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**ALLSTIM**

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Feasibility and Efficacy of Transcranial Direct Current Stimulation (tDCS) and Cognitive  
Training for Executive Dysfunction in Adult Survivors of Childhood Acute Lymphoblastic  
Leukemia

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**Protocol ALLSTIM and Title: Feasibility and Efficacy of Transcranial Direct Current Stimulation (tDCS) and Cognitive Training for Executive Dysfunction in Adult Survivors of Childhood Acute Lymphoblastic Leukemia**

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**IDE Holder:** Soterix Medical

**Brief Overview:** A common and potentially debilitating late effect of childhood cancer treatment is neurocognitive impairment, frequently in the domain of executive dysfunction, which can limit educational attainment, employment, and quality of life. Among the survivors of childhood acute lymphoblastic leukemia (ALL) in the SJLIFE cohort, the rate of executive function impairment has been shown as high as 58.8%, with moderate to severe impairment rates as high as 33.5%, and risk for impairment increased with time from diagnosis. Given the potential of pervasive impact of neurocognitive impairment on daily life, interventions directed at reducing neurocognitive dysfunction among childhood cancer survivors with long-term follow-up are needed. Transcranial Direct Current Stimulation (tDCS), a form of non-invasive brain stimulation, is a potentially useful tool to enhance cognitive function. tDCS involves modulation of cerebral cortex excitability by the application of weak direct current through the scalp.

Researchers at St. Jude Children's Research Hospital want to evaluate the influence of tDCS and cognitive training on cognitive performance in long-term survivors of childhood ALL.

**Intervention:** Transcranial Direct Current Stimulation

In phase I, the short-term effect of tDCS intervention will be evaluated in the clinical setting using a randomized cross-over trial. The survivors will be randomized to receive either the tDCS intervention at the current dose level of 1mA or Sham for 15 minutes on day 1, with the other treatment given on day 2 (i.e. those who got tDCS intervention on day 1 will get sham on day 2 and vice versa). The tDCS intervention will be delivered by the Soterix Transcranial Direct Current Stimulator Clinical Trials (1x1-CT). Neurocognitive testing using the NIH Toolbox will be conducted within two hours of completing stimulation each day.

In phase II, the feasibility and potential efficacy of self-administration of the tDCS intervention paired with cognitive training will be evaluated over 5 weeks. Research participants will be taught to use the mobile tDCS device and will be provided one to take home. The device will be programmed by the investigators in advance to control the intensity and duration of the stimulation. The research participants will use the device twice per week as directed, and will be required to obtain a unique access code from the investigators prior to each stimulation session. Each stimulation session will be monitored using FaceTime on an institutional iPad given to the participants. Within two hours of completing each tDCS session participants will complete 20 minutes of cognitive training using a mobile app installed on the iPad. Neurocognitive testing will be conducted pre- and post- intervention using remote assessment.

**Study Design:** Pilot study

**Sample Size:** 45 research participants

**Data Management:** Data management for this study will be supervised by the Neuropsychology Research Team Clinical and Survey Research Center in the Department of Epidemiology and Cancer Control. Statistical analysis will be provided

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locally by the Biostatistics Department at St. Jude Children's Research Hospital.

**Human Subjects:** There is low risk to participants related to the tDCS. Potential side effects include redness and slight tingling at the site of stimulation, and all side effects are reversible. Recent meta-analyses show side effects to occur no more frequently than placebo conditions. Time commitment could be seen as a burden and some of the questions may make the participant uncomfortable. Adverse events will be monitored, reported, and treated accordingly.

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## 1.0 OBJECTIVES

### 1.1 Primary Objectives:

- 1.1.1 To evaluate the feasibility of a home-based intervention using tDCS and cognitive stimulation in adult survivors of childhood ALL participating in the SJLIFE study.

Hypothesis 1: A home-based tDCS and cognitive training intervention will be a feasible intervention strategy to improve executive function in long-term survivors of childhood ALL.

### 1.2 Secondary Objectives

- 1.2.1 To estimate the efficacy of a tDCS intervention paired with cognitive stimulation.

Hypothesis 2: The home-based tDCS and cognitive training intervention will result in improved executive function in adult survivors of childhood after a five week intervention.

- 1.2.2 To explore the short-term effect of tDCS on measures of executive function among adult survivors of childhood ALL participating in the SJLIFE study.

