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Transcranial Direct Current Stimulation Therapy for Sleepiness Related to Shift Work Disorder (tDCS SWORD)
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Title: Transcranial Direct Current Stimulation Therapy for Sleepiness Related to Shift Work Disorder (tDCS-SWORD)

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Not applicable

IDE: non-significant risk (NSR) investigational device that meets the abbreviated Investigational Device Exemptions (IDE) requirements at 21 CFR 812.2(b)

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I. Objectives

1) To determine the effects of tDCS on subjective measures of sleepiness in night-shift workers with shift work disorder.

2) To determine the effects of transcranial direct current stimulation (tDCS) on vigilance in night-shift workers with shift work disorder.

The objectives of this study are to determine if active tDCS treatment will improve vigilance and subjective measures of sleepiness in patients with shift work disorder. This is a preliminary, single-arm efficacy study which will serve as the basis of a larger, confirmatory trial if the findings are positive.

The risks associated with this study are minimal compared to the potential benefits. Knowledge about the effects of tDCS on vigilance and subjective sleepiness would be an important advance in the care of patients suffering from shift work disorder.

II. Background and Rationale

Shift Work Disorder (SWD) is a circadian rhythm sleep disorder characterized by complaints of insomnia during hours allotted for sleep or excessive daytime sleepiness that occur during work hours that are scheduled during the usual sleep period.[1,2] SWD has been estimated to affect 10-23% of the approximately 22 million Americans currently estimated to be shift workers.[2-4] Among night-shift workers, the prevalence of SWD is estimated to be about 14%.[3] SWD is considered a public health risk, as the impaired functional ability due to excessive sleepiness in persons with SWD may result in impaired occupational performance.[2] Excessive sleepiness associated with SWD has been shown to be associated with impairments in cognition and psychomotor performance, which in turn may contribute to increased accidents during work and motor vehicle crashes during the morning commute.[3] One-third of night workers admit to regularly nodding off or falling asleep at least once a week while working and half admit to falling asleep while commuting.[5] About one third of nurses are estimated to have SWD.[6]

While there are two medications (modafinil and armodafinil)[7,8] approved by the Food and Drug Administration (FDA) for sleepiness during the work hours for those with SWD, they are associated with adverse events.[9] Caffeine plus naps reduces sleepiness during the night shift, but the quality of evidence is considered low.[9] Therefore, there is a need to develop non-pharmacologic treatment strategies for sleepiness related to SWD.

Multiple recent studies have used transcranial direct current stimulation (tDCS) as a novel therapy for central nervous system disorders including depression, anxiety, Parkinson's disease, and chronic pain.[10-13] tDCS is a form of noninvasive, painless, brain stimulation that uses a mild direct electrical current passed between electrodes on the scalp to modify neuronal membrane resting potential in a polarity dependent manner, elevating or lowering neuron excitability in a region.[14] It has several advantages over other brain stimulation techniques because it is noninvasive, painless and safe. It is also easy to administer and the equipment is easily portable. The most common side effect of tDCS is a slight itching or tingling on the scalp.[15] Importantly, no studies thus far have provided evidence that tDCS produces more than a minimal risk.[16] **An updated review that consolidated evidence on the safety of tDCS found that to date, the use**

of conventional tDCS protocols in human trials (≤40 min, ≤4 milliamperes, ≤7.2 Coulombs) has not produced any reports of a Serious Adverse Effect or irreversible injury across over 33,200 sessions and 1000 subjects with repeated sessions. This review included a wide variety of subjects, including persons from potentially vulnerable populations.[16] In addition, several studies have shown that tDCS can be used safely in the home environment.[17-21]

Thus, tDCS is a non-significant risk (NSR) investigational device that meets the abbreviated Investigational Device Exemptions (IDE) requirements at 21 CFR 812.2(b) addressing labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion for an NSR device study. An expert panel has stated that in the US, IRBs overwhelmingly designate tDCS trials as non-significant risk.[22]

Studies using tDCS have demonstrated improvements in vigilance and cognitive function under conditions of sleep deprivation and in a case of a patient with organic hypersomnia.[14,15,23] These studies suggest potential benefit in those with sleepiness related to SWD. Our hypothesis is that patients with sleepiness related to SWD will demonstrate improvements in vigilance and self-reported sleepiness as co-primary outcomes after receiving active stimulation.

