Morpheus - Manipulating and Optimizing Brain Rhythms for Enhancement of Sleep

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Study Title: Manipulating and Optimizing Brain Rhythms for Enhancement of Sleep

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Protocol Date and Version	Major Changes
08 Jul 2020 (Version-2)	Original protocol submitted to IRB
17 Aug 2020 (Version-3)	IRB Modification-02 (IRB Approved 08 Sep 2020) The modification includes: Addition of Dr. Bryan Klassen's curriculum vitae to the DoD portion of the IRB application. The Reviewer determined the modification(s) pose no more than minimal risk to subjects.
27 Jan 2021 (Version-4)	IRB Modification-04 (IRB Approved 10 Feb 2021) The modification includes: 1) editorial changes and 2) editorial clarification that data will be used to support an IDE submission. The Reviewer noted the revised protocol version 4 dated January 27, 2021reflecting the modification. The modification constitutes a

	minor change to previously approved research, and therefore was eligible for expedited review in accordance with 45CFR46.110(b)(2), 21CFR56.110(b)(2) & 32 CFR 219.110(b)(2). The Reviewer determined the modification(s) pose no more than minimal risk to subjects.
22 Jun 2021 (Version-5)	IRB Modification-08 (IRB Approved

The authors declare no conflicts of interest.

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1. KEY CONTACTS

Principal Investigator	Greg Worrell MD, PhD
Funder(s)	Names and contact details of all the organisations providing funding and /or support in kind for this study). United States Army Medical Research and Development Command (USAMRDC) [redacted]
Statistician	Full contact details including phone, email and fax numbers

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2. LAY SUMMARY

Treatment of sleep disturbances is mainly attempted through behavioral modifications or drug administration. However, behavioral approaches may fail, and certain drugs are associated with unwanted side effects or residual effects upon awakening (e.g. sleepiness, ataxia) which can increase the risks of falls and fractures. In addition, there can be systemic consequences of long-term medication use. An alternative method of manipulating sleep is by electrically stimulating the brain to directly influence the brain circuits underlying behavioural state. To date, there have been mixed results from stimulating superficial areas of the brain and, as far as we know, there has been no systematic attempt to influence deep brain activity using deep brain stimulation.

Many patients suffering from neurological diseases, such as Parkinson's Disease (PD), Multiple Systems Atrophy (MSA), Essential Tremor, Chronic Pain, and Epilepsy also have disrupted sleep. Currently, at stages where drug treatment do not offer adequate control of their primary neurological symptoms, these patients are implanted with a deep brain stimulation (DBS) system. This involves depth electrodes implanted into specific brain locations to deliver electrical stimulation to the targeted area..

The aim of this feasibility study is to investigate whether we can improve sleep quality in patients who have DBS devices implanted for existing neurological indications by delivering targeted stimulation patterns during specific stages of sleep using their existing DBS device. We will only use electrical stimulation frequencies that have been proven to be safe for patients. We will perform these studies in patients admitted to the hospital in order to examine the structure and quality of sleep as well as how alert patients are when they wake up, while also monitoring physiological markers such as brainwave activity, heart rate and blood pressure. Upon awakening, we will ask the patients to provide their subjective opinion of their sleep and complete some simple tests to see how alert they are compared to a night of no electrical stimulation.

We hope that our study will open new ways of optimizing sleep in patients with neurological disease who are implanted with DBS devices. We also believe that our findings will broaden the understanding of how the activity of deep brain areas influences sleep and alertness.

3. SYNOPSIS

Study Title	Manipulating and Optimising Brain Rhythms for Enhancement of Sleep		
Sponsor	Mayo Clinic		
Funder	United States Army Medical Research and Development Command (USAMRDC) [redacted]		
Study Design	Feasibility study		
Study Participants	Patients with existing DBS systems implanted for their neurological disease, e.g. Parkinson's, pain and epilepsy.		
Sample Size	Aim to enroll up to n = 15 patients in total The minimum acceptable number per primary target area of interest is n=3 to investigate the presence of an effect. We will start at n=15 of cases of interest. Overall, we expect to recruit 30-50 participants over duration of the study.		
Planned Study Period	Total length of the project: 07/09/2020 to 11/03/2030 (archiving of the study) Duration of an individual participant's involvement: two study visits in the hospital each composed of two nights. Patients will be either screened/consented following scheduled clinic visits or at a separate visit arranged for their convenience. Follow up will be through routine care.		
Recruitment period	07/09/2020 to 07/03/2022		
Objectives	Feasibility of study	Outcome Measures	Timepoint(s)
Primary	Effect of electrical stimulation on sleep stages	Recruit participants and carry out scheduled experiments in reproducible fashion	• Analysis completion at study end • Interim group analysis
Secondary	Effect of stimulation on sleep inertia Controlling sleep depth and sleep-wake transitions	EEG changes (frequency, patterns and sleep structure)	• During stimulation • Post-stimulation for specific sleep stages

