Title: Home-based tDCS for Prevention of Suicidal Ideation

Study Protocol and Statistical Analysis

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Study Title: Home-based transcranial direct-current stimulation (tDCS) for prevention of suicidal ideation relapse after inpatient treatment

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Site: University of Rochester Medical Center

1. PURPOSE OF STUDY

Aim 1: To examine the feasibility of the home-based transcranial direct-current stimulation (tDCS) apparatus and protocol (as well as the home-based tDCS sham protocol) for future use as an adjunctive treatment to prevent suicidal ideation (SI) relapse in adult patients with mood or bipolar disorders after discharge from the Comprehensive Psychiatric Emergency Program (CPEP) or inpatient unit to which they were admitted with SI or attempt.
Hypothesis 1: We expect at least 70% of the subjects to complete at least 5 of recommended 10 RS-tDCS sessions within three weeks of receiving the home-based tDCS device.

Aim 2: To detect a preliminary signal of the effect of adjunctive home-based tDCS on indices of SI measured with The Columbia-Suicide Severity Rating Scale (C-SSRS) in adult patients with mood or bipolar disorders after discharge from the CPEP or inpatient unit of which they were admitted with SI or attempt.
Hypothesis 2: Subjects in the active tDCS arm will report less suicide ideation intensity (as measured by C-SSRS) than subjects in the control (sham) group at the end of treatment, which will help to determine an effect size for use in the sample size calculation for a full randomized controlled trial.

2. BACKGROUND AND RATIONALE

Suicide is one of the main causes of mortality worldwide, and its rates have increased in the US (1-3). There is no single cause of suicide and suicidal behavior, rather it is the result of a complex interaction between social, environmental, and individual risk factors (4). Approximately 90% of those who died by suicide had a psychiatric disorder, mainly a mood disorder (5), which allows for a small narrowing of intervention selection insofar as components of evidence-based treatments for mood disorders may be helpful for SI and behavior. Indeed, SI (i.e., thoughts about death or wanting to be dead) is present in approximately 20% of individuals with mood disorders and is an independent risk factor for a suicide attempt (6, 7).

Neuroimaging studies demonstrate an association between SI and alterations in neural circuits, including increased functional connectivity in the default mode network (DMN) (8-12). The DMN is a large-scale brain circuit that shows activity when the brain is at rest and not engaged in goal-directed activities (13). The DMN is related to self-oriented patterns of thought, which include rumination and introspective states, and comprise medial, lateral, and inferior parietal cortices, medial prefrontal cortex (mPFC), and precuneus/posterior cingulate cortex (PCC) (13, 14). Chase et al. (2017) have tested if individuals with SI would present different patterns of connectivity within the DMN compared with healthy controls. Indeed, participants with SI evince altered functional connectivity in the cingulate cortex and between ventral and

dorsal posterior cingulate cortex (PCC) and dorsal anterior cingulate cortex (ACC) (10). Taylor et al. (2015) have investigated whether suicidal thoughts are associated with gray matter volumetric and white matter microstructural differences comparing depressed participants with or without SI and healthy controls. These investigators found that alterations in parietal white matter microstructure observed in depressed individuals with SI compared to those without SI are potentially related to the DMN's posterior hub (8). Interestingly, studies with ketamine, an intervention that rapidly reduces SI (15), showed decreased functional connectivity in the DMN (16-18). Transcranial direct-current stimulation (tDCS), a non-invasive, non-pharmacologic neurostimulation intervention that has demonstrated efficacy for the treatment of mood disorders (19-21), has also been associated with alteration of cerebral connectivity in the DMN; for instance, reducing synchrony in DMN components (22, 23), and hence may prove to be a useful adjunct in treating SI.

In a randomized controlled trial (RCT), Brunoni et al. (2013) evaluated the efficacy and safety of tDCS and sertraline, compared to each treatment in isolation, in patients with major depressive disorder (MDD) and found that tDCS was significantly superior to placebo on the Montgomery-Asberg Depression Rating Scale (MADRS) scores (21). A systematic review and meta-analysis for tDCS in treating bipolar depression also noted significant findings for reducing depressive symptoms, even after controlling for sample sizes. In addition, results suggested that effects could be achieved within one week of treatment (24). tDCS twice a week was also associated with low relapse rates in a 6-month follow-up with individuals who had responded to the treatment (25).

The mechanism of action of tDCS is still unknown. However, as mentioned above, some studies show an association between tDCS and modulation of brain connectivity in the DMN (22, 23), a neural network associated with several psychiatric disorders and maladaptive behaviors, including SI (26-29). Pena-Gomez et al. (2012) have investigated whether the activity of the "anticorrelated network" (AN), brain regions that have a negative correlation with DMN, would predominate over DMN with tDCS over the dorsolateral prefrontal cortex (DLPFC). These authors found a reduction in synchrony within DMN components and increased synchrony within its AN (23). The influence of tDCS in resting-state networks was also tested by Keeser et al. (2011), who showed that, compared with sham tDCS, active tDCS induced changes in the functional connectivity of the DMN (22).

Prior history of suicide attempt is the main risk factor for suicide behavior. Nanayakkara et al. (2013) used public data to investigate risk factors for adolescent suicide and found that prior-year suicide attempt was the greatest risk factor for re-attempt, even controlling for current or past depression (30). Data from a 5-year study of individuals who have attempted suicide show that almost 40% of participants made at least one suicide attempt during the study period. In this same study, 6.7% of the 302 participants died by suicide during the 5-year follow-up (31). In a retrospective-prospective cohort study with 1,490 participants who attempted self-harm, Bostwick et al. (2016) reported 81 (5.4%) deaths by suicide during the study follow-up, representing 62.3% of the total deaths in the period (32).

Luxton et al. (2013) have investigated suicide rates among U.S. military service members after a psychiatric hospitalization and reported an almost 5-fold higher suicide rate in this population compared to the general population of active-duty U.S. military personnel. In addition, the highest suicide rate was in the first 30 days after hospitalization, 8.2 times higher than the risk one-year post hospitalization. In this study, almost one-third of those who died by suicide had an episodic mood disorder (33). Another study showed a suicide rate of 263.9

suicides per 100,000 person-years soon after hospital discharge among U.S. Army soldiers, almost 14-fold higher compared with the total U.S. Army. Previous suicidal behavior was one of the main predictors (OR=2.9) (34). Forte el al. (2019) addressed suicidal risk after hospital discharge in a review paper that included 48 studies with a total of 1,700,785 participants followed for almost 8 years after a psychiatric hospitalization (35). The authors noted that about 20% of the suicides and attempts had occurred within 15 days following hospital discharge and more than a quarter in the first month. The results also showed that mood disorders were associated with the highest risk (35).

