Safety and Feasibility of Transcranial Direct Current Stimulation to Enhance Auditory Rehabilitation in Cochlear Implant Recipients

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1) **Protocol Title:** Safety and Feasibility of Transcranial Direct Current Stimulation to Enhance Auditory Rehabilitation in Cochlear Implant Recipients

2) Purpose of the Study:

a) To evaluate the safety and feasibility of reliable Transcranial Direct Current Stimulation (tDCS) administration at home in combination with home-based auditory training therapy and practice in Cochlear Implant (CI) patients

b) To evaluate changes in speech perception performance after a 4-week intervention consisting of tDCS combined with auditory rehabilitation and training.

3) Background & Significance:

Hearing loss is a prevalent source of disability in the population, particularly with advancing age (Goman and Lin 2016). Data from the National Health and Nutrition Examination Survey suggests that 10.5% of adults aged 55 to 64 years have hearing loss sufficiently disabling to warrant amplification, increasing to 25% for those 65 to 74 years and 50% for those 75+ years of age (NIDCD). There is increasing evidence of a strong correlation between sensorineural hearing loss in older adults and declines in general health including cognitive decline, social isolation, depression, and early mortality (Deal et al. 2017; Genther et al. 2015). Hearing restoration using cochlear implant (CI) technology and post-operative rehabilitation for moderately severe or greater hearing loss has proven crucial for improving quality of life, and reducing isolation and depression, which may serve as precursors for associated cognitive and general health declines (Contrera et al. 2017; Rutherford et al. 2018).

Nevertheless, there is substantial variability in the efficacy of hearing restoration interventions by CIs. Almost all CI patients improve dramatically after its activation, but some patients will reach a plateau in their performance even with a full auditory rehabilitation program. A recent meta-analysis was only able to explain 22% of the variability in speech perception results (Zhao et al. 2020). Some patients might even grow reluctant to wear the external part of the implant and become non-users (Távora-Vieira, Acharya, and Rajan 2020). Poor speech understanding in noise is a common complaint of patients using CIs and remains a major source of disability in these individuals. Therefore, there is an unmet need for approaches that can boost patients' speech perception performance with CIs more than current standard rehabilitation programs.

As for individuals using hearing aids (Chisolm et al. 2013; Smith et al. 2016), auditory rehabilitation after cochlear implantation has been associated with higher speech perception results (Fu and Galvin 2008; Stacey et al. 2010) and better quality of life (Tang et al. 2017). Neurocognitive functioning has become increasingly recognized as an important determinant of speech perception performance in older adults with CIs (Moberly, Castellanos, and Mattingly 2018). The history of hearing deprivation appears to be a prominent determinant of speech perception gain in the first few months after CI activation (Francis, Yeagle, and Thompson 2015). The subsequent gains are slower and appear to be more strongly associated with general health and a variety of psychosocial factors. This study proposes to evaluate an intervention that may facilitate adaptation of auditory brain circuits in response to salient but novel auditory stimulation with a CI, while engaged in auditory therapy and practice.

tDCS is a non-invasive brain stimulation technique that delivers low-intensity current via electrodes on the scalp to modify neuronal excitability in the underlying cortex (Paulus, Peterchev, and Ridding 2013). Over the past two decades, tDCS has been studied extensively in healthy subjects, patient populations, as

well as animal models, demonstrating robust safety (Antal et al. 2017) and promising efficacy (Buch et al. 2017). Previous neurostimulation studies have demonstrated that tDCS improves motor learning, cognition, and memory for healthy participants as well as in stroke patients (Ciechanski et al. 2019; Elsner et al. 2017; Shaker et al. 2018). Members of this study team have also reported faster acquisition of manual laparoscopic surgical skills among trainees receiving tDCS therapy (Cox et al. 2020) (see Fig. 1).

