Walter Reed Army Institute of Research
Consent for Research Participation

Title: CNS Correlates of Extended Sleep Restriction

Sponsor: Center for Military Psychiatry and Neuroscience,
Walter Reed Army Institute of Research (WRAIR)

Funder: U.S. Army Medical Research and Development Command
Military Operational Medicine Research Program

Principal Investigators (PI): Samantha M. Riedy, Ph.D.
WRAIR

COL Vincent F. Capaldi, II, M.D.
WRAIR

Contact Info: Email: samantha.m.riedy.civ@health.mil
Phone: (301) 337-1323

Email: vincent.f.capaldi.mil@health.mil
Phone: (301) 319-9098

Study Locations: WRAIR Sleep Research Center
503 Robert Grant Avenue
Silver Spring, MD 20910

National Institute of Mental Health (NIMH),
National Institute of Health (NIH) Clinical Center
9000 Rockville Pike
Bethesda, MD 20892

National Intrepid Center of Excellence (NICoE)
4494 North Palmer Road
Bethesda, MD 20889

You are being asked to take part in a research study. This study is being conducted by the United States Department of Defense. The box below tells you important things you should think about before deciding to join the study. We will provide more detailed information below the box.

Please ask questions about any of the information before you decide whether to participate. You may also wish to talk to others (for example, your family, friends, or your doctor) about this study, before agreeing to join.

As part of the exclusion criteria, you will be excluded from participating if you are not able to read and sign the consent form.

Please contact one of the investigators below if you have any questions concerning the study or if you have any other questions or concerns.

Samantha Riedy, Ph.D. **(301) 337-1323**
COL Vincent Capaldi, II, M.D. **(301) 319-9098**

Key Information for You to Consider

- **Voluntary Consent.** You are being asked to volunteer for a research study. It is up to you whether you choose to participate or not. There are no penalties and you will not lose any benefits to which you are otherwise entitled if you decide not to participate, or if after you join, you decide to quit.
- **Purpose.** We are doing this research to better understand how changes in brain chemistry and physiology caused by sleep loss impair performance and alertness. Once we pinpoint the physiological processes involved, we may be able to design ways of preventing or reversing them.
- **Duration.** Your participation in the study will last approximately 8 weeks (55 days). There will be two periods of at-home sleep monitoring and two in-laboratory phases. The first at-home monitoring period lasting 10-15 days (phase 1) will be followed by a 16 day stay at the WRAIR Sleep Research Center (phase 2). A second at-home monitoring period lasting 20 days (phase 3) will be followed by a final, 5 day stay at WRAIR (phase 4), after which you will be discharged from the study. During phase 2 and phase 4, you will not be able to leave the laboratory or building except for scans at the NIH and NICoE.
- **Procedures and Activities.** We will use state of the art brain imaging methods – including positron emission tomography (PET), magnetic resonance imaging (MRI), electroencephalography (EEG), and polysomnography (PSG) – to obtain information about brain chemistry and physiology throughout this period. We will also conduct behavioral tests (mostly administered via computer and smartphone) and collect blood samples that reflect the level of sleep loss and recovery.

  This research study will involve three radiolabeled drugs during the PET scans—[11C]ER176, [11C]UCB-J, and [18F]Florbetaben—that will be used to examine the effects

of sleep restriction on neuroinflammation, synaptic density, and beta-amyloid plaque accumulation. [11C]ER176 and [11C]UCB-J are investigational drugs, which means they are not approved by the U.S. Food and Drug Administration (FDA) for clinical use. [18F]Florbetaben is a U.S. FDA approved drug.

- **Risks – Imaging.** Most studies have some possible harms that could happen to you if you join. In this study, exposure to radioactive chemicals (in PET) and strong magnetic fields (in MRI) represent potential risks. A total of nine PET scans across six scanning sessions and 30-50 MRI scans across five scanning sessions will be conducted. However, the doses we will use and the safety precautions we will take – all of which conform to standards of care in medical research – should significantly minimize these risks.

- **Risks – Venous Catheters, Arterial Lines, and Blood Draws.** A venous catheter will be inserted five times on five different days for blood draws, and six times on six different days for injection of the radiotracer prior to PET scans. Venous catheter risks may include some pain, discomfort, dizziness, as well as minor bruising, swelling or irritation at the insertion site. Pain, itching, inflammation of the vein, infiltration (when small amounts of fluid leak out of the vein into the surrounding tissue), or infection are also possible though rare. An arterial line will be inserted three times across three different days throughout the study. The placement of an arterial line may cause discomfort, bruising, swelling, and fainting. There is also a chance of forming a blockage though this is rare. A total of 730 mL of blood will be drawn across the study. Dizziness, nausea, fainting, and rapid breathing are possible with this blood draw volume though this is rare.

- **Risks – Sleep Restriction.** Sleep restriction risks may include slowed response time, difficulty staying awake, increased subjective sleepiness, and mild negative effects on mood, as well as hypnagogic or hypnopompic hallucinations though this is rare.

- **Benefits.** Participation in this study will provide no direct benefit to you, but the information we gain may help us provide ways to prevent performance and alertness deficits, and thus improve the safety and well-being, of soldiers

- **Alternatives.** Participation is voluntary and the only alternative is to not participate.

Why is this research being done?

Sleep loss causes impairments of alertness and performance. Although it is assumed that these impairments reflect temporary neurochemical or other physiological changes in the sleep-starved brain, the exact changes in brain function that occur following sleep loss are poorly understood. Recent animal studies have provided clues, but specific physiological effects of sleep loss in the brains of humans have not yet been identified.

The purpose of this research study is to learn what we can about these physiological effects. Our ultimate goal will be to use what we learn about the underlying mechanisms to design ways of preventing the root causes of sleep loss related decreased alertness and performance.

In this study – which is described in greater detail below – we will use state of the art

brain imaging methods to obtain direct information about brain physiology before, during, and after one week of moderate sleep restriction, during the immediate post-restriction recovery period and following full recovery, approximately 4 weeks later.

Over this period of time, volunteers will undergo positron emission tomography (PET), magnetic resonance imaging (MRI), electroencephalography (EEG) and polysomnography (sleep studies) as well as behavioral tests (mostly administered via computer and smartphone). Three radiolabeled drugs will be used during the PET scans during the study: [^{11}C]ER176, [^{11}C]UCB-J, and [^{18}F]Florbetaben.

[^{11}C]ER176 and [^{11}C]UCB-J are investigational drugs, which means they are not approved by the U.S. Food and Drug Administration (FDA) for clinical use. [^{18}F]Florbetaben is a U.S. FDA approved drug. We are using these drugs and methods to determine a) which physiological processes correlate best with decreased performance and alertness and b) what physiological changes accompany improved functioning following recovery sleep relative to that during sleep restriction. We will also measure substances in the blood that may reflect level of sleep loss and recovery.

You are being asked to take part in this research study because you are a member of the target population – young, healthy individuals with no known sleep abnormalities. Overall, a total of 18 volunteers ranging in age from 18-39 will complete this study.

As you read this consent form, if you are unsure about anything, please ask questions.

How long will I be in this research study?

We expect that your participation will last approximately 8 weeks (55 days).

In addition to a 3-4 hour screening process which will take place at WRAIR, you will take part in two periods of at-home sleep monitoring and two in-laboratory phases.

Following the first at-home monitoring period (which will last 10-15 days depending on scheduling considerations) you will return to WRAIR where you will spend 16 days (14 full days and 2 partial days) in the Sleep Research Center. You will be released on the sixteenth day following an examination by a medical investigator and will return home for the second at-home monitoring period (which will last 20 days).

At the end of this monitoring period, you will return to WRAIR where you will spend the next 5 days (3 full days and 2 partial days). On the fifth day you will be examined by a medical investigator and if cleared for release, you will be discharged from the study.

What will happen if I decide to be in this research study?

THE SCREENING VISIT (today's visit)

This visit will last about 3-4 hours and its purpose is to determine whether you are able to safely participate in the study.

During this visit, you will read this consent form and receive answers to any and all questions that you may have. You will then be given a formal briefing by an investigator or qualified representative. This briefing will describe the purpose of the study, key points, your participation and what it includes, criteria for including or excluding you from the study, and potential risks and/or benefits of participating.