Tertiary	Effect of stimulation on other measures of arousal	Performance on short and long test battery (see section 9.6.3) Effect on sleep and REM latencies, sleep cycles, sleep stage duration, number of awakenings, sleep efficiency	• On awakening (post-baseline night and post-intervention) • During day (post-baseline &intervention) • During intervention nights
Interventions	Open and closed-loop electrical modulation triggered and based on ongoing sleep staging by researcher as well as automated closed-loop algorithm for stimulation.	Effect on autonomic measures such as heart-rate variability and blood pressure, as well as salivary cortisol levels	• On awakening (post-baseline night and post-intervention) • During day (post-baseline & intervention) • Salivary cortisol levels measured on awakening each day 6am).
Comparator	Within-subject: their usual stimulation settings (stimulation at high/low frequency, as per established practice) Between-subject: different nuclei (stimulation sites)		

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4. ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AMG	Amygdala
ANT	Anterior Nucleus of Thalamus
CL	Centro lateral Nucleus of Thalamus
CMT	Centro median Nucleus of Thalamus
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance
DBS	Deep Brain Stimulation
DHRPO	Department of Defence Human Research Protection Official (U.S.)
DoD	Department of Defense (U.S.)
EMG	Electro-myogram
EOG	Electro-oculogram
GCP	Good Clinical Practice
GPi	Globus Pallidus Interna
HF	High-Frequency
HIP	Hippocampus
HRPO	Human Research Protection Officer
ICF	Informed Consent Form
IRB	Institutional Review Board
KSS	Karolinska Sleepiness Scale
LF	Low-Frequency
MSA	Multiple Systems Atrophy
MTLE	Medial Temporal Lobe Epilepsy
NREM	Non-Rapid Eye Movement Sleep
N1	Stage 1 of NREM
N2	Stage 2 of NREM
N3	Stage 3 of NREM
REM	Rapid Eye Movement Sleep
PAG/PVG	Periaqueductal Grey/Periventricular Grey matter
PD	Parkinson's Disease

PPN	Pedunculopontine nucleus
PI	Principal Investigator
SOP	Standard Operating Procedure
Stim	Stimulation
STN	Subthalamic Nucleus
USAMRDC	U.S. Army Medical Research and Development Command

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5. BACKGROUND AND RATIONALE

Sleep disturbances such as insomnia, whose worldwide prevalence is approximately 35%, pose a heavy burden on communities by affecting quality of life through reduced sleep quality, disturbed diurnal functioning, as well as a bidirectional interaction with other diseases (reviewed in Morin et al 2015). Neurological disease in particular has a high association with sleep comorbidities. Movement disorders, apart from their well-known motor sequelae, are often accompanied by poor sleep quality and architecture. Notably, prevalence of sleep disturbances in Parkinson's Disease (PD) varies from 40 to 98% (Dhawan et al 2006), while both drug-naïve patients and those receiving treatment exhibit a decrease in delta oscillatory power compared to age-matched controls (Brunner et al 2002). Similarly, epilepsy has a bi-directional relationship with sleep (Bazil et al. 2017; Manni R, et al. 2010) and possibly a mechanistic role in epileptogenesis (Bower et al 2015 & 2017).

Currently, DBS is a treatment option for patients with movement disorders and epilepsy that show poor response to drug therapies. Patients are able to titrate the amplitude of stimulation under guidance, to help control disease symptoms. However, these stimulation parameters are constant (do not vary according to wake/sleep cycles or intrinsic brain activity), while the applied stimulation parameters are largely tailored based on disease symptom response only. Indeed, DBS targets a variety of regulatory networks with an involvement in sleep maintenance and regulation (including thalamo-cortical, basal ganglia, and connectivity to brain stem regions), the specific networks depending on disease state and mechanism of therapy (e.g. Sharma et al 2018). Thus, whether and how we can harness DBS for treatment of sleep disturbances is a question that remains largely unexplored.

In this study, we will investigate the feasibility of targeting DBS to modify sleep in patients with a range of brain areas implanted. The patients will have already been implanted with a DBS device for approved clinical indications, e.g. PD and epilepsy. We will aim to tailor the stimulation parameters according to available evidence (by changing the frequency and/or off periods according to sleep stage), in a way that optimizes sleep. More specifically, we wish to determine if amplitudes and frequencies of electrical stimulation that are clinically available to our patients might be beneficial for sleep induction and maintenance, or in fact disrupt sleep quality. Furthermore, we wish to minimize sleep inertia (the period of reduced alertness and performance capability upon awakening), ease sleep-wake transitions as well as control sleep depth. The population of the study will be patients with PD, other movement disorders, pain and epilepsy patients who have a DBS device already implanted.

We plan on recruiting patients with DBS leads in six primary targets of interest: STN, ANT, CMT, CL, HIP, AMYG. There are indications from previous findings (basic science/animal studies as well as some involving human participants) that these brain sites play roles in sleep modulation (summarized in table 1 below). These participants will be chronically implanted and thus not naïve to the effects of stimulation, but will have an established sleep pattern that has been influenced by their clinical programming. First, we will record baseline brain activity during sleep overnight and we will afterwards proceed to apply different stimulation patterns (low vs. high frequency) during different sleep stages. This will allow us both within-subject comparisons as well as greater efficacy and familiarity with individual sleep patterns.

