Complete Research Protocol (HRP-503)

PROTOCOL TITLE:

Include the full protocol title.

Response: Role of transcranial direct current stimulation in appetite and weight control, a prospective randomized study.

PRINCIPAL INVESTIGATOR:

Response:

Paresh Dandona, MD PhD

Division of Endocrinology, Department of Medicine

Phone: 716-535-1850

Email: pdandona@kaleidahealth.org

Sub Investigators:

Miguel Alonso Alonso, MD PhD

Chi Tang, MD

VERSION:

Include the version date or number.

Response:

08/01/2017

GRANT APPLICABILITY:

Indicate whether this protocol is funded by a grant (e.g. NIH, foundation grant). For a grant with multiple aims, indicate which aims are covered by this research proposal.

NOTE: This question does not apply to studies funded by a sponsor contract.

Include a copy of the grant proposal with your submission.

Response:

The project is not funded by a grant

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Template Instructions

Sections that do not apply:

In several sections, the addition of checkboxes for ***Not Applicable*** *have been added to the template as responses.*

If an N/A checkbox is present, select the appropriate justification from the list.

If an N/A checkbox is not present, or if none of the existing checkboxes apply to your study, you must write in your own justification.

In addition:

For research where the only study procedures are records/chart review: Sections 19, 20, 22, 23, 24, 25, 31, and 32 do not apply.

For exempt research: Sections 31 and 32 do not apply.

Studies with multiple participant groups:

If this study involves multiple participant groups (e.g. parents and children), provide information in applicable sections for each participant group. Clearly label responses when they differ. For example:

Response: This study does not involve multiple participant groups

Intervention Group:

Control Group:

Formatting:

Do not remove template instructions or section headings when they do not apply to your study.

If you are pasting information from other documents using the "Merge Formatting" Paste option will maintain the formatting of the response boxes.

Amendments:

- *When making modifications or revisions to this and other documents, use the* ***Track Changes*** *function in Microsoft Word.*
- *Update the version date or number* ***on Page 3.***

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RESEARCH REPOSITORY:

Indicate where the research files will be kept, including when the study has been closed. The repository should include, at minimum, copies of IRB correspondence (approval, determination letters) as well as signed consent documents. This documentation should be maintained for 3 years after the study has been closed.

Response:

Location:1000 Youngs Road, Suite 105, Williamsville NY 14221

Department: Diabetes Endocrinology

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives of this research.

Response: To study the effects of transcranial direct current stimulation (tDCS) on weight and appetite.

Aim:

1. *To compare weight loss over one month in active tDCS group with sham tDCS group. We will measure weight of every participants at the beginning of the study and one month after the last session of tDCS*
2. *To compare change in insulin sensitivity over one month in active tDCS group with sham tDCS group. We will measure fasting insulin and glucose level, and calculate homeostatic model assessment-insulin resistance (HOMA-IR)*
3. *To compare change in cognitive performance as a response to food over one month in active tDCS group with sham tDCS group. We will evaluate performance in a computerized task that measures executive functions under the presence of food (working memory, inhibitory control and a combination of both). We will assess changes in accuracy and speed in the task under active tDCS versus sham tDCS.*
4. *To compare change in post-prandial glucose excursion and average meal counts per day. We will use continuous glucose monitor to record the frequency and amplitude of glucose excursion.*

1.2 State the hypotheses to be tested, if applicable.

NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

Response:

Hypothesis:

1. *Active tDCS will result in more weight loss, appetite reduction and improved insulin sensitivity compared with sham tDCS over one month period.*
2. *The effect of tDCS on weight, appetite, glucose tolerance and cognitive response to food varies according to the underlying allele status of BDNF and COMT gene*

2.0 Scientific Endpoints

2.1 Describe the scientific endpoint(s), the main result or occurrence under study.

NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should ***not*** *be a date.*

Response:

Primary endpoints: change in weight, measured as a percentage of baseline body weight.

Secondary endpoints: change in HOMA-IR, change in average daily meal counts based on frequency of glucose excursion on continuous glucose monitor, change in average amplitude of glucose excursion curve after meals, change in cognitive performance in response to food

3.0 Background

3.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute to existing knowledge. Describe any gaps in current knowledge. Include relevant preliminary findings or prior research by the investigator.

Response:

Transcranial Direct current stimulation (tDCS) is a procedure in which a pair of electrode pads is applied over the scalp to deliver mild direct electric current to a specific area of the brain. It changes spontaneous firing rate of neurons underlying the pads[1], and the persistence of this modification in excitability of neurons can last up to 1 hour after the cessation of electric current[2]. This effect can be prolonged with repetitive stimulation over several consecutive days, most likely mediated by synaptic changes[3].

Left dorsolateral prefrontal cortex is a subregion of the prefrontal cortex considered to be involved in taste[4] and satiation[5]. Previous studies also demonstrated left dorsolateral prefrontal cortex in response to meal is different in lean men and women from obese subjects[6, 7], with obese subjects mounted a more significant response after meal. Therefore, this region of brain is a potential target for obesity intervention.

A recent study showed that tDCS inhibit craving for food[8]. Another prospective study of 9 obese subjects reveal that tDCS is associated with weight loss[9]. Our proposed study will explore the effect of tDCS on weight, appetite and glucose tolerance in long term (over 1 month period) and in a larger study population. We will apply sham tDCS as control. In sham tDCS, the duration of stimulation will be limited to 15 seconds instead of 30 minutes in the active tDCS group. According to previous study, subjects are the not able to differentiate sham from active tDCS [9].

Polymorphism of the catechol-O-methyltransferase (COMT) gene was found to interact with tDCS intervention and change its effect on higher level executive function[10]. The brain derived neurotrophic factor (BDNF) gene polymorphism was also shown to modulate the effect of tDCS on motor cortex plasticity [11]. Therefore, these genes can potentially alter the effect of tDCS on weight, appetite and cognitive response to food.