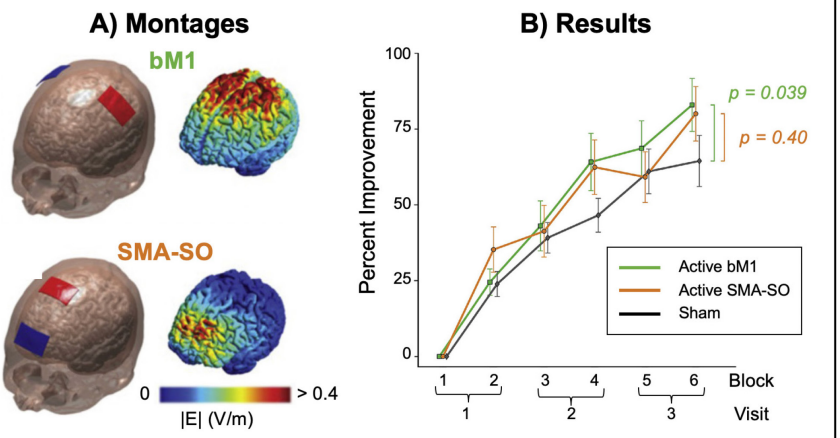

Fig. 1. Beneficial effects of tDCS during training on the acquisition of manual skills. A) tDCS electrode montages and associated electric field distribution in cortex. B) Results showing significantly greater improvement for the bM1 montage (green) over sham (black) (Cox et al, 2020).

Importantly, anodal tDCS can modulate linguistic abilities in healthy individuals and improve language performance in patients with post-stroke aphasia, via modulation of effective connectivity in the brain (Fiori et al. 2018). Indeed, anodal tDCS affects structural plasticity in the auditory cortex of normal-hearing and noise-exposed rats (Paciello et al. 2018). These effects are thought to result from enhanced neuroplasticity that can occur as relevant groups of neurons are stimulated to fire together, thereby strengthening neural pathways and improving signal processing. Studies of tDCS and transcranial magnetic stimulation of auditory cortex are limited to normal hearing subjects and have demonstrated several perceptual effects including modulation of the mismatch negativity evoked response potential component, increased temporal resolution, phonetic categorization, and pitch discrimination (see review by (Heimrath et al. 2016)) as well as modulation of the right ear advantage in dichotic listening (Heimrath et al. 2020). However, tDCS has not been studied for enhanced rehabilitation of speech perception in patients with hearing loss.

4) Design & Procedures:

This prospective study involves the completion of a 4 week computer-based auditory training program while administering tDCS. Patients with a unilateral Cochlear Implant will be asked to complete 30-minute sessions of self-directed auditory training while administering tDCS, at least five times per week for 4 weeks. Subjects will be asked to complete daily electronic logs for adverse event reporting and documentation of auditory training compliance. Subjects will be provided with a customized learning and practice plan during the initial baseline visit and given instructions on use of the tDCS device. Subjects will be selected whose sentence recognition scores (AzBio) have plateaued below 65%, which provides an opportunity to detect a measurable improvement in response to the proposed intervention.

The following assessments/procedures will be performed at the MOSCH lab located in the Hock Building on Erwin Road:

Auditory training methods: Subjects will be provided customized auditory training program using materials from two existing computer-based auditory training programs that can be completed in the home. Specifically, we will use consonant and vowel discrimination and recognition modules from Speech Banana to focus on bottom-up processing tasks. This will allow for practice in discriminating between letters/words (e.g., bat/pat/mat or hid/hood/had). Additionally, modules from the Sound Success program

will be used, which focuses on understanding sentences/conversations in quiet and in noise using different talkers. The latter program also allows the patient to practice listening in familiar contexts (e.g., topics on weather, shopping, and family life). Both programs use an adaptive approach such that the difficulty of training stimuli is adjusted based on performance. Participants will be asked to bring their personal laptop or tablet to the baseline visit (if applicable) so they can download the auditory training software and conduct a practice session before leaving the clinic.

Transcranial Direct Current Stimulation (tDCS): We will use a device that was designed and validated to allow safe and reliable tDCS delivery at home (1x1 tES mini-CT, Soterix Medical, USA). This tDCS system incorporates a customizable headgear for individualized electrode placement and disposable, snap-in electrodes that are easy for the patient to apply at home without assistance. The device also allows the clinical team to control and monitor the home use by the patient. Based on the reports of listening related functional brain imaging (Price 2012), and transcranial stimulation studies (Heimrath et al. 2016), we will deliver anodal stimulation (positive electrode over target) of the primary auditory cortex contralateral to the CI implant.

Patient Reported Outcome Measures will be collected: Speech, Spatial, Qualities of Hearing (SSQ-12), and Cochlear Implant Quality of Life Questionnaire (CIQOL) will be collected at baseline, and the 1 month and 6 month follow-up visits.

An adverse event questionnaire will be collected continuously during the 4 week auditory training sessions and reviewed during each of the weekly tele-visits with a member of the study team.