You will have the opportunity to ask and have addressed any questions or concerns regarding the study. If you then wish to continue, you will sign this consent form. This will be followed by some questionnaires to complete, after which a study medical investigator will review your medical history and conduct a physical exam.

This screening visit includes collecting approximately 25 mL (about 5 teaspoons) of blood drawn by a qualified staff member for safety tests (complete blood count, kidney and liver function tests) and a polymorphism test (described below). We will also collect urine and saliva samples to test for the presence of nicotine, drugs and alcohol. If either of these tests is positive during the screening process, a medical investigator or the PI will inform you of your results and you will not be able to enroll in the study.

Additionally, for women, we will do a urine pregnancy test. Women who are pregnant or breast feeding will not be able to participate.

We will call you within 7-10 business days to let you know whether you are qualified and to schedule you for the next phase if you are still interested. You may request copies of your screening lab results.

If you agree to be in this research, you will be expected to return for enrollment and participation in the activities described below:

ENROLLMENT VISIT (Day 1)

If you pass the initial screening process you will report back to the WRAIR Sleep Research Center within 180 days to enroll in the first portion of the study (Day 1).

The enrollment visit will take about 4 hours. You will need to stop consuming alcohol and any prescription or over-the-counter medications or supplements (unless previously approved by the study medical investigator) for the entire study. Do not stop using prescription medication without consultation and approval of the prescribing physician.

We will again collect urine and saliva samples to test for the presence of nicotine, drugs and alcohol. If any of these tests are positive, a medical investigator or the PI will inform you of your results and you will not be able to complete the enrollment process. For

women, we will do another urine pregnancy test, and women who are pregnant will not be able to participate.

On the enrollment day, you will complete some additional questionnaires.

You will be fitted with a wrist actigraph (a device that records sleep/wake timing and duration). The actigraph is a commercially-available device that has been cleared by the Food and Drug Administration for this purpose. It records your wrist movements, from which your sleep/wake schedule each day can be determined. During the entire study (from day 1 through day 55, during both at-home and in laboratory phases), your sleep/wake schedule will be recorded with this device.

You will also receive a smartphone, which will be used for vigilance testing (the PVT or psychomotor vigilance test), reporting sleepiness levels (the KSS or Karolinska Sleepiness Scale), and recording of caffeine intake and sleep times. You will receive instructions on how and when to use these apps during the at-home monitoring phases.

All data collected on the actigraph and smartphone will be stored on the devices and will not be stored in the cloud (a remote server that can be accessed by the internet). Additionally, these data will never be accessible by the device manufacturers.

You will review an information sheet at WRAIR that will describe the portion of the study that will be conducted at the National Intrepid Center of Excellence (NICoE) and complete a form that will be used to register you as a research volunteer at the Walter Reed National Military Medical Center (WRNMMC).

You will be transported to Bethesda in a government vehicle driven by a civilian or military member, where you will register as a research volunteer at the National Institutes of Health (NIH) Clinical Center. While at the NIH Clinical Center, you will review another consent form that specifically includes information on the portion of the study that will be conducted at the NIH Clinical Center. Members of the NIH study team will talk with you about the information described in that document.

When this is completed, you will be transported back to WRAIR and return home to begin Phase 1 of the study.

<u>PHASE 1 – At Home Monitoring (Days 1-16)</u>

Throughout Phase 1, you will maintain your usual activities and your normal schedule and maintain a consistent sleep schedule.

You must leave the actigraph in place (on your non-dominant wrist) at all times – e.g. during bathing/showering, swimming, exercising/engaging in sports, etc.

The smartphone you received at enrollment will be used to take short (5-minute) reaction time tests and to report your sleepiness levels during each day of the at-home monitoring phase. You will take 4 to 6 of these reaction time tests and sleepiness ratings per day. The reaction time tests are simple to do - your task is to touch the

smartphone screen as quickly as possible each time a signal on the screen appears. You will be asked to minimize distractions by taking the task in a quiet location.

You will be able to choose when to take these reaction time tests each day, with the only restrictions being (a) you will take at least 4 tests and no more than 6 tests per day, and (b) after you take one test you must wait at least 90 minutes before taking the next test. The smartphone will remind you to take the 5-minute test approximately every 2-3 hours. You must complete at least 80% of all the smartphone-administered 5-minute tests across the initial at-home phase to qualify for Phase 2 of the study.

You will also be asked to use the smartphone to document the amount of caffeine that you consume on an ongoing basis (e.g., "12 ounces of coffee at 8:00 AM"; "one Red Bull at 1:00 PM") and record nightly sleep times (i.e. every morning you will input the amount of sleep you obtained over the past 24 hours).

It is your responsibility to prevent damage or loss and keep the phone charged during Phase 1 at home. The phone must be returned to the study staff when you arrive for the beginning of Phase 2. The study staff will at that time verify that you have completed at least 80% of the required tests at home during Phase 1.

If you lose or damage the smartphone and/or the wrist actigraph, you will not be responsible for the cost of replacing or repairing these items. However, you will also not be eligible to receive the payments associated with wearing the wrist actigraph and/or taking the performance tests on the smartphone (since there will be no way to confirm the number of performance tests completed and/or the number of nights that the actigraph was worn). Also, because the data from these devices will be missing, your participation in the study session could be terminated.

You will also be asked to call a voicemail box with your bed and wake times, and report if the actigraph was removed temporarily (if applicable). Study staff will provide a phone number to call to report these times. The staff may call you if there are any questions, and to remind you of your upcoming visit to the laboratory for Phase 2.

<u>PHASE 2 – In-Laboratory Testing: Sleep Restriction and Recovery (Days 16-31)</u>

See the figure at the end of this document.

You will report to the WRAIR Sleep Research Center on the afternoon of Day 16, the first day of the second phase of the study, and will remain there for the approximately two weeks (14 full days and 2 half days). You will be released after lunchtime on Day 31 following evaluation and clearance for discharge by a medical investigator.

When you arrive at WRAIR for Phase 2, your actigraph will be reviewed to make sure that your recorded sleep times do not differ greatly from what you reported during screening. If it is determined that your recorded sleep times do differ significantly from what you initially told us, you will not be able to continue in the study. The study staff will also check results on the smartphone to verify that you have completed at least 80% of the required tests at home during Phase 1.

Depending on availability of PET ligands and imaging facilities, PET and MRI scans and other study procedures described throughout may be moved to different days or times of day, or specific PET scans may be removed from the study schedule, for any logistical reason, the required PET ligand is not available for a scheduled PET scan.

Sleep schedules:

On nights 16-18 (baseline) you will be allowed to sleep from about 11:00 PM until about 7:00 AM the following morning. On nights 19-25 (sleep restriction) you will be allowed to sleep from about 2:00 AM until about 7:00 AM. On nights 26-30 (recovery) you will again be allowed to sleep from approximately 11:00 PM until about 7:00 AM the following morning.

Recording electrodes:

Your sleep will be monitored during the in-laboratory phases by placing electrodes on your scalp, chest, and face. The electrodes connect to a computer, and their purpose is to monitor your brain activity, eye movements, muscles, and heart during times when you are asleep and awake. The electrodes do not penetrate your skin, are not painful, and do not deliver electricity.

Electrodes will be applied on day 16 and removed on day 31. Electrodes will also be removed at multiple points during the study including before shower opportunities and reapplied the same day. Electrodes used during sleep recordings may be removed prior to PET/MRI scans and reapplied after the scans, or left on during the scans. New electrodes compatible with the scanning equipment may be applied for the scans.

It is requested that braids are not worn during recordings with these electrodes.

Electrophysiological and video monitoring during sleep and wake:

Recording from these electrodes gives us information about activity of your brain, your heart and your muscles during sleep. We will obtain this information every night during this phase.

We will also record the same information for brief periods while you are awake – just before you go to sleep and just after you awaken. These waking EEG recordings will take place while you are sitting comfortably in a chair in your bedroom and will take about 15 minutes in each case. Additional recordings may also be conducted during MRI scans or during sleep restriction.

During sleep periods, a trained staff member may be able to see you via an infrared camera (which provides images in the dark). This is done so that while you are in bed the study staff can see from a distance if you have any problems sleeping and whether you remain in bed as instructed. The images recorded during the sleep periods will be stored on a computer as part of your sleep recordings.

During scheduled nighttime sleep periods, you are allowed to leave the bedroom to use the restroom.