III. Procedures

A. Research Design

This is a single-arm preliminary study involving those with SWD.

Informed consent will be obtained from all participants. If the subject is agreeable, the consent form will be sent to them via mail or electronically so that they will have the opportunity to read the document ahead of time.

A separate informed consent for the purpose of screening potential candidates will be obtained.

B. Subject Selection:

1. Inclusion/Exclusion Criteria

A. Key Inclusion Criteria

- age 18-65 years
- works 5 or more night shifts per month (each shift lasting at least 10 hours, with ≥6 hours worked between 10 pm and 8 am) with plans to maintain this schedule for the duration of the 3-week trial
- meets the criteria for SWD according to the International Classification of Sleep Disorders[24] and evaluation of a sleep medicine provider (physician or nurse practitioner) during a screening evaluation:

  a) affirmative answers to Do you experience excessive sleepiness? (yes/no); "Do you experience difficulties with falling asleep during opportunities for sleep? (yes/no); "Is the sleep or sleepiness problem related to a work schedule where you

have to work when you would normally sleep? (yes/no)"; and "Has this sleep or sleepiness problem related to your work schedule persisted for at least three months? (yes/no)
b) based on the evaluation of the sleep medicine provider, the sleep and/or wake disturbance are not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, poor sleep hygiene, or substance abuse disorder.

- Stable medication dosage over previous 4 weeks.
- Able to understand English and give a written informed consent document.

B. Key Exclusion Criteria

- Currently taking stimulant medications such as Modafinil, Armodafinil, Methylphenidate, or Dextroamphetamnie.
- History of automobile accident due to falling asleep while driving
- Inability to understand or read English
- Self-reported Substance abuse (current)
- Excessive alcohol consumption defined as:
    - More than 3 glasses of wine a day
    - More than 3 beers a day
    - More than 60 mL of hard liquor a day
- Presence of cardiac pacemaker or automatic implantable cardioverter-defibrillator (AICD).
- Pregnancy, lactation (will be screened with urine pregnancy test)
- Non-removable metal or tattoos around head
- Use of implantable birth control device such as Implanon
- History of frequent severe headaches
- Unstable coronary artery disease
- Uncontrolled Seizure disorder
- Uncontrolled hypertension
- Any other clinically significant condition that, in the opinion of the Investigator, might put the subject at risk of harm during the study or might adversely affect the interpretation of the study data.

b) Screening Procedures

A screening visit will be scheduled to determine eligibility as above. A separate informed consent for the purpose of screening potential candidates will be obtained. Female patients of childbearing potential will be required to have a negative pregnancy test result at screening. Those with known sleep apnea are eligible for the study provided they are compliant with therapy (defined as > 4 hours of average nightly use for at least 30 days).

The modified neck circumference (MNC) score will be obtained during the screening visit. The MNC is calculated as the neck circumference measured in centimeters and adjusted if the patient has hypertension (4 cm is added), is a habitual snorer (3 cm is added), or is reported to choke or gasp most nights (3 cm is added). Those with an MNC score >48 cm water which indicates an increased risk of having obstructive sleep apnea (OSA) will have home sleep apnea testing (HSAT).

Those with an apnea-hypopnea index of ≥15/hour based on the HSAT will be excluded and referred to their primary care physician for treatment discussion.

3. Vulnerable Populations

- Children, fetuses, neonates, or prisoners are not included in this research study.

4. Populations vulnerable to undue influence or coercion

Should an OSU employee or student (or their surrogate) be approached for enrollment, they will be given the opportunity and time to consider participation and will be reassured that declining to participate will not jeopardize or hinder their standard of care at the OSU Wexner Medical Center, nor will it have any bearing on either their student status or employment.

e) Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study.

