THE UNIVERSITY OF ARIZONA Research Innovation & Impact

IRB Protocol for Human Subjects Research

Basic Information	
Title of Study:	Toward personalized treatment of Chronic pain using transcranial direct current stimulation paired with deep learning
Short Title:	tDCS and Pain
Principal Investigator Name:	Allison Huff
Principal Investigator's Department/Unit:	Department of Family and Community Medicine

1.0 Background (Limit 1,000 words):

Provide the scientific or scholarly background for the proposed Human Research. Discuss relevant prior experience or preliminary data (e.g., existing literature).

There is an urgent need for effective, non-opioid treatment to manage pain. Particularly, for those whom pharmacologic pain treatments may be harmful, such as those with substance use disorders, PTSD, and other co-morbid mental health issues. The clinical standards for diagnosing and treating pain is based on an incomplete biological understanding of pain, and there are well documented problems with and inefficacy of the current treatment modalities, including dependence, addiction, and cognitive decline. Traditionally, pain treatment is localized, but to effectively treat pain we need to shift our focus to the underlying mechanisms of pain in the brain. Research shows that only 40-60% of all patients that receive pharmacological treatments for pain have a significant positive outcome [15]. Opioids have varying levels of effectiveness depending on type of pain, underlying etiology, and genetics. One of the main reasons for lack of efficacy is that current pharmacological approaches have limited to no effect on the neural mechanisms underlying pain and, in some cases, may make pain worse. For example, opioids tend to be more effective for acute pain, but can actually worsen chronic pain by inducing central sensitization (hyperalgesia) and hypersensitivity [13-17]. This predominant pharmacologic approach ignores the brain's neuroplasticity and ability for cell-regeneration and fails to consider the individual impacts on brain regions where pathological disorders related to pain are subserved. The use of tDCS, which emits a constant, low intensity current through electrodes placed over the head which modulates neuronal activity, lacks these side effects and has shown promise in promoting neuroplasticity 11-12 16-18]. The mechanisms of cortical modulation by tDCS may activate certain neuronal networks such as increasing glutamine and glutamate under the stimulation, effects on the μ-opioid receptor, and restoration of the defective intracortical inhibition. Precision medicine is a national priority and using technology to identify and treat differences in disease states should move forward as an alternative to pharmacological treatments [16-18]. TDCS is a non-invasive brain stimulation that uses electrical currents to stimulate specific areas of the brain. A constant, low intensity current passes through two to four electrodes, which can be placed on various locations on the head, to modulate neuronal activity. tDCS can administer anodal and cathodal stimulation to excite (depolarization) or inhibit (hyperpolarization) neuronal activity, respectively. Using low amplitude direct currents applied via scalp electrodes to alter cortical excitability is not a novel concept. This non-pharmacological approach has held promise for decades as a way to treat a plethora of neurological and psychiatric disorders. Although tDCS is not currently FDA approved it is considered a non-significant-risk therapy with no record of serious adverse effects [45,46,55]. Health Canada, the European Union, Israel, Singapore and many other regulatory bodies around the world have approved tDCS for medical treatment applications [44,46]. Although there are many neurostimulation devices available on the market only a few have been cleared recently by the FDA for medical use, including the Fisher Wallace Stimulator which is FDA cleared to treat depression, anxiety and insomnia

[47] and Neurostar which is FDA cleared to treat depression [49]. Studies have repeatedly shown clinical benefits of tDCS as a therapy for major depression [16–20], bi-polar disorder [21,22], anxiety [23,24], Parkinson's Disease [26] TBI [28,29], ADHD [30,31], stroke [32,33] and pain [13,25,34–42,50-54] as well as reduction in opioid use [43,44] with no major side effects.

(References listed at end of Protocol document)

2.0 Lay Summary:

Provide a brief description of the proposed research using terms that someone who is not familiar with the science or discipline can understand.

Pain is a severe and growing problem in the United States with more than 116 million Americans suffering from chronic pain and more than $635 billion spent annually on pain and its related healthcare costs [1]. Additionally, opioid addiction has become a national crisis with nearly 50,000 deaths every year as a result of opioid-involved overdoses and nearly $78.5 billion spent annually on opioid misuse and addiction [2–4]. Currently available treatments for pain, namely opioid analgesics, have limited effectiveness and can lead to a significant number of side effects and complications including dependence, pharmacodynamic tolerance, sedation, gastrointestinal issues, respiratory depression, immunosuppression, and hormonal changes [5–7]. Effectively treating pain requires an accurate assessment of pain, however current methods of diagnosing and evaluating pain depend on subjective self-reporting including the use of visual and numerical pain scales [8–10]. The subjective nature of describing pain makes it virtually impossible to quantify and therefore difficult to treat and monitor. To overcome this subjectivity, through a non-invasive neuromodulation technique called transcranial direct current stimulation (tDCS) and deep learning, pain can be measured objectively using electroencephalograph (EEG) to assess and personalize treatment. *The overarching goal of this project is to apply transcranial direct current stimulation (tDCS) as an alternative to opioids for the reduction in chronic pain.* Our long-term goal is to use these data to analyze EEG signals and generate personalized tDCS treatment in real-time.

3.0 Purpose:

Describe the purpose, specific aims, objectives, questions to be answered, hypotheses, and/or primary and secondary study endpoints of the Human Research.