Neuroimaging studies:

On certain days during Phase 2 of the study, you will be transported from WRAIR in a government vehicle driven by a civilian or military member to the NIH Clinical Center for positron emission tomography (PET) studies, or to the National Intrepid Center of Excellence (NICoE) for PET and magnetic resonance imaging (MRI) studies. You will return to WRAIR on the same day, following completion of these tests.

Urine samples will be obtained at WRAIR for pregnancy screening within 24hr prior to PET and MRI scans.

During transport to/from NIH and NICoE, you may be asked to wear light blocking goggles to minimize the effects of light exposure on sleep, performance, and other measures.

Magnetic resonance imaging, or MRI, uses a strong magnetic field and radio waves to take pictures of the brain.

The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. A device called a "coil" will be placed over your head. Before functional MRI (fMRI) scans, you will be told about tasks that you may do during the scan and you will have the chance to practice.

Some of the MRI studies provide information about brain structure (white or grey matter, fiber tracts or fluids). Others such as Magnetic Resonance Spectroscopy (MRS) give us information about brain chemistry. Functional MRI (fMRI) allows us to see what parts of the brain are active when you are completing a task.

While in the scanner you will hear loud knocking noises and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan and you may ask to be moved out of the machine at any time.

During some of the scans, you may be asked to do behavioral tasks while in others you may be asked to just lie still. The behavioral tasks either replicate some of those you will have been doing at home or at WRAIR (such as the continuous performance task) or are designed to check your level of attention while you're in the scanner (e.g. asking you to identify and/or count auditory or visual stimuli).

During Phase 2, you will be asked to complete four MRI sessions across four different days (on days 18, 22, 25, and 30). Each session will be at NICoE and will be broken into three periods in the scanner with rest breaks of approximately 15 minutes in between. During each session, the three periods in the scanner will last approximately 1 hour and consist of 6-10 MRI scans of variable duration for a total of 3-4 hours.

During your first MRI session at NICoE, we will perform a required annual clinical scan.

This clinical scan is performed to look for abnormalities. You will be informed about any finding that may require further evaluation or care. We are not able to provide evaluation or treatment for these conditions. If needed, we will refer you to a health care provider. These results will not be shared with your chain-of-command/supervisor.

During MRI scans, respiration and skin conductance data may be collected, and images of just the eye may be collected.

Positron emission tomography, or PET, uses a small amount of a radioactive chemical that is injected into a vein in your arm and can be detected in your brain by the PET scanner. PET scans give us information about brain chemistry and function.

The PET scanner is shaped like a donut. You will lie on a bed that slides in and out of the scanner. A head strap will help you hold your head still during the scan. We will start the scan by taking an X-ray-like picture (transmission scan).

A PET ligand (the radioactive chemical) will be injected through an intravenous catheter (a thin plastic "i.v." tube) in your arm. The i.v. will be inserted by a certified technician or medical support staff member at the NIH or NICoE and will be removed when the studies are completed.

During each scan you will be asked to lie quietly without sleeping. As in the MRI studies, you may be asked to perform tasks that are designed to check your level of attention while you're in the scanner (e.g. asking you to identify and/or count auditory or visual stimuli). After the scan, you will be told about drinking fluids and voiding (urinating) to limit your exposure to radioactivity.

You will have three types of PET scans in this study. One type (C-11 ER176) measures small amounts of inflammation in your brain, another (C-11 UCB-J) measures the density of synapses - the connections between brain cells - and the third (F-18 Florbetaben) provides information about the clearance of protein substances from the brain.

For PET scans that use C-11 ER176 (two of the six PET scans that you will have in this part of the study) we will sample arterial blood in order to quantify our measurements making them statistically reliable. About 80 ml (5-6 tablespoons) of blood will be sampled during each of these PET scans. For the other PET scans (C-11 UCB-J and F-18 Florbetaben) arterial sampling will not be required.

For these C-11 ER176 scans, another thin plastic tube (catheter) will be put into an artery at your wrist or elbow crease area. Before inserting a catheter into the wrist, a simple test will be done to ensure that both arteries in your wrist are working. We will inject a local anesthetic to numb the skin over the artery. Then, the catheter will be placed in the artery with a needle. The needle will be removed, leaving only the thin catheter in the artery. The catheter will be fastened to the skin with tape. During the time the catheter is in place, you should try not to move your arm. A physician or nurse will be available at all times and you should tell them immediately if you have pain or discomfort.

During phase 2, you will be asked to complete four PET sessions across four different days – two sessions at the NIH (on days 19 and 26), two sessions at NICoE (on days 18 and 25). Each session will range from 2 ½ to 8 hours depending on the number of scans and the amount of downtime between scans. The two sessions at the NIH will consist of two scans. Each scan is approximately 2 ½ hours in length. The two sessions at NICoE will consist of a single scan which will last approximately 2 ½ hours.

If we cannot do the PET scan because of technical problems or if the scan is cancelled for other reasons and you had no radioligand exposure for the cancelled scan, we may ask you to have another PET scan. It could be on the same day or another day. We would also need to repeat the transmission scan. You will remain in the study and continue to undergo all of the other procedures described here.

Blood sampling for biomarkers:

We will collect additional blood at four different time points during this portion of the study in order to measure plasma levels of compounds that give us information about the effects of sleep loss on your body and brain. You will start fasting at 23:00 (11:00 PM) the night before these blood sampling days. Food intake timing will also be tracked on blood sampling days.

In order to collect blood samples without multiple needle sticks, we will insert an intravenous line (a small flexible plastic catheter) into a vein in your arm (most likely your non-dominant arm). A small saline lock adapter is connected to the line and taped to your arm (there is no IV bag or long IV tube). Blood is sampled from this line (also known as a peripheral venous catheter, or PVC) and the line will be flushed with a solution several times a day to keep it from clotting.

The PVCs will be inserted in the morning on the four days with scans at NICoE and removed prior to bedtime on these same days. If it is not possible to collect a blood sample from the PVC, the PVC may be replaced with a new PVC or venipuncture may be performed. The medical support staff may also choose to use venipuncture in place of a PVC. Prior to the first blood draw on at least two of the four days with PVC insertions, a finger prick will be conducted to assess hemoglobin levels.

While the PVCs are in place blood samples will be taken approximately every three hours. Approximately 372 ml of blood will be taken during this phase of the study.

Behavioral tests:

On days 16-31, you will periodically perform batteries of cognitive and behavioral tests and tests of motor function. These batteries will take between 15-120 minutes.

On the days that you will travel to the NIH or NICoE for brain imaging studies, the performance batteries will be administered a limited number of times – typically in the morning before you leave, and in the evening, after you return to WRAIR.

On the other days, when you remain at WRAIR, you will receive additional tests at various times throughout the day. On day 31, when you are scheduled to leave, you will be tested until the time of discharge.

These tests are being administered because behavior – cognitive abilities such as memory, attention or language as well as motor skills such as speed and balance – can be affected by sleep restriction. An important part of this study involves measuring these effects.

Your mood, sleepiness and other physical symptoms will be periodically assessed via questionnaires, as well. One task will include audio recorded interactions with a study team member; these audio recordings will be used to assess language-based communication.

Most of the tests in this battery will be administered via computer. These will include, for example, determining how fast you respond to visual stimuli, how well you recall words that had been presented to you previously, remember visual patterns for short periods of time, and so on. These tests do not require any special skills. Other tests – for example determining how well you are able to maintain your balance – are performed on specialized pieces of equipment.

PHASE 3 – At Home Monitoring (Days 31-51)

Activities during the 20 days of this phase are essentially the same as those described for Phase 1 above:

You will maintain your usual activities/schedule and a consistent sleep schedule, leaving the actigraph on your wrist at all times.

You will use the smartphone to take the short reaction time tests and to report your sleepiness levels – between 4 to 6 tests per day - on each day, of this phase, with the same stipulations (e.g., at least 90 minutes between tests) described above. You will be asked to minimize distractions by taking the task in a quiet location.

You must complete at least 80% of all the smartphone-administered 5-minute tests across the approximately 20 days at home to qualify for Phase 4 of the study.

You will again use the smartphone to document the amount of caffeine that you consume and record nightly sleep times.