C. Study Plan

This is a preliminary single-arm study. The study will last up to 6 weeks including the screening period. Subjects will receive active tDCS for 30 minutes before their scheduled work hours at least 3x/week for two consecutive weeks.

Outcome measures will include: psychomotor vigilance test (PVT) and the Karolinska Sleepiness Scale (KSS)[25,26] which will be obtained during the shift work.

Visit Schedule

A) Screening visit

During this visit, the following will be obtained for all subjects:

a. Screening Informed consent (if not obtained on a prior separate visit)
b. Evaluation for SWD by investigator
c. Pregnancy test, if applicable
d. Height and weight
e. Blood pressure and pulse rate
f. Medication list
g. Cognitive Tasks results
h. Epworth sleepiness scale (ESS)
i. CPAP compliance for those who are known to have sleep apnea
j. MNC score
k. HSAT, if applicable as explained above
l. Expected visit length: 60 minutes

The following are the reasons why subjects may not proceed with the study after screening:

a) If they are determined to have significant sleep apnea, this will end their participation in this research study. The home sleep study results will be provided to research participants or their health care provider for referral for appropriate treatment.
b) The investigators determine that the subject does not have shift work sleep disorder.

Those who remain eligible will then sign a separate informed consent for the remainder of the study. They will be requested to complete a baseline PVT and KSS during their shift work prior to the tDCS stimulation sessions. The PVT is a test that measures the speed with which subjects respond to a visual stimulus. It is a simple task where the subject presses a button as soon as the light appears. The light will turn on randomly every few seconds for 3 minutes. The KSS is a subjective measure of sleepiness. They will be provided with a mini-IPAD that contains the PVT and KSS apps. The PVT and KSS will only take 4 minutes and will be collected around 6 pm, 12 midnight and 4 am.

B) Visit 1 (stimulation #1)

During this visit, the following will be obtained for all subjects:

a. Study Informed consent (if not already obtained)
b. Resting blood pressure and pulse rate
c. Changes to Medication

They will then receive active tDCS for 30 mins. PVT **during** the active tDCS

d. Side effects questionnaire **after** the active tDCS
e. Actigraphy equipment will be provided to be worn throughout the duration of the study. Instructions on how to wear an actigraph device around their wrist that measures both the rest-activity cycle will be provided.
f. Expected visit length: 60 minutes

C) Visit 2 (stimulation #2)

During this visit, the following will be obtained for all subjects:

a. Resting blood pressure and pulse rate
b. Changes to Medication

They will then receive active tDCS for 30 mins. PVT **during** the active tDCS

a. Side effects questionnaire **after** the active tDCS
b. Expected visit length: 60 minutes

D) Visit 3 (stimulation #3)

During this visit, the following will be obtained for all subjects:

a. Resting blood pressure and pulse rate
b. Changes to Medication

They will then receive active tDCS for 30 mins. PVT **during** the active tDCS.

c. Side effects questionnaire after the active tDCS
c. PVT and KSS (6 pm, 12MN, and 4 am)
g. **Expected visit length: 60 minutes**

Visits 1-3 will occur during a one week period. Subjects will then be asked to obtain the KSS score and PVT during their shift work at 6 pm, 12 MN, and 4 am at the end of Visit 3.

E) Visits 4, 5, 6 represent the second week of tCDS active stimulation and will be similar to Visits 1-3 with an expected visit length of 60 minutes per visit and will occur over a one-week period.

