objectivity. This committee will be selected from the pool of expert consultants on the analytics committee and will be overseen by the STAGES study's PI, Dr. Mignot. The Publication and Presentations Committee will serve as an advisory capacity to the STAGES Steering Committee, which meets every month and will approve formally the recommendations of the publication committee or decide in case of disagreement. For fast tracked decisions when there is not enough time to query the Steering Committee, the Executive Committee will have the authority to make a decision.

Publications and presentations that are part of the study design or primary outcomes are not subject to the approval process.

The responsibilities of the Publication and Presentation Committee include (but are not limited to):

- Provides a guideline for "Primary Publications" originating from STAGES related material (section 3)
- Provides a guideline to define the Role of Authors and Contributors (section 3.1)
- Planning and supervising of proposals for publication topics (section 3.3)
- Provides a guideline for assigning Writing Groups, as well as a list of responsibilities for these members to ensure that each proposed and approved publication topic is addressed in a thorough manner (section 3.3.1)
- Provides a guideline for manuscript preparation (section 3.3.3)
- Provides a guideline for defining authorship rules (section 3.6)
- Relies upon the Data Center (DC) for the validation of all data for manuscripts or presentations (see section 3.7)
- Provides a guideline on Conflict of Interest disclosure (section 3.8)
- Verifies that all investigators have the opportunity to participate and be recognized in study-wide STAGES publications (section 3.1, section 3.3.1, section 3.6, and section 5.1)
- Arranging the conference calls, distribution of the agendas, and policies is the shared responsibility of this committee and the DC
- Maintains a current list of all STAGES presentations and publications for distribution to STAGES investigators on a regular basis (section 4)

14.3 Guidelines for "Primary" Publications

14.3.1 Defining the Role of Authors and Contributors

To ensure that contributors with substantive intellectual contributions to a paper are given credit as authors, we use the following definition of the International Committee of Medical Journal Editors (ICMJE) to define the role of authors and contributors (ICMJE 2017). Authors need to fulfill all of the 4 below-mentioned criteria.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All contributing parties, who meet less than all 4 criteria, don't qualify as authors and should be listed, with their permission, in the acknowledgements or in an appendix. The acknowledgement can be stated on an individual level or as a group under the umbrella of the STAGES investigator group, see section 5.1 for STAGES acronym.

14.3.2 Types of Primary Publications and Presentations

The Publication and Presentation Committee is also responsible for resolving any uncertainties as to which category a specific presentation or publication belongs.

There are several types of publications and presentations for which approval procedures are established. These include:

Publications/Abstracts:

- Any publication using STAGES data.
- Major descriptions of results, addressing the main objectives of the STAGES study
- Major descriptions of results, addressing issues other than the main objectives of the STAGES study
- Articles to appear in proceedings of meetings for which no abstract was required.

Presentations:

- Invited presentations for which no abstract is submitted and for which there are to be no published proceedings
- Press releases or discussions with the media
- Lectures or other informal presentations

Ancillary Publications:

Publications that result from an additional protocol, where data was collected from at least one collaborating site

14.3.3 Guidelines for Publications

When an investigator or a group of investigators wishes to use STAGES data for analysis and publication, a formal proposal should first be submitted to the Publication and Presentation Committee (see template for new proposal attached in Appendix **Error! Reference source not found.**). The committee reviews all publication proposals for overlap with other submitted proposals. If overlap exists, the investigator may be encouraged to collaborate on the existing project. Publication proposals approved by the Publication and Presentation Committee will then be reviewed by the STAGES Steering Committee. The review process should be completed within two weeks from the original date that the proposal was submitted. To ensure this timeline is met, email communications will be used and decision can be taken based on quorum approval if need be.

Once a publication proposal has been approved by the Steering Committee, the Publication and Presentation Committee will assign a Writing Group, see also section 3.3.1 below. The author of the initial proposal, as well as other investigators, may recommend Writing Group members for a particular topic; however, the final assignment of members will be recommended by the Publication and Presentation Committee and approved by the Steering Committee. Once a proposal is approved, the Writing Group is then authorized to submit abstract or presentations for congress or symposium. It is also in charge of moving the proposed primary publication along as outlined below.

An investigator may only have two proposals in which he or she is the Writing Group Chairperson active at a time.