There are no known risks of tailoring the stimulation frequency to sleep stage. Regarding the potential risks, the biggest risk would be provocation of an epileptic seizure by the electrical stimulation. This risk will be minimized by using previously established safe stimulation parameters determined by the clinicians caring for the patient. Other risks include possible disruption of sleep architecture and/or arousal during the first attempt to optimize the parameters. However, in this event, these settings would not be used further, and may help establish an algorithm for optimal sleep depth and appropriate arousal times. All frequencies and amplitudes that we plan to use in this study are already available on devices and clinical programmers, therefore ensuring patient safety. We will not use novel frequencies that have not been clinically tested. In participants with epilepsy we will avoid stimulation of epileptogenic foci to avoid seizure induction. In participants with chronic pain, we will test stimulation parameters while the patient is awake, to ensure good levels of pain relief and tolerability of the protocol.

With regards to the potential benefits, improving sleep depth and architecture through stimulation could lead to physical, psychological and cognitive benefits in our target clinical populations. The most immediately obvious benefits may be a reduction in sleep inertia, with better cognitive functioning after waking up from sleep. However, better sleep quality has also been associated with working memory improvements in older adults (Ellenbogen, 2005).

Target Area	Disease	Role in Sleep (if known)
AMG	Epilepsy	Consolidation of emotional memory. Possible relevance for PTSD (Van Der Helm et al. 2011)
ANT	Epilepsy	HF can disrupt sleep cycles (Voges et al. 2015)
CL	Epilepsy	Control of arousal. HF stimulation facilitates arousal from N3 (Redinbaugh et al 2020)
CMT	Epilepsy	CMT neurons can modulate brain-wide cortical activity during sleep and provides dual control of sleep-wake states (Gent et al. 2018)
Cortical	Epilepsy & Pain	Steriade (1997), McCormick & Bal (1997)
HIP	Epilepsy	Critical role in memory consolidation during slow-wave sleep
Other Potential Areas		
GPi	Dystonia & PD	HF Arousal from anesthesia (Moll et al. 2009)
HYP	Cluster HA	Control of sleep and arousal. (Saper et al. 2001)

Target Area	Disease	Role in Sleep (if known)
PAG/PVG	Pain	
PPN	PD & MSA	HF stimulation increased REM (Moro et al 2009)
STN	PD	HF stimulation improves sleep quality (Baumann-Vogel et al. 2017)

Table 1: Target brain areas of interest, neurological condition of participant group and roles in sleep modulation if known.

In addition to the patients with FDA approved DBS devices we will also analyze previously collected data from patients implanted with an investigational RC+S Summit device. The sleep and wake data from these patients was previously collected as part of an ongoing FDA-IDE G180224. The analysis of these previously collected data will focus on how low and high frequency stimulation impacts sleep electrophysiology. The analysis of the RC+S data will be included in the FDA-IDE G180224 yearly submissions.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of outcome measure
Primary Objectives Feasibility of study	Ability to recruit planned participant number and carry out scheduled experiments in reproducible fashion	• Analyses post-study completion • Some evidence during interim analyses per group
Effect of stimulation on sleep stages	EEG changes (frequency changes, changes in EEG patterns and sleep structure)	• During stimulation • Post-stimulation at specific sleep stages

Secondary Objectives Effect of stimulation on sleep inertia and vigilance & performance during the day Controlling sleep depth and sleep-wake transitions	Performance on short and long test battery (see section 9.6.3) Assessment of effect on latency to sleep onset and REM sleep, number of sleep cycles, duration of sleep stages, number of awakenings per night, sleep efficiency	• Upon awakening (post-baseline night and post-intervention) • During the day (post-baseline and intervention) • During intervention nights
Tertiary Objectives Effect of stimulation on other measures of arousal	Effect on autonomic measures such as heart-rate variability and blood pressure, as well as salivary cortisol levels	• Overnight measurements • Salivary cortisol levels measured upon awakening each day (6am).

7. STUDY DESIGN

This is a feasibility study that will take place in Mayo Clinic Rochester, MN. A parallel study will also be conducted at a UK site (Oxford University, UK) and University of California San Francisco (UCSF) under the same funding but this will be reviewed by their local IRB. Anonymized data will be shared between sites for analyses purposes.

Participants will be identified during their routine clinic visits and care and invited to participate in the study. Screening of interested potential participants will take into account pre-operative assessment data.

Testing will ensue (within a variable period from screening, but within the study timeline), over two visits to the epilepsy monitoring unit in Saint Marys Hospital (SMH), each consisting of two nights. Baseline sleep recordings will be obtained over the first night of the first visit, with the remaining nights consisting of stimulation trials. Questionnaires, daytime vigilance testing, autonomic parameters and cortisol levels will be collected as described in the sections to follow. No long-term follow-up is planned at this stage.

With regards to data collection processes, our population of patients have already been implanted with a DBS system (such as an FDA approved Medtronic Activa PC, Boston Scientific Vercise, Abbot Infinity systems). In addition, we will analyze data previously collected from patients with the RC+S Summit System under FDA-IDE G180224. The analysis of the RC+S data will be included in the FDA-IDE G180224 yearly submissions.

Note: A parallel study DBS devices currently under IDE investigations (such as Medtronic RC+S devices) will be pursued separately. Inclusion of patients with investigational devices under FDA investigational device exemptions will require prior approval from FDA.

We will leverage rules from the current AASM guidelines, technologies and methods for manual and automated sleep scoring using standard scalp polysomnography as well as novel methods we previously developed for sleep scoring using intracranial electrophysiology.