It is your responsibility to prevent damage or loss and keep the phone charged during Phase 3 at home and the phone must be returned to the study staff when you arrive for the beginning of Phase 4. The study staff will at that time verify that you have completed at least 80% of the required tests at home during Phase 3.

As in Phase 1, if you lose or damage the smartphone and/or actigraph, you will not be responsible for the cost of replacing or repairing these items. However, you will also not be eligible to receive the payments associated with wearing the actigraph and/or taking

the performance tests on the smartphone. Again, because the data from these devices will be missing, your participation in the study session could be terminated.

You will also be asked to call a voicemail box with your bed and wake times and report if the actigraph was removed temporarily (if applicable). The study staff will provide a phone number to call to report these times. The staff may call you if there are any questions, and to remind you of your upcoming visit to the laboratory for Phase 4.

PHASE 4 – In-Laboratory Testing: Post-Recovery (Days 51-55)

You will report to the WRAIR Sleep Research Center in the afternoon on Day 51 of the study and will remain there for approximately 5 days (three full days and two half days). You will be released after lunchtime on Day 55 following evaluation and clearance for discharge by a medical investigator.

When you arrive at WRAIR for Phase 4, the study staff will review your actigraph to make sure that your recorded sleep times do not differ greatly from what you reported during screening. If it is determined that your recorded sleep times do differ significantly from what you initially told us, you will not be able to continue in the study. The study staff will also check results on the smartphone to verify that you have completed at least 80% of the required tests at home during Phase 3.

During Phase 4, you will undergo a number of the same electrophysiological, neuroimaging, food tracking, and behavioral and blood tests that you did in Phase 2.

PET ligand synthesis is not always successful, and timely delivery from offsite laboratories cannot always be assured. Depending on availability of PET ligands and imaging facilities, PET and MRI scans and other study procedures described throughout may be moved to different days or times of day, or specific PET scans may be removed from the study schedule, for any logistical reason, the required PET ligand is not available for a scheduled PET scan.

Sleep schedules:

Throughout this phase, you will be allowed to sleep from about 11:00 PM until about 7:00 AM the following morning.

Electrophysiological and video monitoring during sleep and wake:

Recording electrodes will be put in place during the evening of day 51 and removed on day 55. Electrodes will also be removed at multiple points during the study including for shower opportunities and reapplied the same day. Electrophysiological recording and video monitoring will take place during sleep each night. Waking EEG recordings will be made just before you go to sleep and shortly after you awaken on days 51-55. Recordings may also be conducted during MRI scans.

It is requested that braids are not worn during recordings with these electrodes.

Neuroimaging studies:

On day 53, you will be transported from WRAIR in a government vehicle driven by a civilian or military member to the National Intrepid Center of Excellence (NICoE) for a PET session that will include one PET scan and an MRI session that will include 6-10 MRI scans of variable duration.

On day 54 you will be transported from WRAIR in a government vehicle driven by a civilian or military member the NIH Clinical Center for a PET session that will include two PET scans. During the C-11 ER176 scan an arterial line will be inserted for blood sampling, as outlined above. About 80 ml (5-6 tablespoons) of blood will be sampled during this final PET scan.

Urine samples will be obtained at WRAIR for pregnancy screening within 24hr prior to MRI and PET scans.

During transport to/from NIH and NICoE, you may be asked to wear light blocking goggles to minimize the effects of light exposure on sleep, performance, and other measures.

Blood sampling for biomarkers:

A PVC will be inserted in the morning prior to scans at NICoE on day 53 and removed prior to bedtime on the same day.

Blood samples will be taken approximately every three hours while the PVC is in place. Approximately 93 ml will be taken during this phase of the study.

Behavioral tests:

On days 51-55, you will periodically perform batteries of cognitive and behavioral tests and tests of motor function. These batteries will take between 15-120 minutes.

On the days that you will travel to the NIH or NICoE for brain imaging studies, the performance batteries will be administered a limited number of times – typically in the morning before you leave, and in the evening, after you return to WRAIR.

On the other days, when you remain at WRAIR, you will receive additional tests at various times throughout the day. On day 55, when you are scheduled to leave, you will be tested until the time of discharge.

How will my eligibility for this research study be determined?

You may be allowed to participate in the study if you are a healthy adult between 18 and 39 years of age, without any ongoing symptoms of insomnia or other sleep disorders or disqualifying abnormalities identified by tests and interviews conducted during the screening visit when we will ask you questions and have you fill out forms as described below.

You may be excluded from participating for your own safety, if you have ever had any of the following: heart disease, hypertension (high blood pressure), a neurologic disorder (for example, seizures or multiple sclerosis), a history of a major psychiatric disorder, a history of claustrophobia, certain allergies or immune disorders, asthma or other airway diseases, liver disease, kidney disease, metabolic disorder or diabetes, illicit drug use, regular use of nicotine within the past year, excessive use of alcohol or caffeine, and/or excessive sleeping problems.

You will also be excluded if you have had a PET scan or participated in research involving exposure to a significant amount of radiation in the past year.

Because you will be providing blood samples during this study, you will not be able to enroll in the study for at least 56 days (8 weeks) after your last blood donation and you will not be able to donate blood during the study, including blood donations for other clinical trials. It is also recommended that you do not donate blood for at least 56 days (8 weeks) after completing the final in-laboratory portion of the study.

If you are a woman, you must not be breast-feeding, not be lactating, not actively be trying to conceive, and must test negative for pregnancy. Additionally, for females of childbearing potential, you must be taking or using some form of birth control (e.g., condom, oral contraception (the pill), intrauterine device (IUD), etc.) during your participation in this study.

For your own safety, you must tell the person conducting this screening visit of *any* medical or mental health problems you now have, or had in the past, no matter how minor.

During the screening visit, a study medical investigator will review with you any current medications you are taking to let you know if their use is permitted while you are in the study. For your safety, it is very important that you disclose all of the medications you are currently taking, to include prescriptions, over-the-counter medications, and nutritional supplements; and that you DO NOT stop taking prescription medications without consulting your personal physician in order to participate in the study. During the study, you must not be taking any medications, with the exceptions of birth control for females, and any medications previously discussed with and approved by the medical investigator. (See the following section).

You must consent to the storage of your blood for future research, which may include genetic testing or other research purposes. Additional information is provided below. You must consent to neuroimaging, behavioral, and other data being made available for future research.

A portion of the blood sample collected during screening will be used for genotyping of a specific polymorphism; that is, a natural variation in one of the genes that are of interest in this study. You may be excluded based on the presence of this polymorphism. This is for research purposes only and the presence or absence of the polymorphism does not provide benefits nor does it indicate any additional risks.

In addition - for active duty military, you must have written approval to participate from your supervisor, unit commander (or equivalent), and company commander (or equivalent). If you are active duty military or federal personnel, you must be off duty or on approved annual leave during your participation in the continuous in-laboratory phases of this study. No data collected during the study (including health-related data) will be shared with your supervisor or anyone in your chain-of-command. For additional information regarding participation and compensation for Federal personnel, please see the document entitled, "Information Sheet Regarding Compensation to Federal Personnel When They Participate in Research as Human Subjects."

What are my responsibilities as a participant in this research study?

Some things you should know about the study phases that might influence your decision whether to participate are listed below:

1. For the duration of the study:

You must stop consuming alcohol. Additionally, unless previously approved by a medical investigator, you must not be consuming certain vitamins, dietary supplements, herbal remedies, prescription drugs and over-the-counter drugs. One exception to this, for example, is that women should continue to take their birth control.

For your own safety, it is critical that you tell the medical investigator who conducts your physical exam if you are taking ANY of these items and that you DO NOT stop taking prescription medications without consulting your personal physician.

Note: A study medical investigator will be on-call throughout the study for any medical issues.

2. When you are in the laboratory:

- You are not allowed to do strenuous activity or to exercise.
- You may not make or receive phone calls, use a cell phone/Blackberry/pager/computer, iPad, or other electronic devices. We will store your mobile devices in a locked cabinet in the laboratory during your stay.
- You are not allowed to have visitors.
- A staff member is with you at all times except when you must go to the bathroom or attend to similar needs.
- You may not bring in outside food or beverages, take dietary supplements, vitamins, or medications (except those approved by the study medical investigator). We supply all food and beverages, which you are allowed to have at any time except when you are testing, sleeping, or fasting prior to blood draws.
- You will be expected to perform all tasks, activities, etc., to the best of your ability and as you are instructed.