Hearing and Speech Evaluation: Hearing thresholds and speech perception performance will be measured during the baseline visit, and 1 month and 6 month follow up visits using standard, validated and standard word and sentence lists presented in quiet and in noise (AzBio Quiet, AzBio +5/+10dB; CNC 50-item list) while the patient is wearing an appropriately programmed CI alone and/or with appropriately fitted contralateral hearing aid (if this is typically worn by the patient).

5) Study Schedule:

Visit 1/Baseline:

Subjects will undergo a screening visit to determine eligibility. The screening visit may be combined with a standard of care visit for patients already being seen for cochlear implant evaluation. Each participant will sign an informed consent before committing to any study-related tests or procedures and will include the following assessments:

- Obtain and document consent from potential participant on informed consent form (ICF).
- Conduct baseline hearing threshold and speech perception testing using standard audiological procedures (e.g., AzBio Quiet, AzBio +5/+10dB; CNC 50-item list) for screening for eligibility and baseline assessment
- Obtain patient reported outcome questionnaires (SSQ-12 and CIQOL)
- Auditory training and assignment of home-based personalized, computer-based rehabilitation/practice plan
- Orientation to tDCS equipment, determination of appropriate stimulation levels and electrode placement

- Conduct integrity evaluation of device using telemetry during initial tDCS trial.
- Repeat subset of speech perception assessment before, during and after the initial tDCS application.
- Instructions for completion of electronic daily diary to record adverse events and compliance of auditory training

The tDCS current will be programmed to 2.5mA prior to the start of integrity testing. If 2.5mA is intolerable, then the current will be reduced to 2.0mA. If a participant is still not able to tolerate 2.0mA, then this will be considered a screen fail and the subject will be removed from study.

Study participants meeting the screening criteria upon completion of the baseline visit will continue on study. Enrolled participants will be given a tDCS device to take home to complete study procedures with instructions to return it at the 1 month post-treatment visit to be completed in person.

Weeks 2-5 (Visits 2 – 5)

During the 30-day treatment period, subjects will be expected to complete the following:

- Complete daily web-based auditory training with tDCS stimulation for 30-minute sessions, at least five times per week for 4 weeks.
- Completion of a daily diary to record compliance of auditory training with tDCS, as well as to document adverse events that may occur during or after the sessions.
- Video visits will be conducted at least weekly by a member of the research team, starting more frequently in the first week, to provide technical assistance as needed, review reported adverse events, and give reminders regarding completion of the daily diary.

One-Month post-treatment (Visit 6)

Participants will be asked to return at the end of the 30-day treatment period for an in-person visit and undergo the following assessments:

- Hearing threshold and speech perception testing using standard audiological procedures (AzBio Quiet, AzBio +5/+10dB; CNC 50-item list)
- Obtain patient reported outcome questionnaires (SSQ-12 and CIQOL)
- Conduct integrity evaluation of device using telemetry
- Review of adverse events
- Return tDCS device

Six-Month post-treatment (Visit 7)

Participants will be asked to return for an in-person visit and undergo the following assessments:

- Hearing threshold and speech perception using standard audiological procedures (AzBio Quiet, AzBio +5/+10dB; CNC 50-item list)

- Obtain patient reported outcome questionnaires (SSQ-12 and CIQOL)
- Conduct integrity evaluation of device using telemetry
- Review of adverse events since the last visit

Schedule of Events Table							
	Baseline	Week 2 (televisit)	Week 3 (televisit)	Week 4 (televisit)	Week 5 (televisit)	1 month post-assessment (in-office visit)	6 month post - assessment (in-office visit)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Consent	X						
Hearing and Speech Reception Thresholds	X					X	X
Patient Reported Outcome Measures (SSQ12 and CIQOL)	X					X	X
Auditory Training in office – establish therapy plan	X	X					
In-office tDCS – establish protocol, patient training	X						
Home Auditory training and tDCS (daily)		→	→	→	→		
Weekly video visit to review use & compliance of training		X	X	X	X		
Review of symptoms and adverse events		X	X	X	X	X	X
Subject Compensation	X					X	X

6) Selection of Subjects:

Inclusion Criteria

1. Age ≥ 18 years of age
2. Patients with a unilateral Cochlear Implant device in use for a minimum of 1 year
3. Sentence recognition scores (AzBio) are below 65% in quiet and/or word recognition scores (CNC) are below 75% in the implanted ear for ≥ one year following cochlear implant activation.
4. Ability to access internet to conduct computer-based auditory trainings and weekly video visits with study team weeks 2–5