For perturbations, we will use the FDA approved clinician programmer and patient programmer. In this study, we specify as high frequency (HF) a stimulation range from 40 Hz to 250 Hz, while low frequency (LF) will be defined as 2 Hz to 40 Hz. All perturbations will be within the clinical range used and approved for DBS patients.

We will use a combination of subjective and objective measurements of sleep quality and efficiency to measure the impact of any sleep perturbations. The following objective metrics will be derived from visual/manual polysomnography (gold standard) & automated algorithm sleep staging:

1. Total sleep time.
2. Number of sleep cycles (switches of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep).
3. Initial sleep and REM latencies (Time from beginning of study to the first stage of sleep, and from beginning of sleep to first REM sleep onset).
4. Duration of N1, N2, N3, and REM stages, and the duration of NREM (sum of N1,N2,N3)stages.
5. Sleep efficiency (100*total sleep time/time in bed).
6. Number of awakenings during night, including arousals per hour and duration of time spent awake after initial sleep onset (i.e., wake after sleep onset time)
7. Apnea-hypopnea and respiratory disturbance indices (the frequency of stop or reduced breathing episodes, and respiratory arousals per hour)
8. Periodic limb movement indices (the frequency of periodic leg movements of sleep per hour)
9. Measures of arousal during sleep
    a. behavioural macrostate observations such as eye opening or blinking that can be assessed in video recordings

b. microarousal observations defined exclusively by cortical fast frequency shifts (ie, >14 Hz rhythms) lasting 3 seconds or longer, with or without added autonomic measures of tachycardia.

c. Spectral composition of the sleep stage specific EEG over the 0.25-32 Hz frequency range

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10. Salivary samples to characterize awakening levels of cortisol will be obtained in the morning (~6AM) at the end of each night.

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12. Questionnaires will be administered to patients as per the list below:

- Upon enrollment/prior to their visit:

- The following questionnaires or tasks will be administered to or completed by both the Epilepsy and Parkinson's disease Cohort at specified time points (see schedule of events)

1. Neurological Exam & Mini-Mental State Examination (MMSE).

2. Current medications and medication history. Medications will be kept stable

3. Mood assessment with Beck Inventory for Anxiety and Depression

4. Quality of life evaluation (QOLIE-31) questionnaire.

5. Patient sleep diary (bedtime, awakening time, arousals/sleep disturbances, perceived sleep quality).

6. Karolinska Sleepiness Scale (KSS) (Akerstedt and Gillberg, 1990).

7. Profile of Mood States Scale (POMS) (McNair, Lorr and Doppleman, 1971)

8. Psychomotor Vigilance Task (PVT) (as in Santhi et al. 2013

9. Karolinska Drowsiness Test (KDT) (Akerstedt and Gillbert, 1990)

These questionnaires are specific to the Epilepsy Cohort only:

10. Liverpool Seizure Severity Scale and Seizure Severity Questionnaire (LSSS).

11. Seizure Severity Questionnaire (SSS).

12. Mayo Epilepsy Short Assessment.

13. These questionnaires are specific to the Parkinson's disease Cohort only:Movement Disorder Society Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al 2008).

14. Parkinson's Disease Sleep Scale (PDSS) (Trenkwalder et al. 2011). This will be completed by the Parkinson's Disease Cohort only. Tasks and questionnaires are described in more detail in section 9.6.3.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Patients suitable for this study will be identified by either the clinical and research teams. Suitable candidates will be reviewed with the clinicians responsible for the clinical care of the patients. The participants will be allowed to exit the study at any point without any changes to their routine medical care. The initial assessment will be carried out by the research team working with the patient's primary neurologist.

8.2. Inclusion Criteria

- DBS in one of the defined nuclei of interest during the period of the study
- Male or female, aged 18 years and above
- Be willing and able to give written and oral informed consent
- Ability to complete all required study procedures including travelling to Mayo Clinic and staying overnight
- All women of childbearing potential and women who have been amenorrheic for less than 1 year must practice effective contraception during the study. This includes a barrier method such as condom or diaphragm with spermicide; barrier intrauterine device (IUD) or abstinence.

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Cognitive impairment (judged by the clinician taking consent as not having sufficient mental capacity to understand the study and its requirements). This is including anyone who, in the opinion of the clinician taking consent is unlikely to retain sufficient mental capacity for the duration of their involvement in the study.
- Patients with any other medical condition that would interfere with study conduct or make it unsafe for them to participate

9. PROTOCOL PROCEDURES

9.1. Recruitment

Potential participants will be identified by the clinical and research team as suitable candidates. Recruitment will take place in outpatient or pre-operative assessment clinic, as well as during assessment for suitability for DBS surgery. They will first be approached by the clinical team and if they indicate that they are interested in taking part, will then be approached by a researcher.

9.2. Visit-1 Screening and Eligibility Assessment

Screening and eligibility will be assessed during the patients' clinic visit schedule or with a telephone interview. They will therefore have already had a detailed medical and drug history as per inclusion/exclusion criteria to this study, and this information will be available to their clinician

(recruiting for the study). If a potential participant is interested and agrees to further screening (to exclude medical conditions making participation unsafe, as per listed exclusion criteria), this will be documented in the patient's notes (relevant to the clinic visit) by the recruiting clinician.