3.2 Include complete citations or references.

Response:

1. *Wassermann, E.M. and J. Grafman,* Recharging cognition with DC brain polarization. *Trends Cogn Sci, 2005.* ***9****(11): p. 503-5.*

2. *Priori, A.,* Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clin Neurophysiol, 2003.* ***114****(4): p. 589-95.*

3. *Stagg, C.J. and M.A. Nitsche,* Physiological basis of transcranial direct current stimulation. *Neuroscientist, 2011.* ***17****(1): p. 37-53.*

4. *Kringelbach, M.L., I.E. de Araujo, and E.T. Rolls,* Taste-related activity in the human dorsolateral prefrontal cortex. *Neuroimage, 2004.* ***21****(2): p. 781-8.*

5. *Tataranni, P.A., et al.,* Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. *Proc Natl Acad Sci U S A, 1999.* ***96****(8): p. 4569-74.*

6. *Gautier, J.F., et al.,* Differential brain responses to satiation in obese and lean men. *Diabetes, 2000.* ***49****(5): p. 838-46.*

7. *Gautier, J.F., et al.,* Effect of satiation on brain activity in obese and lean women. *Obes Res, 2001.* ***9****(11): p. 676-84.*

8. *Fregni, F., et al.,* Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite, 2008.* ***51****(1): p. 34-41.*

9. *Gluck, M.E., et al.,* Neuromodulation targeted to the prefrontal cortex induces changes in energy intake and weight loss in obesity. *Obesity (Silver Spring), 2015.* ***23****(11): p. 2149-56.*

10. *Plewnia, C., et al.,* Effects of transcranial direct current stimulation (tDCS) on executive functions: influence of COMT Val/Met polymorphism. *Cortex, 2013.* ***49****(7): p. 1801-7.*

11. *Puri, R., et al.,* Duration-dependent effects of the BDNF Val66Met polymorphism on anodal tDCS induced motor cortex plasticity in older adults: a group and individual perspective. *Front Aging Neurosci, 2015.* ***7****: p. 107*

4.0 Study Design

4.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, observational).

Response:

Single center, double blinded, controlled, randomized, prospective study

There are two groups to which participants are being randomized, one with active transcranial stimulation and one with sham stimulation.

5.0 Local Number of Subjects

5.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed locally.

Response:

20

5.2 If applicable, indicate how many subjects you expect to screen to reach your target sample (i.e. your screen failure rate).

Response:

40

5.3 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response:

In our clinics, we will see about 20 patients every week that meet the inclusion criteria. We only need to recruit 10% of them over 10 weeks.

6.0 Inclusion and Exclusion Criteria

*6.1 Describe the criteria that define who will be **included** in your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:

1. Men and women 18 to 80 years of age
2. Body mass index > 30 kg/m2

*6.2 Describe the criteria that define who will be **excluded** from your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:

1. Current participation in any other concurrent clinical trials or previous participation within 30 days before the screening visit
2. Pregnancy or premenopausal women who are trying to be pregnant
3. Patients who are incompetent to give consent
4. Obesity due to a known secondary cause (Cushing's syndrome, hypothyroidism, etc) or a history of weight loss surgery

5. Have taken any of the following medications within the past 3 months:

phentermine, naltrexone, bupropion, topiratmate, lorcaserin, phendimetrazine, methamphetamine, benzphetamine, diethylpropion

6. Any contraindication to receive transcranial direct current stimulation (tDCS):

a. Personal or family history of seizures, epilepsy or other unexplained loss of consciousness.

b. Current or past history of skin disease or damaged skin on the scalp at the site of stimulation (i.e. eczema, skin with ingrown hairs, acne, razor nicks, wounds that have not healed, recent scar tissue, broken skin, etc.).

c. Prior neurosurgical procedure or radiation.

d. Known diagnosis of brain lesions, such as tumor, stroke or multiple sclerosis

e. Implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, Transcutaneous Electrical Nerve Stimulation unit, ventriculo-peritoneal shunt or any metallic implant on the head.

6.3 Indicate specifically whether you will include any of the following special populations in your study using the checkboxes below.

NOTE: Members of special populations may not be targeted for enrollment in your study unless you indicate this in your inclusion criteria.

Response:

☐ Adults unable to consent

☐ Individuals who are not yet adults (infants, children, teenagers)

☐ Pregnant women

☐ Prisoners

6.4 Indicate whether you will include non-English speaking individuals in your study. ***Provide justification if you will exclude non-English speaking individuals.***

In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may ***not*** *be routinely excluded from research as a matter of convenience.*

In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.

Response:

We will not enroll non-English speaking individuals. Enrollment in this study is not large (20 participants in total) and there is no reason to believe that the study would be withholding benefit from non-English speaking subjects.

7.0 Vulnerable Populations

If the research involves special populations that are considered vulnerable, ***describe the safeguards included to protect their rights and welfare.***

NOTE: You should refer to the appropriate checklists, referenced below, to ensure you have provided adequate detail regarding safeguards and protections. You do not, however, need to provide these checklists to the IRB.

7.1 For research that involves ***pregnant women,*** *safeguards include:*
NOTE CHECKLIST: Pregnant Women (HRP-412)

Response: We will not be using subjects from vulnerable populations

☒ **N/A**: This research does not involve pregnant women.

7.2 For research that involves ***neonates of uncertain viability or non-viable neonates,*** *safeguards include:*
NOTE CHECKLISTS: Non-Viable Neonates (HRP-413), or Neonates of Uncertain Viability (HRP-414)

Response:

☒ **N/A:** This research does not involve non-viable neonates or neonates of uncertain viability.

7.3 For research that involves ***prisoners****, safeguards include:*
NOTE CHECKLIST: Prisoners (HRP-415)

Response:

☒ **N/A:** This research does not involve prisoners.

7.4 For research that involves ***persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children")****, safeguards include:*
NOTE CHECKLIST: Children (HRP-416)

Response:

☒ **N/A:** This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

7.5 For research that involves ***cognitively impaired adults****, safeguards include:*
NOTE CHECKLIST: Cognitively Impaired Adults (HRP-417)

Response:

☒ **N/A:** This research does not involve cognitively impaired adults.

7.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. ***Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.***

Response:

Not applicable

8.0 Eligibility Screening

8.1 Describe ***screening procedures*** *for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.*

📎 *Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaire).*

Response: We will first look at the electronic medical record of our clinics to identify potential candidates and this will be followed by patient doctor interaction at the time of their visit. Potential candidates will be scheduled to come to the research unit for a screening visit. Please see the screening documents

☐ **N/A:** There is no screening as part of this protocol.

9.0 Recruitment Methods

☐ **N/A:** This is a records review only, and subjects will not be recruited.
NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections.

9.1 Describe when, where, and how potential subjects will be recruited.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. Include specific methods you will use (e.g. searching charts for specific ICD code numbers, Research Participant Groups, posted advertisements, etc.).

Response:

Participants will be identified by prescreening clinical charts prior to their clinic visit, and patient doctor interaction at the time of their visit at the Diabetes Endocrinology Center of WNY and Western New York VA Hospital. If the patient expresses interest after speaking with their physician and provide their contact information, they will be scheduled for a screening visit. The recruitment will start immediately after approval by IRB. Advertisements and flyers will be posted at these locations with the contact phone number for the patient to call the research team, if interested in participating.