## 2.0 BACKGROUND AND RATIONALE

### 2.1 Background

With recent advances in treatment the survival rate of childhood cancer exceeds 80%,<sup>1</sup> such that 1 in 640 young adults in the United States is estimated to be a pediatric cancer survivor. A common and potentially debilitating late effect of childhood cancer treatment is neurocognitive impairment, particularly executive dysfunction, which can limit educational attainment and employment.<sup>2</sup>

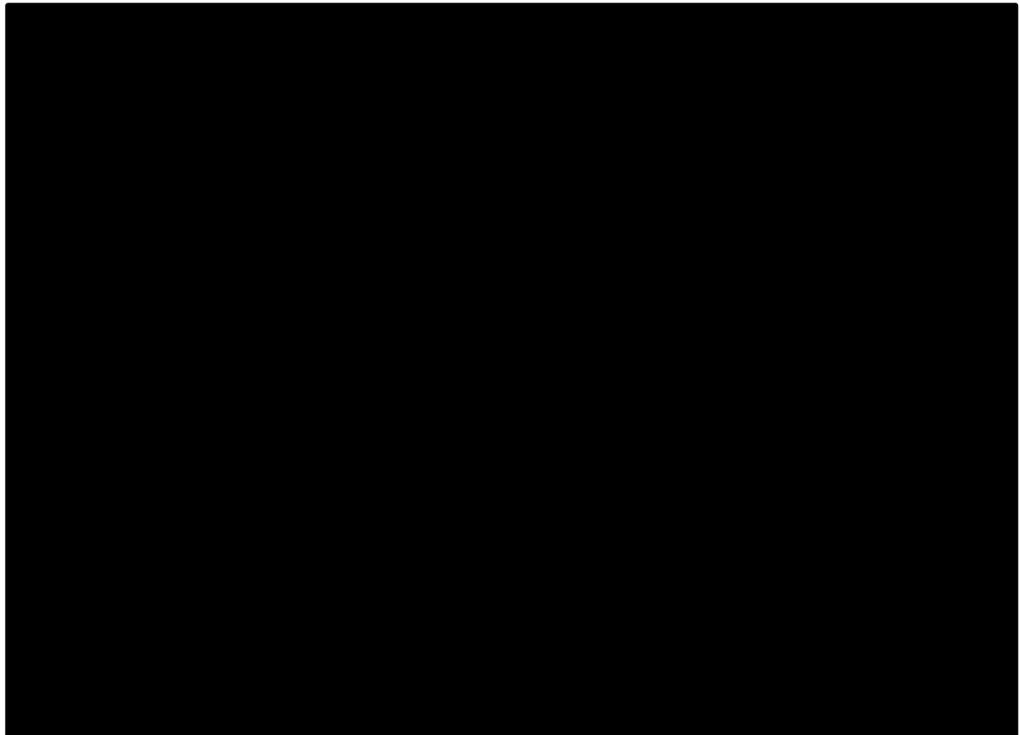
Prevalence estimates of neurocognitive dysfunction range from 20% to 80% of the population of cancer survivors, depending on the diagnoses, treatment, cognitive assessment procedure, and definition of impairment.<sup>3-6</sup> Treatments such as cranial radiation, antimetabolite chemotherapy (i.e. methotrexate) and corticosteroids increase the risk of neurocognitive impairment.<sup>3,7-9</sup> A recent study<sup>2</sup> among the survivors of childhood acute lymphoblastic leukemia (ALL) in the SJLIFE cohort showed that the rate of neurocognitive impairment to be as high as 58.8% for executive functions, the most common domain of impairment, with moderate to severe impairment rates as high as 33.5%. Furthermore, risk of impairment increased with time from diagnosis. Across individual skills, moderate to severe impairment (defined as a score <7<sup>th</sup> percentile compared to the normal population) rates of 25%, 18%, and 3.5% were seen for cognitive flexibility, cognitive fluency and working memory, respectively.<sup>2</sup> Neurocognitive impairment impacts multiple areas of adult functioning, including educational attainment<sup>3</sup>, employment,<sup>3</sup> health behaviors,<sup>10</sup> quality of life<sup>11</sup> and social functioning.<sup>3,12</sup> Given the potential of pervasive impact of neurocognitive impairment on daily life, interventions directed at reducing neurocognitive dysfunction among long-term survivors of childhood cancer are needed. Even though many studies have characterized neurocognitive impairment in long-term survivors of childhood cancer, limited research has focused on developing interventions to improve these well-established late effects.<sup>13-15</sup> Thus there is a strong need for intervention studies that will improve the neurocognitive impairment among these survivors.

### 2.2 Rationale:

Cognitive training has been used in an attempt to improve neurocognitive impairment in cancer survivors. We recently completed a pilot study of a cognitive stimulation trial to improve function in adult survivors of childhood cancer. Twenty-one survivors completed six months of regular cognitive exercises, with pre- and post-neurocognitive testing. Compared to an equated

reference group tested at a similar interval, those who completed training exercises demonstrated significant improvement in cognitive flexibility and processing speed. However, the effect sizes were relatively small and, given the long-standing nature of the impairment, extended training, more intensive training, or an additional intervention to support the training may be necessary to enhance effects.