The patient will be provided with all relevant study information and resources (such as the consent form and patient information sheet). They will be offered the choice of being screened after a future scheduled clinic visit, or at a separate visit solely for study purposes. This will ensure optimal comfort and minimal travel time.

Prior to any screening assessments we will obtain written consent. Upon screening, they will be asked for any changes/updates on their medication schedule or if any other conditions have developed. In addition, physical examination (at point of entry, in addition to the prior one as per pre-operative protocol) will ensure participant fitness for participation.

There will be no exceptions made regarding eligibility, i.e. each participant must satisfy all the approved inclusion and exclusion criteria of the protocol. Changes to the approved inclusion and exclusion may be made by substantial amendment only. We do not anticipate rescreening excluded potential participants.

9.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information (at least 24 hrs.), and the opportunity to question the PI, research team, or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorized to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

9.4. Enrollment

Patients enrolling in the study will be recorded in an encrypted study database on a password-protected Mayo Clinic computer. The team will identify patients who have been previously implanted with a DBS device and a contact call will be scheduled after liaison between the clinical team. During this, visit times and traveling arrangements will be discussed.

9.5. Blinding and code-breaking

There will be no blinding in the study and therefore no code-breaking procedure is required.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

9.6.1.Description of study intervention(s)

We will use both an open and a closed-loop approach to investigate sleep perturbations through stimulation deep brain targets. As previously mentioned, FDA approved clinician or patient programmers specific to the implanted device will be used at the open-loop stage, to explore the effect of available stimulation patterns when they are synchronized with different sleep stages. A physician/sleep technician team will be overseeing the delivery of stimuli during real-time sleep scoring on testing nights. See Appendix A. for example stimulation paradigms

9.6.2.Description of comparator(s)

We will use both within- and between-subject comparators. As within-subject comparators, these will primarily be the usual patient settings of low frequency (LF) or high frequency (HF) continuous stimulation (ON) at the clinically prescribed amplitude and frequency. Therefore, we will be able to make assumptions both about these settings (beneficial/disruptive) and the intervention, with regards to effects on EEG patterns, autonomic activity, behavioural measures etc. In addition, since we will be applying a number of exploratory patterns per night (according to sleep stage), each of these will be used as a comparator to others. Where electrical stimulation will be switched off (OFF), this will be compared to individual stimulation configurations as well as all (ON) states. Where comparable stimulation patterns will be used in different patient groups (e.g. HF stimulation during NREMS2 in both HC and ANT), these will serve as between-subject comparators. In addition, given the exploratory nature of this study, the responses of different participants to the same stimulation pattern will be compared (e.g. effects on sleep stages/EEG rhythms of stimulation during REM, between patients with hippocampal electrodes).

9.6.3.Description of study procedure(s)

1. Smart Watch (Empatica https://www.empatica.com/research/e4/)

After consent, on the patient's initial visit, the patient will be provided and instructed in the use of the Empatica E4 watch. The purpose of the watch will be to track various bio signals in the outpatient environment. These signals will be used to assess how the patient is sleeping prior to the admissions to the hospital for the overnight polysomnography studies.

2. Questionnaires and testing

Questionnaires and tasks that will be used during the study visit (as have been listed in prior sections) are described in more detail below. In addition, a short note is provided on the rationale for their selection.

Sleep inertia is a period of reduced performance and alertness following awakening. This period may be as short as 30 minutes or as long as an hour or more depending on the performance task. For a good quantification of sleep inertia, it is important to do repeat assessments with a high temporal resolution, and as such, the tests used cannot be too long. For DBS in patients with motor symptoms one needs to consider that for a between-stimulation-condition comparison of sleep inertia, tasks with a motor component are probably not best suited to the task, since it will be difficult to differentiate an effect of impaired motor performance from a deficit in alertness.

We have selected an array of measures that have been previously tested and might be applicable in accurately quantifying changes in sleep inertia in our populations of interest.

The Karolinska Sleepiness Scale (KSS, measuring vigilance and lasting a few seconds) also had good sensitivity as does the Psychomotor Vigilance Test (PVT) (Santhi et al 2013).. Finally, we will use the Karolinska Drowsiness Test (KDT) which assesses waking resting EEG, eyes open 1 min; eyes closed 1 min.

3. EEG and polysomnography

Scalp EEG electrodes are individually attached while additional electrodes record EMG, EOG and ECG signals (detecting muscle activity, eye movements and the electrocardiogram respectively). We will also use sensors to monitor breathing parameters such as airflow and respiratory effort and EKG. Video recordings with video being time-locked to the polysomnography EEG data.

4. Autonomic measures:

In addition to data captured with the polysomnography system described above. Systems such as an FDA Empatica E4 watch can be used where available and tolerated. These sensors capture high-resolution data relevant to heart rate and blood pressure.

5. Biological sampling and analyses:

Patients will provide a single salivary sample for cortisol measures upon awakening (6am) on each visit.

6. Other devices and procedures:

Subjects will be wear a "smart" watch, Empatica E4 or Empatica II watch, which are FDA approved device for tracking electrodermal activity (EDA), heart rate (HR), and photoplethysmography (ppg). Participants may also wear a commercially available smart watch, such as the Apple Inc. watch or Fitbit. The patient will already be familiar with their FDA approved patient programmer used with their DBS device from prior clinic visits, as well as instructions and advice offered during their hospital stay. This tablet-like or pager-like device allows for adjustment of stimulation settings (amplitude, pulse width and frequency) by its operator, by communicating wirelessly with the implanted battery and DBS system.