Subjects will be asked to obtain the KSS score and PVT during their shift work at 6 pm, 12 MN, and 4 am at the end of Visit 6. In addition, at the end of Visit 6, the following will be obtained **after** the active tDCS

i. Cognitive Tasks results
ii. Epworth sleepiness scale (ESS)

Visit Schedule

Procedures	**Visit #**						
	S	1	2	3	4	5	6
Screening consent	x						
Study consent		x					
Medication list	x	x	x	x	x	x	x
Height and weight	x						
BP and Pulse rate	x	x	x	x	x	x	x
MNC	x						
HSAT, if applicable	x						
Pregnancy test, if applicable	x						
Cognitive tasks	x						x
ESS	x						x
Actigraphy		x	x	x	x	x	x
tDCS		x	x	x	x	x	x
Side-effects		x	x	x	x	x	x
*PVT		x		x			x
*KSS		x		x			x

*obtained during the subjects' shift work at baseline at baseline prior to stimulation and after every 3 tdcs stimulation session
S= screening visit (requires a separate consent)
BP= blood pressure
MNC= modified neck circumference
HSAT= home sleep apnea test
tDCS= transcranial direct current stimulation
PVT= psychomotor vigilance test
KSS= Karolinska sleepiness scale
ESS= Epworth Sleepiness Scale

Detailed Procedures

a) Medication List

For all subjects we will obtain information about their medications or any changes to their medications.

b) Height and Weight

Weight and height measurements (to calculate BMI) will be done without shoes.

c) Blood Pressure

The standard operating procedure for obtaining sitting blood pressure will be followed.[27]

Medical Alert Procedure. Subjects in these protocols may be identified to have clinical abnormalities that require medical attention. Research staff would notify Dr. Magalang or a physician co-investigator immediately for Systolic BP >200 mmHg or diastolic BP >120 mmHg.

d) Modified Neck Circumference (MNC) score

This will be obtained during the screening visit. The MNC is calculated as the neck circumference measured in centimeters and adjusted if the patient has hypertension (4 cm is added), is a habitual snorer (3 cm is added), or is reported to choke or gasp most nights (3 cm is added).

e) Home sleep apnea testing (HSAT)

This is part of the screening procedure. Subjects with an MNC score >43 cm high, indicating a moderate to high probability of having obstructive sleep apnea (OSA), will have home sleep apnea testing (HSAT). Those with an apnea-hypopnea index of ≥15/hour based on the HSAT will be excluded and referred to their primary care physician or the sleep medicine clinic for treatment discussion. Subjects will be given a copy of the HSAT report. Subjects will be given instructions on how to use the HSAT equipment which is used routinely in clinical practice for home sleep apnea testing by clinical staff of the OSU Lung Center. The device will be preset to turn on automatically at home at the desired time. HSAT includes recordings of nasal pressure, thorax and abdominal movements, oxyhemoglobin saturation, and pulse rate. Subjects will be provided a telephone number to call should they have any questions about the device.

HSAT will be scored according to standard criteria. Briefly, an apnea is scored when all of the following criteria are met: a drop in airflow sensor excursion by > 90% of baseline, the duration of the event lasts at least 10 sec, and at least 90% of the event's duration meets the amplitude reduction criteria. An apnea is classified as obstructive if it is associated with continued or increased respiratory effort throughout the entire period of absent airflow, central if it is associated with absent respiratory effort throughout the entire period of absent airflow, and mixed if it is associated with absent respiratory effort in the initial portion of the event, followed by resumption of respiratory effort in the second portion of the event. A hypopnea is scored if the following criteria are met: the airflow signal excursion drops by >30% of baseline, there is a >4% desaturation from pre-event baseline, and at least 90% of the event's duration meets the amplitude reduction criteria.

f) Questionnaires

The following questionnaires will be completed by the subjects:

a. Karolinska Sleepiness Scale (KSS). Values will be collected prior to their shift work (around 6pm) and during shift work (around 12 midnight and around 4 am). These data will be obtained prior to tDCS stimulation, after the third stimulation and after the 6th stimulation sessions. They will be asked to rate how sleepy they are according to the following scale:

9. Extremely sleepy, fighting sleep
8. Sleepy, some effort to keep alert
7. Sleepy, but no difficulty remaining awake
6. Some signs of sleepiness
5. Neither alert nor sleepy
4. Rather alert
3. Alert
2. Very alert
1. Extremely alert

b. Epworth Sleepiness Scale Score (ESS) at baseline and after the 6th stimulation session.
c. Side Effects

g) **Actigraphy**

This device is the size of a small wristwatch that measures activity and is a non-invasive method of monitoring human rest/activity cycle. The instructions for the device use as well as a sleep diary will be provided. The data is then downloaded into a computer.

h) **Psychomotor Vigilance Test (PVT)**

The PVT is a sustained-attention, reaction-timed task that measures the speed with which subjects respond to a visual stimulus. The PVT is a simple task where the subject presses a button as soon as the light appears. The light will turn on randomly every few seconds. The purpose of the PVT is to measure sustained attention and give a numerical measure of sleepiness.[28] The purpose of the PVT is to measure sustained attention, and give a numerical measure of sleepiness by counting the number of lapses in attention of the tested subject. Subjects will be provided with a min-IPAD and the PVT will be done prior to their shift work (around 6pm) and during shift work (around 12 midnight and around 4 am). Values will be obtained prior to tDCS stimulation, after the third stimulation and after the 6th stimulation sessions.

i) **Cognitive Performance**

In addition, subjects will also be asked to make judgements or decisions on stimuli such as words or images presented on a computer screen to track memory and thought process (cognitive performance).

j) Transcranial Direct Current Stimulation (tDCS)

The neuroConn DC stimulator (neuroCare Group, Munchen, Germany) will be used to provide the tDCS stimulation. This battery-powered device will be controlled with a microprocessor to ensure constant current at up to 2000 μA. For safety, multistage monitoring of the output current and electrode/tissue impedance will be included. The device automatically shuts off if the impedance becomes greater than 50 kΩ to prevent electric shocks or burns. This device will be investigational only (not FDA approved). As above, tDCS is a non-significant risk (NSR) investigational device that meets the abbreviated Investigational Device Exemptions (IDE) requirements at 21 CFR 812.2(b) addressing labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion for an NSR device study.

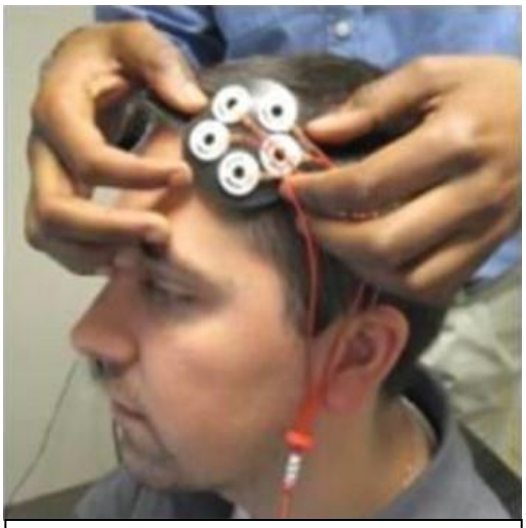

Figure 1. tDCS electrode array (anode only pictured). All five elements are standard silver-silver chloride EEG electrodes placed in a plastic cup which is then filled with a conductive gel.

We will use a custom set of silver/silver chloride electroencephalographic (EEG) electrodes (at location F3 according to the 10-20 system) as described in McKinley et al.[28] These new electrodes were shown to be more stable over time, produce lower sensation levels, and produce fewer skin reactions when compared to standard sponge electrodes. Both the anode and cathode consist of a separate array of 5 EEG electrodes as pictured in Fig. 1. Each electrode has an inner diameter of 1.6 cm yielding a contact area of 2.01 cm^2 for each electrode. At 2 mA of supplied current, the average current density will be 0.199 mA/cm^2 as calculated by current (2 mA) divided by area (10.05 cm^2).