The primary objective of the proposed study is to determine the impact of tDCS on pain in substance use disorder (SUD) subjects. The long-term goal of the study is to address the underlying neurobiological deficiencies caused by SUD and provide a more personalized adjunctive SUD treatment.

***Aim 1*: to compare changes in brain waves during tDCS treatment sessions in the treatment (tDCS) and placebo (sham) arms. This aim will be achieved by capturing EEG readings of the entire brain for subjects in each treatment arm at baseline, during the treatment phase, and at final study visit 1 week post treatment.**

***Aim 2*: to compare changes in self-reported pain perception in the treatment and placebo (sham) arms. We will achieve this aim by comparing the baseline pain perception scales results of subjects in treatment and placebo arms to pain perception scales results on the final day of the treatment and again one week later, enabling investigators to determine any short-term change or durable change to pain.**

***Aim 3*: to compare the safety and tolerability of the tDCS system (tKIWI) versus placebo (sham) in terms of any unwanted side effects or adverse events. We will achieve this aim by monitoring subjects' vitals during the entire session and evaluating results of a**

questionnaire after each treatment session and after the final study visit, enabling us to capture reported discomfort.

Our central hypothesis is that applying transcranial direct current stimulation using the patented tKIWI system will safely reduce self-reported chronic pain with little to no side effects. If this hypothesis is accurate, the next steps are to identify mechanistic biomarkers to improve our understanding and ability to accurately diagnose pain disorders which would facilitate the development of pharmacologic and non-pharmacologic treatment modalities using deep learning architecture built into the tKIWI.

Treatments focus entirely on pharmacological and behavioral approaches without evaluating the brain itself [9,10] even though chronic pain has been shown to be significantly related to brain function [8-11]. This creates significant limitations, such as imprecise treatment modalities, medicine side effects, and decreased treatment adherence due to slow progression and increased patient frustration [12-14]. This predominant approach ignores the brain's neuroplasticity and ability for cell-regeneration and fails to consider the individual impacts on brain regions.

Expected Endpoint / Outcome Measures: The primary *efficacy endpoint* in this RCT is chronic pain participants in the treatment arm feel a reduction in symptoms of pain and a self-reported reduction in opioid use, or the desire for opioid use. The primary *safety endpoint* of this RCT is that after both single and multiple treatments, no participants experience clinically significant side effects or adverse events.

4.0 Funding Information:

Indicate all sources of funding for the project, including gift funds, departmental funds, or other internal funding. For each funder, list the name of the funder, and the institutional proposal number or award number you received from Sponsored Projects. For externally funded projects, the information below should match the Study Funding Sources in eIRB.

☐ **No Funding**	
☐ **Federal Funding**, including flow-through federal funding (i.e., NIH, NSF, DoD, etc.)	Name of funding source:
	Institutional Proposal or Award Number:
	eDoc # (for multi-site projects):
☐ **Industry Funding**	Name of funding source:
	Institutional Proposal or Award Number:
	eDoc #:
☐ **Foundation Funding**	Name of funding source:
	Institutional Proposal or Award Number:
✓ **Department Funding**	**Name of funding source:** Career Development Award, UAHS

☐ **Gift Funding**	Name of funding source:
☐ **Other**	Name of funding source:

5.0 Resources Available to Conduct the Human Research:

Describe the resources (facilities, time, emergency resources, etc.) available to recruit, consent, conduct study procedures, and analyze data.

Research will be conducted at the UArizona Comprehensive Pain and Addiction Center in Dr. Vanderah's lab room 641 with the full support and funding of Family and Community medicine. The CPAC has all the resources required to fulfill this study. We will hire a research coordinator in addition to the PI and Co-I.

Timeline of Study:

Phase	Milestone	Start/Finish	sks Overview
Phase 1 Planning Months 1-6	Finalize Clinical Protocol	Month 1 - 2	• Work with FDA consultants, Dr.Baraniuk, study coordinator and other personnel to finalize protocol
	Regulatory Approval	Month 1-2	• Submit UArizona IRB • Submit UAHS Contracts • Submit IDE application to the FDA • Submit to DOD Human Research Protection Office [HRPO]
	Recruitment strategies meetings	Month 1-3	• Establish access to patient populations • Work with clinical network, local enterprises, and providers • Develop marketing material, informed consent etc.
	Finalize tKIWI units and software for clinical trial	Month 3-6	• Adapt tKIWI software for double blind clinical trial, prepare for data anonymization, HIPAA etc. • Manufacture 4+ tKIWI systems in different sizes • Prepare for data collection and storage
	Training	Month 6	• Train Clinical Research Coordinator, Study Coordinator, Research Assistants on administering tKIWI blinded, monitoring vitals, administering questionnaires etc.
Phase 2 Clinical Trial Month 7-20	Recruit Patients	Month 7+	• Recruit 40 chronic pain patients • Informed consent • Medical questionnaires/surveys etc.
	Baseline Session and Preparation for data collection	Month 10+	• Collect baseline EEG readings • Create patient profiles, anonymize personal information • Randomize treatment assignment • Preliminary EEG biomarker analysis

	Clinical trial (2 weeks)	Month 11-12	• Each patient has one daily treatment session (blinded treatment or sham)
	Follow up	Month 12-13	• Follow up with each patient one week and two weeks after clinical trial
	Statistical analysis	Month 14	• Statistical analysis of data collected including questionnaires, vital monitoring, EEG etc. • Publish findings in an academic journal • Transition plan for next phase of clinical trial
	Publish	Month 16	• Publish findings in an academic journal • Present findings internally and at conference • Plan for next phase of clinical trial • Publish biomarkers data in academic journal
	Transition	Month 17+	• Prepare and submit R01