A potentially useful tool to enhance cognitive intervention is transcranial Direct Current Stimulation (tDCS). tDCS involves modulation of cerebral cortex excitability by the application of weak direct current to the scalp<sup>16</sup>. tDCS is a technique that applies safe, low level direct current through large pads on the scalp to stimulate the underlying brain region, with current level  $< 0.10 \text{ C/cm}^2$  (as a reference, tissue damage occurs at levels of  $\sim 200 \text{ C/cm}^2$  or higher).<sup>16</sup> The schematic below demonstrates the manner in which the tDCS intervention is delivered to the participants.



A cross-over study of tDCS on working memory using healthy volunteers showed that tDCS modulated working memory performance (measured by letter n-back) by altering dorsolateral prefrontal cortex (DLPFC) brain activity in a polarity-specific way, in that anodal tDCS enhanced the performance related to working memory.<sup>17</sup> Another study<sup>18</sup> in healthy volunteers found that anodal tDCS of DLPFC or the primary motor cortex (M1) increased performance on a cognitive or motor task, respectively.<sup>18</sup>

tDCS is also a safe method for enhancing cortical responsivity. A recent meta-analysis<sup>19</sup> looked at over 200 studies for adverse events (AE) related to active

tDCS and found that 56% of studies reported mild AEs and no studies reported more than mild AE's. The most common AE's reported were itching, tingling, mild headache, and discomfort, however, none of the AE's differed in frequency between the placebo (sham application) and active treatment groups. Levels of less than 2 mA of current over 5-20 minutes for 1-10 days has been used in various studies without significant adverse events. In addition, clinical studies have demonstrated efficacy of tDCS intervention in reducing neurocognitive impairments among patients suffering from strokes,<sup>20</sup> depression,<sup>21,22</sup> psychosis, and Alzheimer's disease<sup>23</sup>. However, the usefulness of tDCS has not been evaluated in long-term adult survivors of childhood cancer exhibiting neurocognitive impairments. Since these adults have likely experienced neurocognitive impairment for many years, we believe the application of tDCS will enhance their ability to benefit from cognitive training.

We propose to conduct a pilot study to assess the feasibility and potential efficacy of a 5-week tDCS intervention paired with cognitive training to improve executive function in long-term adult survivors of childhood ALL. Stimulation and training will be conducted at home twice per week for five weeks. However, prior to initiating the home trial, we propose to conduct a trial in the clinic in order to evaluate the short-term effect of tDCS on measures of executive function. This clinic-based trial will also provide participants with on-sight experience with tDCS under direct observation prior to beginning the home-based intervention under remote observation.

### **3.0 RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT**

According to institutional and NIH policy, the study will accession research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

#### **3.1 Inclusion Criteria**

- 3.1.1 Current St. Jude LIFE Participant
- 3.1.2 Long term survivor of acute lymphoblastic leukemia (ALL)
- 3.1.3 Currently  $\geq$  18 years of age
- 3.1.4 Wi-Fi internet access at home (estimated at >75% of the SJLIFE cohort)
- 3.1.5 History of executive dysfunction, documented by SJLIFE neurocognitive testing, and defined as having an age-adjusted standard

score <20<sup>th</sup> percentile on Trail Making Test Part B, Verbal Fluency, or Digit Span Backward.

3.1.6 History of self-reported executive dysfunction in daily life, defined as having a standardized score <20<sup>th</sup> percentile on BRIEF Initiate, Shift, or Working Memory domains OR having scored <20<sup>th</sup> percentile on the Childhood Cancer Survivor Study Neurocognitive Questionnaire Task Efficiency or Memory domains.

3.1.7 Participant is able to speak and understand the English language.

### **3.2 Exclusion Criteria**

3.2.1 Any survivor with full scale IQ <80

3.2.2 Currently on stimulants or other medications intended to treat cognitive impairment

3.2.3 History of seizures

3.2.4 No implanted medical devices or implanted metal in the head

3.2.5 Currently pregnant or planning to become pregnant.

3.2.6 Inability or unwillingness of research participant or legal guardian/representative to give written informed consent.

### **3.3 Research Participant Recruitment and Screening**

We propose to utilize the SJLIFE alumnus dataset to identify evaluable adult long-term ALL survivors. Following review of the SJLIFE patient database, we have identified 333 participants with documented executive function impairment. Participant eligibility will be identified through hospital admission records and consultations with the SJLIFE study team prior to the patient's SJLIFE clinic visit. Individuals eligible for this study will be mailed a letter to introduce the study and inform him or her that they are eligible for enrollment. The letter will state that an interviewer will be contacting them within two weeks to discuss the study and inquire about their desire to participate. A second letter and a second phone call will be attempted two to four weeks after the original letter if no initial response is received.