For the active anodal stimulation condition, tDCS will be applied at 2mA for 30 min. The anode will be applied to scalp location F3 according to the 10-20 EEG electrode placement system while the cathode will be placed over the contralateral (i.e. right) bicep. Electrodes will be secured using medical bandages, and connectivity will be ensured using highly conductive gel.[14]

IV. Data Analysis

Sample size:

The sample size is selected such that we have power to detect differences in the mean reciprocal reaction time (mean 1/RT) and KSS, which are our co-primary endpoints. Differences from baseline in the co-primary endpoints will be assessed at Visit 6.

We plan to enroll a total of 45 subjects. We assume a screen failure rate and a loss to follow up rate of 40%. Thus, we anticipate at least 27 evaluable subjects. Once 27 evaluable subjects have completed the study, enrollment will stop. We will control the type I error rate at 0.10 for assessing the primary endpoints conservatively using a Bonferroni correction.[29] With this sample size, we have 80% power to detect an improvement of 0.50 standard deviations in mean 1/RT with an alpha level of 0.05 using a one-sided t-test. For the KSS, we assume a standard

deviation of 2 [9] and have 80% power with this sample size to detect a reduction in KSS of 1 with an alpha level of 0.05 using a one-sided t-test.

Statistical Methods:
The primary analysis will examine the difference in KSS and mean 1/RT at 4 AM at Visit 6 and baseline. To analyze differences in KSS at Visit 6 and baseline, and differences in mean 1/RT at Visit 6 and baseline, we will use paired t-tests using the worst values during the shift work. We will use Holm's Method to account for multiple testing and control the familywise error rate.

Secondary analyses will include the mean inverse response time and additional outcomes from the PVT and subjective questionnaires. To analyze differences in the number of lapses at Visit 4, we will use a Poisson regression model to compare the lapse rate at Visit 6 to the baseline rate. Additional questionnaires (ESS) will be assessed using paired t-tests.

We will also build longitudinal models to fully explore changes in outcomes both across weeks and within shifts. We may also explore joint models of subjective and objective outcomes to better characterize correlation between outcomes and their changes over time. Characteristics of participants will be summarized by randomized treatment group using appropriate descriptive statistics. We will also summarize any reported side effects of treatment. Additional exploratory analyses may be conducted at the discretion of the study team.

Interim Analysis:
An interim analysis will be conducted when 50% of the evaluable patients have reached the primary endpoint at Visit 6. That is, it will be conducted after 14 patients have an evaluable primary endpoint. The analysis will assess both co-primary endpoints using the error spending approach described by Lan and Demets.[30,31] The study will be stopped early for efficacy if the p-value is less than 0.006 for both co-primary endpoints. If only one endpoint reaches the efficacy boundary, the trial will not be stopped early and will enroll the full planned number of participants.

V. Event Reporting

(a) Adverse Events
The ICH Guideline for Good Clinical Practice E6(R1) defines an adverse event (AE) as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

As this is a study that does not include a pharmaceutical product intervention, this definition would include AEs that occur as a result of protocol procedures and protocol treatment.

A serious adverse event (SAE) is any AE that:
- Results in death
- Is immediately life-threatening

This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that may have led to death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
  In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting.
- Results in persistent or significant disability/incapacity
  The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

  Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

1. Collecting and reporting adverse events:
All AEs occurring after subject has signed consent and up to the study completion visit must be recorded on specific data collection forms.

2. Collecting and reporting Serious Adverse Events:
The OSU Event Reporting Form should be used to report untoward events that may affect participants in research approved by an OSU IRB. Events requiring prompt reporting include adverse events, protocol deviations, and other unforeseen problems or findings that suggest participants, research staff, or others are placed at greater risk by the research than previously expected. These events, classified broadly as unanticipated problems involving risks to participants or others, must be reported promptly to the IRB. Unanticipated problems can occur in any type of research and may involve physical, psychological, social, legal, or economic harms.

Events Requiring Prompt Reporting
Events that may represent unanticipated problems involving risks to participants or others and therefore require prompt reporting include the following:

- Adverse events or injuries that are serious, unexpected, and related;
- Events requiring prompt reporting according to the protocol or sponsor;
- Reports, interim analyses, or other oversight committee/monitoring reports altering the risk/benefit profile;

These events should be promptly reported (see below), regardless of whether they occur during the study, after study completion, or to a participant who has withdrawn from or completed study participation.