During times you are assigned to be in your bedroom (sleep periods, testing, etc.), you

will be expected to remain in your bedroom except to use the bathroom. During all other times, you must remain in the same area (the common living room area) with the technicians.

What happens to the information and specimens collected for this research?

As part of this study, we are obtaining data – e.g. neuroimaging (PET and MRI) scans, behavioral information and blood samples – from you. These data will be shared with researchers at the NIH, NICoE, and other WRAIR labs to better understand the physiological effects of sleep loss as described in this consent form.

When data are stored at WRAIR, NIH and NICoE we take precautions to protect your personal identifiable information. These include the use of double locked cabinets and encrypted, password-protected computers.

We will also store and use these data for studies other than the ones described in this document that are going on right now, as well as studies that may be conducted in the future.

NIH policies require that your clinical and other study data collected at the NIH be placed in an internal NIH database that is accessible to other NIH researchers for future research. Usually, these researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether these data are placed in this database or not. If you do not wish to have these data placed in this database, you should not enroll in this study.

In addition, your data may be submitted to open-access repositories. Such open-access repositories (e.g., OpenNeuro, sponsored by NIMH) allow anyone to access the data for any purpose. If we do, while we maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

Your data may be shared with other collaborating research laboratories, not yet identified, without asking for your permission. These researchers – at other research centers and institutions, or commercial entities – may be doing research in areas similar to this research or in other unrelated areas

Nevertheless, personally identifiable information will never be shared with these groups. That is, we will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your data with a code so that you cannot easily be identified.

The code will be linked through a key to information that can identify you. However, if we share your coded data with other researchers, we will maintain the code key so that the other researchers will have no way to link the data back to you.

Future studies may lead to the development of research tests, treatments, drugs, or devices that may lead to development of a commercial product by the DOD or NIH and/or their research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you. We will not contact you to ask your permission or otherwise inform you before we do this.

Your name will not appear in any published paper or presentation related to this study. You will not have access to the results of neuroimaging or cognitive/neurophysiological testing that takes place during the study.

Other than any medically relevant abnormalities detected during screening, the overall results and findings from this study will not be shared with you. However, a summary of the overall results and findings from this study will be provided to you upon request.

As noted, a portion of your blood samples will be stored for future research studies. It has not yet been determined how this blood will be used. But it is anticipated that at some future date your blood may be tested for as-yet-unspecified genes, proteins, markers of immune function, hormones, etc. – in short, anything in the blood that could be tested as a biological marker that changes as a function of sleep schedule, and/or anything that may reflect your sleep preferences or "type" (for example, whether you are a "morning" or "evening" person) information that will help us better understand the biological consequences of sleep restriction.

Blood specimens retained for possible use in future analyses for genetic testing and to test for sleep-related biomarkers will be stored indefinitely, until they are used. Again, all personally identifiable information will be removed from the samples and any identifying information will be kept under lock and key or on a secured computer at WRAIR.

The research plan describing the storage and potential future use of your blood has been reviewed by the Institutional Review Board (IRB) (committees responsible for protecting human subjects in research studies) at WRAIR. The data protections for privacy and confidentiality described in this document apply to any future use of your stored data and samples. Legal protections specifically regarding genetic information are described in the following section

Once the study is complete, records will be kept in secure storage at WRAIR, the NIH and NICoE and maintained until it has been deemed no longer necessary to retain them by the Center for Military Psychiatry and Neuroscience, NIH or NICoE. They will then be destroyed in accordance with Federal regulations.

What are the potential risks and discomforts if I participate in this research?

If you choose to take part in this study, there are risks associated with the following

procedures:

Sleep restriction: During the 7 nights/days of sleep restriction (Study Phase 2) when you will spend only 5 hours in bed each night, you might feel physical, emotional or mental changes. In previous studies, including those conducted in our sleep research laboratory, volunteers have previously undergone these same levels of sleep loss. The most commonly experienced effects have been feelings of sleepiness, tiredness, and fatigue. Engaging in conversation, watching movies, and walking around the laboratory corridors help alleviate these feelings. These feelings generally occur only during the sleep loss periods, and are reversed once you are allowed to sleep again. Study staff may try to help you stay awake by interacting with you socially (e.g. playing games, talking to you) and asking you to walk with them around the laboratory corridors. Though rare, sleep loss can sometimes cause mild auditory or visual hallucinations.

MRI and PET scanning:

Radiation Exposure Risks – During your participation in this research study, you may be exposed to radiation from [^{11}C]ER176, [^{11}C]UCB-J, [^{18}F]Florbetaben and the transmission scans (necessary for data correction) each year. The amount of radiation exposure from these procedures is equal to approximately 3.67 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called “background radiation.” No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The PET/CT scans that you will get in this study will exposure you to roughly the same amount of radiation as 12.2 years worth of background radiation. Most of the time, this amount of extra radiation is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects. This could include getting a new cancer. We estimate that this could happen in about 1 out of every 1000 people who get a very large amount of extra radiation.

Please tell us if you have had any radiation exposure in the past year so we can make sure that you will not receive too much. Exposure could either be from other research studies or from medical tests or care. Exposure includes x-rays, cardiac catheterization, and fluoroscopy. It also includes nuclear medicine scans where radioactive materials were injected into your body.

Because of potential risk to a fetus, all women able to get pregnant must be on some form of birth control and have had a negative urine pregnancy test during each pregnancy test taken prior to the scan.

PET Scanning Procedure – There are no medical risks from the PET scan other than the radiation exposure. The strap or mask that helps hold your head may be a bit uncomfortable. You may also be uncomfortable staying still during the scan itself. You

can stop the scan at any time. You can ask to be taken out of the PET scanner if you are uncomfortable.

MRI Scanning Procedure – People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner or older tattoos (that used metallic ink), implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware. You will be screened for these things before having a scan using a standardized screening instrument approved by the American College of Radiology. If the screening suggests that you have such a history, you will be interviewed by a study medical investigator and will likely not get an MRI scan. If you have a question about any metal objects in your body, you should tell the staff. You will be asked to complete an MRI screening form before each MRI scan you have. Also, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before you go into the MRI scan room.

It is not known if MRI is completely safe for a developing fetus. Thus, as noted above, women able to get pregnant must be on some form of birth control and have had a negative urine pregnancy test during each pregnancy test taken prior to the scan.

People afraid of small spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will get hearing protection. If the hearing protection comes loose during the scan, you should let us know right away. Please tell the investigators if you have hearing or ear problems.

There are no known long-term risks of MRI scans.

Placement of an Arterial Line: There is usually some discomfort when the needle is inserted. Bruising or swelling at the site of the arterial catheter occurs in 5 to 20 percent of volunteers. But it is only temporary. Fainting is uncommon, but possible. The catheter can cause blockage of the artery, but that is unlikely because the catheter is left in for only a short period of time. There have been two delayed complications from wrist arterial catheters at NIH. One person developed a small radial artery aneurysm 2 years after arterial catheterization. A second person developed a blocked artery a few days after arterial catheterization. Both required surgical repair. These two cases occurred across more than 3,000 subjects for a frequency of less than 0.07%.

Peripheral Venous Catheter and Blood Draws: The insertion of the peripheral venous catheter (PVC) prior to blood draws and the intravenous line inserted for injection of radiotracers prior to PET scanning may cause some pain or discomfort, dizziness, as well as minor bruising, swelling and/or irritation at the insertion site. Also, some people may feel faint. It is possible that you may experience some discomfort or stinging during the injection of the radiotracer through the PVC. The intravenous lines inserted for the PET scanning will be removed immediately after the scans have been

completed. However, PVCs used for blood collection will remain in place for approximately 15 hours, and you may experience some discomfort. Please let the PI or a medical investigator know if you are uncomfortable. Other risks of keeping in the PVC include pain, itching, inflammation of the vein, infiltration (when small amounts of fluid leak out of the vein into surrounding tissue), or infection, but these are uncommon for PVCs left in place for less than a week. A small blood clot can form or a small amount of air can enter the vein, but these will not hurt you. It is also possible for a piece of the PVC equipment to break off, but this is extremely rare. Trained personnel will insert and flush the PVC, as well as perform the blood draws. If the PVC is not working properly, blood will be taken from a different vein, the PVC will be removed and a new one may be placed in a different vein for later use, or venipuncture will be used. The medical support staff may also choose to use venipuncture in place of a PVC.

