Effects of Transcranial Direct Current Stimulation (tDCS) and Transcranial Ultrasound (TUS) on the Perception of Pain and Functional Limitations Due to Non-Specific Chronic Low Back Pain (NSCLBP)

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ORGANIZATION OF DETAILED PROTOCOL

Title: Effects of Transcranial Direct Current Stimulation (tDCS) and Transcranial Ultrasound (TUS) on the perception of pain and functional limitations due to Non-Specific Chronic Low Back Pain (NSCLBP) (phase II)

Sponsors

This study is funded by the NIH NIA and conducted in conjunction with Highland Instruments (co-applicant in this grant proposal). Highland Instruments is a company focused on developing neurostimulation technologies for treatment of neural pathologies.

[redacted]

II. SUBJECT SELECTION

In phase II, we will recruit about 80 subjects in order to randomize 40 patients with NSCLBP for this study. Subjects will need to meet all of the following inclusion criteria and none of the following exclusion criteria:

Inclusion Criteria:

1. Providing informed consent to participate in the study
2. 18 to 85 years old
3. Having non-specific chronic low back pain as defined by [6, 7] (existing pain for at least 3 months and having pain on at least half the days in the past 6 months) with an average of at least 3 on a 0-10 VAS scale
4. Pain resistant (partial or no response) to common analgesics and medications for chronic pain such as Tylenol, Aspirin, Ibuprofen, Soma, Parafon Forte DCS, Zanaflex, and Codeine
5. Must have the ability to feel sensation by Von-Frey fiber on the forearm

Exclusion Criteria:

1. Subject is pregnant
2. Contraindications to tDCS in conjunction with TUS:
    a. Metallic implant in the brain
    b. Implanted brain medical devices
3. History of alcohol or drug abuse within the past 6 months as self reported
4. Use of carbamazepine within the past 6 months as self reported
5. Suffering from severe depression (with a score of >30 in the Beck Depression Inventory)
6. History of neurological disorders as self reported (including epilepsy (note patients will also be evaluated via EEG at baseline and any patient showing abnormal EEG activity will be removed))
7. History of unexplained fainting spells as self reported
8. History of severe head injury resulting in more than a momentary loss of consciousness as self reported
9. History of neurosurgery as self reported
10. Unstable pain (defined as a difference in pain intensities larger than 4 points on a 0-10 VAS scale between the average over the week prior to visit 2 and the average over the week prior to visit 4a [96])
11. Large placebo responder: having a reduction of pain greater than 72.52% (VAS pain now post stimulation on V3 compared with VAS pain now pre stimulation on V2) or VAS now of 0 or 1 following any stimulation during Run-in period.
12. Low Adherence during the Run-in stimulation visits (ie. not attending both Run-in stimulation visits within approximately one week)
13. Low baseline pain: VAS pain weighted average < 3 prior to randomization during visit 4a

III. STUDY PROCEDURES

Because our protocol involves a run-in phase (Part I), we expect that up to 90 patients may enter the run-in phase so we will be able to randomize 40 eligible subjects to participate in this study (in phase II). When the target number of 40 subjects (for phase II) entering the randomized phase

(Part II) is completed, enrollment will end. Subjects who passed the run-in phase (Part I) successfully will then be randomly assigned to receive treatment in Part II with active tDCS+active TUS (n=20) or sham tDCS+sham TUS (n=20, inactive transducers)

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General Study Outline: This two-Part study will consist of 23 visits over the course of about 15 weeks. After Visit 1, the remaining Part I of the study will take about a week (Visits 2-4a). Prior to any assessments, the subject will consent to participate in both Part I and Part II, pending that the subject fits the additional eligibility criteria* of the run-in period. After completion of Part I, eligible subjects will continue onto Part II, the main interventional portion of the trial. Part II of the study will take place over the remaining weeks (Visits 4b-23).

Part I Study Flow – Run-in Period (Visits 1-4a):

- Screening Visit
- Run-in Visit 2&3 – sham stimulation visits
- Rescreening Visit

Part II Study Flow – (Visits 4b-23):

- 10 sessions of tDCS stimulation over 2 weeks
- Bi-weekly sessions of tDCS stimulation over 3 weeks
- 4 Follow-Up Visits – 2 week, 4 weeks, 6 weeks, and 8 weeks post-stimulation

Eligibility criteria for Part II include:

- VAS pain score greater than 1 following either of the two SHAM stimulation sessions [97] during Part I and pain reduction not greater than 72.52% (i.e. not a large placebo response)
- Stable pain intensities (defined as a difference in pain intensities less than or equal to 4 (on a 0-10 VAS scale) between the average over the week prior to visit 2 and the average over the week prior to visit 4a [96])
- High adherence during the Run-in stimulation visits (defined as completing both Run-in stimulation visits within approximately one week)
- VAS pain weighted average ≥ 3 prior to randomization during visit 4a (i.e. not exhibiting low baseline pain)