Locations include:

1. 1020 Youngs Road, Williamsville NY 14221
2. 705 Maple Road, Williamsville NY 14221

3. 462 Grider Street, Buffalo NY 14215

4. 3495 Bailey Avenue, Buffalo NY 14215

9.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.

NOTE: Privacy refers to an individual's right to control access to him or herself.

Response: HIPAA waiver is being requested, so that we will be able to use identifiable health information for subject recruitment. Any potential participant's personal health information will be kept solely between the study team and handled just as clinic patients' personal health information is handled. Locked file cabinets in locked offices for written data, password protected logins for electronic data, private rooms for any patient discussion. The data will only be shared with the study team who have all taken CITI training and will follow University privacy policies. We will not retain personal identifiers once the candidate is identified in the electronic medical record and contacted, no matter if the candidate agrees or declines to participate.

9.3 Identify any materials that will be used to recruit subjects.

NOTE: Examples include scripts for telephone calls, in person announcements / presentations, email invitations.

For advertisements, include the final copy of printed advertisements with your submission. When advertisements are taped for broadcast, attach the final audio/video tape. NOTE: You may submit the wording of the advertisement prior to taping to ensure there will be no IRB-required revisions, provided the IRB also reviews and approves the final version.

Response: Please see attached document

10.0 Procedures Involved

*10.1 Provide a description of **all research procedures or activities** being performed and when they are performed once a subject is screened and determined to be eligible. Provide as much detail as possible.*

NOTE: This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research. For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response.

Screening Day

All subjects will have completed the following procedures prior to participating in the study:

1) Informed consent

2) Medical history

3) Physical exam (including body mass index measurement)

We will collect general demographic data regarding years of education, race/ethnicity.

A continuous glucose monitor will be calibrated with finger blood glucose result and the probe of the monitor will be inserted into the abdominal subcutaneous tissue. Patient will be instructed on how to use continuous glucose monitor, they will be instructed to wear it and document the time and the types of food of every meal for at least 72 hours after the screening visit.

Subjects will be instructed not to change their medications during the whole study period and not to take insulin for at least 4 hours before visit 1, visit 5 and visit 6.

Visit 1:

Subjects will come back within 2 weeks and will arrive after having fasted overnight (10 hours) at 7 to 7:30 am. They will then be randomized to either active tDCS or sham tDCS with block randomization (block size of 10). We will test urine pregnancy test to rule out pregnancy. Pregnant subject will be excluded from the study. We will also administer the three-factor eating questionnaire (Stunkard and Messick, 1985), which measures eating habits and attitudes toward food, weight and dieting, and a personality questionnaire, the Big Five (Costa and McCrae, 1989). We will evaluate cognitive responses to food with a 20-minute computerized task designed to engage the inhibitory control circuit when confronted with food stimuli, as well as engaging the other two components of executive function: working memory and cognitive flexibility. The task consists of 3 parts: a version of a Go/No-Go (GNG) task modified for food; an N-back memory task with food images, similar to a task used in a previous study; and a combined N-back and GNG task. In the food modified GNG task subjects have to press the space bar of a computer in response to pictures of low-calorie food, refraining from pressing when the pictures are of high-calorie food (25% of the time). In the N-back task, subjects will press the space bar when the picture displayed matches the picture displayed two images before. In the combined task, the subject will press the space bar when a picture of low-calorie food matches the picture displayed two images before, while refraining from pressing when a high-calorie food matches the picture displayed two images before.

Blood sample for BDNF and COMT gene test will be collected. We will also collect blood sample for plasma insulin and glucose level. We will download data from the continuous glucose monitor.

Subjects assigned to active tDCS group will receive 30 min of anodal tDCS delivered with a neuroConnVR DCSTIMULATOR device (neuroConn GmbH, Ilmenau, Germany), at a constant current of 2 mA (with a 30-second ramp at on- and offset) using two sponge electrodes soaked in a sterile 0.9% sodium chloride solution. The anode electrode will be placed over F3 (10–20 EEG system), with the cathode electrode placed over the contralateral supraorbital area, above the right eyebrow. This montage was used in a recent study that showed reduction of body weight and intake of soda and fat in a sample of obese subjects.

Subjects assigned to sham tDCS group will receive 15 seconds of anodal tDCS delivered with a neuroConnVR DCSTIMULATOR device (neuroConn GmbH, Ilmenau, Germany), at a constant current of 2 mA (with a 30-second ramp at on- and offset) using two sponge electrodes soaked in a sterile 0.9% sodium chloride solution. However, they will stay at the research center for 30 minutes with electrodes on their scalp. Before starting the stimulation, a code will need to be entered into the tDCS machine which will decide whether a sham or active stimulation will be performed by the machine automatically in the next 30 minutes. At the beginning of the study, a code that is associated with either active stimulation or sham stimulation will be assigned to the subject based on the randomization. However, neither the subject or the operator of tDCS machine will know what does the code represent.

Visit 2: Subjects will come back next day to receive the second session of the same intervention.

Visit 3: Subjects will come back next day to receive the third session of the same intervention.

Visit 4: Subjects will come back next day to receive the fourth session of the same intervention.

Visit 5: Subjects will fast overnight (10 hours) and come back next morning at 7 to 7:30 AM to receive the fifth session of the same intervention. We will then measure body mass index, plasma insulin and glucose, appetite and cognitive function in response to food. Continuous glucose monitor will be reinstalled, and subjects will be instructed to wear it and document the time and types of food of every meal for at least 72 hours after this visit and 72 hours before the next visit. Subject will be instructed on how to insert and remove continuous glucose monitor again.

Visit 6: Subjects will fast overnight (10 hours) and come back next morning at 7 to 7:30 AM in 4 weeks after visit 5. We will measure body mass index, plasma insulin and glucose, appetite and cognitive function in response to food again. We will download data from the continuous glucose monitor. We will also ask if the subject believed that he/she received active or sham tDCS.

10.2 Describe what data will be collected.

NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

Response:

We will collect general demographic data regarding years of education, race/ethnicity. We will also administer the three-factor eating questionnaire (Stunkard and Messick, 1985), which measures eating habits and attitudes toward food, weight and dieting, and a personality questionnaire, the Big Five (Costa and McCrae, 1989).

Plasma glucose and insulin level during screening visit, visit 5 and visit 6

COMT and BDNF gene during screening visit

Weight, height and body mass index (BMI) during screening visit, visit 5 and visit 6

Cognitive response to food during screening visit, visit 5 and visit 6.