Blood Draw Volume: Over the course of the study, a total of 730 mL of blood will be drawn. This total volume is 180 mL over standard guidelines, but it is considered reasonably safe given the additional precautions in place.

Electrodes: The electrodes may cause some skin irritation (redness or bumps at the application sites). This goes away once the electrodes are removed.

Actigraphy: There are no known risks with wearing an actigraph (a watch like device to measure your activity).

Behavioral Tests*:* Performing the majority of tasks and activities may be frustrating, particularly when done during the sleep restriction period, and the laboratory may seem confining. These effects, if they occur, are temporary.

Screening Questions: You may feel uncomfortable answering sensitive questions during the screening procedure, such as questions related to your medical history. Your medical history will be taken by a study medical investigator and your answers to questions will be included in your confidential file that will be protected throughout the study. Please see the following section for more information on how your privacy will be protected.

Test Results: If you are female, you may learn you are pregnant. Also, both male and female volunteers could receive abnormal test results that require follow-up with your primary physician.

Breach of Confidentiality: Although efforts are made to protect your research study records, there is always a risk that someone could get access to the personal information in your research records or other information researchers have stored about you. The study staff will protect your personal identity and maintain confidentiality to the best of our ability using precautions described below.

Genetic Information: Inadvertent release of personally identifiable genetic information may pose a possible risk of discrimination or increased difficulty in obtaining certain types of insurance for you and your family members. You should know that a Federal law, called the Genetic Information Nondiscrimination Act (GINA) of 2008, generally

makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

a. Health insurance companies and group health plans may not request your genetic information that we get from this research.

b. Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

c. Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

d. All health insurance companies and group health plans and all employers with 15 or more employees must follow this law as of November 21, 2009. All health insurance companies and group health plans follow this law as of May 21, 2010.

The above-listed protections of GINA do not apply to employers with fewer than 15 employees. GINA's protections in employment do not extend to the US military. Nor does it apply to health insurance through the TRICARE military health system, the Indian Health Service, the Veterans Health Administration, or the Federal Employees Health Benefits Program. Lastly, the law does not cover long term care insurance, life insurance or disability insurance.

***Storage and Sharing of Data**:* When we store your data, we take precautions to protect your information from anyone that should not have access to it; these precautions include the use of double locked cabinets and encrypted, password-protected computers. When we share your data, we will do everything we can to protect your identity. For example, when appropriate, we remove any information that could be used to identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your data.

COVID-19: Although precautions are in place to minimize risk as described below, there remains a possible risk of a COVID-19 infection during study participation.

Other risks/discomforts: There may be other risks to you which are currently unknown.

What precautions and safeguards will be taken to minimize risk and discomfort?

Precautions to minimize the possible risks listed above include asking you questions about your health during this screening visit, monitoring your vital signs during the study, and having you under constant supervision by study staff. All study staff are certified to perform CPR (cardiopulmonary resuscitation). Trained medical support staff

will put in your PVC and obtain blood samples. A licensed medical professional will assess your PVC regularly for complications.

Natural replenishment in part mitigates the risks associated with the amount of blood drawn over the two months. To further mitigate these risks, you will be asked to not donate blood in the eight weeks prior to enrollment in the study or during the study and it is recommended that you do not donate blood in the eight weeks following the study. Subjects weighing less than 140 lbs will be excluded. Your pulse, blood pressure, and hemoglobin levels will be checked prior to the first blood draw on two of the five days with PVC insertions. You will be asked to remain seated after each blood draw.

One or more of the study medical investigators will be in the building or on call throughout the study. One or more research technicians will be with you throughout the study, and assistance for discomfort or distress will be available during any portion of the study. Please report any issue or concern to the technician.

For female subjects of childbearing potential, undergoing PET and MRI scanning and extended sleep restriction, there may be risks to the embryo or fetus that are currently unforeseeable. Therefore, use of birth control is required for study participation. Additionally, pregnancy testing will be conducted during the study to verify that you are not pregnant during your participation. If you become pregnant during the study, you will be withdrawn from study participation.

You will be asked to complete an American College of Radiology approved MRI safety screening form before each MRI scan you have. This screening form is designed to identify any potential risks of exposure to the MRI environment. In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) will be removed before you go into the MRI scan room.

Precautions to minimize the possible risk of a COVID-19 infection follow current WRAIR guidelines. During the study, precautions include but are not limited to use of personal protective equipment, regular hand washing and cleaning of facilities, and monitoring of symptoms. During each transport, personal protective equipment and appropriate COVID-19 related precautions will be used by the drivers and passengers.

The sleep suites are divided into two sides with a shared kitchen. It is possible that a second study could be conducted on the other side of the sleep suites while you are in the laboratory, and that you may see each other while in the kitchen or hallway. Please note, that due to this shared space, your identity may be known to other volunteers if there are concurrent studies. Do not identify another volunteer outside of the Sleep Research Center as a volunteer or disclose the identity of study volunteers to others.

How will my privacy and data confidentiality be protected?

We will take measures to protect your privacy. Even with these measures, we can never fully guarantee your privacy will be protected.

We will try our best to protect your privacy by doing the following:

Your personal identity and confidentiality will be protected throughout the study. Data and results obtained from your participation will never be directly associated with your name, social security number, or other personally identifying information. This includes health-related data collected throughout the study, comprising but not limited to results from the screening visit, and additional drug and pregnancy tests.

To help ensure this, all personally identifiable information will be removed from study files and your lab samples and be replaced with an identification code that consists of numbers and letters. Different codes may be used for you during the course of the study. Only the study investigators, study coordinators, and representatives from certain agencies (described below) will be allowed to know which codes belong to you, and to have access to your study information.

One exception to this is that your data collected at NIH and NICoE may reside in a secure database at NIH and NICoE and may be associated with a profile that contains your personally identifying information.

Your study files will be kept in a safe, secure storage area at WRAIR for the duration of the study. While we will do our best to protect your information there are some cases where we cannot guarantee complete confidentiality.

You may be informed of results or given a referral based upon results of health-related tests, but this information will not be shared with your health care provider or chain-of-command/supervisor. No data will be associated with your name or other personally identifying information. Results of this study may be presented at scientific meetings and/or published in the scientific literature; no personally identifying information of the subjects will ever be presented.

All urine samples and saliva samples collected for drug screening are destroyed within about 7-10 business days of collection. Blood samples collected for the polymorphism test and after the initial screening will be stored indefinitely, for possible use in future analyses for genetic testing and to test for sleep-related biomarkers. You will not be provided with any results from blood analyses.

If we deem it medically advisable, abnormal lab results revealed as part of your screening and/or revealed during your participation in the study will be shared with you, and you will be referred to your personal physician for follow-up.

All video recorded during sleep will only be used to help verify sleep versus wake states. As soon as sleep versus wake has been determined, the video recordings will be destroyed.

The National Institutes of Health has specific criteria for disclosure to participants in which collection or use of identifiable sensitive information is covered under a Certificate of Confidentiality. For the present study, National Institutes of Health investigators were issued a Certificate of Confidentiality from the National Institutes of Health. This Certificate stipulates that researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or

local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use.

Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation which is funding this project. You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

We may report some clinical or laboratory results to authorities, to prevent serious harm of yourself or others.

- For volunteers who are in the military, it may be required to report some information bearing on your health – e.g. suicidal or homicidal behavior - to appropriate medical or command authorities.
- Representatives from the following agencies may have access to review research records as part of their responsibility to protect humans in research and oversee the quality of the research efforts. As government agencies, they must also maintain confidentiality of your records within the limits of the law.
- The Study Sponsor, Center for Military Psychiatry and Neuroscience, WRAIR
- The WRAIR Institutional Review Board (IRB)
- U.S. Army Medical Research and Development Command (USAMRDC)
- National Institutes of Health (NIH)
- Office for Human Research Protections (OHRP)
- Office of Research Integrity (ORI)

In order to obtain access to the NIH campus, NIH Police may require your name and date of birth prior to your initial visit for a security check. After the initial visit, they may need your name in order to grant access to the campus and facilities.

Please remember that even though we are doing our best to protect your information, we can never fully guarantee confidentiality of all study information.

What are the possible benefits from this research?