A requirement of ALLSTIM eligibility is to be a participant in the SJLIFE study. Patients will be assessed for the capacity to consent as part of SJLIFE recruitment. If a participant is assessed to be competent to consent for SJLIFE, they will be competent to consent for ALLSTIM.

### 3.4 Enrollment on Study at St. Jude

A member of the study team will confirm potential participant eligibility as defined in Section 3.1-3.2, complete and sign the ‘Participant Eligibility Checklist’. The study team will enter the eligibility checklist information into the Patient Protocol Manager (PPM) system. Eligibility will be reviewed, and a research participant-specific consent form and assent document (where applicable) will be generated. The signed consent/assent form must be faxed or emailed to the CPDMO at [REDACTED] in order to complete the enrollment.

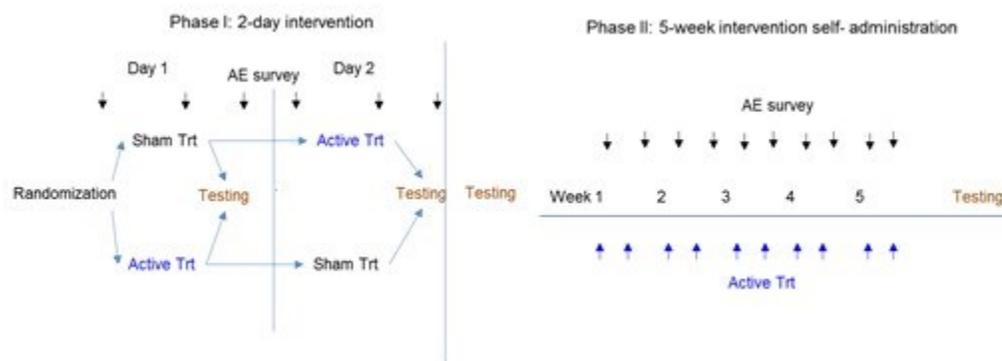
The CPDMO is staffed 7:30 am-5:00 pm CST, Monday through Friday. A staff member is on call Saturday, Sunday, and holidays from 8:00 am to 5:00 pm. Enrollments may be requested during weekends or holidays by calling the CPDMO “On Call” cell phone ([REDACTED]) or referencing the “On Call Schedule” on the intranet).

## 4 DESIGN AND METHODS

### 4.1 DESIGN AND STUDY OVERVIEW

The proposed study will be conducted in two phases. In Phase I, the short-term effect of tDCS on performance on measures of executive function will be evaluated over a two-day period. After assessing the effect in Phase I, and providing participants with a directly observed experience with tDCS, the feasibility of self-administering tDCS over long-term (5 weeks with two sessions per week) using a mobile tDCS device and its potential efficacy will be evaluated in Phase II. The 5-week intervention will be paired with cognitive stimulation using the Lumosity Brain Games program ([www.lumosity.com](http://www.lumosity.com)). This program involves cognitive exercises designed to enhance executive function and processing speed, to be performed on an institutionally provided iPad. Cognitive stimulation activities can be completed in 15-20 minutes per session. The study schema is displayed in the Figure below:

Figure 1. ALLSTIM Study Schema



A cross-over randomized trial will be used in Phase I. The survivors will be randomized to receive either the tDCS intervention at the current dose level of 1mA or Sham for 15 minutes on day 1 and then on day 2 the other treatment will be provided (i.e. those who got tDCS intervention of day 1 will get sham on day 2 and vice versa). The tDCS intervention will be delivered by the Soterix Transcranial Direct Current Stimulator Clinical Trials (1x1-CT). The effect of one session to tDCS is expected to last for about two hours thus conducting the second session the next day will provide sufficient time for the “wash-out” and good justification for using a cross-over design.

In phase II, the feasibility and efficacy of long-term (5 week) self-administration of the tDCS intervention will be evaluated in concurrence with self-administered cognitive stimulation. In this phase the research participants will be taught to use the mobile tDCS device and will be provided with one to take home. The device will be programmed by the investigators in advance to control the intensity and duration of the stimulation. The research participants will use the device twice per week as directed. Before each session, the participant will use an institutionally provided iPad for video conferencing with the study center to obtain a unique access code to start the tDCS device and ensure proper device placement. Each stimulation session for each participant will have a unique access code. An AE evaluation will be conducted by a trained study team member every week. Research participants will complete remote neurocognitive testing via the iPad before and after phase II.

## 4.2 STUDY PROCEDURES:

### 4.2.1 Transcranial Direct Current Stimulation – Clinical System

The system used for stimulation is the Transcranial Electrical Stimulation 1x1 Clinical Trials Device manufactured by Soterix Medical. This system allows for double-blinded application of the intervention or sham treatment. The intervention consists of a direct current of 1 mA applied for 15

minutes. The sham procedure provides the same small current during ramp up to imitate the intervention, but the current is discontinued after ramp up and no intervention is provided.