Timeframe for Reporting
All internal events (those occurring in research at OSU or at a site under an OSU IRB's jurisdiction) as described above should be reported **within 10 days** of the Investigator's or research staff member's learning of the event. Events resulting in temporary or permanent interruption of

study activities by the Investigator or sponsor to avoid potential harm to participants should be reported **immediately (within 48 hours)** whenever possible.

Additional Information
Related adverse events and other problems involving risk that do not meet the reporting requirements and do not represent potential unanticipated problems involving risks to participants or others should be reported in summary form at the time of continuing IRB review. However, any problem or adverse event that an investigator believes could influence the safe conduct of the research should be reported promptly.

(b) Protocol Deviations
Protocol deviations are accidental or unintentional changes to the protocol or procedures. In the event that the protocol deviation involves risk to the subject or potential risk to future participants, or with the potential to recur or significantly impacts the integrity of the research data, the event should be reported to the IRB in a timely manner, in accordance with their reporting guidelines.

1. Ethical Considerations

The study will be conducted in accordance with the ICH guidelines on GCP, the GCPs applicable to any region where the study is conducted, and the ethical principles set forth in the Declaration of Helsinki. Good clinical practice is defined as a standard for the design, conduct, performance, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study participants are protected.

Per GCP, the protocol will be reviewed and approved by the IRB or IEC of each participating center prior to study initiation. The investigator will keep the IRB/IEC informed as to the progress of the study.

(a) Consent procedures
The investigator/study personnel will explain the nature of the study, and will be available to answer questions regarding procedures, risks and alternatives to participation. The consenter will inform the subject that participation is voluntary and that the subject can withdraw or be withdrawn from the study at any time. The principal investigator or his/her entitled designee will obtain written informed consent from each subject. Documentation of the informed consent process along with the original consent form will be maintained in the subject's research folder. A copy of the signed informed consent will be provided to the subject for their records.

(b) Subject compensation
Participants who qualify for the study will receive up to $500 compensation for participating in the study in the form of a check or by direct deposit (optional for OSU employees who may elect to receive payment by check). They will receive $250 after Visit 3 and $250 after Visit 6. If the participant is unable to complete all the visits, compensation will be prorated for the visits that are completed. For check payments, it may take up to 6 weeks for subjects to receive payment. All subject payments are taxable income.

2. Data Handling and Record Keeping

The investigator shall maintain the records of the study e.g.: subject research charts, regulatory documents and all other study specific documentation for a minimum of 15 years or in accordance with currently OSU-IRB regulations.

1. Confidentiality

- Confidentiality of all records will be maintained and data will be kept in a locked filing cabinet and only research staff and authorized members of the IRB will have access.
- Electronic data is protected by codes to which only research staff and authorized members of the IRB and OHR will have access
- The PHI to be collected; who will use the information within the institution and why; who may disclose the information and to whom; the subjects rights to access research information and their right to withdraw authorization (approval) for any future use of personal health information are all listed in the HIPAA form specific to the research
- The names of subjects and any other identifying information will be kept in a different secure location.
- Should publications result from this study all PHI will be removed.

3. Data Safety Monitoring Plan

The risks involved with tDCS, completion of questionnaires, PVT, HSAT, and actigraphy are minimal.

This study will be monitored to ensure participant safety and data integrity. The monitoring for this study will be conducted by the Principal Investigator and the study team. The information that will be evaluated will be the incidence and severity of adverse reactions related to the study procedures, enrollment and efficiency of data capturing. The adverse events will be assessed on a case by case basis at the time the study team is aware of the event.

Overall study monitoring will take place on an ongoing basis with study review meetings taking place at least every 6 months. In the event the side effects suggest the risk outweighs the benefit, the study will be stopped and the IRB notified in order to evaluate possible solutions to the risk problem.

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