These studies clearly show that evidence-based interventions for suicidal behavior prevention offered soon after psychiatric inpatient hospitalization are of major significance, especially for high-risk groups such as individuals with a history of SI and behavior and mood disorders. However, the low rate of outpatient treatment engagement and the high rate of dropout from an outpatient service after discharge from an emergency department is a challenge (36), and speaks to the need to overcome these barriers to care. Effective tDCS stimulation requires daily sessions, typically performed in an outpatient clinic. For some patients, this presents a serious barrier. Specifically, for patients in the first weeks after discharge, residual symptoms, and the need to reorganize personal issues and obligations after a period at the hospital may prevent them from commuting to daily visits at health facilities to complete a non-invasive brain stimulation treatment. Thus, to address low treatment engagement and overcome barriers to care with this population, this study will test the feasibility of a home-based tDCS protocol for preventing SI relapse soon after hospitalization discharge.

Home-based tDCS has proven feasible in treating pain in older adults with knee osteoarthritis. In a study by Ahn et al. (2019), participants provided average ratings of 9.57, 9.67, and 9.8 out of a possible 10 concerning 1) preparation of the device, 2) ease of use of the device, and 3) confidence in the use of home-based tDCS, respectively. In addition, no participants reported adverse effects with the treatment (37). Alonzo et al. (2019) tested the efficacy, tolerability, and feasibility of home-based tDCS for treating depression in an open-label trial monitored remotely. The authors found that the intervention was associated with a significant decrease in depressive symptoms, with minor and transient side effects, and excellent adherence (38). The tolerability and safety of home-based tDCS were assessed over 6,779 sessions from six clinical trials, with daily session, varying from 10 to 60 applications. The authors reported no serious adverse events, a similar proportion of tingling (68%), itching (41%), and warmth sensation (42%) between active and sham groups, and no participant discontinuation due to lack of tolerability (39).

Taken together, previous studies provide evidence that: 1) SI is an independent risk factor associated with suicide attempts; 2) SI has been associated with hyperactivity in the DMN brain circuit, which is related to rumination and self-oriented patterns of thought; 3) tDCS, a safe, non-invasive type of neurostimulation, seems to decrease the synchrony within DMN. To our knowledge, no study has investigated tDCS as an adjunctive intervention for SI or behavior. Considering the safety and ethical concerns about any research that deals with SI and behavior as the primary outcome, best practices treatment must be offered; therefore, we intend to investigate tDCS as an adjunctive treatment for the prevention of SI relapse after discharge from a psychiatric emergency or inpatient unit of which they were admitted with SI or attempt.

3. ADMINISTRATIVE ORGANIZATION

Yeates Conwell, MD, Professor and Vice Chair of Department of Psychiatry at the University of

Rochester Medical Center (URMC), is the Principal investigator (PI) of this study. Alexandre Paim Diaz, MD, Ph.D., a T32 Postdoctoral Research Fellow at the Center for the Study and Prevention of Suicide (CSPS) in the same Department, is the Co-PI of this study. All research procedures will be conducted by Dr. Paim Diaz and URMC staff under Dr. Conwell's and Dr. Paim Diaz's supervision. Research recruitment is conducted by Dr. Paim Diaz and URMC staff at URMC in Rochester, NY. The recruitment will be in-person. tDCS sessions will be conducted at home by the subject, and monitored by the study's staff remotely via HIPAA-compliant videoconference. Thus, we refer to home-based tDCS also as remotely supervised tDCS (RS-tDCS).

4. STUDY DESIGN

This is a single-center, randomized, sham-controlled, double-blind clinical study to investigate the feasibility of delivering RS-tDCS sessions for high-risk patients for suicide in the days following discharge from the CPEP or inpatient unit which they were admitted with SI or attempt. We plan to assess up to 80 adult patients for eligibility over 12 months of which 20 will be enrolled and randomized. Clinical assessments will be performed at baseline, post-treatment day 14 (14 days after the first RS-tDCS session), and follow-up day 30 and 60 (30 and 60 days after the first RS-tDCS session, respectively).
All study outcome measures are described in Table 1.

Table 1. Study's time points and measures.

Time points		**in-person**	**remote**	
	Measures		**S1 to S10**	**C14, C30, and C60**
Eligibility screening		X		
Informed consent		X		
Enrollment		X		
		Baseline		
Demographic data		X		
General medical history		X		
Orientation tDCS session		X		
Loan agreement		X		
	Feasibility		X*	
	C-SSRS	X		X
	RRS	X		X
	CAST	X		X
	MADRS	X		X
	C-SSRS SV		X	
	Side effects questionnaire		X	
	Treatment emergent event review		X	X
	Acceptability questionnaire		X**	
	Blinding assessment		X**	

C14, C30, and C60: clinical assessments at post-treatment day 14, follow-up day 30 and follow-up day 60; CAST: The Concise Associated Symptoms Tracking; C-SSRS: The Columbia-Suicide Severity Rating Scale; C-SSRS SV: The Columbia-Suicide Severity Rating Scale – screening version; MADRS: Montgomery-Asberg Depression Rating Scale; RRS: Ruminative Responses Scale; S1 to S10: remotely supervised transcranial direct current stimulation (RS-tDCS) sessions one to ten.
*Number of completed RS-tDCS sessions per participant within three weeks of the study.
**applied only once, after the final RS-tDCS session (the tenth session).

Primary outcome measures:

1. Feasibility of the intervention – number of completed remotely supervised transcranial direct current stimulation (RS-tDCS) sessions, for both active and sham groups:
We expect at least 70% of the subjects to complete at least 5 of recommended 10 RS-tDCS sessions within three weeks of receiving the home-based tDCS device.
This criterion is based on a study that reported dropout rates between 22% and 25% of home-based tDCS for patients with bipolar depression (40) and that therapeutic effects with tDCS could be achieved within one week of treatment (24).