Direct current is transferred by a pair of saline-soaked sponges, with the anode attached to the left frontal region (F3) and the cathode attached over the right eyebrow (Fp2). Participants will be randomized to receive the intervention on day 1 and the sham on day 2 or vice versa. Within two hour of completing the intervention and sham, participants will complete the NIH Toolbox Cognitive Battery on both days.

#### **4.2.2 Transcranial Direct Current Stimulation – Mobile System:**

The mobile transcranial direct current stimulation system is manufactured by Soterix Medical and consists of a battery pack, control unit and a self-positioning headband with sponges. Participants will be given the device after completing the clinical portion of the study and trained in correct usage. Participants will complete two stimulation sessions per week for 5 weeks. The sessions will provide 1 mA DC for 15 minutes in the same manner as the clinical system. Participants will be supplied iPads for the cognitive stimulation training, and the iPad will be used to monitor correct tDCS usage. The tDCS unit requires a unique code for each stimulation session. Study staff will use video conferencing to confirm correct electrode placement, then provide the code to initiate treatment. Each session will be monitored for compliance and to assess any adverse events.

#### **4.2.3 Cognitive Training:**

Survivors who complete phase I and continue to phase II will begin the 5 week cognitive stimulation program. Participants will use the supplied iPad to complete online cognitive stimulation training within one hour of every at-home tDCS session. The cognitive training program was developed by Lumosity (see Appendix for description of Lumosity program) and involves training of attention, processing speed, working memory, and executive function skill using cognitive tasks. Participants will be asked to engage in training for 20 minutes a day, two days per week. Five cognitive tasks will be presented during each training session. Survivors will complete 5-weeks of stimulation and training. The Lumosity program records the day and time of training and performance on the training activities for each participant, and these records are available to study staff via internet. Adherence to training and

change in performance following stimulation sessions will be examined.

At the end of the 5-week intervention, participants will mail back the iPad and tDCS device in a postage-paid and addressed FedEx box provided to them at their study visit.

#### **4.3 Adverse Event Monitoring:**

Reports of adverse events will be monitored. Adverse events will be surveyed at the beginning of each video conference, with symptoms reports for the prior stimulation session. Adverse event information will be collected by participant reporting and direct questioning using the patient report of incidence of side effects (PRISE), frequency and intensity of side effect rating (FISER), and global rating of side effects burden (GRSEB). The PRISE form assesses the presence of side effects for a variety of biological systems. For each of the nine organ/function systems (gastrointestinal, nervous system, heart, eyes/ears, skin, genital/urinary, sleep, sexual functioning, and other), the participant indicates the presence of a side effect, and if present, the tolerability of the side effect (tolerable or distressing). The FISER and GRSEB assess three domains of side effect impact: frequency, intensity, and burden. Each domain is rated on a 7-point Likert scale (i.e. Frequency, ranging from no side effects to present all the time; Intensity, ranging from no side effects to intolerable; and Burden, ranging from no impairment to unable to function due to side effects). Reliability and validity have been reported.

## **5 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS**

### **5.1 Pre-Study Evaluations**

#### **5.1.1 Baseline Neurocognitive Evaluation**

SJLIFE Evaluation: All participants in SJLIFE undergo neurocognitive testing as part of the SJLIFE parent protocol. This evaluation involves assessment of intelligence, academic skills, processing speed, attention, working memory, long-term memory, and executive functions. Specific tests include:

- Wechsler Abbreviated Scale of Intelligence
- Woodcock-Johnson-III: Tests of Achievement
- Letter-Word Identification

- Calculation
- Wechsler Adult Intelligence Scale-Third Edition
- Digit Symbol-Coding
- Symbol Search
- Digit Span
- Trail Making Test
- Conners' Continuous Performance Test-II
- California Verbal Learning Test-II
- Brief Symptom Inventory
- Verbal Fluency Test
- Test of Memory and Learning Visual Selective Reminding

We will use this testing, which is already ongoing, to identify survivors who are eligible for this study (<10<sup>th</sup> percentile on Digit Span Backward, Trail Making Part B, or Verbal Fluency).

## 5.2 Evaluations During Therapy

### 5.2.1 NIH Toolbox – Cognitive Battery

We will use the three tests from the Cognitive Battery of the NIH Toolbox<sup>24</sup> to evaluate the acute effect of tDCS on executive function. These three measures have a computerized format and are nationally standardized. Testing will occur post-intervention (total 2 times) during phase I.