6.0 Study Population:

- **Select all the categories of participants included in the research:**

☐ Healthy adults	☐ Non-English-speaking subjects
☐ Non-healthy adults	☐ UA staff/faculty
☐ Children (under 18 years old) *	☐ UA students
☐ Pregnant women, neonates, and/or fetuses*	☐ Banner employees
☐ Prisoners*	☐ Refugees
☐ Native Americans, Alaskan Native, and Indigenous Populations*	✓ Other – please explain: Adults ages 18-79 with a self-reported history or diagnosis of chronic pain (>3mo)
☐ Adults unable to consent (i.e., cognitively impaired adults) *	

- **For each of the above selected categories, describe the inclusion and exclusion criteria. Indicate age range, gender, and ethnicity.**

Inclusion Criteria:

Age: 18-79 years old

Gender: Any

Ethnicity: Any

Chronic pain (≥ 3-months); No current use of nonprescription opioids (≤ 1 month); Able and willing to comply with scheduled visits and other study-related procedures to complete the study; Willing and able to give informed consent.

Exclusion Criteria:

- Diagnosis (as defined by DSM-IV) of: any psychotic disorder (lifetime); eating disorder (current or within the past year); obsessive compulsive disorder (lifetime)); mental retardation.

- History of drug or alcohol abuse or dependence (as per DSM-IV criteria) within the last 3 months (except nicotine and caffeine).
- Subject is on regular benzodiazepine medication which it is not clinically appropriate to discontinue.
- Subject requires a rapid clinical response due to inanition, psychosis or high suicide risk.
- Neurological disorder or insult, e.g., recent stroke (CVA), which places subject at risk of seizure or neuronal damage with tDCS.
- Subject has metal in the cranium, skull defects, or skin lesions on scalp (cuts, abrasions, rash) at proposed electrode sites.
- Female subject who is pregnant.
- Participants who are not fluent in English will not be included in the trial for safety reasons: a) It is usually not possible to have an interpreter reliably available every weekday for up to 4 weeks and it is not safe to give tDCS to a subject who cannot tell us immediately of any side effects; Note that translation of the proposed ACT activity into English has not been validated and that we cannot be confident that they would be accurately translated and validated.
- Minors
- Older than 79 years old
- last use >24 months
- history of EEG or any electrical implant (i.e. pacemaker)
- history of Parkinson's, diagnosis of bipolar, schizophrenia/schizo-affective d/o, OCD, epilepsy, alzheimers
- taking antipsychotic drugs

One of the exclusion criteria is recent history of drug abuse or dependence (in the last 3 months). This would include prescription or non-prescription. If someone uses an opioid (prescribed or not) and does not meet that exclusion criteria, they are eligible to participate for that criteria. We would request that if possible, they refrain from using an opioid within a 3 hours of their appointment.

- **Describe the total number of subjects to be enrolled locally. If obtaining specimens, specify the maximum number of specimens needed for this project.**

The total number of subjects to be enrolled locally is 40 subjects.

7.0 Recruitment Methods:

- **Select the methods used to recruit individuals.**

☐ Email	☐ Screening of the Electronic Medical Record (EMR)
☐ Face to face	✓ Social media
✓ Flyers	☐ SONA System
☐ In person presentations	☐ TV, Radio, Print

☐ Online advertisements	☐ Other – please explain: Click or tap here to enter text.
☐ Phone calls	

- **Explain the recruitment process. Describe how potential subjects will be identified, where recruitment will take place, when recruitment will occur, and the methods that will be used to recruit individuals.**

Recruitment Location(s): We plan to recruit participants from clinical settings in Tucson, Arizona, such as the Veterans Affairs Hospital and private clinics and hospitals, private enterprises, such as gyms and health-related facilities (chiropractic offices, yoga/pilates studios). We also plan to recruit participants via local Facebook/Instagram and Twitter.

Recruitment Method(s): Recruitment flyers will be distributed to several health clinics and settings. Additionally, ads will be placed on Facebook and Twitter. At this time, we do not plan to conduct in-person recruitment. The flyers will include a link and QR code to a simple Qualtrics form where the interested person will be able to include their name and contact information. Potential participants will then be contacted to schedule an initial visit.

Site authorizations will be sought for each place we put flyers.

8.0 Diversity, Equity, and Inclusion

8.1 Explain how the research plan (recruitment, study population, data collection, etc.) is equitable and represents the demographic makeup for the location in which the research will be conducted.

This study recruits from the general population seeking treatment for chronic pain in Tucson. There are no exclusionary criteria based on any demographic makeup. All demographics in the population being recruited have an equal opportunity to participate in this study.

8.2 Describe whether non-English speaking subjects will be included in the study. If yes, please explain how your research team is prepared to meet the needs of the population. If not, please explain why non-English speakers will be excluded from the study population.

An inclusion criteria is to be able to read and speak English, as parts of the study material require one to understand English.