14.3.3.1 Writing Groups

The Publications and Presentations Committee will assign the Writing Groups by following the below mentioned guidelines:

- The committee will strive to include representation from each participating site. As a general guidance, this group should be limited to 5 to 7 members, but can be expanded if deemed necessary;
- The committee will ask for and consider all suggestions for writing group members, especially any recommendations by the investigator who submitted the original proposal;
- The Writing group chairperson will generally be assigned to the investigator who submitted the original proposal;
- The committee will attempt to divide the workload for the publications between the participating sites;
- The committee will always keep the best interests of the publication in mind while assigning the Writing Groups;
- For ancillary publications, the committee will attempt to include representation from each site that contributed data, however, this may not always be the case.

Once all Writing Group members are assigned by the Publication and Presentation Committee (and accepted by both the Steering Committee and the individual members) the Publication and Presentations Committee will determine a start date for the manuscript. It is the responsibility of the Writing Group Chairperson to contact each member of the Writing Group to discuss the outline of the publication as well as the assignments for each member. The Chairperson will also

ensure continuous progress for all phases of manuscript preparation from conception through publication. The responsibilities of the Writing Group include the following:

- The preparation of an outline;
- Identification of what data analysis is necessary from the DC and providing the DC with a written request;
- Assignment of tasks to each Writing Group member with clear deadlines for the completion of these tasks;
- The completion of interim progress reports for the manuscript to be submitted to the Publication and Presentation Committee;
- Manuscript approval by each Writing Group member prior to submitting each draft to the Publication and Presentation Committee;
- Attaining a verification of data from the DC once the second draft has been approved by the Publication and Presentation Committee;
- Selection of a journal to which the manuscript should be submitted;
- Maintenance of communication between co-authors, the DC, the Publication and Presentation Committee, the Steering Committee, the Klarman Family Foundation, and the journal editors.

14.3.3.2 Modification of Writing Groups

Each member of the Writing Group is responsible for completing the tasks assigned by the Writing Group Chairperson within the allotted time period. If a member does not accomplish the tasks, he or she may be removed from the Writing Group. In this case, the Writing Group Chairperson should write to the Publication and Presentation Committee requesting the removal of a particular member due to the lack of participation.

The Publication and Presentation Committee also has the discretion to change the composition of any Writing Group that has failed to produce a manuscript according to the schedule originally agreed upon by the Writing Group and the Publication and Presentation Committee. In the event of negligence on the part of an individual or the entire Writing Group, revisions may be made to the Writing Group. This may call for the replacement of one or more members, or in the worst-case scenario, disbandment of the entire group. The Writing Group Chairperson will be kept informed on the deliberations of the Publication and Presentation Committee. The STAGES Steering Committee must approve any recommendations for reassignment developed by the Publication and Presentation Committee.

14.3.4 Preparation of Manuscripts

No manuscript shall be submitted to any journal prior to approval from the Steering Committee. The Writing Group is required to follow the expected schedule for the finalization of a manuscript described below. Deviations from this schedule will be reviewed by the Publication and Presentations Committee and may cause the replacement of the Chairperson and/or other members of the Writing Group.

Schedule for manuscript preparation in the context of an approved proposal

1. After the Writing Group has received the start date for the paper, the group will have 4 months to prepare a first draft. The first draft should consist, at a minimum, of an Introduction, Method, and Results Section. After approval by each of the Writing Group members, the Publication and Presentations Committee should be sent a copy of the draft.
2. The Writing Group has then 3 months to prepare the next draft, which should be adequate for submission to the Steering Committee for review. Once all Writing Group members have signed off, the draft should be sent to the Publication and Presentations Committee along with a cover letter stating that the draft is ready for review.
3. The Publication and Presentations Committee has 14 days to review and approve the final draft manuscript. The manuscript should be reviewed by each of the Publication and Presentations Committee members followed by a discussion during a regular Publication and Presentations meeting.
4. If a manuscript is not approved by the Publication and Presentations Committee, the draft will be returned for revision to the Writing Group Chairperson.
5. In case of approval, it will be forwarded to the Steering Committee for review within 30 days. The Steering Committee will then send a written response with a decision for either approval, approval with modifications or disapproval.
6. The DC will initiate verification of the results after approval from the Publication and Presentations Committee and the Steering Committee.
7. After final sign-off by the Writing Group, the manuscript should be sent to the journal with a copy of the cover letter sent to the DC.

14.3.5 Guidelines for Presentations and abstracts in the context of an approved proposal

Prior to all meeting presentations or congress abstracts related to STAGES, a brief summary must be submitted and subsequently approved by the Publication and Presentation Committee, see Appendix **Error! Reference source not found.** for template for summary of STAGES related presentations. The committee will inform the presenter of their decision within one week from the date that the summary was submitted. To ensure that this deadline is met, the study steering committee may take change and approve the abstract or presentation on behalf of the Publication and Presentation Committee. If necessary, the Executive Committee approve a proposal. Summaries of presentations should be submitted for review up to 30 days prior to the deadline if constructive feedback by the Publication and Presentations Committee is desired.