Prior to both epilepsy monitoring unit (EMU) stays in Saint Marys Hospital female patients will have pregnancy test, unless clinically determined to not be able to become pregnant.

9.7. Visit-2 First EMU study visit

Baseline characterization of sleep and perturbations

Baseline day:

Upon the first day of their arrival to Saint Marys Hospital, patients will be familiarized with the testing battery and EEG equipment. We will run the battery of questionnaires and tests while participants are on their usual stimulation parameters and medications, to ensure that delays/errors when this is repeated upon awakening are not a result of task novelty.

Based on each patient's sleep diary and actigraphy from their Empatica watch, we will determine a bedtime that corresponds with their usual schedule. The gold standard polysomnography will be used to measure scalp EEG and sleep over two nights in each participant. One night will be used to characterize a patient's sleep state with their typical therapy parameter settings (stimulation on) or off stimulation, while during the other night effects of defined perturbations (examples outlined in Figures 1-5 in the Appendix) on sleep we be assessed. Medications and other influences will be controlled as much as possible between the control and the experiment (i.e. consistent with their daily medication dose). Patients will be under supervision of trained clinical personnel.

For these two nights, we will configure each subject with the polysomnography system and programmer. This will provide a consistent environment over both nights.

Baseline night: The main purpose of this first night of recording is for the researcher to become familiar with the patient's typical sleep patterning /sleep stages and their electrophysiological and polysomnographic correlates. For this we will capture and quantify the EEG in different stages (WAKE, N1, N2, N3, REM) and observe respiratory and autonomic parameters. Should we be able to recruit patients with DBS devices that enable us to sample intracranial data, we will also record samples of data during different sleep stages.

At the end of the night, we will define the dominant EEG characteristics for each sleep stage and translate this to transition models for each patient. The outcome of this analysis will be used to generate the patient-specific stimulation perturbations based on sleep stages. Data collected during the first (baseline) night will be used as the baseline for the remainder of the protocol.

Upon awakening (at a time decided based on the sleep diary), a salivary sample will be obtained for morning cortisol. Participants will complete specific tasks at the time of awaking, and again at 30 minutes and 60 minutes post awaking.. These tasks will consist of the KSS, Mood, KDT, , , and PVT.

During the intervening day, the patients will be allowed to read, watch television, and socialize with caregivers, as well as complete tasks and questionnaires.

Testing/stimulation night:

We will use the programmers in an initial open-loop approach during the first visit, to see if a pattern can help optimize sleep stages and perturb sleep patterns. We will reconfigure each subject with polysomnography system and ensure it is still operating per requirements. The intent is to provide a consistent environment over both nights. We will again capture EEG (and if available, intracranial data). We will use real-time classification of sleep architecture to perturb the networks with variants of stimulation (see tables per target in Appendix A). For the initial sleep cycles, we will be using manual (open loop) interventions by the sleep monitor and the site clinician and scientist. In parallel, the laptop algorithm will be running a prototype closed-loop control to demonstrate the bridge to automated closed loop control. The output of the algorithm and stimulation commands will be logged and compared to the manual interventions.

Upon waking, a salivary sample will be obtained for measuring of early morning cortisol. The cognitive tasks will be performed as listed previously, to assess sleep inertia and other response variables. Subjective questionnaires will be administered post-cognitive screen. Cognitive tests will continue throughout the day to assess variation in the patient's performance.

9.8. Visit-3 Second EMU visit

The second visit will also consist of two nights of sleep recordings. We will once again connect the participant to the equipment and capture standard behavior and electrophysiological nature of brain in different stages (AWAKE, N1, N2, N3, REM) as well as intracranial data where available. This will happen at the beginning of both nights and be compared to the baseline. This visit will be largely informed by the sleep characteristics and stimulation results of the first visit.

Adaptive night: We will use real-time classification of sleep architecture to perturb the networks with variants of stimulation. The perturbations will be automatically generated by the adaptive algorithm, which will be informed from the data gathered during the first visit.

Control night: open loop stimulation (or off) will be applied, guided again by data obtained during the first visit.

Upon waking, salivary cortisol samples will be obtained as before. The cognitive tasks will be performed again to assess sleep inertia and other response variables. Subjective questionnaires will be administered post-cognitive screen. Cognitive tests will continue for an additional post-wake to fully gauge impacts on sleep inertia. Testing and questionnaire schedule will be the same during both visits.

9.9. Sample Handling

9.9.1 Sample handling for study purposes

Salivary samples (2mls in a universal container pot) will be obtained for measuring of salivary cortisol levels, for study purposes only. Samples will be obtained upon awakening after each night (e.g. at 6am).

9.10. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw or be withdrawn early from the study at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with study procedures
- Participant decision

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. According to the design of the study, participants can withdraw but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal.

In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (arising during the study)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Clinical judgement

We do not expect significant adverse events from the stimulation patterns applied. However, there may be an impact on performance upon awakening in the case where sleep stage/depth perturbations are achieved. When DBS devices are turned off/switched to lower than clinical settings, there may be a transient return to pre-treatment baseline or deterioration in symptoms. With regards to chronic pain patients, this might be uncomfortable. However, this eventuality will be mentioned during recruitment and clearly stated in the patient information sheet. In addition, there will be clinical supervision during the perturbations. If the participant is concerned and/or experiences discomfort because of either this or a deterioration in sleep depth and quality, they will be reminded that they can withdraw at any time without any impact of further care.