Average daily meal counts and type of food based on patient report and continuous glucose meter on visit 1 and visit 6

10.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).

Include copies of these documents with your submission.

Response: Please see form for screening visit, form for follow up visit 1, 2, 5 and 6, eating habit questionnaire, personality questionnaire.

Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).

Response: electronic medical records, clinical charts and research files

*10.4 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.*

Response: Individual participant lab results will be disclosed to the participant upon their request. If the participant requests documentation be shared with another physician, physician office or hospital, the participant must come to the research center to collect said documentation and/or the documentation can be mailed to their given home address.

*10.5 Indicate whether or not **study** results will be shared with subjects or others, and if so, describe how these will be shared.*

Response: Study results will not be shared directly with subjects. However, study results could be published in the form of a manuscript, to an academic journal.

11.0 Study Timelines

11.1 Describe the anticipated duration needed to enroll all study subjects.

Response: 10 weeks

11.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

Response: If the subject was found to meet the eligibility criteria, he/she will come to our research center for 6 appointments. Each appointment lasts for 1 hour and the total length of the study is about 2 months

11.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Response: 18 months

12.0 Setting

12.1 Describe all facilities/sites where you will be conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.

NOTE: Examples of acceptable response may be: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Buffalo General Medical Center, a fully accredited tertiary care institution within New York State with badge access," or, "Community Center meeting hall."

Response:

Research will be conducted at the Diabetes Endocrinology Research Center of WNY, located at 1000 Youngs Road, Suite 105, Williamsville NY 14221. The Diabetes Research Center has facilities and exam rooms available for insulin pump download, continuous glucose monitor device download, meal and infusion studies and presence of study coordinator and registered nurse for data collection and blood work at all times. One of the investigators will be available at all times to address patients' related issues. Equipment include ultra-low freezers for sample storage, centrifuges, microscopes for sample preparation, infusion pumps, ELISA, PCR and immunoblotting instrumentation. CTRC location is a fully equipped laboratory

12.2 For research conducted outside of UB and its affiliates, describe:

- *Site-specific regulations or customs affecting the research*
- *Local scientific and ethical review structure*

NOTE: This question is referring to UB affiliated research taking place outside UB, i.e. research conducted in the community, school-based research, international research, etc. It is not referring to multi-site research. UB affiliated institutions include Kaleida Health, ECMC, and Roswell Park Cancer Institute.

Response:

☒ **N/A:** This study is not conducted outside of UB or its affiliates.

13.0 Community-Based Participatory Research

13.1 Describe involvement of the community in the design and conduct of the research.

NOTE: Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

Response:

☒ **N/A:** This study does not utilize CBPR.

13.2 Describe the composition and involvement of a community advisory board.

Response:

☒ **N/A:** This study does not have a community advisory board.

14.0 Resources and Qualifications

*14.1 Describe the qualifications (e.g., education, training, experience, expertise, or certifications) of the Principal Investigator **and** staff to perform the research. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.*

NOTE: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify a person by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that the person meets the qualifications described to fulfill their roles.

Response:

Dr. Paresh Dandona is the chief of endocrinology division and a distinguished professor of University at Buffalo. He has published multiple articles in the field of obesity. Staff members at our research unit at Erie County Medical Center are well trained to conduct this type of research. Further, all study personnel are educated, trained, and licensed as required for their delegated role in this study. All study personnel have also received the required university training and will be trained by the PI before the study starts

Dr. Miguel Alonso-Alonso is an expert in transcranial direct current stimulation. He will provide transcranial direct current stimulation device, computer tasks and questionnaires training. He will also review the protocol and participate in manuscript preparation. He and his staff at Harvard university has trained and will continue to train our staff if there is a need.

Describe other resources available to conduct the research.

14.2 Describe the time and effort that the Principal Investigator and research staff will devote to conducting and completing the research.

NOTE: Examples include the percentage of Full Time Equivalents (FTE), hours per week. The question will elicit whether there are appropriate resources to conduct the research.

Response:

The principal investigator supervises the research project and weekly research meetings are conducted to discuss the recruitment rate, resolve and discuss issues related to the conduct, safety, analysis of the study and related publications. PI is expected to spend 5% of his academic time on this research. The co-investigators and study coordinator provide coverage to the research related activity for 365 days a year.

14.3 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable.

NOTE: One example includes: on-call availability of a counselor or psychologist for a study that screens subjects for depression.

Response:

Available medical literature will be provided as deemed appropriate or requested by patient through UB libraries, Pubmed, Google scholar as all the investigators have access to medical literature through listed resources above

The patient will also have access to physician (Investigators and Co-Investigators) who will be available to address any adverse effects or other questions during the course of the study

14.4 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response: Education through meetings, conferences and discussions

15.0 Other Approvals

15.1 Describe any approvals that will be obtained prior to commencing the research (e.g., school, external site, funding agency, laboratory, radiation safety, or biosafety).

Response:

☒ **N/A:** This study does not require any other approvals.

16.0 Provisions to Protect the Privacy Interests of Subjects

16.1 Describe how you will protect subjects' privacy interests during the course of this research.

NOTE: Privacy refers to an individual's right to control access to him or herself. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

Examples of appropriate responses include: "participant only meets with a study coordinator in a classroom setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Response:

Patients who agree to be contacted for potential participation in a research study will have their information given to the research coordinator to be contacted.

Participant will arrive at the Diabetes Endocrinology Research Center of WNY,and will be placed in a private area to review the consent. They will be allowed to address their question and concerns in private with the research coordinator, study nurse and/or research physician. At any time during the study the patient is able to place privacy restriction to their protected heath information (i.e. telephone message, PHI release forms) which the study personnel document and respect.

Additionally, when patients are seen in the clinic for the first time they sign the "Consent to use and disclosure of protected health information". This form clearly states that their protected health information (PHI) can be used for review in preparation for possible research.

We will not be accessing any medical information of the patients for whom the services are not provided by our clinic providers

16.2 Indicate how the research team is permitted to access any sources of information about the subjects.

NOTE: Examples of appropriate responses include: school permission for review of records, consent of the subject, HIPAA waiver. This question ***does apply*** *to records reviews.*

Response: Consent of the subject and HIPAA waiver.

17.0 Data Management and Analysis

17.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.