NIH Toolbox Dimensional Change Card Sort Test (DCCS): The DCCS specifically taps cognitive flexibility, with performance generally increasing through childhood and then declining across the adult age. A total of 40 trials require 4 minutes. Scoring is based on a combination of accuracy and reaction time. This combination score is then converted to a scale score with mean of 100 and SD of 15, where higher scores indicate higher levels of cognitive flexibility.

NIH Toolbox Flanker Inhibitory Control and Attention Test: The Flanker taps inhibitory control and attention, the capacity for new learning and information processing in novel situations – measure, in which performance reaches a peak in early adulthood, and then tends to decline across the life span. A total of 40 trials require 4 minutes. Scoring is based on a combination of accuracy and reaction time, this combination score is then converted to a scale score with mean of 100 and

SD of 15, where higher scores indicate higher executive function.

NIH Toolbox List Sorting Working Memory Test: List Sorting is tapping both information processing and storage, with performance tending to peak in early adulthood and then declining across the life span. The raw score obtained is converted to Age-Adjusted to the national norms. Higher scores on each of these indicate higher levels of working memory. This task assesses working memory and requires the participant to sequence different visually- and orally-presented stimuli. The list scoring task takes approximately 7 minutes to administer. List Sorting is scored by summing the total number of items correctly recalled and sequenced on Lists-1 and -2, which can range from 0-26.

### **5.2.2 Gray Oral Reading Test**

The Gray Oral Reading Test (GORT) will be used to measure reading comprehension. The GORT is one of the most widely used measures of oral reading fluency and comprehension in the United States. Participants will be asked to read a set of passages and recall specific details from the stories. Responses to the test require literal as well as inferential comprehension, the latter of which involves executive function. Two stories will be given each day, one day from Form A and one day from Form B. Raw scores will be calculated for total accuracy, and compared within participants. Total testing time will be approximately 5 minutes after each clinical tDCS session.

### **5.2.3 Woodcock Johnson Understanding Directions**

The Woodcock Johnson Understanding Directions is a measure of listening comprehension. The task requires the participant to listen to a series of complex instructions and then follow the directions by pointing to various objects in a colored picture. Directions require sequential and logical reasoning, components of executive function. Four complex instructions will be administered each day, from alternate test forms, and raw scores will be calculated and compared within participants. Total testing time will be approximately 5 minutes after each clinical tDCS session.

### **5.2.4 Remote Assessment Procedures**

We have recently completed a pilot study to evaluate the accuracy of remote cognitive assessment, using web and phone based procedures.<sup>25</sup> We will employ these procedures prior to

and following the initiation of phase II of the trial. Specifically, the following tests will be administered:

**Televideo-based assessment:**

Neurocognitive testing will be conducted via video conferencing with the iPad. At a scheduled time, an examiner will contact the participant. The following clinical measures will be administered:

- Digit Span Test
- Verbal Fluency Test
- Oral Trail Making Test
- CCSS Neurocognitive Questionnaire

## **6 CRITERIA FOR REMOVAL FROM PROTOCOL**

### **6.1 Off Study Criteria:**

**6.1.1** All protocol interventions are complete

**6.1.2** Request of the Participant/Legally Authorized Representative

**6.1.3** Death

**6.1.4** Lost to follow-up

**6.1.5** Discretion of the Study PI, such as the following:

- The researcher decides that continuing in the study would be harmful
- A treatment is needed that is not allowed on this study
- The participant misses so many appointments that the data cannot be used in the study
- New information is learned that a better treatment is available, or that the study is not in the participant's best interest

## **7 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS**

### **7.1 Reporting Adverse Experiences and Deaths to St. Jude IRB**

**Only “unanticipated problems involving risks to participants or others” referred to hereafter as “unanticipated problems” are required to be reported to the St. Jude IRB promptly, but in no event later than 10 working days after the investigator first learns of the unanticipated problem.**

**Regardless of whether the event is internal or external (for example, an IND safety report by the sponsor pursuant to 21 CFR 312.32), only adverse events that constitute unanticipated problems are reportable to the St. Jude IRB. As further described in the definition of unanticipated problem, this includes any event that in the PI's opinion was:**

- Unexpected (in terms of nature, severity, or frequency) given (1) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, as well as other relevant information available about the research; (2) the observed rate of occurrence (compared to a credible baseline for comparison); and (3) the characteristics of the subject population being studied; and
- Related or possibly related to participation in the research; and
- Serious; or if not serious suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unrelated, expected deaths do not require reporting to the IRB. Though death is “serious”, the event must meet the other two requirements of “related or possibly related” and “unexpected/unanticipated” to be considered reportable.

Deaths meeting reporting requirements are to be reported immediately to the St. Jude IRB, but in no event later than 48 hours after the investigator first learns of the death.