Secondary outcome measures:
1. Intensity of suicidal ideation as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) (41) (time frame: day 14 [+ 7 days], day 30 [+ 7 days], and day 60 [+ 10 days] from the first RS-tDCS session):
The C-SSRS is a suicidal ideation and behavior rating scale with yes/no responses. For each of the 5 items of the C-SSRS related to suicidal ideation intensity, an individual's degree of suicidal ideation is rated on a 0-5 scale. The total score is the sum of the 5 intensity item scores (total score ranges from 0 to 25), with higher scores indicating more severe suicidal ideation.
2. Acceptability based on subject's readiness, self-confidence, and satisfaction in dealing with the device and RS-tDCS sessions. Acceptability based on subject's readiness, self-confidence, and satisfaction will be considered if at least 60% of all subject's rate "strongly agree" or "agree" on the questionnaire item 11: "Overall, I felt that transcranial electrical stimulation treatment benefited me" (the questionnaire is a 5-item Likert scale with the following response options "Strongly agree", "Agree", "Neither agree nor disagree", "Disagree", "Strongly disagree") (42). These questions were adapted from other studies with home-based tDCS (37, 43) and will be presenting as following: 1) "It was easy to prepare the device and accessories"; 2) "I felt confident setting up the stimulation sessions"; 3) "I felt confident using the device"; 4) "I needed to learn a lot of things before I could get going with this device"; 5) "The device was unnecessarily complex"; 6) "I could find a convenient time to do the stimulation sessions"; 7) "I would imagine that most people would learn to use this device quickly"; 8) "The stimulation sessions interfered with my everyday life"; 9) "It would have helped to have more in-person, one-on-one instruction"; 10) "I felt that the remote supervision sessions were helpful"; 11) "Overall, I felt that transcranial electrical stimulation treatment benefited me". Questions 4, 5, 8, and 9 will be reverse coded. This information will be collected after the final RS-tDCS session (that is, the tenth RS-tDCS session).15
3. Proportion of patients who answered "no" for both questions 1 ("Have you wished you were dead or wished you could go to sleep and not wake up?") and 2 ("Have you actually had any thoughts of killing yourself?") of the C-SSRS (time frame: day 14 [+ 7 days], day 30 [+ 7 days], and day 60 [+ 10 days] from the first RS-tDCS session). This will help to determine the proportion of subjects who presented suicidal ideation relapse since the negative answer for both questions will be an inclusion criterion for this study.
4. Intensity of rumination as assessed by the Ruminative Responses Scale (RRS) (44) (time frame: day 14 [+ 7 days], day 30 [+ 7 days], and day 60 [+ 10 days] from the first RS-tDCS session):
The RRS encompasses 22 items. Each item is rated on a 4-point Likert scale: 1, almost never; 2, sometimes; 3, often; 4, almost always. The score on this scale is obtained by simply summing the scores on the 22 items.
5. Symptoms associated with suicidal ideation as assessed by the Concise Associated Symptoms

Tracking (CAST) scale (time frame: day 14 [+ 7 days], day 30 [+ 7 days], and day 60 [+ 10 days] from the first RS-tDCS session):
The 16 items of the CAST Scale assess symptoms across five domains: anxiety (three items, subscore range 3-15), irritability (five items, subscore range 5-25), mania (four items, subscore range 4-20), insomnia (two items, subscore range 2-10), and panic (two items, subscore range 2-10). The total CAST score ranges from 16 to 80. Each item is rated on a 5-point Likert scale: 1, strongly disagree; 2, disagree; 3, neither agree nor disagree; 4, agree; or 5, strongly agree, with higher scores indicating more severe symptoms.
6. Depressive symptoms as assessed by the Montgomery-Asberg Depression Rating Scale (MADRS) (time frame: day 14 [+ 7 days], day 30 [+ 7 days], and day 60 [+ 10 days] from the first RS-tDCS session):
MADRS is a 10-item questionnaire that includes questions on the following symptoms: 1. Apparent sadness 2. Reported sadness 3. Inner tension 4. Reduced sleep 5. Reduced appetite 6. Concentration difficulties 7. Lassitude 8. Inability to feel 9. Pessimistic thoughts 10. Suicidal thoughts. Each item yields a score of 0 to 6. The overall score ranges from 0 to 60. A higher MADRS score indicates more severe depression. The usual cutoff points are:
0 to 6 - normal/symptom absent; 7 to 19 - mild depression; 20 to 34 - moderate depression; >34 - severe depression.
7. The level of side effects will be assessed at the end of each session on a 0 (not at all) to 10 (highest degree) scale used by Ahn et al. (2019) (37), which includes the following symptoms: 1. Itching; 2. Burning; 3. Headache; 4. Fatigue; 5. Nervousness; 6. Dizziness; 7. Difficulty concentrating. The total score is the sum of the 7 items, varying from 0 to 70. Higher scores indicate higher levels of side effects.
8. Treatment emergent event review: after each RS-tDCS session and clinical assessment, subjects will be asked “Have you had any new symptoms, new medical conditions or been started on new medication/treatment since we last saw you?”. This information will help research staff to judge about potential adverse events related to the trial. In addition, changes in treatment will help researchers to account for them in data analysis and the study’s results interpretation.

4.1. **STUDY INTERVENTION**

The study intervention is tDCS treatments delivered by the Soterix Medical mini-CT device (https://soterixmedical.com/research/remote/mini-CT). The device is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk device under §812.3 (m) of the investigational device exemptions (IDE) regulation (21 CFR §812) (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.3).

The Soterix Medical mini-CT device for the RS-tDCS includes: (1) 1 x 1 mini-CT tDCS device; (2) SNAPstrap headgear, a “cap”-like placement for simple positioning and uniform electrode placement; (3) SNAPpads (individually-packaged pre-moistened sponge), and snap connectors (Figure 1) (39).