9.0 Consenting Process:

- **Indicate the informed consent process(es) and/or document(s) for the study. Check all that apply.**

Written Consent
✓ Informed Consent (ICF) – written or electronically signed form
☐ Parental Permission – written or electronically signed form
☐ Assent (participants under 18) – written or electronically signed form
☐ Combined ICF/PHI Authorization – written or electronically signed form
☐ Protected Health Information [2] Authorization – written or electronically signed

☐ Translated Consent/Assent – written or electronically signed form(s)
☐ Short Consent Form – written or electronically signed form (see guidance on **Short Form process**)
☐ Debriefing Script or Form – document used to properly inform subjects of the study's purpose when intentionally deceived

Oral/Online/Unsigned Consent
☐ Informed Consent – oral script/online/unsigned
☐ Parental Permission – oral script/online/unsigned
☐ Assent – oral script/online/unsigned
☐ Translated Consent/Assent – oral script/online/unsigned

Waivers of Informed Consent and/or PHI Authorization
☐ Waiver of Consent
☐ Full Waiver of PHI Authorization
☐ Partial Waiver of PHI for Screening Purposes

- **Describe in detail the consent processes checked above, including any waiting period for subjects to sign the consent, steps to minimize the possibility of coercion or undue influence, and the language used by those obtaining consent.**

The subjects will be asked to sign an electronic informed consent form during their first study visit. Prior to coming in for the first visit, they will be provided an electronic copy of the informed consent and will have the opportunity for any questions regarding the consent prior to the initial visit where they will sign. Upon signing they will receive a paper copy of their signed consent. The electronic consenting will be done in Qualtrics.

- **Where will the original signed consent and PHI authorization documents be stored?**

The electronic informed consent will be stored in a protected UA Box Health.

- **Acknowledgement of consent form storage.**

x I will store original signed consent and/or PHI authorization documents for at least 6 years past the time the study is concluded.
☐ For studies involving minors, I will store original signed consent and/or PHI authorization documents for at least 6 years after the youngest participant turns 18.
☐ Not applicable – I am not collecting signed documents.

10.0 Research and Data Collection Procedures:

- **Select the methods of data collection that will be used in this study (select all that apply):**

☐ Anthropometric measures (e.g., height, weight, waist circumference, etc.)	☐ Participant observation
☐ Audio/video recording	✓ Screening data
☐ Benign interventions	☐ Self-health monitoring (e.g., pedometers, food diaries, etc.)
☐ Biological specimens – blood draws	☐ Surveys – paper
☐ Biological specimens – clinically discarded blood or specimens	X Surveys – internet (including online and email-based data collection)
☐ Biological specimens (urine/feces, tissue, saliva, skin, hair, nails, nasal swab)	☐ Surveys – telephone
☐ Clinical Data Warehouse (CDW)	X Randomization with control and experimental groups
☐ Cognitive or behavioral measures, including daily diaries	☐ Records – billing
☐ Data collected using other communication/electronic devices (e.g., cell phones, pagers, and texting devices)	☐ Records – educational
☐ Data previously collected for research purposes	☐ Records – employee
☐ Deception	☐ Records – lab, pathology and/or radiology results
X Instrumentation, equipment, or software not approved by the FDA	☐ Records – mental health
☐ Interviews – focus groups	☐ Records – substance abuse
☐ Interviews – in person	☐ Research imaging protocols
☐ Interviews – virtual/online	☐ Recombinant DNA
☐ Medical records review	☐ Social networking sites
☐ MRI/ultrasound with contrast	☐ Stem cells
☐ MRI/ultrasound without contrast	☐ Radiation Scans (X-Ray, CT Scans, etc.)
✓ Non-invasive instruments (e.g., external sensors applied to the body)	X Other activities or interventions – describe: We will collect EEG data, Vitals (heart rate, blood pressure, Pulse O2, repiratory rate, and temperature), responses to pain surveys (VAS and FACES) as well as responses to a cognitive evaluation (MMSE). Click or tap here to enter text.

- **Description of research procedures.**

The proposed study employs a randomized, double-blind, sham-controlled design to evaluate the effects of the tDCS using the tKIWI device on chronic pain. We will be randomly assigned to treatment (tx) or sham/placebo group.

Up to 40 participants will be recruited and randomly placed in either the treatment or the sham group. The randomization ratio is 1:1. Each participant has an equal chance of being assigned to each condition and each participant will be assigned to a condition independently of the other participants. The sample is small (20 each group), so in order to ensure random assignment, we will assign a unique number to every participant of the study's sample. Then, we will use a lottery method to randomly assign each number to the control or experimental group.

The screening will be in redcap where the potential participant will respond to inclusion and exclusion criteria. If the participant is eligible, they will be emailed or provided the consent and enrolled in the study. They will sign the consent during their first visit where demographic data will also be collected and entered into Qualtrics.
Demographics Collected will include:

- Age
- Sex
- Race/Ethnicity
- City, State, Zip
- Phone
- Email
- First Drug Use
- Most Recent Drug Use
- Preferred/Most commonly used drug
- Mental Health diagnoses (including SUD)

The study will occur in 7 visits over an 11 day-period. (see table 2). At the beginning of each visit, the participants will answer a very brief "Pre-Study Session Update" survey to ensure no changes to eligibility have occurred between visits.
Visit 0 will consist of informed consent review and signature, collection of demographic data, baseline self-report pain using the pain surveys (FACES and VAS), brief cognitive survey (MMSE), and baseline EEG recording. Visits 1-5 will consist of initial EEG recording, three sessions of ramped up tDCS followed by EEG recording and self report pain surveys. Session 1 will be 5 minutes, session 2 will be 5 minutes, and session 3 will be 10 minutes. Details on mAs are listed under tDCS application. The final post visit (V7), on day 11 will consist of no treatment, but a repeat of the data collected on Visit 0.