Detailed Study Outline

Pre-screening Procedures:

During the pre-screening process, the subject will contact a co-investigator usually via a phone call. During this call, the co-investigator will discuss in greater depth the details of the study, explain the study procedures and encourage the subject to ask questions. In the privacy of the laboratory, the co-investigator will ask the subject questions from the following:

1) Phone screening questionnaire

Once this information is collected, the co-investigator will consult with the PI regarding the eligibility of the subject, who will then give approval for the subject to come to our laboratory for the screening procedure.

Part I – Run-in Period

Visit 1

Screening Visit – (Approx Time: ¾ hour)

Screening Procedures:

At Screening, the PI and/or a co-investigator will once more conduct a review of inclusion/exclusion criteria to determine the subject's eligibility for enrollment. Study procedures will be reviewed with the subject, and documentation of informed consent will be obtained.

At Screening the following procedures will be completed:

- Discuss study-specific procedures with the subject.
- Review inclusion and exclusion criteria.
- Obtain a signed and dated consent form.
- Conduct a Demographics Survey and the Beck Depression Inventory.
- Urine pregnancy exam (if applicable).

This visit can be done remotely (There will be an electronically signed consent form, using Mass General Brigham REDCap eConsent and the visit will be done either by telephone or Zoom Healthcare)

Visit 2

Baseline Testing/1st Run-in SHAM stimulation visit (Approx Time: *1 ¼* hours)
The first baseline testing might be completed on the same day as the screening visit if time allows and the subject agrees.

There will be 2 SHAM stimulation visits to be completed approximately 48 hours apart over about one week (this visit will include the first SHAM stimulation session). The subject will receive 20 minutes of SHAM tDCS in conjunction with SHAM TUS.

Before SHAM stimulation, the subject will complete the following assessments:

- Urine pregnancy exam (if applicable)
- Visual Analog Mood Scale (VAMS)
- Mini Mental State Examination (MMSE)
- Neurological and Physical Exam
- Visual Analogue Scale (VAS) for Pain
- Pain/Medication Diary
- EEG recording
- NIH CLBP RMD instrument
- 29-PROMIS short form
- Beck Depression Inventory (BDI)

After SHAM stimulation subjects will complete the following assessments:

- Adverse Events (AE)

- Visual Analogue Scale (VAS) for Pain
- Screening Form for Part II

Visit 3
2nd Run-In SHAM Stimulation Visit/ End of Run-In Week – (Approx Time: ¾ hour)

Before SHAM stimulation, the subject will complete the following assessments:
- Visual Analogue Scale (VAS) for Pain
- Pain/Medication Diary
- 5 minute training session for motion tests to be performed during Part II

After stimulation subjects will complete the following assessments:
- Adverse Events (AE)
- Visual Analogue Scale (VAS) for Pain
- Screening Form for Part II

Visit 4a
Rescreening Visit – (Approx Time: 1 ¼ hours)
This study will be scheduled ~1 week after the first baseline measurements were done.

The subject will complete a series of assessments:
- Urine pregnancy exam (if applicable)
- Visual Analog Mood Scale (VAMS)
- Mini Mental State Examination (MMSE)
- Stroop test
- Neurological and Physical Exam
- Visual Analogue Scale (VAS) for Pain
- Pain/Medication Diary
- Quantitative Sensory Testing (QST)
- Walking Test
- Postural Stability/Standing Test
- One Leg Stance Test
- Trunk Mobility Test
- Screening form for part II*

* If the subject is eligible for part II, then they will complete visit 4b in the same day.

Note, patients who exhibit large placebo effects (defined as exhibiting VAS=0 or VAS=1)following either of the two SHAM stimulation sessions[97]during Part I and score reduction higher than 72.52%; unstable pain intensities (defined as a difference in pain intensities larger than 4 (on a 0-10 VAS scale) between the average over the week prior to visit 2 and the average over the week prior to visit 4 [96]), low baseline pain (defined as weighted VAS avg < 3) prior to randomization during visit 4) or who are not compliant with the Run-In protocol (defined as not completing both Run-in stimulation visits within approximately one week) will be excluded from the full trial [96-98], and thus will not receive MRIs and will not come for

additional visits. By following this Run-in strategy, we will maximize trial resources by excluding patients who demonstrate poor compliance and are less likely to complete the trial. More importantly, we will increase the likelihood that the effects we are measuring in the full trial are biological in nature and directly caused by the stimulation intervention [97, 98]. Note, a patient can be screened out in any of the visits prior to Visit 4b.