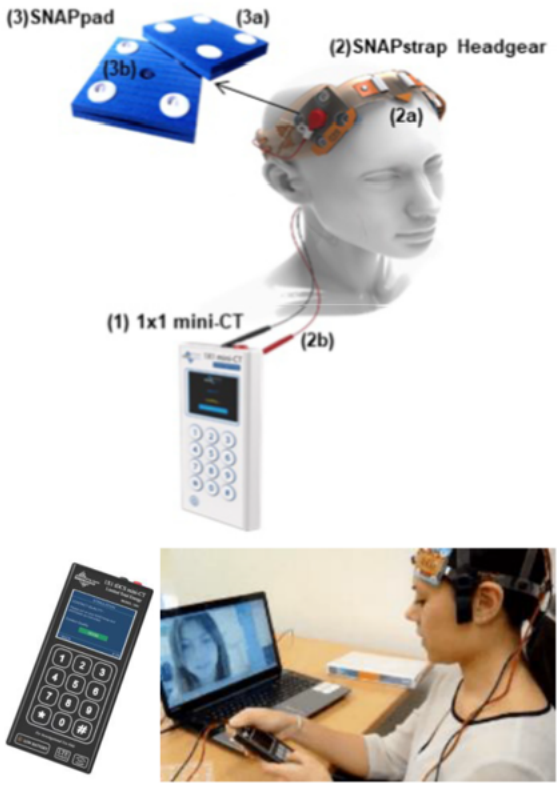

Figure 1. Remotely supervised (RS-tDCS) Equipment. (1) 1 x 1 mini-CT tDCS device; (2) SNAPstrap headgear: "cap"-like placement for simple positioning and uniform electrode placement; (2a) markers for guidance in placement; (2b) electrode polarity labeling with fixed wiring. (3) SNAPpad: (3a) individually-packaged pre-moistened sponge; perforated packaging for easy opening; (3b) snap connectors. (adapted from Pilloni, G., A. et al., Brain Stimul 15(3): 707-716, http://creativecommons.org/licenses/by-nc-nd/4.0/, DOI: 10.1016/j.brs.2022.04.014). The figure at the bottom simulates an RS-tDCS session.

Subjects will be randomized 1:1 to either active or sham RS-tDCS. The active RS-tDCS delivers a constant current intensity of 2mA on the subject's scalp, with SNAPstrap headgear and 5x7 (35cm2) SNAPpads positioning bilaterally (anodal-left and cathodal-right), on the DLPFC, for 30 minutes. A similar protocol's administration was found effective, safe, and tolerable as an add-on intervention to decrease depressive symptoms in patients with bipolar depression (45). Sham tDCS looks identical to a typical RS-tDCS cap but delivers a 30-second ramp-up (0-2 mA) stimulation followed by a 30-second rampdown (2-0 mA) at the beginning and end of the application. Figure 2 shows a representation of the electric current delivered by the active and sham RS-tDCS.

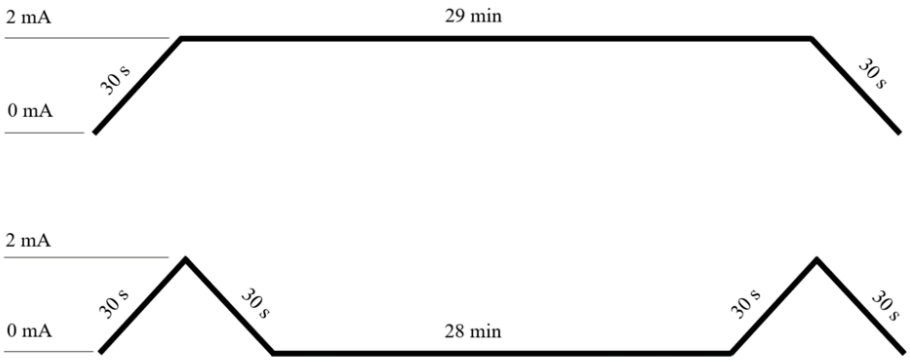

Figure 2. Stimulation protocol. Active tDCS (upper) and sham tDCS (lower).

The tolerability and safety of home-based tDCS were assessed over 6,779 sessions from six clinical trials. Sessions were administered daily, with treatment ranging from 10 to 60 sessions per subject. The authors reported no serious adverse events, a similar proportion of tingling (68%), itching (41%), and warmth sensation (42%) between active and sham groups, and no participant discontinuation due to lack of tolerability (39).

5. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria:

- age between 18 and 65 years
- diagnosis of mood or bipolar disorder registered in the electronic hospital medical record
- history of suicidal ideation and/or suicide behavior at the time of admission registered in the electronic hospital medical record
- absent of suicidal ideation at the time of enrollment (defined as questions 1 and 2 of the C-SSRS answered “no”).
- ability and willingness to provide information and permission to contact at least one person in the case of a need to contact them to promote subject safety or inability to reach the subject for follow-up
- a living situation with access to a private space suitable for administration of the RS-tDCS sessions in next three weeks
- agree to use a medically acceptable form of birth control while receiving the treatment if you are an individual able to become pregnant
- living in Monroe County region, as this is the area covered by the Mobile Crisis Team, a URMC psychiatric emergency team serving anyone within Monroe County
- device or computer with internet access for a URMC-approved remote RS-tDCS supervision
- ability to manage proper use of the device in a practice session

Exclusion criteria:

- acute psychiatric instability or substance abuse (e.g., psychotic symptoms, alcohol misuse in the previous three months, use of any illicit drugs in the previous three months)
- unstable medical condition with reduction of functional capacity
- history of epilepsy or seizures in the last year
- history of neurodegenerative diseases registered in the electronic hospital medical record
- presence of or implanted any ferromagnetic metal in the head or the neck
- pregnant or breastfeeding or willingness to become pregnant in the next month

- history of head trauma (e.g., head injury, brain injury) or neurosurgery
- history of skin disorder or sensitive skin area near stimulation locations
- the presence of pacemaker
- current treatment with electroconvulsive therapy or transcranial magnetic stimulation

Although concurrent treatment with medications or psychotherapy is not an exclusion criterion, we will measure changes in medication and psychotherapy for descriptive and planning purposes (please, see "Secondary outcome measures", item 9).

6. RECRUITMENT METHODS

We will recruit potential subjects (i.e., those with a history of suicidal ideation and/or suicidal behavior at the time of admission registered in the electronic hospital medical records) from inpatient units and the Comprehensive Psychiatric Emergency Program (CPEP) of the URMC. After pre-screening the electronic hospital medical record to identify potential subjects, research staff will contact unit staff in-person, providing information about the study. Then, the research staff will ask unit staff to determine the most appropriate time for research staff to meet with the patient based on knowledge of the patient status and needs.