Exclusion Criteria

1. Non-English speaking
2. Diagnosis (documented or self-reported) of a psychiatric or neurologic condition, or any other comorbidities that may interfere with the study or increase the level of risk (such as dementia, seizures, legal blindness, brain tumor)
3. Implants, other than CI, above collar bone level that may interact with delivery of tDCS
4. Inability to or unwillingness to use electronic devices/computers, participate in video visits, or make required visits

7) Subject Recruitment and Compensation:

10 patients from the Duke Head and Neck and Communication Science clinics and/or the Duke Raleigh HNSCS Clinic will be recruited. Patients who meet the inclusion and exclusion criteria listed above will be approached for possible study participation after a member of the clinical care team asks the patient's permission to be contacted by the study team. The study coordinator (or member of the research team) will then review the records, and upon determination that the patient is deemed eligible for this protocol, the clinical research coordinator (CRC) will contact the patient. This may occur in clinic or via phone using an IRB approved phone script. If the patient indicates interest in study participation, the study coordinator will thoroughly explain the required elements of informed consent and all aspects of the study to the subject including inclusion/exclusion criteria, risks, benefits, and alternative to study participation. Up to 14 patients will be enrolled, allowing for 4 drop-outs.

Subjects will be compensated $75 upon completion of the baseline visit (visit 1), $100 upon completion of the one-month f/u visit (visit 6) and $75 upon completion of the six-month follow up visit (visit 7) for total of $250.

8) Consent Process:

The principal investigator, cochlear implant audiologist/coordinator, study coordinator, or authorized key personnel will explain all aspects of the study in lay language and answer all questions regarding the study. The consent process will occur in a private room or via phone and eConsent. eConsent is available via REDCap. This functionality provides the ability to consent remote participants or participants in clinic via tablets or touchscreen device.

Participants will have the capability to sign electronically with a stylus, mouse, or finger. Once the consent form is submitted, participants will receive an email that includes a PDF attachment with a copy

of the signed consent form. The PDF will be emailed to Health Information Management from REDCap for incorporation into Epic.

The subject will be asked for permission to proceed if other people are in the room. The potential subject will have as much time as they need to decide if they would like to participate or not. The potential subject will be encouraged to review the consent and discuss it with any family members if they wish. The subject and will be given the contact information of the study coordinator and PI to call with any questions before or after consent is signed. The investigator will discuss all treatment options with potential subjects and they will be informed that participation in this study is voluntary and will not affect access to their health care at Duke, and that they may stop participating at any time.

If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. No study procedures will be conducted without prior written informed consent. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

9) Subject's Capacity to Give Legally Effective Consent: It is not anticipated that we will enroll subjects who do not have the capacity to give legally effective consent. Non-English speaking subjects will not be approached for the study.

10) Study Interventions:

Refer to the Design and Procedure section.

11) Risk/Benefit Assessment:

Safety of Stand-Alone tDCS

tDCS uses low voltage (typically < 20 V) and direct currents (typically < 2 mA) applied through scalp surface electrodes. Thus, it is comparable to connecting a conventional 9 V battery to the electrodes. The low voltages and currents contribute to an excellent safety profile of tDCS. According to a recent review paper (Bikson et al 2016) there are no known long-term health risks from the use of tDCS, per se, when operated within consensus safety guidelines. However, minimal, acute side effects of tDCS may include discomfort, skin irritation, lightheadedness, and headache.

- *Potential risk of skin irritation.* The most commonly reported side effect is skin irritation at the sites of the tDCS electrodes. This may include reddening of the skin underneath the electrodes or itching at the site of stimulation. Skin lesions, such as burn-like lesions or contact dermatitis, have also been observed.
- *Potential risk of lightheadedness.* While rare, feelings of pre-syncope, or lightheadedness, with stimulation can occur. This condition can sometimes occur during the "ramp-up" or "ramp-down" phase at the beginning and end of the protocol as the current is changing.
- *Potential risk of headache.* A potential side effect of tDCS is a headache that could develop during or immediately after the stimulation and may last for minutes to hours following the end of the stimulation. It is typically limited to the day of stimulation, and usually responds promptly to single doses of over-the-counter analgesics.
- *Potential risk of impairments in cognitive function.* There has been no evidence of neuronal damage or cognitive impairment induced by tDCS as demonstrated in Nitsche and Paulus (2001) and Nitsche et al. (2003).