Participation in this study will provide no direct benefit to you, but the information we gain may help us provide ways to prevent performance and alertness deficits, and thus improve the safety and well-being, of soldiers. This study may also help us identify better treatment for soldiers who face sleep disturbances such as extended sleep restriction.

Will I be paid to take part in this research study?

Yes, for your participation you will receive reimbursement according to the following schedule:

TABLE 1

PHASE	NON-COMPLIANCE COMPLETION	FULLY SUCCESSFUL COMPLETION
Initial Screening Visit	$50.00	$50.00
Enrollment Visit	$100.00	$100.00
Phases 1 – At-home actigraphy (10-15 days)	$5/day x 10-15 days = $50-$75	$10.00/day x 10-15 days = $100.00-$150.00
Phase 1 – At-home PVT Testing (10-15 days) (min 4/day and max 6/day)	$5/at-home PVT (min 4/day and max 6/day) = $0 $360	$20.00-$30.00/day x 10-15 days =$200.00-$450.00
Phases 2 In-laboratory hours (baseline, restriction, acute recovery) = 15 days (14 full days, 2 half days) = 360 hours	$16.00/hour	$16.00/hr x 360 hrs = $5,760.00
Phase 3 – At-home actigraphy (22 days)	$5/day x 20 days = $100	Phase 3: $10.00/day x 20 days = $200.00

Phases 3 – At-home PVT testing (20 days) (min 4/day and max 6/day)	$5/at-home PVT (min 4/day and max 6/day) = $0-$480	$20.00-$30.00/day x 20 days =$400.00-$600.00
Phases 4 – In-laboratory hours (extended recovery) = 4 days (3 full days,2 half days) = 96 hours	$16.00/hour	$16.00/hr x 96 hrs = $1,536.00
Performance Bonus	$0.00 to $1,000.00 Phases 2 and 4	$0.0 to $2,000.00 Phases 2 and 4
***TOTAL:**	$50.00 to $8,210.00	$8,346.00 to $10,846.00

You are compensated $50 for the screening evaluation (today's visit). If you successfully complete all required activities from the remainder of the study and follow all restrictions outlined in this consent form or given to you by the study staff, your compensation will be between $8,346 and $10,846, depending on how many performance tests you complete at home during the initial 2 weeks of the study, and depending on whether you earn the $2,000.00 performance bonus.

However, if you withdraw (drop out) from the study once it has begun, or are withdrawn by the investigator once it has begun because you did not follow study procedures, your recorded sleep times during Days 1-16 (the initial at-home monitoring phase) or Day 31-51 (the second at-home monitoring phase) differ greatly from what you reported during screening, and/or you withheld any kind of information, based on your time in the study, you will be compensated $100.00 for the Day 1 Enrollment Visit, $5.00/day per actigraphy at-home, and $16.00 per hour during the in-lab portion. If you are withdrawn by the Investigator from the study due to health concerns or due to difficulty drawing blood, you will be compensated based on the amount of time you participated in the study, but you will not be eligible for the bonus.

Back-ups: Study sessions may be scheduled with up to one extra volunteer. "Back-up" volunteers would enroll (in-lab) and complete Phase 1 (at-home) concurrently with another volunteer. If scheduled as a "back-up" volunteer, you would then be scheduled to come in for Phase 2. If needed, you would continue with Phase 2. Otherwise, if the back-up volunteer is asked to reschedule, your study participation would be put on pause until study activities are resume. You would be compensated for Phase 1 participation as well as $50 if you have to come into the lab prepared to participate in Phase 2. Volunteers may serve as "back-ups" multiple times until they participate.

Participation following Phase 4: In the rare instance that it is not possible to conduct a PET scan during Phase 4, you may have the option to return within 14 days of the conclusion of the study to complete the PET scan. This depends on your availability as well as the availability of staff and the imaging facility. In this occurs, a wrist-actigraph would be worn until the scan can be conducted. A pregnancy test would be completed

(if female) along with tests for drugs, alcohol, and nicotine upon reporting to the lab. You would be compensated an additional $300 for the scan and $10/night for actigraphy.

Additionally, if you are military or a federal employee, you will also receive a document entitled, “Information Sheet Regarding Compensation to Federal Personnel When They Participate in Research as Human Subjects,” which explains that federal personnel can only be compensated for a maximum of $50 per blood draw if they are not on leave during study participation. This document informs you that all military and federal personnel participating as research subjects must be on leave or off-duty during the screening, enrollment, and in-laboratory phases to receive full compensation for participation in those phases.

Please note, if you receive more than $600 for your participation in the study, you will be required to report your compensation as income to the IRS via a Form 1099.

Other than medical care that may be provided and any other payment specifically stated in this informed consent, there is no other compensation available for your participation in this research study; however, you should also understand that this is not a waiver or release of your legal rights.

Are there costs for participating in the research?

No, there are no costs to you for taking part in this research study.

Are there disclosures of financial interests or other personal arrangements from the research team?

Neither WRAIR nor or any research team member or members of their immediate families have any financial interests or personal arrangements with sponsors, funding sources, manufacturers of biologic or medical supplies, or storage banks where any study specimens could be subsequently sent.

What happens if I am injured as a result of this research?

If you are injured because of your participation in this research and you are a Department of Defense (DoD) healthcare beneficiary (e.g. active duty in the military, military spouse or dependent, retiree), you are entitled to medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are entitled to medical care for your injury at an Army hospital or clinic; medical care charges for care at an Army hospital or clinic will be waived for your research-related injury. You are also entitled to care for your injury at other DoD (non-Army) hospitals, but such care for your injury at other DoD (non-Army) hospitals or clinics may be time-limited, and your insurance may be billed. It cannot be determined in advance which Army or DoD hospital or clinic will provide care. If you obtain care for research-related injuries outside of an Army or DoD hospital or clinic, you or your insurance will be responsible for medical expenses.

Transportation to and from hospitals or clinics other than the NIH Clinical Center and NICoE will not be provided. No reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights.

If you believe that you have sustained a research-related injury, please contact the PI COL Vincent F. Capaldi, II, M.D. (Email: vincent.f.capaldi.mil@health.mil. Phone: 301-319-9098) or Samantha M. Riedy, Ph.D (Email: samantha.m.riedy.civ@health.mil. Phone: 301-337-1323).

What happens if I withdraw from this research?

You are always free to withdraw from the study at any time without prejudice or loss of benefits to which you are otherwise entitled. You are not required to disclose a reason for your decision. Leaving the study will not impact your ability to receive care or any other benefits that you would have received otherwise.

If you withdraw from the study, data and specimens that were already collected may be retained.

If you withdraw yourself from the study, you will receive pro-rated adjusted compensation at the base rate as indicated in the table above.

Please note that withdrawing your consent to participate in this research does not fully revoke your HIPAA (Health Insurance Portability and Accountability Act) Authorization Form to use/disclose your protected health information. To make that revocation, please send a letter to the principal investigator as discussed in the HIPAA Authorization Form.

The principal investigators, COL Vincent F. Capaldi, II, M.D. and Samantha M. Riedy, Ph.D. may decide not to allow you to continue participating in this study under the following conditions:

- If you develop health conditions that would make it dangerous to you or others if you were to continue participating
- If other situations or conditions arise that would make participation harmful to your own health, or compromises the safety of other volunteers or study staff members, and/or compromises the integrity of study data.
- If your ability to provide continued consent to study procedures has been compromised.
- If you fail to comply with the procedures as outlined in this form.
- If you become pregnant during the study, you will be withdrawn from the

study and followed for safety.

Failing to comply with all study procedures includes (but is not limited to) things such as: you took prohibited substances (alcohol, nicotine, etc.), you did not follow study procedures, or you withheld or falsified any kind of information (for example, failed to disclose a medical condition or actual recorded sleep varied significantly from reported sleep during screening process). If your participation is terminated due to non-compliance, you will receive pro-rated adjusted compensation at the base rate as indicated in the above table.

You could be terminated (removed) from the study should you become incarcerated during Phases 1 or 3.

You could also be terminated from the study at any time without your consent for any technical difficulties, e.g. a problem obtaining blood specimens. In rare circumstances, your participation may be terminated without your consent if unplanned conditions occur (for example, loss of electrical power or water to the building, hazardous weather conditions, etc.).