Response:

The demographic features of the population and screening lab results will be displayed in tables. Statistical analysis will be conducted using SigmaStat software version 3.1 (SPSS Inc., Chicago, IL). Data will be represented as mean±S.E. Sample size cannot be estimated as this is a pilot study. Generalized linear mixed model will be applied to compare the difference in weight, average amplitude of glucose excursion curve, average daily meal count, HOMA-IR, reaction time and percentage correct response in computerized cognitive tests. Predicting variables include time in the study (baseline, visit 5 and visit 6) and type of intervention (active tDCS vs sham). Sensitivity analysis will be performed to evaluate baseline imbalance, outliers, protocol violation, and missing data. The proposed covariants to be evaluated for baseline imbalance includes age, gender, COMT and BDNF gene status, baseline weight, baseline HOMA-IR, baseline average amplitude of glucose excursion curve, baseline average daily meal count, baseline reaction time and percentage correct response.

17.2 If applicable, provide a power analysis.

NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

Response: This is a pilot study, so we are not able to estimate sample size. However, previous shorter term study showed a small effect of tDCS on appetite and weight (see reference 9) in nine patients. We consider that by recruiting 20 participants, it will be more likely to detect a significant change, while the total expense will still be within the limit of our fund.

17.3 Describe any procedures that will be used for quality control of collected data.

Response:

Date entered by research staff will be verified by another person independently.

18.0 Confidentiality

A. Confidentiality of Study Data

*Describe the local procedures for maintenance of confidentiality of **study data and any records that will be reviewed for data collection**.*

*18.1 A. Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, and separation of identifiers and data, as applicable. Include physical (e.g. paper) **and** electronic files.*

Response:

All data records will be stored on password protected computers and or in locked cabinets within the research department. These files will only be accessible by authorized study personnel.

Each subject will be assigned a randomization number (1 to 20) depending on the sequence of their visit, and each subject will also be assigned a stimulation code which decides whether he/she will receive active or sham stimulation. This stimulation code is determined at the time of randomization. After that, we will only retain the subject's intials, randomization number, and a stimulation code. These identifiers will not be separated from the data.

The data recorded on the paper forms will be transferred to Excel file and will be verified by another staff member at the research center.

18.2 A. How long will the data be stored?

Response: Data and specimens storage has no expiration date and will be stored for a minimum of 7 years. The researchers may continue to rely on this for future use in research study

B.Who will have access to the data?

Response:

Those physicians, nurses, and laboratory staff that are on all documentation for the study will have access to the data and specimens

18.3 A. Who is responsible for receipt or transmission of the data?

Response: Those physicians, nurses, and laboratory staff that are on all documentation for the study will have access to the data and specimens and can handle transfer of data and samples

18.4 A. How will the data be transported?

Response:

All data are stored at one location and is not transported unless it is being archived. At that point files will be transferred to Iron Mountain for storage and archiving. Samples that are transported will be done so using dry ice in a properly labeled Styrofoam container by the laboratory technician.

B. Confidentiality of Study Specimens

*Describe the local procedures for maintenance of confidentiality of **study specimens**.*

☐ **N/A:** No specimens will be collected or analyzed in this research.
(Skip to Section 19.0)

18.5 B. Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.

Response: The data and specimens will be stored in the laboratory located at 1000 Youngs Road, Suite 105, Williamsville NY 14221 and at the CTRC located in 875 Ellicott St. Buffalo NY14203. Samples will be stored in a locked -80º C freezer.

18.6 B. How long will the specimens be stored?

Response: Data and specimens storage has no expiration date and will be stored for a minimum of 7 years. The researchers may continue to rely on this for future use in research study

18.7 B. Who will have access to the specimens?

Response: Those physicians, nurses, and laboratory staff that are on all documentation for the study will have access to the data and specimens

18.8 B. Who is responsible for receipt or transmission of the specimens?

Response: Those physicians, nurses, and laboratory staff that are on all documentation for the study will have access to the data and specimens and can handle transfer of data and samples

18.9 B. How will the specimens be transported?

Response: Samples that are transported will be done so using dry ice in a properly labeled Styrofoam container by the laboratory technician

19.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

NOTE: Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments that elicit suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.

19.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response:

According to previous studies, active tDCS was associated with a higher prevalance of skin redness compared with control group. Other possible adverse reaction reported in the past include scalp burning, tingling, sleepiness, difficulty with concentrating, heachache, neck pain and scalp pain, but the prevalence of these reactions was not found to be different from control group. These side effects are generally transient and resolve with time without active intervention. Contraindications for the use of tDCS include underlying psychiatric illness, personal or family history of seizures, underlying skin disorders, history of implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, TENS unit, ventriculoperitoneal shunt or any metallic implant on the head. Although not a direct contraindication, scarring within the brain may modify the effects of the tDCS and therefore prior neurosurgical procedures or radiation treatment to the brain are also considered contraindications. Subjects with any of these known medical conditions will be excluded. Immediately before and after tDCS administration, we will systematically monitor the presence of adverse events using a standard tDCS safety questionnaire that has been previously published (Brunoni et al., 2011). Subjects who report significant side effects related to the tDCS may also be excluded based on the investigator's judgement.

Continuous glucose monitor use is occasionally associated with insertion site discomfort or skin irritability. The effect is generally mild and resolve without intervention. We will demonstrate the correct way of using continuous glucose monitor to subjects to minimize the side effects. We will also ask them if they experience any side effects on the visit after continuous glucose monitor use and they are encouraged to report side effects over telephone.

The principal investigator Paresh Dandona, MD,PhD and co-investigators Miguel Alonso Alonso MD, PhD and Chi Tang, MD will review the data of adverse reaction every 3 months to assess the safety and potential benefits to the participant. Furthermore, they will also assess other risks including the physical, psychological, social, legal and economic harm to these patients. The investigators listed above will carefully watch for any invasion of privacy and breach of confidentiality.

19.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response:

Height, Weight, and adverse reaction reported by subjects are monitored every visit to ensure safety.