Part II –Interventional Period

Visit 4b
1st Stimulation Visit – (Approx Time: 1 hour)

There will be 10 stimulation visits to be completed over the next 2 consecutive weeks (ideally Monday to Friday of each week). The subject will receive either 20 minutes of active tDCS in conjunction with active TUS, or sham tDCS in conjunction with sham TUS per day for the course of their stimulation visits.

Randomization:
Once eligibility and consent have been approved and completed, after all baseline evaluations and immediately before the first stimulation session of Part II, stratified blocked randomization will occur using the randomized list generated by an automatic web-based randomization program (www.randomization.com). Randomization will be based on placebo effect above or below -17.3% according to preliminary data. A staff member who is not involved in any of the study procedures will be responsible for creating the randomization list and monitoring it during the study. Subjects will be randomly assigned to treatment or placebo groups in a 1:1 allocation ratio. We will use permuted blocks of variable sizes (4) in a random manner to minimize the risk of study staff guessing at the next allocation. Randomization order will be kept in sealed envelopes.

Blinding:

All subjects and investigators will be blinded to the group assignment except for the co-investigators providing stimulation and staff involved in the randomization process (the latter would otherwise not be involved in study procedures). Only the staff involved in the randomization will be authorized to break the blind if there is a clinical need as requested by the PI, clinical care providers, Medical Monitor, or IMC. The patients will remain blinded until they have completed all visits (whether they complete all 23 visits or drop out early), or in the case of an adverse event necessitating un-blinding.

If the subject receives sham stimulation during Part II, he/she may re-enroll into an open label portion of the study, where he/she will receive 10 days of active tDCS/TUS. Un-blinded co-investigators (e.g., who provided stimulation) will coordinate with subjects electing to enter into the open label phase, which will be conducted by the un-blinded study staff. In the open label phase, we will complete the VAS assessments on Day 5 and Day 10 of stimulation. This

collected data will not be analyzed with the main data collected in the study. This data will be used for exploratory analyses only.

After stimulation subjects will complete the following assessments:

- Visual Analog Mood Scale (VAMS)
- Mini Mental State Examination (MMSE)
- Stroop test
- Neurological and Physical Exam
- EEG recording *
- Adverse Events (AE)
- Visual Analogue Scale (VAS) for Pain

* *The EEG can be performed at anytime during the first week of stim (V4b-V8).*

Visits 5-7

2-4th Stimulation visits – (Approx Time: ¾ hour)

During the next 3 stimulation sessions – the subject will receive either 20 minutes of active tDCS in conjunction with active TUS, or sham tDCS in conjunction with sham TUS.

Before stimulation, the subject will complete a series of assessments:

- Visual Analogue Scale (VAS) for Pain
- Pain/Medication Diary

After stimulation subjects will complete the following assessments:

- Visual Analog Scale (VAS) for Pain
- Visual Analog Mood Scale (VAMS)
- Mini Mental State Examination (MMSE)
- Stroop Test
- Adverse Events Questionnaire (AEs)
- MRI at Martinos Center***

*** *The MRI will be taken at most one time for each subject that is eligible for Part II at any time during the remaining of the study, even after the last follow up visit.*

Visit 8

5th Day of stimulation – (Approx Time: 1 ¾ hours)

Before stimulation, the subject will complete a series of assessments:

- Visual Analogue Scale (VAS) for Pain
- Pain/Medication Diary

After stimulation subjects will complete the following assessments:

- Visual Analog Mood Scale (VAMS)
- Mini Mental State Examination (MMSE)
- Stroop test
- Neurological and Physical Exam

- EEG recording**
- Adverse Events (AE)
- Visual Analogue Scale (VAS) for Pain
- Quantitative Sensory Testing (QST)
- NIH CLBP RMD instrument
- 29-PROMIS short form
- Beck Depression Inventory (BDI)

Visit 9
6th Day of Stimulation – (Approx Time: ¾ hour)

Before stimulation, the subject will complete a series of assessments:
- Urine pregnancy exam (if applicable)
- Visual Analogue Scale (VAS) for Pain
- Pain/Medication Diary

After stimulation subjects will complete the following assessments:
- Visual Analog Scale (VAS) for Pain
- Visual Analog Mood Scale (VAMS)
- Mini Mental State Examination (MMSE)
- Stroop test
- Adverse Events Questionnaire (AEs)

Visits 10-12
7-9th Day of Stimulation visits – (Approx Time: ¾ hour)