If this happens and you have otherwise successfully completed the study up to the point of termination, you will receive pro-rated adjusted compensation at the fully-complete rate. If this happens and you have not otherwise successfully completed the study up to the point of termination, you will receive pro-rated adjusted compensation at the base rate indicated in the above table.

If your participation is stopped before the end of the study (either by you or by us), during the period of extended sleep restriction and recovery, you will be asked (and encouraged) to remain in the WRAIR Sleep Research Center so that you can obtain recovery sleep and be evaluated and cleared for release by an appropriately licensed Investigator. Due to the potential cognitive and behavioral effects of sleep loss, it is unsafe for you to leave the laboratory until you have obtained sufficient recovery sleep.

If you wish to withdraw from the study against medical advice (AMA), a study staff member will request that you speak to, and are evaluated by, an appropriately licensed medical investigator, who will explain the risks to you and will recommend a course of action for your safety.

Who can I contact if I have questions about my rights as a research participant?

If you have questions about your rights as a research volunteer in this study, you may contact the Human Subjects Protection Branch, Walter Reed Army Institute of Research 503 Robert Grant Avenue, Silver Spring, MD 20910, phone number 301-319-9940 and email usarmy.detrick.medcom-wrair.mbx.hspb@health.mil.

To summarize:

Taking part in this research study is your decision. Your participation in this study is voluntary. You do not have to take part in this study, but if you do, you can stop at any

time. You have the right to choose not to participate in any study activity or completely withdraw from continued participation at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If there is any portion of this document that you do not understand, ask the investigator before signing the form. Signing this form means that you consent to participate in this research, at this time.

A signed and dated copy of this document will be given to you.

SIGNATURE OF PARTICIPANT

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Permanent Address of Participant

****

SIGNATURE OF INDIVIDUAL ADMINISTERING CONSENT
(Can only be signed by an investigator or staff approved to administer consent)

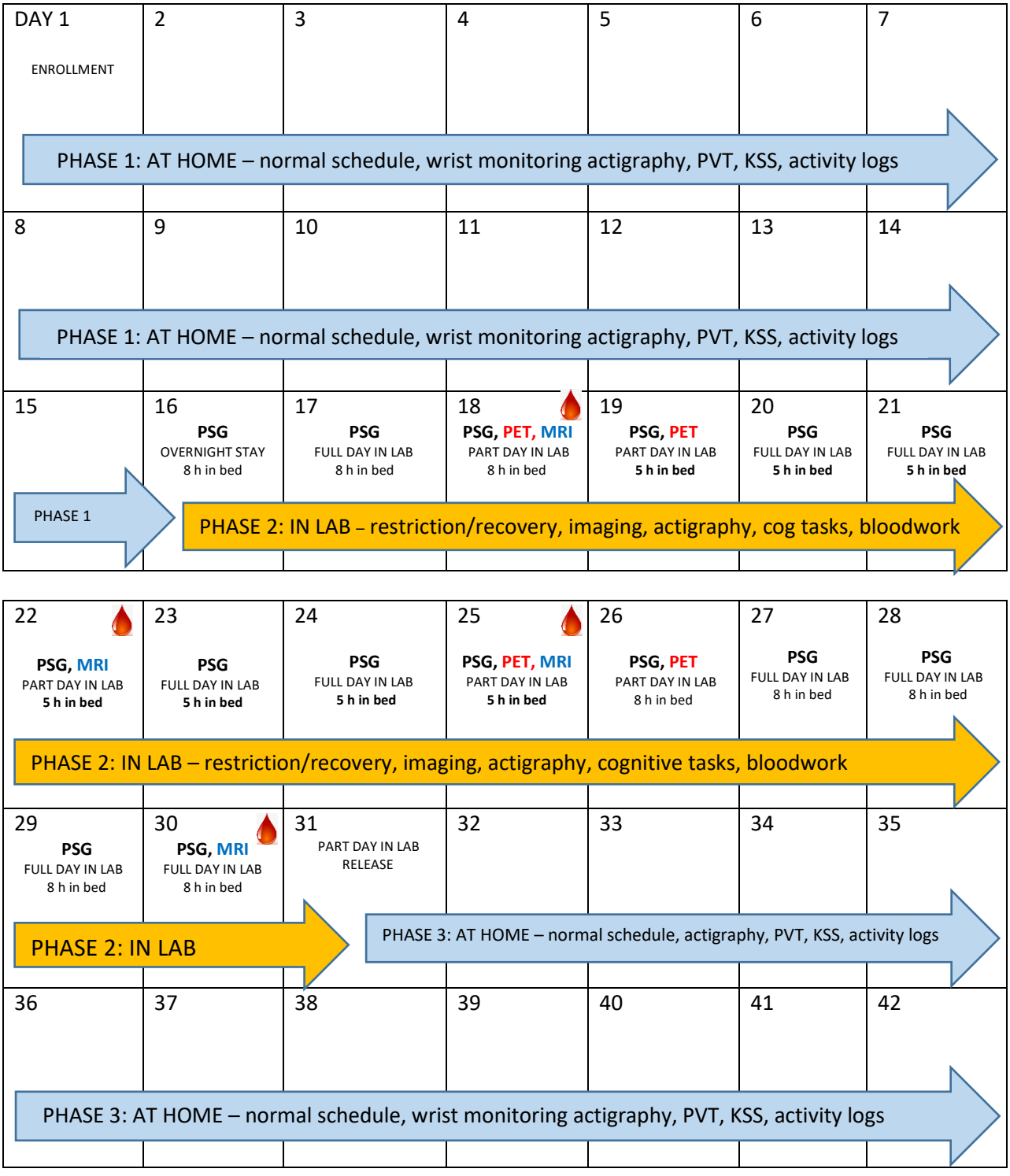
_____
Printed Name of Administering Individual

_____ _____
Signature of Administering Individual Date

Quality Control conducted by _____ on _____.
Name Date

_____
Signature

FIGURE 1


DAY 1
ENROLLMENT
2
3
4
5
6
7
PHASE 1: AT HOME – normal schedule, wrist monitoring actigraphy, PVT, KSS, activity logs
8
9
10
11
12
13
14
PHASE 1: AT HOME – normal schedule, wrist monitoring actigraphy, PVT, KSS, activity logs
15
16
PSG
OVERNIGHT STAY
8 h in bed
17
PSG
FULL DAY IN LAB
8 h in bed
18
PSG, PET, MRI
PART DAY IN LAB
8 h in bed
19
PSG, PET
PART DAY IN LAB
5 h in bed
20
PSG
FULL DAY IN LAB
5 h in bed
21
PSG
FULL DAY IN LAB
5 h in bed
PHASE 1
PHASE 2: IN LAB – restriction/recovery, imaging, actigraphy, cog tasks, bloodwork
22
PSG, MRI
PART DAY IN LAB
5 h in bed
23
PSG
FULL DAY IN LAB
5 h in bed
24
PSG
FULL DAY IN LAB
5 h in bed
25
PSG, PET, MRI
PART DAY IN LAB
5 h in bed
26
PSG, PET
PART DAY IN LAB
8 h in bed
27
PSG
FULL DAY IN LAB
8 h in bed
28
PSG
FULL DAY IN LAB
8 h in bed
PHASE 2: IN LAB – restriction/recovery, imaging, actigraphy, cognitive tasks, bloodwork
29
PSG
FULL DAY IN LAB
8 h in bed
30
PSG, MRI
FULL DAY IN LAB
8 h in bed
31
PART DAY IN LAB
RELEASE
32
33
34
35
PHASE 2: IN LAB
PHASE 3: AT HOME – normal schedule, actigraphy, PVT, KSS, activity logs
36
37
38
39
40
41
42
PHASE 3: AT HOME – normal schedule, wrist monitoring actigraphy, PVT, KSS, activity logs

43	44	45	46	47	48	49
50	51 **PSG** OVERNIGHT STAY 8 h in bed	52 **PSG** FULL DAY IN LAB 8 h in bed	53 **PSG, PET, MRI** PART DAY IN LAB 8 h in bed	54 **PSG, PET** PART DAY IN LAB 8 h in bed	55 RELEASE	

PHASE 3: AT HOME – normal schedule, wrist monitoring actigraphy, PVT, KSS, activity logs

PHASE 3: AT HOME

PHASE 4: IN LAB - post recovery imaging, bloods, cog tests