19.3 Describe any safety endpoints.

Response:

***Adverse event (AE)**: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research*

***Serious adverse event (SAE)**: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria: 1) results in death;*

2) is life-threatening (places the subject at immediate risk of death from the event as it occurred); 3) requires inpatient hospitalization or prolongation of existing hospitalization; 4) results in a persistent or significant disability/incapacity; 5) results in a congenital anomaly/birth defect; or any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse)

The following table represents the time frames for reporting serious events at the State University of New York at Buffalo:

TIMEFRAMES FOR REPORTING ON-SITE "SERIOUS" EVENTS/PROBLEMS (SEPs)	
Type of Report	**When to Report**
Deaths - except when death is the endpoint of the study	**Within 24-hours** of knowledge or notification
Life-threatening (i.e., events/problems that place the subject at immediate risk of death from the event as it occurred)	**Within 72-hours** of knowledge or notification
Required hospitalization or prolongation of existing hospitalization	**Within 72-hours** of knowledge or notification
Resulted in persistent or significant disability or incapacity	**Within 72-hours** of knowledge or notification
Resulted in congenital anomaly or birth defect	**Within 72-hours** of knowledge or notification

Based on appropriate clinical judgment, the event required or may require medical or surgical intervention to: • prevent a life-threatening event/problem (the subject is at immediate risk of death from the event as it occurred) • Required hospitalization or prolongation of existing hospitalization • Resulted in persistent or significant disability or incapacity • Resulted in congenital anomaly or birth defect	**Within 72-hours** of knowledge or notification
Deviation, in an emergency situation, from the approved investigational plan initiated in order **to protect the life** or physical well-being of a subject	**Within 5 days** of the emergency
Deviation, in an emergency situation, from the approved investigational plan initiated in order **to eliminate an apparent hazard to a participant**	**Within 5 days** of the emergency
Increased Risk of Harm to subjects or others than was previously known or recognized (whether or not actual harm has occurred). Risks may be physical, psychological, economic, or social: *Examples:* • *Theft or loss of stored research data* • *A subject complaint indicates unexpected risks* • *Unexpected subject withdrawal poses increased risks to the subject or others* • *Incarceration of an enrolled subject, in a study not approved for participation of prisoners, where ceasing all study involvements or interventions with the now-incarcerated prisoner-subject may increase risks to his/her health or safety.*	**Within 10 working days** of knowledge or notification
Breach of Confidentiality that caused harm or places subjects or others at **increased risk of harm** (physical, psychological, economic, or social harm (even if actual harm has not occurred).	**Within 10 working days** of knowledge or notification
Significant impact on the integrity of the research data *Examples:* • *Unplanned destruction of study records* • *Withdrawal of subject(s) impacts data integrity or causes inability to complete the study*	**Within 10 working days** of knowledge or notification
Unanticipated Adverse Device Effects Any serious adverse effect on health or safety of any life-threatening problem or death caused by, or associated with, an FDA regulated device, if that effect problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.	**Within 10 working days** of knowledge or notification

Any event/problem that would cause the sponsor to modify the investigator's brochure, informed consent document or would prompt other action by the IRB to assure protection of subjects.	**Within 10 working days** of knowledge or notification.
Any other "Serious" Event/Problem not described above	**Within 10 working days** of knowledge or notification

19.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response:

On site during the visit. We also encourage participants to call us if they develop any adverse reaction

19.5 Describe the frequency of safety data collection.

Response:

The data collection will be done at all study visits. The patients, however, will be asked to report any adverse event or safety related information via phone as soon as it occurs.

19.6 Describe who will review the safety data.

Response: The safety data will be reviewed by the principle and sub investigators as well as the research coordinator.

19.7 Describe the frequency or periodicity of review of cumulative safety data.

Response: Safety data will be reviewed every three months during the duration of the study. Study endpoint data will be reviewed once after half of the recruited patients have completed the study and then at the end of the study.

19.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: We will calculate the percentage of participants that developed any adverse reaction during the course of the study. We will use Fisher exact test to compare the percentage of participants that developed serious adverse reaction (which leads to withdrawal of subject) between group with active tDCS and sham tDCS. We will use two sample exact test for incidence rate data to compare the incidence of mild adverse reaction (which did not lead to withdrawal of subjects) between the two groups.

19.9 Describe any conditions that trigger an immediate suspension of the research.

Response: Inability to tolerate the tDCS administration, continuous glucose monitor or blood draw

20.0 Withdrawal of Subjects

☐ **N/A:** This study is not enrolling subjects. This section does not apply.

*20.1 Describe **anticipated** circumstances under which subjects may be withdrawn from the research without their consent.*

Response: Inability to tolerate the tDCS administration, continuous glucose monitor or blood draw. The principal investigator of the study can remove a participant from the research study without their approval if for any reason he/she feels is appropriate, including: severe side effect, injury or medical condition which may place subjects at risk of further complications if he/she continues to participate, failure to keep scheduled appointments, or other administrative reasons.

If any of the subjects become pregnant during the period of study, he/she will need to withdraw from the study.

20.2 Describe any procedures for orderly termination.

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Response:

We will recommend that the subject come back for an exit visit to make sure he/she is not experiencing side effect from tDCS. However, they can also follow up with us in the clinic since the subjects are recruited from our clinic patients. They will also be asked to return the continuous glucose monitor after the study.

20.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Response: If a subject withdraws from the research, the data collected to that point will be used toward the research finding.

21.0 Risks to Subjects

21.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

Response: Insertion of cannula or drawing blood may result in pain, a feeling of faintness, irritation of the vein, bruising, bleeding, or later infection at the puncture site.

However, risk of infection is very small and treatable. Too much blood collection can potentially lead to hypotension and dizziness. If subjects develop these symptoms, we will stop blood draw.

According to previous studies, active tDCS was associated with a higher prevalence of skin redness compared with control group. Other possible adverse reaction reported in the past include scalp burning, tingling, sleepiness, difficulty with concentrating, headache, neck pain and scalp pain, but the prevalence of these reactions was not found to be different from control group. These side effects are generally transient and resolve with time without active intervention. Difficulty with concentrating is mild and transient. And according to previous study (reference 9), all patients who received sham stimulation also developed difficulty with concentrating, which means this is probably not a side effects of tDCS. However, we list it as a possible effect because the sample size of previous study is small and this symptom was reported by study participants.

Continuous glucose monitor use is occasionally associated with insertion site discomfort or skin irritability. The effect is generally mild and resolve without intervention. Another potential risk is breach of confidentiality. The measures to prevent it are mentioned above.

21.2 Describe procedures performed to lessen the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.

Response: We will collect no more than 50 ml of blood on each visit. We will follow standard sterilization procedure.

Contraindications for the use of tDCS include underlying psychiatric illness, personal or family history of seizures, underlying skin disorders, history of implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, TENS unit, ventriculoperitoneal shunt or any metallic implant on the head. Although not a direct contraindication, scarring within the brain may modify the effects of the tDCS and therefore prior neurosurgical procedures or radiation treatment to the brain are also considered contraindications. Subjects with any of these known medical conditions will be excluded. Immediately before and after tDCS administration and on the last visit of the study, we will systematically monitor the presence of adverse events using a standard tDCS safety questionnaire that has been previously published (Brunoni et al., 2011). Subjects who report significant side effects related to the tDCS may also be excluded based on the investigator's judgement.