14.3.6 Guidelines for Ancillary Publications

In general, investigator groups of ancillary studies are subject to the STAGES guidelines for Primary Publications with the following exceptions:

- Should utilize their own resources for data analysis; however, the Publications and Presentations Committee will provide assistance if necessary (yet this data analysis will be assigned a lower priority than analysis for other publications);
- Should define their own Writing Groups, determine the order of Authorship within the group, and establish their own timelines for receipt by the Publications and Presentations Committee; however, the Publications and Presentations Committee can assist if

necessary (yet this will be assigned a lower priority than other internal STAGES publications);
- Must include a statement that the publication results from an additional protocol of STAGES and that STAGES is supported by the Klarman Family Foundation.

14.3.7 Authorship Rules

The Publication and Presentation committee will keep the following guidelines in mind:

- "Prominent" authorship is defined as first, second, and last authors.
- The Writing Group should occupy the initial author positions; if applicable, two or more first and last authorship positions can be assigned as "Contributed Equally."
- Determination of the order of authorship is based primarily on effort and the contribution made by each author. If the order of authorship cannot be resolved by the Writing Group Chairperson, it will be resolved by the Publication and Presentation Committee, with the Steering Committee as the final arbitrator.
- Following the Writing Group members, the representatives of the individual sites should be listed:
    - Grouped by site
    - In alphabetical order of site
- According to the agreed number of authors per site as indicated in Table 1 below.
- The final author positions should be occupied by the PI, and the senior author (if applicable); the two final positions can be assigned as "Contributed Equally" (if applicable).
- If the number of authors exceeds an acceptable standard (e. g. 25 authors), the Presentations and Publications committee may decide to mention the three prominent authors and the STAGES acronym (see section 5.1).
- Acknowledgement/Appendix: colleagues actively helping in sample collection, analysis and technical work, who do not meet authorship criteria may be thanked at the end of the manuscript.

Table 1. Number of authors per site

Site	Number of Authors
Stanford	5
St. Luke's	2
Bogan Sleep	2
Mayo	2
MedSleep	5
Geisinger	5

14.3.8 Analyses by the DC

Investigators should utilize the guidelines below for dealing with data analysis by the DC:

- The DC should be sent written notification clearly defining all data that needs to be analyzed for any publication. It is recommended that this notification is sent by the Writing Group Chairperson at least two months prior to the deadline for the first draft;
- If the results from the data analysis lead to a split of the original paper into more than one manuscript, a new proposal should be submitted to the Publication and Presentations Committee. The same Writing Group members will usually be retained for the second manuscript;
- The Writing Group Chairperson should submit a written request to the DC for a validation of results once the second draft has been approved by the Publication and Presentation Committee;
- The Publication and Presentation Committee will consult with the DC to assign priorities for data analyses related to publications or presentations; however, the DC will strive to analyze all data as quickly as possible.
- If the DC falls behind with data analysis, the Writing Group Chairperson should inform the Publication and Presentation Committee. If a delay in attaining the data analysis causes problems with the Writing Groups deadline, the deadlines may be modified without penalty to the Writing Group, provided that the requests to the DC were submitted as recommended.

14.3.9 Conflict of Interest Disclosure

Prior to submission of any kind of STAGES related publication or presentation, all authors are responsible to disclose any kind of financial and personal relationships that might bias or be seen to bias their works. To facilitate and standardize authors' disclosure, the STAGES study encourages authors to use the Conflicts of Interest Form created by the ICMJE (ICMJE - Conflict of Interest Form).

14.4 Current List of all STAGES Publications and all other Presentations

The DC will maintain a current list of all STAGES related publications and other forms of presentation via a RedCap form. The list will be posted to the projects website. The DC will use the following measures to ensure completeness of this list:

- All investigators using data originating from STAGES related material are asked to provide a copy of their publication or other form of presentation to the DC
- Once the first publications have been published, the DC will perform a periodically search on PubMed and on Web of Science for STAGES related publications using the search term: *STAGE* OR "Stanford Technology Analytics and Genomics in Sleep" in topics and authors. The search term may be subject to change over the time – we will use the MeSH (Medical Subject Headings) database on PubMed to establish the most accurate search term.

- All results and records will be maintained in a RedCap database and periodically checked for duplicates.