Decision for withdrawal of participants who experience an effect but wish to continue will lie with the site PI and the clinical team. If the participant is withdrawn due to an adverse event, the Investigator will arrange for a follow-up clinic visits or telephone calls until the adverse event has resolved or stabilized. The type of withdrawal and reason for withdrawal will be recorded in the

CRF. Should the minimum required number of participants per cohort not be met, or if there is a relative imbalance per patient number per cohort, withdrawn participants will be replaced.

9.11. Definition of End of Study

The end of study will be the date of the last visit of the last participant.

10. SAFETY REPORTING

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favorable opinion of the study where in the opinion of the Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Investigator becoming aware of the event.

It is a requirement of the funder that unanticipated problems involving risk to subjects or others must be promptly reported. This will be done by telephone ([redacted]), by email ([redacted]), or by facsimile ([redacted]) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the Funder, at a designated address (US Army Medical Research and Development Command, [redacted]).

Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the Institutional Review Board (IRB), the institution, the Sponsor, or regulatory agencies will also be promptly reported to the USAMRDC ORP HRPO.

The results of the analysis of previously data from the investigational RC+S device will be submitted to the FDA.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The plan for the statistical analysis of the study are outlined below. There is not a separate SAP document in use for the study.

11.2. Description of the Statistical Methods

All analyses will be performed using commercially available software including MATLAB and SPSS. We will use a combination of novel techniques as well as existing and previously published approaches to signal analysis of EEG data, classification and testing for statistical significance. Parametric and non-parametric statistical testing procedures may be employed.

A Hidden Markov Model (HMM) can be generated for each patient, to assist in a statistical comparison of the effect of electrical perturbation of the brain. HMM states will be based on observations made by currently utilized metrics, such as EEG activity in different frequency bands, while the algorithm used for HHM will be based on literature (Vidaurre et al. 2018). A Hidden Markov Model (HMM) will be updated for each disease state, and patient, to add additional data for the stimulation matrix.

We will further assess correlations between stimulation perturbations and observed cognitive measures, physiological biomarkers (cortisol), subjective questionnaires, and post-hoc analysis of sleep patterns. Comparisons between patients control nights will provide a general assessment of in-patient variability. With the limited dataset, areas of statistical significance will be assessed. Where statistical analysis is not possible, consistency and data trends will be evaluated.

Outcomes (primary, secondary, tertiary) have been described in section 6 page 14, while comparators and interventions described in section 9.6 page 20.

11.3. Sample Size Determination

This is a feasibility study into recruiting and conducting the study procedures in patient populations. Given the exploratory and novel nature of this study, effect sizes are as of now, unknown. We are collecting from different groups bearing in mind that a minimum n=3 is required for the most rudimentary statistics based on patient number. We therefore expect 15 patients to be the lowest bound for 5 different DBS electrode locations. There will be multiple comparable stimulation epochs per patient, across three nights (second night of first visit and both nights of second visit). The number of sleep stages and cycles per night will vary between participants, with an added unknown being the effect of the disease state on sleep. However, this within- and across-subject comparison will boost statistical power. Further support that an N-of-1 trial design can be used for closed-loop DBS research and provide individualized, precision data to inform device development, was published recently (Stevens and Gilbert 2020).

11.4. Analysis populations

All data collected from participants who have completed the full study will be included in the analysis.

11.5. Decision points

As specified in section 9.7., interim analyses of each patient's baseline data will be performed after the first night of the first visit. This will help establish a familiarity with each participant's sleep stage duration and EEG morphology, their maximum sleep depth as well as the presence of pathological sleep features. Based on this knowledge, decisions on the timing of the stimulation during the second night will be made by the PI and sleep scientist team, as well as basic assumptions on the desired effects. Following the first visit, further interim analyses will determine to what degree these assumptions were correct, so that stimulation patterns can be explored further during the second visit.

11.6. Stopping rules

As a basic science study, this study will finish at the point at which the target sample size has been recorded.

11.7. The Level of Statistical Significance

Statistics will use standard conventions for reporting of significance, including effect size, and multiple testing statistics for experimental effects.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

All data will be pre-processed and screened for gross abnormalities/poor data quality. In the case where experimental conditions prohibited sufficient quality recordings to be made then all (or a subsection) of a participant's data will be excluded from the study.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Should a deviation from the original statistical plan imply a deviation from the pre-specified recruitment and testing protocol, the Funder and IRB members will be contacted by the Chief Investigator and the Study Steering Committee. No such deviation will be carried out without prior approval from these parties.

12. DATA MANAGEMENT

The plan for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarized into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations. Reports and anonymized data may also be shared with named collaborators (Prof. Tim Denison, PhD Oxford UK and Assistant Professor Dr Simon Little, University of California, San Francisco).

The USAMRDC ORP HRPO conducts site visits as part of its responsibility for compliance oversight (as also stated in other relevant sections). Accurate and complete study records will be maintained and made available to representatives of the USAMRDC as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

12.3. Data Recording and Record Keeping

A unique code will be assigned to each patient, which will consist of group, random number generator sequence, and number of participants during the recruitment process. A side file (Excel) will be created containing patient-specific data and code breakdown –it will be stored in lab premises, on a research computer with backup copy on a password-protected server.