**The following definitions apply with respect to reporting adverse experiences:**

**Serious Adverse Event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:**

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;

- 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: any substantial disruption of the ability to conduct normal life functions, 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), a congenital anomaly/birth defect, secondary or concurrent cancer, medication overdose, or is any medical event which requires treatment to prevent any of the medical outcomes previously listed.

**Unexpected Adverse Event:**

- Any adverse event for which the specificity or severity is not consistent with the protocol-related documents, including the applicable investigator brochure, IRB approved consent form, Investigational New Drug (IND) or Investigational Device Exemption (IDE) application, or other relevant sources of information, such as product labeling and package inserts; or if it does appear in such documents, an event in which the specificity, severity or duration is not consistent with the risk information included therein; or
- The observed rate of occurrence is a clinically significant increase in the expected rate (based on a credible baseline rate for comparison); or
- The occurrence is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

**Internal Events: Events experienced by a research participant enrolled at a site under the jurisdiction of St. Jude IRB for either multicenter or single-center research projects.**

**External Events:** Events experienced by participants enrolled at a site external to the jurisdiction of the St. Jude Institutional Review Board (IRB) or in a study for which St. Jude is not the coordinating center or the IRB of record.

**Unanticipated Problem Involving Risks to Subjects or Others:** An unanticipated problem involving risks to subjects or others is an event which was not expected to occur and which increases the degree of risk posed to research participants. Such events, in general, meet all of the following criteria:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. An unanticipated problem involving risk to subjects or others may exist even when actual harm does not occur to any participant.

**Consistent with FDA and OHRP guidance on reporting unanticipated problems and adverse events to IRBs, the St. Jude IRB does not require the submission of external events, for example IND safety reports, nor is a summary of such events/reports required; however, if an event giving rise to an IND safety or other external event report constitutes an “unanticipated problem involving risks to subjects or others” it must be reported in accordance with this policy. In general, to be reportable external events need to have implications for the conduct of the study (for example, requiring a significant and usually safety-related change in the protocol and/or informed consent form).**

**Although some adverse events will qualify as unanticipated problems involving risks to subjects or others, some will not; and there may be other unanticipated problems that go beyond the definitions of serious and/or unexpected adverse events. Examples of unanticipated problems involving risks to subjects or others include:**

- Improperly staging a participant’s tumor resulting in the participant being assigned to an incorrect arm of the research study;

- The theft of a research computer containing confidential subject information (breach of confidentiality); and
- The contamination of a study drug. Unanticipated problems generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

All anticipated Grade III or IV adverse events will be reported to the IRB in the continuing review report and/or summary. The study teams will monitor accrual and toxicities every six months.

## **7.2 Recording Adverse Events and Serious Adverse Events**

All serious adverse events will be recorded in the source, database and/or case report form. Adverse events unrelated to the trial will not be recorded unless they are grade III or above (CTCAEv4). Adverse events that are related to the trial will be captured in the source document, database and/or case report form. Adverse events related to the trial will be collected until the time the study completes.

# **8 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY**

## **8.1 Data Collection**

Data for this study will be managed by the Neuropsychology Research Team in the Department of Epidemiology and Cancer Control. Data collected at baseline and follow-up assessments will be entered by optical scanning. The optical scanning program has the capacity for designer specific error checks, flagged at the time the questionnaires are scanned. After data are scanned, they are processed and converted into a SAS (Cary, NC) format where a second error check is completed. Data from neurocognitive tests are double-entered into a separate secure Access database and compared for accuracy. All data mismatches will be reviewed by two members of the survey center staff and compared to the original documents (when applicable) for resolution. NIH Toolbox data will be stored on remote computer servers and will be completely de-identified. Data from the tDCS mobile units and the cognitive training (Lumosity) will be downloaded and processed by the study team using software provided by the product manufacturers.

## 8.2 Study Monitoring

The study team will hold monthly meetings and review case histories or quality summaries on participants. The PI and study team will be responsible for ensuring protocol compliance. Continuing reviews by the IRB and CT-SRC will occur at least annually.

This study is associated with an Investigational Device Exemption (IDE) and will be monitored by the St. Jude Clinical Research Monitors accordingly. The monitors will review up to 15% of the study participants semi-annually for appropriateness of the informed consent process, eligibility, adverse event recording and participant's status. Additional information may be monitored at the request of the Internal Monitoring Committee (IMC), the IRB, or other institutional administration.

Source document verification of eligibility and informed consent for 100% of St. Jude participants will be performed by the Eligibility Coordinators within 5 working days of completion of enrollment. The Clinical Research Monitor will review all SAE reports and other applicable essential regulatory documentation. The Monitor will generate a formal report which is shared with the Principal Investigator (PI), study team, and the Internal Monitoring Committee (IMC).