Before stimulation, the subject will complete a series of assessments:
- Visual Analogue Scale (VAS) for Pain
- Pain/Medication Diary

After stimulation subjects will complete the following assessments:
- Visual Analog Scale (VAS) for Pain
- Visual Analog Mood Scale (VAMS)
- Mini Mental State Examination (MMSE)
- Stroop test
- Adverse Events Questionnaire (AEs)

Visit 13
10th Day of stimulation – (Approx Time: 2 hours)

Before stimulation, the subject will complete a series of assessments:
- Visual Analogue Scale (VAS) for Pain
- Pain/Medication Diary

After stimulation subjects will complete the following assessments:

- Visual Analog Mood Scale (VAMS)
- Mini Mental State Examination (MMSE)
- Stroop test
- Neurological and Physical Exam
- Adverse Events (AE)
- Visual Analogue Scale (VAS) for Pain
- Quantitative Sensory Testing (QST)
- NIH CLBP RMD instrument
- 29-PROMIS short form
- Beck Depression Inventory (BDI)
- Walking Test
- Postural Stability/Standing Test
- One Leg Stance Test
- Trunk Mobility Test

Visit 14, 15, 16, 17 and 18

Bi-weekly stimulation visits– (Approx Time: ¾ hour)

Before stimulation, the subject will complete a series of assessments:

- Visual Analogue Scale (VAS) for Pain
- Pain/Medication Diary

After stimulation subjects will complete the following assessments:

- Visual Analog Scale (VAS) for Pain
- Adverse Events Questionnaire (AEs)

Visit 19

Last bi-weekly stimulation visit– (Approx Time: 2 hours)

Before stimulation, the subject will complete a series of assessments:

- Visual Analogue Scale (VAS) for Pain
- Pain/Medication Diary

After stimulation subjects will complete the following assessments:

- Visual Analog Mood Scale (VAMS)
- Mini Mental State Examination (MMSE)
- Stroop test
- Neurological and Physical Exam
- EEG recording
- Adverse Events (AE)
- Visual Analogue Scale (VAS) for Pain
- Quantitative Sensory Testing (QST)
- NIH CLBP RMD instrument

- 29-PROMIS short form
- Beck Depression Inventory (BDI)
- Walking Test
- Postural Stability/Standing Test
- One Leg Stance Test
- Trunk Mobility Test

Visit 20, 21, 22, and 23

Follow-Up Visit – Approximately 2 week, 4 weeks, 6 weeks, and 8 weeks post-stimulation – (Approx Time: 1 ¾ hours)

- Visual Analog Mood Scale (VAMS)
- Mini Mental State Examination (MMSE)
- Stroop test
- Neurological and Physical Exam
- Adverse Events (AE)
- Visual Analogue Scale (VAS) for Pain
- Pain/Medication Diary
- Quantitative Sensory Testing (QST)
- NIH CLBP RMD instrument
- 29-PROMIS short form
- Beck Depression Inventory (BDI)
- Walking Test
- Postural Stability/Standing Test
- One Leg Stance Test
- Trunk Mobility Test

[redacted]

DESCRIPTION OF ASSESSMENTS:
A rater blind to the treatment arm will administer the following tests (also used in our previous study [102]:

Visual Analogue Scale (VAS) for Pain: The VAS is a common assessment used which asks subjects to self-reportedly measure their pain on a visual scale (i.e., unbearable to none). This will help us to monitor changes in subjects' pain levels when they come in for sessions.

Pain/Medication Diary: To help monitor pain levels, as well as safety, subjects will keep a diary listing their daily medications and pain levels when not at the laboratory.

Quantitative Sensory Testing (QST) for Pain: The QST is a common assessment used which measures the detection threshold of accurately calibrated sensory stimuli. It consists of assessing: Mechanical Pain Threshold (MPT), Mechanical Temporal Summation (TS), and Pressure Pain Thresholds (PPT). The QST is founded on:

- *Von Frey Assessment:* This test does not pose a risk to subjects and will help us to monitor whether there are changes in subject's ability to perceive nociceptive stimuli.
- Mechanical temporal summation (TS): "TS is assessed by having the participant rate their pain after a single stimulus is applied for ~0.5 s and then again after a series of 10 stimuli are applied at ~1-s intervals. Temporal summation is

calculated as the difference between the rating of the series of 10 stimuli and the rating of the single stimulus."[103] A 6.65, 300 g Von Frey filament will be used as the stimulus unless the subject does not feel comfortable performing the test with the heaviest fiber. If so, we will reduce the weight of the fiber until it is tolerable by the subject or we will perform the test with the fiber the subject rated as painful, as long as it is tolerable, during the Von Frey Assessment.