Research staff assess eligibility using standardized questions and enter potential subjects' answers on a dedicated REDCap form. Eligibility data are retained for regular reporting and PI oversight. If there is interest in participation, research staff asks permission to collect their name and phone number on the contact information form. This identifiable information is marked with REDCap's "identifier" designation, which allows it to be automatically removed in data exports. This individual form is only accessible to staff who need to contact the subjects. This precautionary measure is described to potential subjects at the interview's beginning. Those who are eligible and interested undergo the informed consent process described below (see Consent Process).

7. CONSENT PROCESS

Informed consent will be obtained using the institutional review board (IRB)-approved form in-person, in a private setting, and through a paper copy.

Inform consent process includes a detailed description of the study procedures, and statements regarding subjects' rights to withdraw from the procedure at any time without consequences. It is explained to subjects in easy-to-understand language. Consent is documented by the subject's signature on the consent form, accompanied by the signature of a research team member. During consent and throughout the study, it is emphasized that participation or non-participation in the study does not affect the patient's treatment at the hospital. Likewise, they are advised to withdraw their participation in the study at any time. The limits of confidentiality are also explained, including the potential to break confidentiality in the event of acute risk of suicidal behavior or violence or disclosures of unreported physical or sexual abuse of a child.

Consent includes an authorization for staff to access subjects' electronic hospital medical records. Research staff collects information from records related to admission and discharge dates, suicidal ideation, method and circumstance of self-harming behavior, diagnoses, and medication.

Subjects who consent to research participation are given a full research assessment battery. Those who do not consent to participate in the research study return to receiving routine

care provided by the referring clinical service.

To minimize the possibility of coercion or undue influence, the consent process is carried out by research staff employed for the study and will not involve any members of the patient's treatment scheme. Patients are encouraged to ask questions about participation in the study. They may take as much time as necessary to consider participation and consult with family members or the treatment team. Patients are reminded that participation is voluntary, and they may withdraw from the study anytime.

Once the consent form is signed, subjects will receive a printout of the paper copy signed consent form. The PI and the Co-PI of the study will be responsible for maintaining all approved pages of the signed consent forms for at least 6 years after the research is completed and the Research Subjects Review Board (RSRB) file is closed, or for a longer term if required by FDA regulations or other contractual agreements. A link will be maintained between the consent document and subject number in order to be able to link signed consent documents to study data. In addition, we will keep a blank approved copy of all RSRB approved consent documents at the time of every approval. The signed consent forms will be stored in chronological order in a locked cabinet in the Co-PI's office. If the PI leaves the institution, the original signed consents will remain at the University of Rochester. Certificate of Confidentiality: as an added protection, the study is covered by a Federal Certificate of Confidentiality from the Department of Health and Human Services (DHHS). The appropriate language is included in the consent form.

8. STUDY PROCEDURES

The pre-screening will be carried out through the electronic hospital medical record to identify potential subjects. Once the potential subject is identified, research staff will visit the unit where the patient is receiving treatment (inpatient unit or CPEP) and talk with unit staff in person, providing information about the study. Then, the research staff will ask unit staff to determine the most appropriate time for the research staff to meet with the patient based on knowledge of patient status and needs.

After screening and signing consent, the research study staff will collect demographic and general medical history data, apply the clinical questionnaires, and conduct the orientation tDCS session as part of the in-person baseline assessment (Table 1 and Figure 3). This demographic, general medical history, and clinical data will be collected and stored in the REDCap through a tablet or another portable electronic device. Per subject need/request, research study staff reads aloud instructions and questions while subjects hold the tablet to record their answers. If the REDCap site is down or malfunctioning, screening, consent, and questionnaires are completed on paper and later entered into REDCap.

The orientation session includes presenting the Soterix Medical mini-CT device to the subject to show how to turn it on/off, how to insert the device unlock codes for one-time use, how to correctly adjust the SNAPstrap headgear, and answer any questions they may have. As part of the orientation session, research staff will also conduct a 90-s tolerability test, with 2.0 mA as the starting point (electrical current intensity of the study protocol). During this test, the current intensity is ramped up to 2.0 mA and the subject will receive the stimulation for 90 seconds. The tolerability will be determined by subject rating below 7 on the 0-10 Visual Analogue Scale (VAS) of pain. If the subject finds the target tDCS dose intolerable (i.e., VAS 7 or higher), subjects will have the option of another test, with the amperage dose decreased by 0.5 mA (i.e., to 1.5 mA). If this lower amperage is also intolerable, the subject will be excluded from the study (39, 46). Thus, the orientation session aims to 1) familiarize the subject with the

device, how to turn it on/off, and insert the unlock codes for one-time use; 2) to assess if the subject tolerates the protocol electric current through the tolerability test; 3) answer any questions the subjects may have. As the Soterix Medical mini-CT device will be with the subjects during the RS-tDCS sessions, subjects will be asked to sign an IRB-approved device loan agreement at the baseline.

Clinical questionnaires will be re-administered at day 14 [+ 7 days], day 30 [+ 7 days], and day 60 [+ 10 days] from the first RS-tDCS session session15 (Figure 3). While we aim to reach subjects on the phone for follow-up, research staff may email or text subjects to schedule the RS-tDCS sessions and clinical assessments. Subject identifying information and protected health information (PHI) is not exchanged in the text messages themselves. Detailed information about text messaging is included under the "Privacy and Confidentiality of Subjects and Research Data" section. Security risks associated with text messaging are described in detail during consent.

After baseline assessment, research staff not involved in the RS-tDCS supervisions and clinical assessments will randomize the subject to active or sham control group and set up the device condition (active or sham), program the intensity for the active condition (either 2.0 mA or 1.5 mA, according to the tolerability test) and duration (30 minutes) of each session, and get the device unlock codes for one-time use to be provided by the research staff to the subject immediately before each session. The discharge day will be tracked daily by the research staff through the electronic hospital medical record. Once the subject is discharged, research staff will deliver the RS-tDCS device by mail to the subject's address in a pre-paid FedEx package to send it back and contact the subject once the device has arrived at their home (by using the mail tracking number) to schedule the first RS-tDCS session.