Clinical Trial Protocol: Baseline V0, Tx V0-5, Post V7 (11 days)

⇒ Pre-Questionnaire (15 min)
  - Cognitive Eval (MMSE)
  - Rate Pain (VAS & FACES)
  - Record medication, activity, symptomology past 24 hours

⇒ Monitor vitals (5 min)
  - HR, BP, PulseO^2, respiratory, temp, etc (set up continuous measure)
  - Put on device and log into patient portal

⇒ EEG Recording (5 minutes)

⇒ Treatment/Sham (20 min max)

⇒ EEG Recording (5 min)
  - Rate pain using VAS & Faces)
  - Record symptoms, side effects, complaints

⇒ Visit 11, 5-day lapse return for EEG and VAS and FACES

The visits will take place in Dr. Vanderah's lab, room 645 in the UArizona Life Sciences Building. This laboratory is approximately 600sq/ft in size. All Vanderah's labs are located next to each other in the Life Sciences North building (Rms 632, 621, 619, 614, 615, 601). All biohazards are disposed according to institutional guidelines. Through Dr. Vanderah, we will also have access to shared laboratories that include a molecular biology laboratory of 1,000 sq. ft, an analytical laboratory of 1500 sq. ft. and a radioligand binding laboratory of 1,000 sq. ft. The laboratories include seating space for students and research personnel.

Table 2. Study Visit Schedule T-Arm and P-Arm	
V0 Baseline Week 1	• Consent+Demographics • Cognitive Eval (MMSE) • Rate Pain (VAS & FACES) • Pain Medication Use Survey • EEG (4 min)
V1-5 Week 2	• Pre-session survey • Vitals • Rate Pain using VAS and FACES • Pre-EEG (2 min) • tDCS1 - .5mA to .75mA (5 min) → EEG (8 sec) • tDCS2 - .75mA to 1.0mA → EEG (8 sec) • tDCS3 - 1.0mA to 1.75mA (10 min) → EEG (8 sec) • Post-EEG (2 min) • Vitals • Rate Pain using VAS and FACES • Side-Effect Self-Report Survey *For the Sham group - the first 1 minute of every tDCS session they receive a negligible current titrated from 0mA up to and not to exceed .5mA to give the impression they are receiving the treatment. The remaining treatment times will be followed by no current.
V6 Final Day 11 Week 3	• MMSE • Rate Pain using FACES and VAS • Pain Medication Use Survey • EEG (4 min)

tDCS Application:

EEG: The tKIWI uses sensors placed on specific locations of the head for the EEG reading. The first time the headset is applied, our research staff will do some minor fitting. There are sensors that run along a strap front to back (base of skull to forehead) and another side to side (ear to ear). The device uses the standard 10-20 system for both location and names of the sensors. Flat sensors will be placed on the forehead. The headband should come down about a half inch above the eyebrows in front. Once all sensors are green, they are ready to record EEG data.

The hair and dry skin act as a resistor between the sensor and the skull. The more resistance the lower the amplitude of the measured signal. Normally this resistance which is also referred to as impedance in the literature is in the realm of 10-100K ohms. Ensuring a snug fit and moving the hair will decrease impedance and improve EEG readings.

tDCS: The anode and cathode are two large 5 cm by 5 cm gel-based pads which are placed on the scalp. This reduces the risk of burn or irritation and increases conduction. The 2 electrodes are connected to the tKIWI device which delivers a low intensity electrical current (</=2A), thereby polarizing membrane potential of neurons in the stimulated area. Current that flows from the cathode to the anode has an inhibitory effect on the stimulated area, while current that flows from the anode to the cathode is typically excitatory. We will be initiating bilateral stimulation of the Dorsolateral pre-frontal cortex (DLPFC), which has been shown in the literature to elicit a significant decrease in ambiguous risk-taking behavior in healthy human subjects and a decrease in pain on a non-ambiguous risk task.

Both anodal and cathodal stimulation is used. Anodal is the negative or inhibiting electrode and cathode is the positive or oxidizing. tDCS is polarity-dependent.

In order to help minimize the stinging feel of the treatment, we have chosen to ramp up time and frequency. For visits 1-5 (tDCS treatment visits), we will start with .5mA ramping up to .75mA for 5 minutes. Followed by a brief (8 sec) EEG recording. Then, we will apply .75mA to 1mA for 5 minutes. This will also be followed by 8 second EEG recording. The final application of current will be 1mA to 1.75mA for 10 minutes followed again by 8 second EEG recording. The sham group will receive 1 minute from 0.0mA to no more than 0.5mA at the initiation of the treatment after which the current will be turned off. This is to maintain a blind trial. 0.5mA is negligible current, but mimics treatment with an initial small tingle. The current delivered by tDCS is not strong enough to trigger an action potential in a neuron; instead its "sub-threshold" changes the pattern of already active neurons. The device has built-in protections to prevent more than 2mA from being inadvertently administered at any time. The Clinical Trial Protocol table demonstrates the study procedures for each day.

Vitals (heart rate, pulse, blood pressure, temperature) will also be taken at the beginning and end of each treatment visit along with an open-ended verbal self-report of any side-effects, which the researcher will document in redcap.