- *Pain-Pressure Tests (PPT):* PPT will be determined using an FDA approved algometer as described in the research strategy. This assessment is often used as a measurement for pain-pressure thresholds in pain patients. Thus, it poses no significant risk to subject safety. The FDA approved algometer will be alternately applied three times, in counter-balanced fashion, ipsilateral to the most painful low back area (if bilateral pain, performed contralateral to the dominant side) to determine participants' baseline pressure pain thresholds (PPTs). Participants will indicate when the increasing pressure stimulation first became painful (via PPT).
- Conditional Pain Modulation (CPM): Following the baseline PPT determination, participants will undergo a series of cold water immersions that will consist of placing the contralateral hand, up to the wrist, into cold water for about 1 minute. The cold water will be maintained at a temperature that produced a moderately painful sensation as during initial health assessment. Participants will be told they can remove their hand from the water at any time. Approximately 30 seconds after initiation of each cold water immersion, while the hand is still immersed, the algometer will be used to deliver noxious mechanical stimulation to either the palm or the back. Participants will indicate when the increasing pressure stimulation first becomes painful, which represented their conditioned PPTs. There will be a 2-minute rest period between each CPM trial [60].

EEG recording: EEG recordings will be taken at the first baseline visit before the first sham stimulation session, one time at any point during the first week of stimulation of Part II and one in the last stimulation visit, to monitor brain activity and saved for post recording evaluation.

MRI: Patient MRIs will be assessed to correlate brain anatomy with patient pain characteristics and response to treatment.

Neurological and Physical Exam: Trained study staff will conduct baseline and follow-up neurological examinations focused to ensure subject safety one week prior to stimulation, on the first day of stimulation, at the end of each stimulation week, and during each follow up visit [104].

Visual Analog Mood Scale (VAMS): This is a self-assessment scale in which subjects rate their own emotions, including anxiety, depression, stress, and sleepiness along a 100 mm line.

Mini Mental Status Exam (MMSE): This is a sensitive, valid and reliable 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. This instrument will be used as a brief screening of cognitive abilities. The MMSE will be administered at the baseline evaluation and every subsequent visit.

Stroop test: 4-Choice Reaction Time: Patients will be seated in front of a computer screen placed at eye level. Subject will we ask to identify the colors of each word that will appear on the screen. The Stroop test will be administered at the baseline evaluation and every subsequent visit.

Adverse Effects Questionnaire: At each session after stimulation begins, subjects will complete a questionnaire to evaluate potential adverse effects of stimulation (headache, neck pain, mood alterations, and seizures) on a 5-point scale. The scale will also be administered at the follow-up. The subjects will be asked whether they have experienced any side effects in an open-ended manner and they will then be specifically asked about headache, neck pain, scalp pain, scalp burns, tingling, skin redness, sleepiness, trouble concentrating, and acute mood change. If any side effects are reported, the degree of relatedness to the intervention will be assessed.

We will be investigating adverse effects using open-ended questions. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a treatment, whether or not considered related to the product.

Examples of AEs are as follows:

- Subjective symptoms offered by or elicited from the subject
- Objective signs observed by the Investigator or other study personnel

All concurrent diseases that occur after the start of the study, including any change in severity or frequency of preexisting disease will be investigated in several domains including: seriousness, severity, length of duration, and if any causal relationship exists with the intervention [53].

Walking Test: Patients will be asked to walk at comfortable speed for 10 meters to assess gait patterns. Quantitative objective metrics of walking will be extracted from the recorded data such as walking speed, gait asymmetry, stride length, and walking smoothness [105-108].

[redacted]

NIH CLBP RMD and PROMIS 29 instruments- Patients will fill out questionnaires are designed to assess the low back pain and the impact of pain on function, psychological, sleep, and related activities. The NIH CLBP Research Task Force (RTF) Recommended Minimum Dataset (RMD) instrument is made of the components of the Patient Reported Outcomes Measurement Information System (PROMIS) instrument [116], the Subgroups for Targeted Treatment (STarT) Back instruments[117], and the RTF Impact classification (see NIH Research Task Force (RTF) for low back pain assessment recommendations [5]). Components of the 29-PROMIS short-form [116] not included as part of the NIH Minimum Data Set Instrument (e.g., elements of anxiety and fatigue) will also be assessed.

Beck Depression Inventory (BDI) is used for assessing the severity of depression [95].

If a subject is not comfortable to perform one of the described assessments or subject schedule doesn't allow, any assessment not performed other than VAS pain, will be noted in the study binder and proceed with the visit.