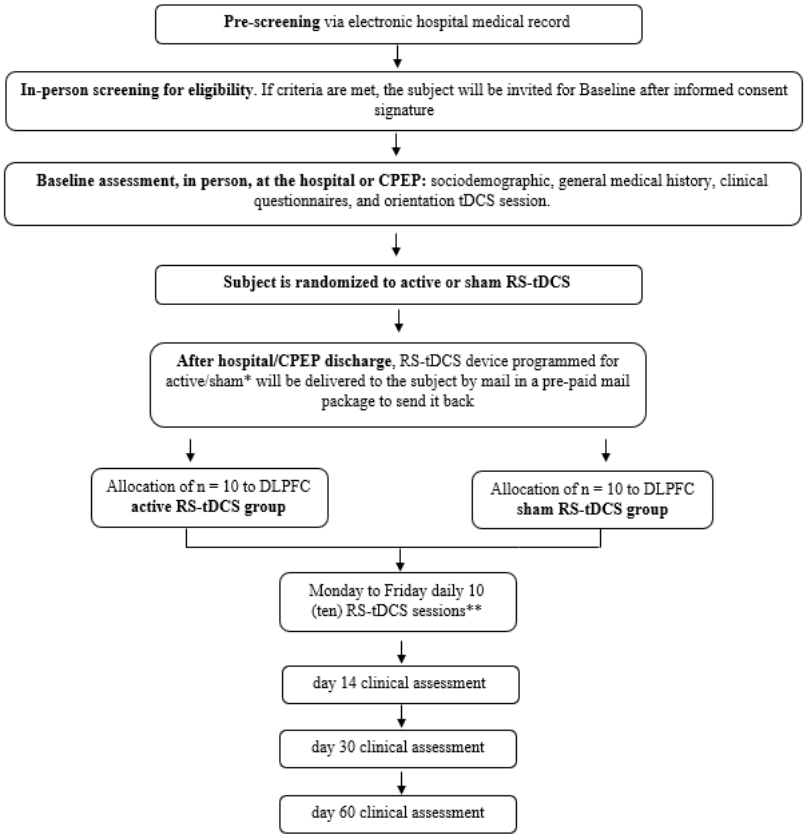

Figure 3. Study flowchart.
*device set up for the condition (active or sham), and locked (unlock codes for one-time use will be provided before each session); **day 1 being the first RS-tDCS session and no sessions on weekends. CPEP: Comprehensive Psychiatric Emergency Program; DLPFC: dorsolateral prefrontal cortex; RS-tDCS: remotely supervised transcranial direct current stimulation.

RS-tDCS sessions:

Research staff with training in using home-based tDCS by the Soterix Medical will meet with the subject via HIPAA-compliant videoconference previously scheduled. Subjects will be encouraged to find a distraction-free setting to complete treatment sessions. After guiding the subject with the proper adjustment of the SNAPstrap headgear and turning on the 1 x 1 Mini-CT device, research staff will provide the device unlock codes for one-time use to the subject. All ten device unlock codes for one-time use (one for each tDCS session) are obtained previously, just after the device is programmed to active or sham. The device unlock codes for one-time use allow the device to function only once a day, just after the inclusion of the code, with the level of electric current and duration of the session determined by the protocol, both (electric current level and duration of the session) pre-programmed on the device before it is delivered to the subject. Thus, the subject cannot alter the electric current level, the duration of the session, or use the device more than once a day. After each RS-tDCS session, research staff will apply the side effects questionnaire, review the subject's current treatment ("treatment review"), ask about any new or updated mental or physical symptoms since the last assessment (adverse events review), and apply the C-SSRS - screening version (C-SSRS SV) as part of the risk assessment (please, see more details on item "9. RISK TO SUBJECTS"). After the last RS-tDCS session (the tenth session), research staff will apply the feasibility questionnaire and blinding assessment. (Table 1). To assess blinding, the subjects will be asked the following question, "What treatment do you believe you have received??"(47). There will be three possible answers: 1) "active-tDCS"; 2)

"sham-tDCS" or 3) "Don't know". If the answer is "Don't know", research staff will ask "Would you be willing to provide your best guess about the treatment you received?", and could choose from two possible replies: 1) active-tDCS; 2) sham-tDCS (47, 48). We will use the Bang Blinding Index, which varies from -1 to +1, being 1 complete lack of blinding, +1 the opposite guessing, and 0 being related to perfect blinding (48). After the tenth session, the subject will be asked to send back the equipment in the pre-paid mail package to send it back.

Clinical assessments:
Clinical assessments with be performed at day 14 [+ 7 days], day 30 [+ 7 days], and day 60 [+ 10 days] from the first RS-tDCS session with the questionnaires described in Table 1. Thus, the duration of and individual's participation in the study will be up to 70 days.

9. RISKS TO SUBJECTS

Based on inclusion criteria of suicide crisis and the psychiatric inpatient recruitment setting, participants in this study are likely to have some increased risk for suicidal behavior (6, 33, 35). Thus, subjects must consent to remain in outpatient mental health care during the study. Consistent with URMC policy 5.4 (Patient Safety Plans Policy), a safety plan will be created for all inpatients enrolled in the study and reviewed by the subject's clinician prior to discharge. The plan includes a list of resources that the subject can call on when in need or at increased risk. If the subject declines to complete the safety plan, the clinician will make a note of this declination and provide crisis/safety resources. Finally, a copy of the safety plan is provided to the patient (subject), (and family/support person, as appropriate), and bookmarked in the patient's chart. There is a risk that the assessment and intervention may cause stress or discomfort. Subjects are informed of this during the consent process and given the option to decline to answer questions or discuss topics they do not wish to discuss. They can take breaks or stop a clinical assessment at any time. Research staff will promote subject comfort, including appropriate pacing of assessments and interventions, providing breaks, and discontinuing any clinical assessment when requested by a subject or it is clinically indicated.