As noted above, the primary side effects of tDCS are mostly related to interactions between the electrodes and the scalp skin. These side effects however are mitigated by the proper selection and application of the electrodes. To minimize chemical reactions at the electrode–skin interface, non-metallic, conductive rubber electrodes, covered completely with saline-saturated sponges will be used in this study, as recommended by Nitsche and Paulus, 2000. The electrodes will be single-use and packaged for convenient and safe use at home by the patients.

The team has experience with the application of tDCS in healthy volunteers and patients at Duke. For example, as part of IRB Protocol #00078782 "Laparoscopic Skills Training", Dr. Appelbaum and colleagues ran over 69 healthy subjects in 191 sessions with no adverse events. As well, Dr. Peterchev consulted on tDCS device application in a multi-center trial, including Duke, of tDCS in patients with depression (Loo et al, 2018). That study included 130 participants (27 at Duke). The most common side effects were tingling, redness, burning sensation, itching, and light-headedness/dizziness.

Safety of Combining tDCS and CI

Dr. Peterchev has evaluated the safety of interactions between various transcranial and implanted stimulation devices, including tDCS and CIs (Peterchev, Dhamne, et al. 2012; Deng et al. 2010; Deng, Lisanby, and Peterchev 2010; Rossi et al. 2009). The tDCS device does not emit a significant electromagnetic field and the CI implant is electrically insulated from the patient except for the cochlear electrode contacts and reference electrode. Therefore, the primary safety question for the novel combination of tDCS and a CI in this study is whether the electric field generated by tDCS in the patient's head injects significant currents in the CI electrodes. Dr. Peterchev and post-doc Dr. Dannhauer conducted computer simulations of the maximum electric fields for the proposed tDCS device (for illustration of tDCS electric field simulations, see Fig 1A). The simulations indicated that the upper bound of the voltages between the CI electrodes (1.75 V at 2.5 mA tDCS current, the maximum output of the tDCS device) is below the intrinsic voltages applied by the CI (6.5 V). Further, the capacitive coupling of the CI electrodes blocks the direct current applied by tDCS. Safety testing conducted as part of the original FDA approval by one of the CI manufacturers (MED-EL Corporation) showed that the implant can tolerate external voltages of at least 20 V. Finally, there are reports of patients with CI that developed Parkinson's disease and were implanted with a deep brain stimulation device, which did not interfere with the CI (Buell et al. 2015). These technical assessments and empirical evidence support the safety of combining tDCS with CI. Therefore, the combination of tDCS and CI is not expected to increase the low risk of tDCS alone.

It's possible that tDCS pads may cause damage to hearing aid microphones if they get wet. Therefore, participants who wear a contralateral hearing aid will be instructed to remove it prior to and during the use of tDCS.

Participants will record daily symptoms via a link to a REDCap survey. REDCap will be programmed to alert the PI and/or SC of symptoms with an intensity level reported at 8 or above on the AE/symptom survey, regardless of the duration indicated (refer to table below). The PI, SC, or delegate will contact the patient to obtain additional information and determine if tDCS should be discontinued, and if a referral for medical evaluation is needed.

In conclusion, given the low risk of tDCS and its combination with CI, the risk/benefit is favorable since improvement in the patients' speech perception due to the administration of tDCS could improve their quality of life.

12) Costs to the Subject:

The study does not involve any costs to subjects. Costs for the audiological assessments will be covered by the study. tDCS devices for in-home use will be provided to study participants at no charge and returned at the end of the 1-month follow-up visit.

13) Data Analysis & Statistical Considerations:

The primary outcome measures of feasibility are: 1) proportion of eligible CI patients who expressed interest in the study; 2) proportion of selected participants who completed tDCS training and demonstrated competence in the office and subsequently at home during remote visits; 3) proportion of participants who completed most or all of the proposed intervention protocol; 4) proportion who completed relevant appointments, and reasons for any missing data; 5) acceptability of patient incentive; 6) patient report of ease/difficulty carrying out the protocol via a patient survey at Visit 2; 7) proportion of people with any adverse events, and 8) other feasibility and acceptability metrics consistent with the latest guidelines on pilot studies (Eldridge et al. 2016). After each in-office tDCS application and at the immediate one month post-intervention Visit 6, the site of tDCS stimulation and the CI site will be visually examined for any skin irritation or tenderness and the internal and external CI devices will be examined for signs of abnormal function. Adverse effects of tDCS will be measured by the intensity and duration of symptoms recorded on the daily diary.