IV. BIOSTATISTICAL ANALYSIS

Data forms and questionnaires will be coded in a standardized manner, and double-entered into our database. Digital measures/recordings will be similarly tracked in our database and regularly backed up. Analyses will be conducted using standard statistical software such as SAS and Matlab.

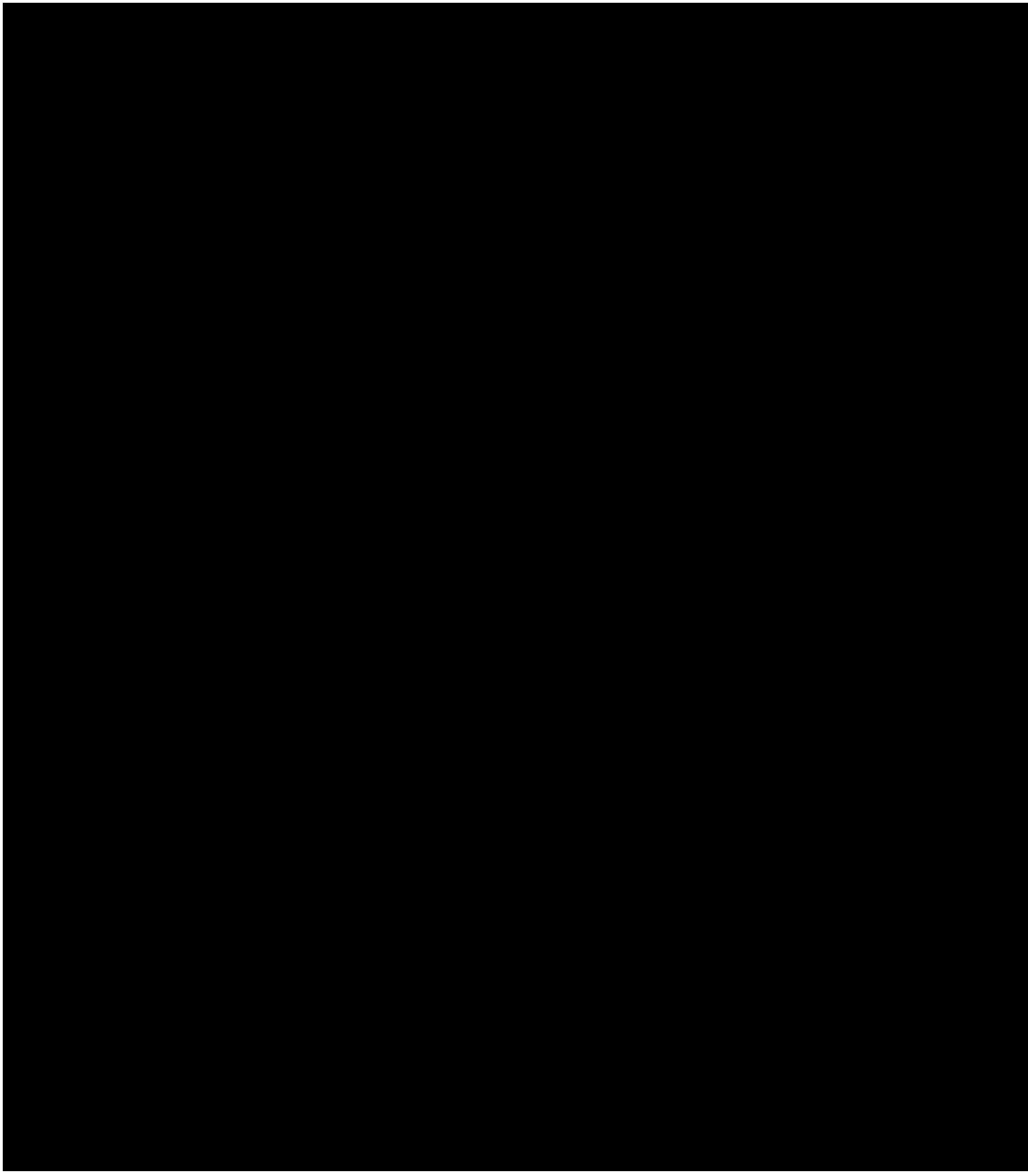
Sample size calculations and data analysis:

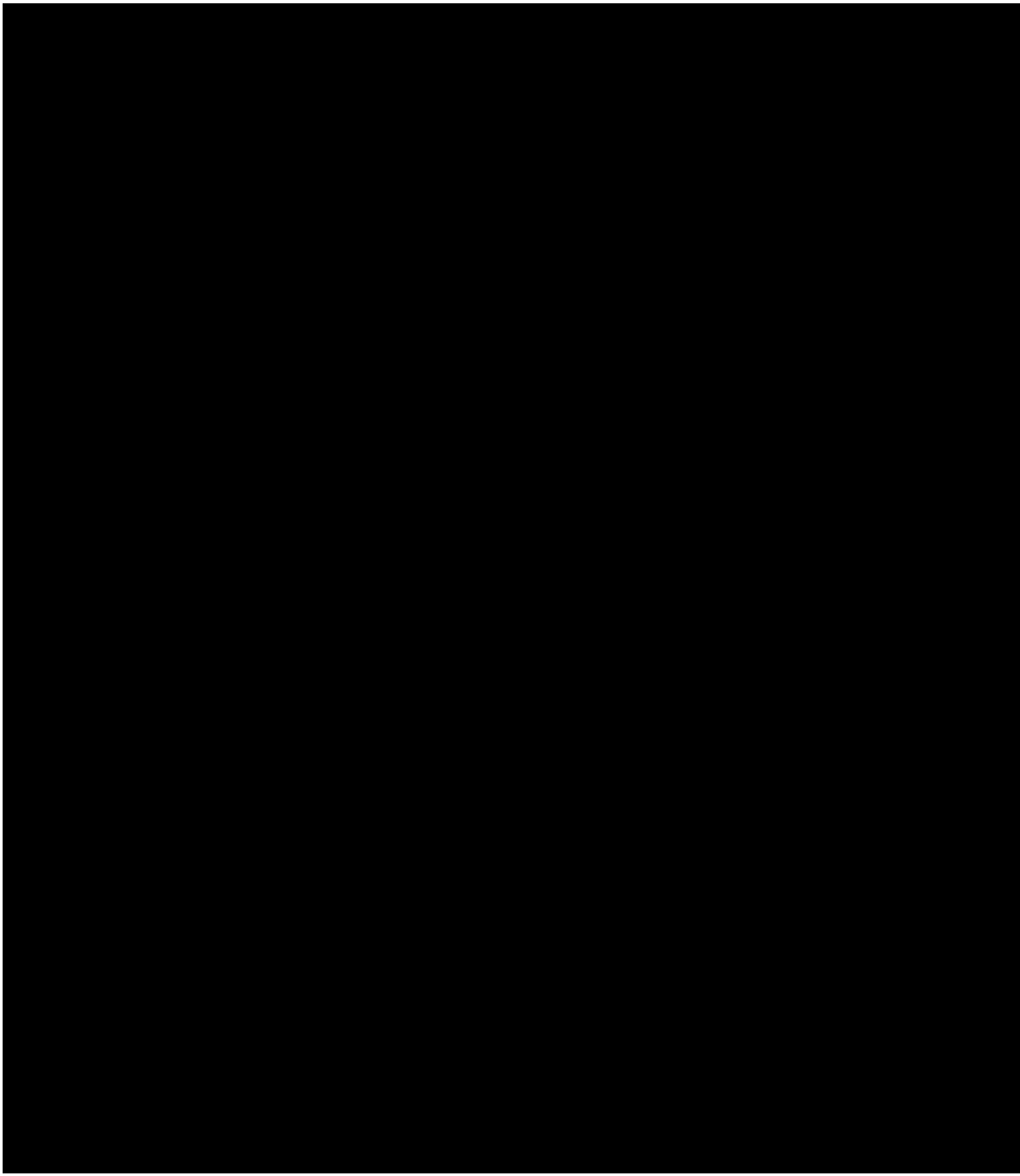
Aim 1:

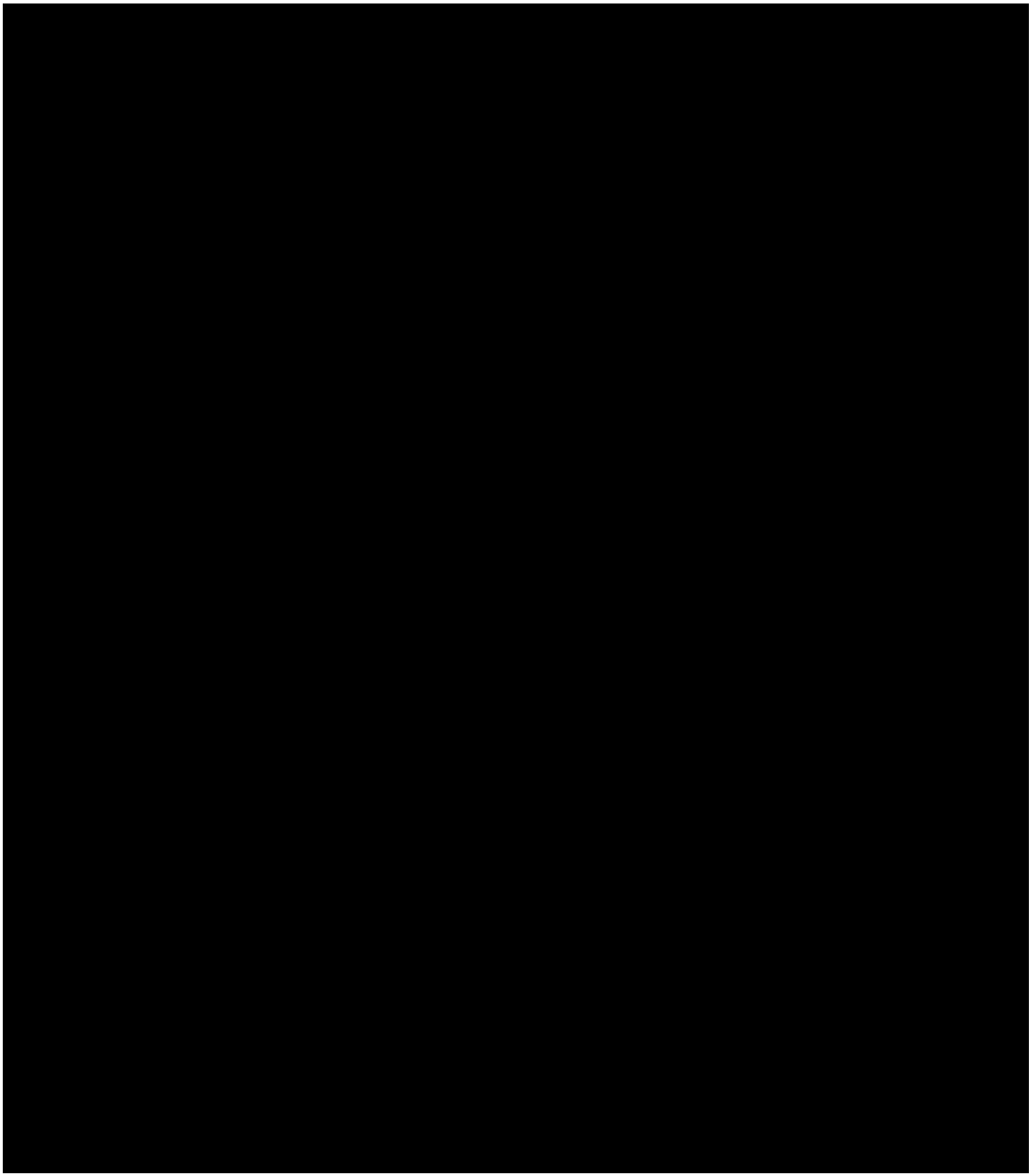
For planning sample size calculation for this study, we considered the surrogate pain outcomes as the main outcome for such analysis; considering the two studies showing significant alterations of these outcomes in NSCLBP [118], an effect in the active tDCS in conjunction with active TUS that is twice of the effect in SHAM tDCS in conjunction with SHAM TUS would be adequate. Considering this effect size and a power of 80% and alpha of 5%, we would need 6 subjects per group for a total of 12 subjects. Therefore considering dropouts and also to increase the sample in phase I for the clinical outcome, we increased the sample to 20 subjects (10 for each arm), that would also give a power to detect significant differences of 2 points in VAS between the 2 groups; though the clinical outcome is not the main outcome in phase 1. For Phase 2, we doubled the sample size as to have enough power to detect a difference of 1.3 in VAS between the two groups that would therefore be adequate to demonstrate a clinically meaningful difference between the two groups. We considered differences smaller than that not clinically meaningful.

All analyses will be conducted according to the principle of intention-to-treat (using regression-based single imputation method). We will also perform an additional sensitivity analysis in

which we will use the method of last observation carried forward. The primary outcome will be TS and CPM [118] (in phase 1) and VAS (in phase 2) changes as indexed by VAS scores, biomechanical function changes as indexed with the motion analysis suite, and global self-assessment changes. Differences between the two groups (active tDCS in conjunction with active TUS and SHAM tDCS in conjunction with SHAM TUS) will be tested using Student's t-test and, in addition, we will adjust for important baseline variables and also test the time effect in general mixed longitudinal models. This model will be used for the primary and secondary outcomes. Secondary analyses will be conducted in an exploratory manner (no correction for multiple comparisons). Similar analysis will be conducted for the adverse effects measuring continuous outcome and for the categorical outcomes we will use Fisher’s exact test. In both cases, for safety analysis we will use uncorrected p-value to increase the likelihood of detecting detrimental adverse effects.







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