The tolerability and safety of home-based tDCS were assessed over 6,779 sessions from six clinical trials, with daily session, varying from 10 to 60 applications. The authors reported no serious adverse events, a similar proportion of tingling (68%), itching (41%), and warmth sensation (42%) between active and sham groups, and no participant discontinuation due to lack of tolerability (39). As described in "Study procedures," a tolerability test will be performed as part of the orientation session to verify if the subject can tolerate the electric current established in the protocol. Subjects will be informed that they can stop an RS-tDCS session anytime. During the RS-tDCS session, the stimulation will be stopped if the subject reports a sensation of pain rated as an intensity of 7 or above on a 1-10 scale (46). If the subject reports any event of critical concern related since the last RS-tDCS session, the next RS-tDCS session will not start until clear that the event is not stimulation-related. All devices function only after the inclusion of a unlock code for one-time use. The unlock codes for one-time use allow the device to function only once a day, just after the inclusion of the code, with the level of electric current and duration of the session determined by the protocol, both (electric current level and duration of the session) pre-programmed on the device before it is delivered to the subject.

Imminent risk of suicide, for the purposes of this study, refers to a subject who is currently 1) thinking about suicide; 2) preparing for suicide and/or having planned for suicide; and has 3) some intent to act on the suicide plan within the very near future (generally 48 hours).

This may differ for each case and therefore, clinical judgment along with timely consultation are needed for determination of imminence. Thus, to assess imminent risk of suicide, the following procedures will be undertaken:

a) at the baseline assessment in the hospital:

- after the C-SSRS assessment, research staff will ask the subject if there is current active suicidal ideation with plan and intent. If the subject reports current active suicidal ideation plan and intent at the baseline, research staff will inform the subject that they need to communicate this information (about the active suicidal ideation with specific plan and intent) to the unit staff in charge of the patient due to safety concerns.
- research staff will also communicate with the unit staff in case of any concerns about the subject during the baseline assessment.
- For this assessment, the following questions will be added, and the research staff must provide the answers ("yes" or "no"): "Active ideation with plan and intent *currently*?"; "Are you otherwise concerned about the patient at all?"

b) at the RS-tDCS sessions:

- after the C-SSRS screening version assessment, research staff will ask the subject if there is current active suicidal ideation with plan and intent. If the subject reports current active suicidal ideation plan and intent, research staff will inform the subject that they need to communicate this information (about the active suicidal ideation with specific plan and intent) to a licensed clinician from the research team to discuss the need for a specialized assessment.
- research staff will also communicate the licensed clinician in case of any concerns about the subject during the RS-tDCS sessions.
- For this assessment, the following questions will be added, and the research staff must provide the answers ("yes" or "no"): "Active ideation with plan and intent *currently*?"; "Are you otherwise concerned about the patient at all?"

c) at the clinical assessments (day 14, day 30, and day 60 from the first RS-tDCS session):

- after the C-SSRS assessment, research staff will ask the subject if there is current active suicidal ideation with plan and intent. If the subject reports current active suicidal ideation plan and intent, research staff will inform the subject that they need to communicate this information (about the active suicidal ideation with specific plan and intent) to a licensed clinician from the research team to discuss the need for a specialized assessment.
- research staff will also communicate the licensed clinician in case of any concerns about the subject during the follow-up assessments.
- For this assessment, the following questions will be added, and the research staff must provide the answers ("yes" or "no"): "Active ideation with plan and intent currently?"; "Are you otherwise concerned about the patient at all?"

The licensed clinician will follow the best policies and procedures of URMC and applicable state law for providing resources and determining if emergency evaluation is required. At minimum, the licensed clinician will:

- Advise the subject about emergency contact number
- Ask the subject to review the steps of the discharge safety plan from the inpatient unit or

the safety planning the subject may have with outpatient provider
- Inquire about and reinforce the need to attend existing appointments
- Verify the subject's understanding by asking what steps they will take if their condition deteriorates

There is a risk of loss of confidentiality if safety concerns are discovered (i.e., suicidal intent). Subjects are informed during the consent process that study staff will break confidentiality if subjects are assessed to be at risk for suicidal behavior and take appropriate actions, including alerting the clinical care provider, referring for emergency evaluation, or other actions such as calling 911. Additionally, if we witness or the subject discloses information regarding potential serious harm to others, including child abuse or neglect, abuse of a disabled adult, or elder abuse, we will also contact the appropriate authorities.

10. POTENTIAL BENEFITS TO SUBJECTS

Subjects might not benefit from being in this research study. The potential benefits include learning more about themselves through clinical assessments, decreased risk of suicidal ideation recurrence, and possible reduction of depressive symptoms.

11. COSTS FOR PARTICIPATION

There are no costs that subjects may be responsible for because of participation in this research.

12. PAYMENT FOR PARTICIPATION

Subjects will receive $40 for the baseline assessment, $30 for each clinical assessment (day 14, day 30, and day 60 from the first RS-tDCS session), and $30 for their time when sending the device back in a pre-paid package by mail, receiving a maximum compensation of $160 through Amazon gift card. Subjects will receive either a text message or email with an Amazon gift code, or a mailed Amazon gift card, following the completion of each clinical assessment.

13. SUBJECT WITHDRAWALS

Subjects may be removed from the study without their consent if they appear to be harmed by participating. Subjects will also be removed from the study if they do not tolerate the tDCS stimulation during the tolerability test (please, see "Study procedures"). Subjects will also be removed from the study if they initiate treatment with electroconvulsive therapy or transcranial magnetic stimulation at any moment during the trial. Finally, women subjects will be removed from the study if they become pregnant or planning to become pregnant during the time of the study comprehending the RS-tDCS sessions No new information identifying the subject will be gathered after the withdrawal date. Information that has already been gathered may still be used for research purposes.

14. PRIVACY AND CONFIDENTIALITY OF SUBJECTS AND RESEARCH DATA

Assessment data is stored in REDCap, a software toolset and workflow methodology for the electronic collection and management of research and clinical trial data. REDCap was created specifically around HIPAA-Security guidelines, including a complete audit trail, user- and individual form-based privilege options, and integration with institutional servers. The REDCap database is password protected, and access is limited to relevant study personnel. All research data are coded using a study identification number. Identifying information and protected health information is marked with REDCap's "identifier" designation, which allows it to be

automatically removed in data exports. Additionally, access to any forms containing identifying or protected health information is only granted to those investigators, clinicians, or staff who need to know this information for the study. All identifying data not in REDCap is stored in password-encrypted files. Access to these files is limited to investigators and support personnel with the need to enter or analyze data.