- **Specify the total estimated time commitment for subject participation, and the estimated time commitment for each activity.**

The estimated time commitment for this study is 11 days and approximately 1.5 hours each day over 3 weeks.

- **If any biological specimens (blood, urine, tissue, etc.) are being collected for research, state the amount, method, frequency, and type of specimen to be collected and what the specimen will be used for.**

NA

If the study is a clinical trial, confirm registration with https://clinicaltrials.gov/ has been completed:

This study is not a clinical trial: ☐
Registration complete: ☐
Registration pending: ☒

Responsible Physician Limited Role:

Dr. Hadley will be available via telephone during all treatment sessions. There is no medical or safety need for a physician to administer the tDCS treatment or be present during the tDCS treatments. The application of tDCS is relatively straight forward, using materials that require very minimal training, the treatment is known to be non-invasive and safe, and is widely available on the market for personal home-use. In the proposed study, we will monitor vitals that can be properly done by a lay person. Should any of the most commonly reported side-effects occur, literature indicates the side-effects would not require medical intervention (other than basic first aid) nor a physician to attend to the subject. Dr. Hadley's skills in family medicine and addiction will be instrumental in guiding this study from a medical lens. Dr. Vanderah's skills in neuroscience and addiction will be instrumental in guiding this study from neuro-psychological and neuroscience lens. Dr. Huff's skills in addiction and artificial intelligence will be instrumental in guiding from the technical and behavioral health lens. The tKIWI device has built in safety features to limit the current to +2 or -2 milliamp (mA). These values have been medically shown, over 50 years, to be well within the range that is safe for the treatment of the brain by modulating the neurons but not causing the direct firing of a neuron. A research assistant will be trained on the tKIWI and set up the device. Drs. Vanderah or Huff will be present during administration of tDCS. Dr. Hadley is a practicing physician and will be responsible for monitoring any reported side-effects and interacting with subjects who have questions during the consenting process. Experience of prior studies indicate It is medically and academically unnecessary for her to be present during the treatment sessions, but she will be available telefonically during treatment sessions.

There is a breadth of literature that demonstrates the safety and efficacy of administering tDCS and tCES [8-10,12, 16-18, 32-33]. tDCS has been studied for decades as a promising adjunctive therapy for numerous degenerative brain diseases and disorders due to its ability to modulate neural activity in the human brain painlessly and non-invasively. The literature indicates side effects are minor and transient [18, 32-33]. In fact, only one major adverse event has been reported in the scientific literature related to employing tDCS treatment, which involved a pediatric patient with pre-existing epilepsy and cerebral palsy [34]. In a letter to the Editor, the author of that single case study states, "Unlike transcranial magnetic stimulation, tDCS does not induce neuronal firing by suprathreshold stimuli. Induction of seizure by tDCS has not been reported previously. On the contrary, cathodal stimulation was reported to be well tolerated in children with epilepsy, and is associated with a decrease in seizure frequency" [34]. The case study indicated this patient "remained seizure free with valproate and topiramate, but developed left dominant spastic paresis. He had his last seizure during a viral infection at 3 years of age. Interictal EEG showed absence of active epileptiform discharges. Dosage of valproate was adjusted to 30 mg/kg and topiramate was tapered. Two weeks after completion of topiramate tapering, anodal stimulation with 25-cm^2 electrodes was initiated to right motor cortex for 20 minutes at 1.2 mA." The patient had a seizure 4-hours after his third tDCS treatment and remained seizure free once treatment ceased. The single case study also indicates, "The possible etiologies of the induction of seizure after tDCS in this patient might be related to recent adjustment in antiepileptic treatment regimen, premedication with escitalopram, or anodal stimulation."

Out of hundreds of RCT's conducted worldwide implementing tDCS [35], there is only one single case of severe adverse event correlated with tDCS treatment. The causal relationship between tDCS treatment and induction of epileptic activity in this single case has not been demonstrated. Although this is a significant event, our proposed treatment procedure and eligibility criteria excludes subjects with structural brain disease, excludes subjects taking anti-psychotic medications, and no premedication will be administered. The literature on hundreds of RCT's employing tDCS on patients with and without structural brain diseases indicates the risk of a severe adverse event requiring medical intervention is negligible.

Data Analysis

Aim 1 will be evaluated using a two sample non-parametric t-test to compare the EEG readings of the treatment group to the sham group to measure any differences in EEG waves. The EEGs will also be read by a neurologist to identify pain biomarkers. Dr. Labiner has agreed to read the EEGs and will have no access to any identifiable data.

Aim 2 will be evaluated also using a two-sample t-test to measure changes in self-reported pain level using the data from the pre-post pain surveys. We will measure within one sample comparing the baseline to the post-study surveys and we will also measure the difference between treatment and sham groups.

Aim 3 will be evaluated using Chi-square (fisher exact test) assuming the data is non parametric to identify any reported side-effects or adverse events.

11.0 Potential Benefits to Subjects:

- **Describe the anticipated benefits of this study to society, academic knowledge, or both.**

  The benefit of this study includes implementing non-invasive technology to reduce or eliminate pain and opioid pharmaceutical treatment for pain. Benefits include "ease of use, the simplicity with which long-term changes are induced after one or a few neurons, and the relative freedom from adverse effects"[1]. tDCS is noninvasive and can reduce or increase neuronal excitability using anodes or cathodes in specified brain regions. According to literature, tDCS has demonstrated to be a safe technique, and reported side effects have been minimal and minor.