Anonymized data may be stored in encrypted devices and password-protected laptops for analysis in other collaborating units.

Data will be retained beyond completion of the study until thoroughly analyzed as per objectives, We may also share encrypted and anonymized data with collaborating groups internationally.

The results of analysis that pertains to the data previously collected from patients with investigational RC+S under FDA-IDE G180224 will be included as part of the FDA reporting.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Regular monitoring will be performed by an Independent Study Monitor, in addition to IRB requirements. The Study Monitor will not be a clinical research associate for the study and will be based in an independent institution –however they will share a relevant clinical background and role to the Principal Investigator (Consultant Neurologist) to ensure optimal ability of risk assessment. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

The USAMRDC ORP HRPO also conducts random audits at the time of continuing review. Additional information and documentation may be requested at that time. The USAMRDC ORP HRPO also conducts site visits as part of its responsibility for compliance

oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRDC as a part of their responsibility to protect human subjects in research. Research records reviewed will be stored in a confidential manner so as to protect the confidentiality of subject information.

The final study report, including any acknowledgement documentation and supporting documents, must be submitted to the HRPO when available.

13.3. Study Committees

The USAMRDC ORP HRPO is responsible for conducting the following activities:

- Principal advisor to the Command for human subjects protection.
- Develop and implement human subjects protection policies & regulations.
- Maintain the USAMRDC Volunteer Registry Management System.
- Review and approve intramural and extramural human subjects protocols.
- Conduct human subjects protection site visits.

In that context (and explicitly stated as a requirement by the Funder), it is required that there is an annual IRB report with regards to the study. To facilitate this purpose, as well as ensure that the study runs smoothly across sites and collaborations, a Study Steering Committee (Profs Denison, Green and Worrell) will meet at regular intervals to discuss progress and troubleshoot any issues.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file. In case of non-compliance, details of the incident will be escalated to the central PI team and an assessment of whether it may be a potential Serious Breach will follow, as outlined in the relevant study SoP.

Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation, as per requirements of the Funder. The USAMRDC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review) or a change that could potentially increase risks to subjects.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the research team the serious breach will be reviewed by the P.I. Sponsor and reported to the Mayo Clinic IRB within seven calendar days. In addition, the Funder will be notified as per their requirements and in the ways stated in prior sections (Section 10.2).

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

As per Funder requirements, a DoD Human Research Protection Official (DHRPO) must:

1) Review the research protocol for compliance with DoD Instruction (DoDI) 3216.02 “Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research,” accept the Institutional Review Board (IRB) determination of level of risk, ensure that the study is compliant with applicable DoD regulatory requirements and approve the protocol prior to implementation.

2) Review and accept IRB-approved substantive changes to an approved research protocol before they are implemented.

3) Ensure the IRB conducts an appropriate continuing review at least annually.

16.4. Other Ethical Considerations

Not applicable.

16.5. Reporting

The PI shall submit once a year throughout the study, or on request, an Annual Progress report to the IRB and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Participant Confidentiality

The study will comply with the Mayo Clinic regulations for protecting patient information, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimized by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorized personnel. The study staff will safeguard the privacy of participants' personal data.

16.7. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

17. FINANCE AND INSURANCE

17.1. Funding (see budget)

17.2. Insurance (Patient insurance as needed)

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties. These include the HRA statement of activities and schedule of events, as well as all relevant DARPA documents.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge funding resources for this study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of Mayo Clinic is the property of Mayo Clinic.

20. ARCHIVING

Patient identifiable information will be stored in encrypted files on password-protected computers for 3 years after the study has finished. This excludes any research documents with personal information, such as consent forms, which will be held securely at Mayo Clinic for ten years after the end of the study - the period necessary for their full analysis and writing up of all scientific publications).

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22. APPENDIX A

Stimulation and Medication parameters

Sites: Amygdala (AMG), Hippocampus (HIP), Anterior Nucleus Thalamus (ANT), Centromedian Thalamus (CMT), Central Lateral Thalamus (CL), Cortex, Subthalamic Nucleus (STN), Globus Pallidus Interna (GPi)

Stimulation: Standard (clinical DBS), Low frequency (2 - 30 Hz), High frequency (40 - 200 Hz). The stimulation parameters will be tested with physician at the bedside to ensure that stimulation does not produce side effects or symptoms.

Example of Experimental Stimulation Paradigm

Night 1	Wake	Light Out/Wake	N1	N2	N3	REM	N1	N2	Rem	Awake	Testing
Stim State	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard
Medication	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Hold un il testing completed	
Night 2											
Stim State	Standard	Standard	off	off	low	off	off	low	off	Standard	Standard
Medication	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Hold un il testing completed	

Night 1	Wake	Light Out/Wake	N1	N2	N3	REM	N1	N2	Rem	Awake	Testing
Stim State	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard
Medication	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Hold un il testing completed	
Night 2											
Stim State	Standard	Standard	off	off	off	high	off	off	high	Standard	Standard
Medication	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Hold un il testing completed	

23. APPENDIX B: SCHEDULE OF STUDY PROCEDURES