Continuous glucose monitor use is occasionally associated with insertion site discomfort or skin irritability. The effect is generally mild and resolve without intervention. We will demonstrate the correct way of using continuous glucose monitor to subjects to minimize the side effects. We will also ask them if they experience any side effects on the visit after continuous glucose monitor use. We will discontinue the use of it on a subject if he/she is not able to tolerate it.

In order to lessen the risk of breach of confidentiality, subjects will be allowed to address their question and concerns in private with the research coordinator, study nurse and/or research physician. At any time during the study the patient is able to place privacy

restriction to their protected heath information (i.e. telephone message, PHI release forms) which the study personnel document and respect. All data records will be stored on password protected computers and or in locked cabinets within the research department. These files will only be accessible by authorized study personnel

*21.3 If applicable, indicate **which procedures** may have risks to the subjects that are currently unforeseeable.*

Response: tDCS. There is no long term study on the safety of tDCS. As a result, the long term risk of this procedure is currently unforeseeable.

21.4 If applicable, indicate which research procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response: There is no known risk of using tDCS in pregnant subjects. However, since we do not have long term safety data on this issue, pregnant subjects will be excluded.

21.5 If applicable, describe risks to others who are not subjects.

Response: not applicable

22.0 Potential Benefits to Subjects

22.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.

*NOTE: Compensation **cannot** be stated as a benefit.*

Response: there is no direct benefit to participating in this research study.

23.0 Compensation for Research-Related Injury

☐ **N/A:** The research procedures for this study do not present risk of research related injury (e.g. survey studies, records review studies). This section does not apply.

*23.1 **If the research procedures carry a risk of research related injury,** describe the available compensation to subjects in the event that such injury should occur.*

Response: Routinely, Buffalo General Hospital, Erie County Medical Center, and/or the University at Buffalo, State University of New York, its agents, or its employees do not compensate for or provide free medical care for human subjects/participants in the event that any injury results from participation in a human research project. In the unlikely event that they become ill or injured as a direct result of participating in this study, they may receive medical care, but it will not be free of charge even if the injury is a direct result of their participation.

23.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.

NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with ***different language regarding research related injury****, you must modify your response here and submit an amendment to the IRB for review and approval.*

Response: N/A

24.0 Economic Burden to Subjects

24.1 Describe any costs that subjects may be responsible for because of participation in the research.

NOTE: Some examples include transportation or parking.

Response: transportation fee

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

25.0 Compensation for Participation

25.1 Describe the amount and timing of any compensation to subjects, including monetary, course credit, or gift card compensation.

Response: Each subject will be compensated 50 dollars for each visit they participate.

They will also be compensated 10 dollars for parking. They will receive a check at the end of the study or their last visit.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

☐ **N/A:** There is no compensation for participation. This section does not apply.

26.0 Consent Process

26.1 Indicate whether you will be obtaining consent.

NOTE: This does not refer to consent documentation, but rather whether you will be obtaining permission from subjects to participate in a research study.
Consent documentation is addressed in Section 27.0.

☒ ***Yes*** *(If yes, Provide responses to each question in this Section)*
☐ ***No*** *(If no, Skip to Section 27.0)*

26.2 Describe where the consent process will take place. Include steps to maximize subjects' privacy.

Response: All participants will come to the research department to be consented. Participants will be placed in a private room where they can review the consent. Participant questions and or concerns will be address with a member of the study team or research doctor if applicable.

26.3 Describe how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study.

NOTE: It is always a requirement that a prospective subject is given sufficient time to have their questions answered and consider their participation. See "SOP: Informed Consent Process for Research (HRP-090)" Sections 5.5 and 5.6.

Response: A prospective subject will be given sufficient time to have their questions answered and consider their participation. And we call a potential subject before the screening visit, so they will have sufficient time to think about it before coming to our research unit.

26.4 Describe any process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

Response: Subjects has the right to discontinue participation at any stage of the study

26.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:

1. *The role of the individuals listed in the application who are involved in the consent process*
2. *The time that will be devoted to the consent discussion*
3. *Steps that will be taken to minimize the possibility of coercion or undue influence*
4. *Steps that will be taken to ensure the subjects' understanding*

Response:

☒ We have reviewed and will be following "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects

☒ **N/A:** This study will not enroll Non-English speaking subjects.
(Skip to Section 26.8)

26.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

NOTE: The response to this Section should correspond with your response to Section 6.4 of this protocol.

Response:

26.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

NOTE: Guidance is provided on "SOP: Informed Consent Process for Research (HRP-090)."

Response:

Cognitively Impaired Adults

☒ **N/A**: This study will not enroll cognitively impaired adults.
(Skip to Section 26.9)

26.8 Describe the process to determine whether an individual is capable of consent.

Response:

Adults Unable to Consent

☒ **N/A**: This study will not enroll adults unable to consent.
(*Skip to Section 26.13)*

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent (Sections 26.9 and 26.10) ***and, where possible, assent of the individual should also be solicited*** *(Sections 26.11 and 26.12).*

26.9 Describe how you will identify a Legally Authorized Representative (LAR). Indicate that you have reviewed the "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" for research in New York State.

NOTE: Examples of acceptable response includes: verifying the electronic medical record to determine if an LAR is recorded.

Response:

☐ We have reviewed and will be following "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

26.10 ***For research conducted outside of New York State****, provide information that describes which individuals are authorized under applicable law to consent on*

behalf of a prospective subject to their participation in the research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response:

*26.11 Describe the process for **assent of the adults**:*

1. *Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.*

Response:

2. *If assent will not be obtained from some or all subjects, provide an explanation of why not.*

Response:

*26.12 Describe whether **assent of the adult** subjects will be documented and the process to document assent.*

NOTE: The IRB allows the person obtaining assent to document assent on the consent document using the "Template Consent Document (HRP-502)" Signature Block for Assent of Adults who are Legally Unable to Consent.

Response:

Subjects who are not yet Adults (Infants, Children, and Teenagers)

☒ **N/A**: This study will not enroll subjects who are not yet adults.
(Skip to Section 27.0)

*26.13 Describe the criteria that will be used to determine **whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research** under the applicable law of the jurisdiction in which the research will be conducted **(e.g., individuals under the age of 18 years)**. For research conducted in NYS, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*

NOTE: Examples of acceptable responses include: verification via electronic medical record, driver's license or state-issued ID, screening questionnaire.

Response: The subject's medical record will be accessed to confirm age.

26.14 ***For research conducted outside of New York State****, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response:

26.15 Describe whether parental permission will be obtained from:

Response:

- ☐ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.
- ☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
- ☐ Parent permission will not be obtained. A waiver of parent permission is being requested.

NOTE: The requirement for parent permission is a protocol-specific determination made by the IRB based on the risk level of the research. For guidance, review the "CHECKLIST: Children (HRP-416)."