- **Describe any benefits that individuals may reasonably expect from participation (not including compensation, which cannot be considered a benefit of participation).**

  Individuals may reasonably expect a decrease in pain from participation in the study for the treatment group. For the sham group, they will be contributing to an innovative and non-invasive, non-habit forming, safe treatment for treatment of chronic pain, and may also receive a benefit of reduced pain from a placebo effect.

Risks to Subjects:

- **Describe all physical, psychological, social, legal, and/or economic risk that could be associated with participation in this research.**

  The most common reported side effects/risks include itching, tingling, headache, burning sensation, redness and discomfort. These are similar in adults and children. The physical adverse effects are restricted to the site of stimulation [1]. Other than these reversible minor adverse effects, no severe adverse effects that were irrecoverable or required professional treatment were reported (22). tDCS is known to be safe and non-invasive and is used frequently in human clinical trials. The other potential risk to subjects is an unlikely breach of confidentiality. This will be mitigated by keeping the enrollment data (with identifiers) separate from the study data. Upon enrollment, the research staff will assign each subject a numerical "study number." The PI and device sponsor will not have access to identifiable data once it is coded for deidentification.

- **Discuss what steps will be taken to minimize risks to subjects/data.**

  There are no risks expected to subjects as tDCS in humans has been widely studied for over a decade; however, to ensure that we document the lack of risks, we will be monitoring heart rate,

blood pressure, pulseO2, respiratory rates, and temperature at baseline and post treatment. We will also ask the subjects for self-report of any adverse events or issues that may have arisen.

- **Describe any costs, monetary and non-monetary, that subjects may incur. This includes time.**

There is no monetary cost for subjects other than possible cost to transport themselves to the lab. There is a time commitment, however, and it is required that the subject be able to transport themselves to the study site. There are a total of 7 visits within 3 weeks that subjects will have to make the time for (including transportation time and time spent in the study). The subject will commit to 11 days of coming into the lab over a 3 week period.

Discuss the amount of compensation (monetary and/or non-monetary) subjects may receive. Describe if compensation will be prorated.

Patients will receive $175 in compensation for their time. We will prorate payments based on duration of participation in the research so that participants are able to receive compensation even if they do not complete the entire study. In doing so, each participant will receive $25 cash at the initial visit (V0), $50 in cash after their 4th (V3) visit, and $100 after their final visit (V6.

12.0 Privacy of Subjects and Confidentiality of Data:

- **Describe steps, if any, to protect the privacy of the subjects throughout their participation (e.g., during the recruitment process, consent process, and/or research procedures).**

The raw identifiers will be de-identified by the research coordinator. Each subject will receive a number and the only connection between the identifiers (name, DOB, contact information) and the number assigned each subject will be safe-guarded in a unique UA Box Health. The microdata that will be collected using the tKIWI will all be housed within the device and is deidentified data. The risk is minimal to connect the EEG readout and self-report surveys, data related to vital monitoring, consents, and any other data collected, as the only data held within the tKIWI is the EEG date and study ID. The raw data will be stored in a unique UA Box Health folder. All data will be uploaded and stored in a secure and unique folder hosted on UA Box Health. tKIWI device data will be uploaded to a Google Workspace that is HIPAA compliant.

Describe if data or specimens will be kept for future research, including unspecified future research and genetics. If data or specimens will be stored in a repository, indicate who holds the repository and what information will be sent to the repository. Ensure this information is reflected in the subject's informed consent form.

The deidentified raw data will be stored for future research. The results will be published and shared with industry partner, ni20, inc., as per our data sharing agreement.

- **Discuss how study results will be shared with subjects, families, and/or the institution, both immediately and long-term.**

Study results will not be shared with participants. They will be shared via publication in peer reviewed journals. The data sharing agreement with our industry partner will use deidentified data from tKIWi to strengthen the algorithm and patented machine learning. The data will be stored on an encrypted SD card and shared with our industry partner via upload to HIPAA Compliant Google Workspace.

- **Indicate if the research team will be accessing any of the following records.**

☐ Substance abuse records (HIPAA and 42 CFR Part 2)
☐ Medical records (HIPAA)
☐ Educational records (FERPA)*
☐ Employee records (ABOR Policy 6-912)*
☐ Other, specify: Click or tap here to enter text.

- **For each record source selected above, summarize the data elements to be accessed, who will access them, and how the information will be obtained.**

  N/A

- **Indicate where data will be stored:**

☐ Box@UA	☐ OnCore
x Box@UA Health	☐ PACS medical imaging software
☐ Clinical Data Warehouse (CDW)	☐ Password Protected Drive
☐ Cloud Server	X REDCap
☐ Department Drive	x Transmitting/receiving subject data to/from an outside group
☐ Department Office	☐ UA Records Management & Archives
x Encrypted Drive	☐ Banner Server/Platform, specify:
☐ External Drive (hard drive, USB, disk)	☐ Other, specify: Click or tap here to enter text.
☐ Google Suite for Education	

- **For EACH of the storage locations checked above, discuss the type of data to be stored, including if the data is identifiable, coded, or de-identified upon storage. Discuss who may have access to the data and how long the data will be kept.**

Identified data will be coded and stored in a unique folder in UA Box Health and Redcap by the research coordinator. No one outside the study will have access to this data. It will be destroyed post-study. Coded data will be used for the self-reporting decrease in pain, vital sign monitoring, and EEG read outs. There is miniscule risk that the identified data will be able to be re-identified, as the identified data will be stored separately from the coded data in UA Box Health/Redcap. The data collected within the tKIWI device will be completely deidentified and paired with the coded data by the research team. As per our research sharing agreement, the deidentified data stored in the tKIWI's internal software, including EEG readouts will be shared externally with our industry partners via an encrypted SD drive and using a HIPAA approved cloudbased storage, such as BoxHealth. The identified data will be destroyed post-study, except for the signed consent, which will be maintained for 6 years post-study. The results will be completely de-identified.