## 8.3 Confidentiality

Confidentiality will be maintained. Data forms will be kept in locked file cabinets, in locked offices, accessed only by study staff on an "as needed" hierarchical basis. All electronic files will be stored on a password protected computer and identifying information will be stored in separate electronic files and linked by participant number. Data files downloaded for statistical analyses will not contain personal identifiers.

The medical records of study participants may be reviewed by the St. Jude IRB, FDA, clinical research monitors, etc.

# 9 STATISTICAL CONSIDERATIONS

The sample size justification will be based on evaluating the primary objective, as that objective is the basic design of how the intervention will be delivered in a subsequent randomized controlled trial should this pilot study prove feasible. We will consider the trial to be feasible if at least 50% of the survivors are able to complete 5 sessions (tDCS along with cognitive stimulation) successfully out of 10. Any participant who completes Phase I,

but is unwilling to participate in Phase II due to the tDCS procedure will be counted towards failure. In the testing of hypothesis framework we would like to test the null hypothesis  $H_0: P \leq 0.5$  vs.  $H_1: P > 0.7$ . Then, using Simon's two-stage Minimax design with type I error rate  $\alpha=0.05$  and power  $(1-\beta)=0.8$  we have the following stopping rules. As an additional measure of feasibility, the consent rate must be  $>50\%$  among all participants approached to participate. Study staff will track study enrollment, and the study statistician will make the determination for study continuation.

In the first stage we will recruit 23 survivors and if the number of survivors who complete at least 5 sessions is at least 13 then we will proceed to the next stage and recruit an additional 14 survivors and if at least 24 survivors out of 37 complete at least 5 sessions then the tDCS trial would be considered feasible. However, since we expect that roughly 20% of the survivors may not initiate the trial after leaving the institution (i.e. may not provide any information at all for objective 1.1.1) we anticipate replacing these survivors and, thus, a total of 45 survivors will be needed for evaluating the Phase II objective. Participant accrual will cease when 37 participants agree to participate in Phase II.

With 37 survivors recruited for phase I of the study, we will have roughly 97.7% power for objective 1.2.1 to detect an improvement of 0.65 in standardized units, respectively, with type I error  $\alpha=0.05$ .

### **Analysis:**

Objective 1.1.1: The feasibility of the 5-week tDCS intervention will be evaluated using Simon's two stage Minimax design with stopping rules described above.

Objective 1.2.1: The improvement in scores on symbol digit coding, Stroop test, shifting attention test, digit span and verbal fluency from baseline to 5-week follow up will be done using matched pair one sample t-tests. In addition, the improvement in EF measures over the 5 week period will also be evaluated using longitudinal methods and implemented using PROC MIXED or PROC GEE in SAS 9.3.

Objective 1.2.2: The improvement in the scores on the NIH Toolbox Card Sort, Flanker and Working Memory tasks between tDCS and sham, will be done using matched pair one sample t-test.

It will be important to monitor for AEs in both phases of the study as well. Thus, in an "ad hoc" manner using one sided 95% confidence bounds we will monitor for all grade 3 or higher adverse events (All types of AE's included)

which are related to study interventions. Among the 45 patients enrolled in the study, if at any time point at least 5 patients ( $\geq 5$ ) have grade 3 or higher toxicity, the 95% lower confidence limit would be 0.059 suggesting that the true AE rate could be higher than 5% which would be unacceptable, the feasibility of the 5 week intervention would be questionable and a consideration will be given to stop or amend the trial.

### 9.1 Anticipated Completion Dates

<b>Anticipated Primary Completion Date:</b>	
<b>Anticipated Study Completion Date:</b>	

## 10 OBTAINING INFORMED CONSENT

Participants will be briefly introduced to the study during the consent process for SJLIFE and told there is a possibility they may qualify for this study. Eligible participants will be identified after the completion of the neurocognitive testing done as part of the SJLIFE protocol. The participant will be informed they are eligible to participate in this protocol at that time. A member of the study team will explain the study and review the potential risks and benefits. The study team will assure that the potential participant understands what the research study involves and the potential risks when the participant agrees to participate. Upon agreeing to participate, the consent form will be signed by the subject and/or guardian and investigator/designee.

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**APPENDIX I: SCHEDULE OF EVALUATIONS**

Event	Screening	Phase 1		Mobile Intervention Period						
		Day 1	Day 2	Pre Intervention	Week 1	Week 2	Week 3	Week 4	Week 5	Post Intervention
Informed Consent	X									
Cognitive Assessment	X									
TDCS Clinical Intervention		X	X							
TDCS Mobile Intervention					X	X	X	X	X	
Cognitive Stimulation					X	X	X	X	X	
NIH Toolbox Cognitive Battery		X	X							
Remote Cognitive Assessment				X						X