14.5 Guidelines for "Secondary" Publications and all other Forms of Presentations

The STAGES project's philosophy is to make all resources generated by the study or in collaboration with the study available to the widest potential audience with the least number of restrictions. Details regarding what data is available, where the data will be available and how to access the data will be described through the projects website and through any publications and presentations that we author or co-author.

Stanford University has intentionally removed itself from the process of granting access to STAGES related data or material to ensure there is no perceived bias related to persons either given or denied access to the data, and the bases for such decisions. However, investigators are asked to provide the Stanford DC with a copy of any publications or all other form of presentations originating from STAGES related material/data.

14.5.1 STAGES Acronym

Researchers should acknowledge the STAGES study in the following way. The author line will include "...and the STAGES cohort investigator group*". The asterisk refers to the following sentence:

"This research has been conducted using the STAGES - Stanford Technology, Analytics and Genomics in Sleep Resource funded by the Klarman Family Foundation. The investigators of the STAGES study contributed to the design and implementation of the STAGES cohort and/or provided data and/or collected biospecimens, but did not necessarily participate in the analysis or writing of this report. The full list of STAGES investigators can be found at the project website."

14.5.2 Access to phenotype and genotype data and biological samples

The application and review process to access data from the NDA is reviewed by the NDA Data Access Committee (DAC). Access to controlled data in dbGaP will be granted by an NIH Data Access Committee NIH Data Access Committee (DAC). Access to samples housed at RUCDR will be controlled through the NRGR access request process. PSG files, associated event files and methods for data collection and quality assurance can also be obtained through the National Sleep Research Resource (NSRR).

14.5.3 Access to Electronic Products / Data Analysis Tools

No application process will be required to access electronic products or data analysis tools such as source code or algorithms developed for this project to analyze PSGs. All materials will be included in publications and posted to GitHub and linked to the NSRR Community Tools page.

14.5.4 Access to Other Materials

Details regarding data content, format, and organization will also be made freely available to investigators through the Stanford's project website and any publications related to the project. There will be no application process or restriction on who may utilize these resources. All

manuals, protocols, and descriptions of data elements will be freely available for download to anyone interested via a Stanford Center for Sleep Sciences and Medicine project website.

All commercially purchased antibodies, reagents or kits will be clearly described in publications, including catalog or stock numbers. This data will also be provided in the metadata associated with published datasets.

15 STUDY COMPLETION AND CLOSE-OUT PROCEDURES

To confirm that the site investigator's study obligations have been met and post-study obligations are understood, the DC will perform the following close-out activities that include:

- Verification that study procedures have been completed, data have been collected, and supplies have been returned to the responsible party
- Review of investigator's correspondence and study files against the DC's records for completeness
- Assurance that all data queries have been completed
- Assurance that correspondence and study files are accessible for external audit
- Reminder to investigators of the ongoing responsibility to maintain study records and to report any relevant study information to the DC
- Meeting with the site investigators to ensure that they are aware of regulatory obligations and requirements for record retention
- Assurance that the investigator notifies the IRB of study completion and obtains a copy of the notification
- Preparation of a report summarizing study conduct

15.1 Participant Notification

The STAGES study recognizes the importance of patient portals as a promising mechanism to support greater patient engagement. Therefore, the STAGES study's future intentions are to create a Patient Portal through which subjects can be informed about the status of the study, the latest findings and developments, and where they can also access selected results of their research procedures.

Through this Patient Portal, we also intend to inform patients about the conclusion of the study and to thank them again for their valuable contribution.

15.2 Closure Checks and Database Locking Procedures

Prior to release of any data to the controlled NIH repositories, the data base will go through a cleaning and verification process. The first batch of phenotypic data of the STAGES study will be submitted to the appropriate NIH repositories 6 months after collecting the first full dataset of 10,000 participants. Once data of the first set of 10,000 participants has been collected, sites will be notified, and the database will be "locked" for data entry and modifications for this set of participants for cleaning, verification, and validation purposes.

Since the ongoing data collection for the remaining participants hinders the "complete locking" of the database, the DC will use the database logs to verify that no further changes have been

made to the dataset to be submitted to the repositories. After uploading of the first batch of data, data will be transmitted to the appropriate repositories at 6 months intervals.

The final lock of the database for data entry and modifications will be carried out prior to the submission of the final dataset of the 30,000 participants.

15.3 Final Study Report

The DC at Stanford will prepare the final study report and will send this report to the IRB within 30 days of the study completion, to the Klarman Family Foundation, and other qualified committees and governing entities.