The primary outcome measures of efficacy will be speech perception performance in the best listening condition compared to baseline, progress within the computer-based rehabilitation program and patient report of improved daily communication function. Speech perception performance will be measured using validated and standard word and sentence lists presented in quiet and in noise (AzBio Quiet, AzBio +5/+10dB; CNC 50-item list).

For the primary outcome we are reporting straightforward proportions and will not be conducting any group comparisons. The prevalence with which adverse effects are reported will be determined for the study as a whole and for different time windows during the study. To address efficacy we would compare baseline speech perception and survey results with 1 and 6 month data.

Descriptive analysis will including mean and standard deviations, and may also include evaluate for improvement using paired t-test. Need for statistical consultation is likely to be minimal but will be sought if appropriate.

14) Data & Safety Monitoring:

The PI will ensure proper data and safety monitoring. Any serious adverse events will be reported by the PI to the IRB within 5 business days. Events that are considered both serious and unanticipated will be reported to the IRB within 24 hours of the PI's knowledge of the event. The PI will reconsider study design and procedures in discussion with the IRB should adjustments be warranted.

Adverse events will be monitored from the start of auditory training with tDCS at week 2 until the six-month follow-up visit at visit. The PI and study team will meet frequently to review patient reported adverse events.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject requests to withdraw from protocol-required therapies or the study due to an adverse event.

Definition of unanticipated and serious adverse events requiring prompt reporting to the IRB are described below:

Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

Serious Adverse Events

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

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

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

15) Participant Discontinuation or Withdrawal from the study:

Participants will be removed in the event of a serious adverse reaction to tDCS.

Subjects will have the option of withdrawing from the study at any time for any reason. Reason and date for withdrawal, as well as any adverse events since the last study visit will be documented.

The Principal Investigator may discontinue a subject from study treatment, or withdraw a patient from the study. Reasons for study treatment discontinuation or withdrawal may include but are not limited to the following:

- Adverse event or hypersensitivity reactions thought to be related to the tDCS device
- Patient voluntarily decides to withdraw.
- Patient non-compliance with the study protocol.
- Intercurrent disease, which in the opinion of the patient's treating physician, would affect the ability of the patient to continue on the clinical study.
- Patient lost to follow-up.

16) Privacy, Data Storage & Confidentiality:

Study records that identify subjects will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS).

Potential subjects will be approached and the study will be discussed in a private clinic or hospital room or via phone to protect their privacy and allow them to ask any questions. Subjects' privacy will also be protected by assigning each subject a unique identification code. This code will be used for the completion of all CRFs and study documents.

Prior to dissemination of any information in this database beyond the DUMC's secure servers or firewall, all identifiers will be stripped from the database and data will only be referenced by the study-specific identification numbers. A master log, which links the study-specific identification number to the study subject, will be generated.

Any publications or presentations that result from this research will not identify any subjects individually, and will present data in aggregate form only.

Confidentiality of subject data will be ensured by de-identification of subject data. During data collection, subject identifiers and relevant data elements will be recorded in the database. Then, study-specific identification numbers will be assigned to each subject. We will not record Zoom or Webex sessions and we will not use the chat functions for research purposes, and no PHI will be recorded within the chat window.

Prior to dissemination of any information in this database beyond the DUMC's secure servers or firewall, all identifiers will be stripped from the database and data will only be referenced by the study-specific identification numbers. A master log, which links the study-specific identification number to the study subject, will be generated.

Any data that is stored in paper or non-digital format will be locked in a file cabinet within a key-accessed office. The office will be locked when not in use by the study team. Any data that is stored in electronic format will be housed behind the Duke University Medical Center firewall. Subject data will be entered into a password-protected and encrypted REDCap database. De-identified data may be stored in a secure, study-specific Duke Box folder with access given to only to IRB approved key personnel. In addition, the Surgery Servers plan in which sensitive electronic information (SEI) is stored on a surgery network drive will be used. No SEI will be stored on mobile computing or storage devices.

The adequacy of the Research Data Security Plan (RDSP) will be evaluated and approved by the Surgery CRU and Surgery IT personnel prior to study conduct.

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