Text messages are sent from a study-issued phone purchased by URMC. The texts sent by study staff do not contain PHI. Content of the texts may include a reminder for a follow-up assessment phone call, a REDCap survey link if subjects cannot be reached by phone for a follow-up assessment, or an Amazon gift code for compensation after a follow-up assessment has been completed. Subjects receive texts only if they are willing and able to receive them. Acceptance of text is not a condition of participation in the study. Subjects may decline to receive texts during consent and opt out by sending a STOP reply to any text. Alternatively, emails, letters, and/or calls are used to maintain contact during follow-up. Study staff document the preferred method of contact for each subject and update their preference if it changes over the course of the study.

All research and clinical information obtained is kept confidential unless the subject is at risk for danger to themselves or others as determined by the research team based on available information. Subject well-being is carefully monitored throughout the study. If the clinical information obtained in the course of research assessments pertains to subject safety (e.g., intent to harm oneself or others), then confidentiality will not be maintained, and appropriate treating professionals will be informed. As required to promote subject safety, this clinical information may be provided to other clinicians (or family members) to facilitate appropriate treatment and minimize the risks of self-harm or harm to others. This information may include the subject's medical history, financial and social resources, and history of suicidal behavior if known.

15. DATA / SAMPLE STORAGE FOR FUTURE USE

We are willing to share data with other researchers and have chosen measures that are useful for future analyses; however, the data sharing agreement involves sharing only de-identified data with other investigators and the use of data-sharing agreements that provide for: (1) a commitment to use the data only for research purposes and not to identify any individual subject; (2) a commitment to secure the data using appropriate computer technology; and (3) a commitment to destroy or return the data after analyses are completed.

16. DATA AND SAFETY MONITORING PLAN

Risk to study subjects is minimized by only employing well-trained and clinically experienced personnel. Routine hospital protocols are already in place for handling in-person and over-the-phone crises.

Adverse Events (AEs) and Serious Adverse Events (SAEs)

An adverse event is “any untoward or unfavorable medical occurrence in a human subject…temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.” A serious adverse event (SAE) is an event where a relationship to the research study cannot be ruled out, and the event is life-threatening/results in death OR disabling/incapacitating OR requires or prolongs hospitalization OR involves an overdose OR was otherwise unanticipated, related to the study procedures. Due to the nature of this study, suicide attempts and psychiatric hospitalizations are possible to

happen during its course. These events are considered SAEs and reported as such. In most circumstances, suicide attempts and psychiatric hospitalizations are expected for this population and, as a result, non-study related. As such, these SAEs will be reported at continuing review but only unexpected reported immediately to the IRB. Suicide deaths are reported to the IRB within 48 hours of learning of the death. In addition, the report includes investigators' judgment as to whether a relationship to the research study can/cannot be ruled out.

For all AEs, the date and time of onset and outcome, course, intensity, action is taken, and causality to study treatment will be assessed. Based on the review of the circumstances and as-needed consultation with co-investigators, the PI can reclassify an AE as an SAE. If considered related to the study, unanticipated adverse events involving risks to subjects or others will be reported by the PI to IRB. For each adverse event, the treatment groups are compared in a pair-wise fashion regarding the occurrence of at least one event using Fisher's exact tests; the numbers of individual events will also be described. All subjects are included in these analyses.

Confidentiality

There will be a restriction from unauthorized access to identifiable subject data, storage of data to protect against the inadvertent loss, and use of appropriate database software tools to maintain the integrity of data for subsequent analyses. All research files are coded using a study identification number. Subject identifying information and PHI are marked with REDCap's "identifier" designation so it is automatically removed from any data exports. Additionally, access to any forms containing identifying or protected health information is only granted to those investigators, clinicians, or staff who need this information to conduct the study. All identifying data is stored in locked cabinets, offices, or password-encrypted files. Access to these files is limited to investigators and support personnel with the need to enter or analyze data.

Data sharing agreement will involve sharing only de-identified data with other investigators and the use of data-sharing agreements that provide for: (1) a commitment to using the data only for research purposes and not to identify any individual subject; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed.

All research and clinical information obtained is confidential unless the subject is an immediate danger to themselves or others. Subject well-being will be carefully monitored throughout the study. If the clinical information obtained in the course of research assessments pertains to subject safety (e.g., intent to harm oneself or others), then confidentiality is not maintained, and appropriate treating professionals will be informed. During crisis situations, this clinical information may be provided to other clinicians (or family members) to facilitate appropriate treatment and minimize the risks of self-harm or harm to others. This information may include the subject's medical history, financial and social resources, and history of suicidal behavior if known.

Certification of Research Personnel in the Protection of Human Subjects

To ensure appropriate human research knowledge, all study personnel interacting with subjects or with access to subject research have completed mandatory training in the protection of human research subjects per guidelines issued by the U. S. Department of Health and Human Services, Office for Human Research Protections (see http://ohrp.osophs.dhhs.gov/) and per guidelines of the URMC. Any additional personnel will complete this training before interacting with study subjects. Consistent with RSRB policy, all investigators and research staff will complete

certification by the RSRB—required completion of a course that contains seven modules dealing with topics such as “Ethics and Federal Regulations,” “Roles and Responsibilities of the Investigator and the Study process,” and “Roles and Responsibilities of Institutions in Human Subjects Research,” among others. The program provides a substantial resource to the investigator for understanding the ethics and regulations governing research with human subjects.

ClinicalTrials.gov Requirements
In line with NIH recommendations, our trial was registered with clinicaltrials.gov (NCT05280756).

17. DATA ANALYSIS PLAN

To assess feasibility, the primary outcome of this study, we chose a sample size of 20. To infer feasibility, at least 50% of the sessions should be performed successfully per subject for at least 70% of the subjects. This criterion is based on a study that reported dropout rates between 22% and 25% of home-based tDCS for patients with bipolar depression (40) and that therapeutic effects with tDCS could be achieved within one week of treatment (24). For each time point established, we will compare groups with a t-test or chi-square test, for continuous and categorical data, respectively (a p value<0.05 will be considered significant).

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