- **Describe what security controls (e.g., administrative, physical, technical) are in place to make sure data/specimens are secure.**

We are using an academic data storage standard of UA Box Health and everyone on the research team who will have access to it will have appropriate and up-to-date clearance and trainings. Any personnel who leave the study will be immediately removed from having access to the folders.

- **Indicate how data/specimens will be shared with collaborating entities:**

☐ Data and/or specimens will not be shared between UA and any outside group or collaborating entity.
x Data/or specimens will be transmitted and/or disclosed to an outside group or a collaborating entity.
☐ Data and/or specimens will be received from an outside group or a collaborating entity.
☐ PHI will be transmitted to or received from an outside group or a collaborating entity. *
☐ A Limited Data Set will be transmitted or received from an outside group or a collaborating entity. *
☐ Data/specimens will be sold to pharmaceutical companies.

Only de-identified data will be shared via an encrypted SD drive encapsulated within the device itself and uploaded to HIPAA compliant Google Workspace.

- **Describe what information will be shared, who it will be shared with, and how it will be shared (e.g., secure file transfer, REDCap, etc.)**

As per our research sharing agreement, the deidentified data stored in the tKIWI's internal software, including EEG readouts will be shared externally with our industry partners via an encrypted SD drive and uploaded to a HIPAA Google workspace. Other de-identified data may also be shared with our external partners, as per our research sharing agreement.

13.0 Additional Questions (complete as applicable):

- **<u>Subject Injury</u>: If the research involves more than minimal risk to subjects, describe the provisions for medical care and available compensation in the event of research related injury. If the Human Research has a clinical trial agreement, this language should reflect what is stated in the agreement.**

There is only minimal risk to subjects. No injuries are expected. The literature is clear that tDCS is safe and effective.

- **<u>Withdrawal of Subjects</u>: Discuss how, when, and why subjects may be removed from the study. If abrupt withdrawal is necessary, discuss how subjects will be withdrawn so that they are not put at increased risk. Discuss what happens if a subject is withdrawn from one part of the study but asked to continue with other parts, such as ongoing follow-up.**

Subjects are free to withdraw at any time. Abrupt withdrawal will result in the subject not receiving full compensation. There is no risk of adverse events or increased risk for abrupt withdrawal. There are no separate parts of the study, so the issue of wanting to remain in one part

of study but continue with other parts is not an option. If a subject withdraws, we will retain the data collected up until the point of withdrawal, unless the participant requests it to be discarded.

- **Monitoring for Subject Safety: Provide a brief lay discussion of your plan to monitor for subject safety. Describe what safety information will be collected, including serious adverse events, how safety information will be collected, and the frequency of collection including a timeline of when the data and review(s) will occur, who will review the information, and the plan for reporting findings.**

If there will not be a way to monitor for subject safety, please explain.

At the beginning of each visit, the subjects will fill out a pre-session survey to ensure no changes to exclusion criteria have occurred. Subjects' vitals will be monitored (Heart rate, blood pressure, temperature, breathing rate, pulseO2) for 5 minutes using medical grade devices. After the treatment, the same vitals will be taken for 5 minutes and self-report of side-effects will be collected. These findings will be collected, and aggregate data will be analyzed and reported within publications.

- **Data Management Plan: Please discuss the data management plan if required by your funding agency. For additional resources, reference the HSPP Data Management webpage.**

N/A

- **International Research: Describe site-specific regulations or customs affecting the research, local scientific and/or ethical review structures that differ, and if community advisory boards are involved. If so, describe their composition and involvement. For research being conducted outside of the US, please explain any local laws, regulations, or customs the IRB needs to be aware of.**

N/A

Additional items needed for review:

- Word Versions of applicable subject materials: Consents, PHI Authorization Form(s), Recruitment Materials, Data Collection Materials, additional Participant Materials
- Current PI/Co-PI CVs or biosketch
- Advisor approval (if the PI is a student or medical resident)
- Department/Center/Section Review approval
- Scientific/Scholarly review approval
- Responsible physician approval (if the PI is conducting medical procedures for which he/she is not clinically certified to perform)
- Additional approvals, as needed (e.g., RIA/Banner feasibility, Export Control, Radiation, COI, UA travel registry, CATS, SRC, school district approval, tribal approval, etc.)

Other items as applicable:

- HSPP Appendices
- Data Monitoring Charter and Plan
- Drug/Device information
    - Applicable drug or device appendix
    - Investigator's Brochure, drug product sheet, device manual, user's manual, instructions for use, package insert, IND/IDE documentation, FDA 1572 form, 510k indication, FDA exemption, sponsor determination of device risk, etc.
- Multi-site information (for sites engaged in research where the UA is the IRB of record)
    - Appendix for Multi-site Research
    - Documentation of reliance
    - Copy of the site's human subjects training policy
    - CV and medical license (if applicable) of site PI
- Sponsor protocol, if separate from this form

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