26.16 Describe whether permission will be obtained from individuals ***other than parents****, and if so, who will be allowed to provide permission. Describe your procedure for determining an individual's authority to consent to the child's general medical care.*

Response:

26.17 Indicate whether assent will be obtained from all, some, or none of the ***children****. If assent will be obtained from some children, indicate which children will be required to assent.*

Response:

26.18 When assent of children is obtained, describe how it will be documented.

Response:

27.0 Waiver or Alteration of Consent Process

Consent will not be obtained, required information will not be disclosed, or the research involves deception.

☒ **N/A:** A waiver or alteration of consent is not being requested.

27.1 If the research involves a waiver or alteration of the consent process, please review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure that you have provided sufficient information for the IRB to make the determination that a waiver or alteration can be granted.

NOTE: For records review studies, the first set of criteria on the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" applies.

Response:

27.2 If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response:

28.0 Process to Document Consent

☐ **N/A:** A Waiver of Consent is being requested.
(Skip to Section 29.0)

28.1 Indicate whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not or if there are any exceptions, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

NOTE: If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent. This is sometimes referred to as 'verbal consent.' Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information.

If you will document consent in writing, attach a consent document with your submission. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)". If you will obtain consent, but not document consent in writing, attach the script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).

Response:

☒ We will be following "SOP: Written Documentation of Consent" (HRP-091).

29.0 Multi-Site Research (Multisite/Multicenter Only)

☒ **N/A:** This study is not an investigator-initiated multi-site study. This section does not apply.

*29.1 If this is a multi-site study **where you are the lead investigator**, describe the processes to ensure communication among sites, such as:*

1. *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
2. *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
3. *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
4. *All engaged participating sites will safeguard data as required by local information security policies.*
5. *All local site investigators conduct the study appropriately.*
6. *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response:

29.2 Describe the method for communicating to engaged participating sites:

1. *Problems*
2. *Interim results*
3. *Study closure*

Response:

29.3 Indicate the total number of subjects that will be enrolled or records that will be reviewed across all sites.

Response:

29.4 If this is a multicenter study for which UB will serve as the IRB of record, and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods.

Response:

30.0 Banking Data or Specimens for Future Use

☐ **N/A:** This study is not banking data or specimens for future use or research outside the scope of the present protocol. This section does not apply.

*30.1 If data or specimens will be banked (stored) for **future use, that is, use or research outside of the scope of the present protocol**, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.*

NOTE: Your response here must be consistent with your response at the "What happens if I say yes, I want to be in this research?" Section of the Template Consent Document (HRP-502).

Response: The data and specimens will be stored short term in the laboratory located at 1000 Youngs Road, Suite 105, Williamsville NY 14221and long term at the laboratory at CTRC located in 875 Ellicott St. Buffalo NY14203. Samples will be stored in locked controlled -80^{o} C freezers. Data will be stored on computers that are password protected and only authorized research personnel would have access. All samples and data will be stored for at least 7 years after the end of the study. It may be used outside the scope of the current protocol. Research staff have designated access to data and specimens.

30.2 List the data to be stored or associated with each specimen.

Response: subject ID, visit number and sample type and date will be stored with sample

30.3 Describe the procedures to release banked data or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response: No data or specimens will be released.

31.0 Drugs or Devices

☐ **N/A:** This study does not involve drugs or devices. This section does not apply.

31.1 If the research involves drugs or devices, list and describe all drugs and devices used in the research, the purpose of their use, and their regulatory approval status.

Response: We will use an Eldith/Neuroconn tDCS device that meets the highest safety standards of all the devices commercially available, providing a microprocessor-controlled constant current source. It is medical device for conducting non-invasive transcranial direct-current stimulation (tDCS) on people. While this device has not been approved by the FDA, it is CE-certified, indicating compliance with European Union legislation.

31.2 Describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Response: The device will be stored at the laboratory located at 1000 Youngs Road, Suite 105, Williamsville NY 14221. It will be handled and administered by staff at the laboratory who have been trained on how to use the device. It will be only used on study subjects

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

31.3 Identify the holder of the IND/IDE/Abbreviated IDE.

Response: In the opinion of the investigators, this study fulfills the non-significant risk category under 21 CFR 812. First, the use of tDCS as applied in this protocol is considered safe by current consensus in the use of the technique according to relevant publication (Nitsche at al. Brain Stim 2008;1(3): 206-223; Fregni et al. Clin Res Regul Aff, Early Online: 1–14). Specifically the Nitsche et al 2008 publication contains the following paragraph: *"Extensive animal and human evidence and theoretical knowledge indicate that the currently used tDCS protocols are safe. However, knowledge about the safe limits of duration and intensity of tDCS is still limited."* The protocol to be used in this project will apply stimulation levels that fall within safety standards established by basic research investigating neural tissue damage, as well as numerous studies applying tDCS to human participants. These studies have included patient populations and stimulation schemes of up to 10 consecutive days. No major adverse effects were reported using these parameters. Second, studies that involve the application of tDCS are generally considered non-significant risk, we can provide letters from FDA and IRBs of a number of cases.

We will use an Eldith/Neuroconn tDCS device that meets the highest safety standards of all the devices commercially available, providing a microprocessor-controlled constant current source. While this device has not been approved by the FDA, it is CE-certified, indicating compliance with European Union legislation. http://www.neuroconn.de/dc-stimulator_en/ This tDCS device is being used in several clinical research studies taken place at Beth Israel Deaconess Medical Center. In a study that used a similar neuromodulation protocol, the IRB of Beth Israel Deaconess Medical Center determined that this device is a non-significant risk device according to federal regulation 21 CFR 812.2(b) (5/7/2012; notification attached; http://clinicaltrials.gov/ct2/show/NCT01632280; PI: Miguel Alonso-Alonso).

31.4 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response: Provide assurance that the device is not a banned device

Label the device in accordance with 21 CFR 812.5.

Obtain IRB approval of the investigation as a nonsignificant risk device study after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device and maintain such approval.

Ensure that each investigator participating in an investigation of the device obtains informed consent under 21 CFR 50 for each subject under the investigator's care and documents the consent, unless documentation is waived by an IRB under 21 CFR 56.109(c).

Comply with the requirements of 21 CFR 812.46 with respect to monitoring investigations.

The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and

Comply with the prohibitions in 21 CFR 812.7 against promotion and other practices

32.0 Humanitarian Use Devices

☒ **N/A:** This study does not involve humanitarian use devices. This does not apply.

32.1 For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response:

32.2 For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

Response: