Acupuncture Treatment for Chronic Post-traumatic Headache in Individuals with Mild Traumatic Brain Injury.

Protocol Number: Version 11

National Clinical Trial (NCT) Identified Number: NCT04369911

Principal Investigator: Amanda A. Herrmann, PhD

Site/Sponsor: HealthPartners Neuroscience Center, HealthPartners Clinic St. Paul Como, and Healing Response Acupuncture & Functional Neurology/HealthPartners Institute

Institutional Review Board Number: A19-094

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the terms of the award.

Protocol Amendment Version 3:
Summary of changes to the protocol due to the COVID-19 Pandemic

This protocol has been amended to account for changes due to the COVID-19 pandemic, which has resulted in increased health and safety concerns for study participants and clinical research staff. Specifically, the risks are primarily due to how easily the virus can be transmitted with person-to-person contact.

The specific changes to the protocol are summarized below. The primary rationale for these changes is to reduce contact time between patients and study staff, while maintaining their health and safety.

- **Addition of 3 healthy volunteer practice participants.** Previously, we obtained IRB approval to test our protocol on 3-5 healthy volunteers. Because we tested all 5 practice participants prior to the pandemic, we are requesting an additional 3 volunteer participants. Practicing the protocol on 3 additional participants will ensure that the acupuncturists have recent protocol training prior to recruitment and will allow them to practice under the new COVID-19 policies and procedures (e.g. utilizing appropriate PPE under COVID-19 guidelines).
- **Study visits completed via phone.** All study visits, except for the acupuncture treatment visits, will be converted to phone visits. This will be done to decrease study staff and patient exposure time.
- **Informed consent and study assessments completed electronically.** Informed consent for the study will be obtained through a phone call with study staff and electronically through a Research Electronic Data Capture (REDCap) survey sent via e-mail. All study assessments will be obtained through REDCap surveys sent via e-mail.
- **Appropriate COVID-19 screening procedures and personal protective equipment (PPE) will be utilized for all acupuncture treatment visits.** We will screen participants for COVID-19 by phone 1-2 days before each scheduled acupuncture treatment visit and also the day of the clinic visit. If a patient screens positive for COVID-19, study visits will be postponed for the appropriate amount of time per current guidance, and we will follow the current clinic site process for COVID-19 positive screens, as defined by the medical group. This study will also align with the HealthPartners Neuroscience Center policies regarding PPE for in-person visits. This will be done to ensure the safety of patients and study staff.
- **Finally, this study will align with HealthPartners Neuroscience Center's COVID-19 policies and procedures.**

Protocol Amendment Version 4:
Summary of changes to the protocol due to the COVID-19 Pandemic

- **Addition of COVID-19 Questions.** The addition of questions related to COVID-19 will be done to potentially explore whether acupuncture has an effect on post-COVID-19 symptoms. The questions below will be asked at 2 time points: at the beginning of first acupuncture appointment and at the 4-week post-treatment visit (4 weeks after the last acupuncture treatment). They will be collected electronically via REDCap. As an exploratory analysis, patients who report post-COVID-19 symptoms will be identified using the additional COVID-19 set of questions. Types and severity of post-COVID-19 symptoms present within the group will be described. The t-test or non-parametric equivalent will be used to determine whether acupuncture had an effect on post-COVID symptoms. The protocol has been updated to reflect the changes and the questions are listed below.

Questions:

1) Have you previously received a positive test for COVID-19? (yes/no)
2) Were you exposed to someone with a positive test, subsequently developed symptoms, but did not get a COVID-19 test? (yes/no)
3) Are you currently experiencing any of the following post-COVID-19 symptoms?

   (Drop down list with most common symptoms, select all that apply)

   a. Fatigue
   b. Difficulty breathing
   c. Joint pain
   d. Chest pain
   e. Brain fog, including an inability to concentrate and impaired memory
   f. Loss of taste and/or smell
   g. Sleep issues
   h. Other: Specify – (free text to type in)
4) *If a participant answers yes to any of the symptoms*: How would you rate your symptoms?
   a. Mild: you have symptoms, but they are not a problem
   b. Moderate: your symptoms limit your normal daily activities
   c. Severe: your symptoms make normal daily activities challenging or impossible

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

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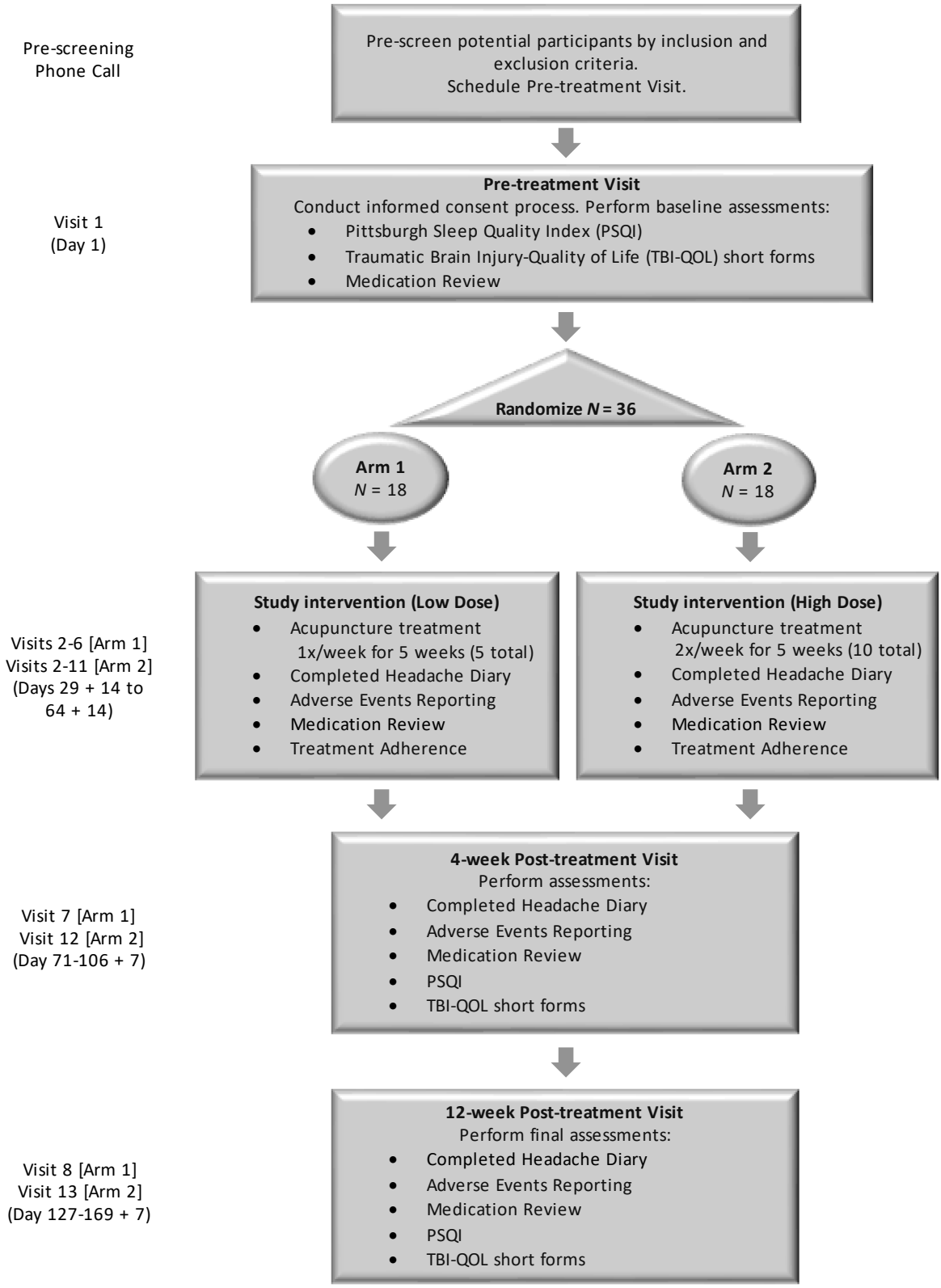
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Acupuncture Treatment for Chronic Post-traumatic Headache in Individuals with Mild Traumatic Brain Injury.
IRB Number:	A19-094
Study Description:	The purpose of the study is to determine the effect of a low vs. high dose of acupuncture treatment in individuals with chronic post-traumatic headache (CPTH). A total of 40 people with mild traumatic brain injury (mTBI) suffering from CPTH will be enrolled in this study to receive acupuncture treatment for 5 weeks. Participants will be randomized into two groups: 1) Low Acupuncture group (5 treatments) and 2) High Acupuncture group (10 treatments). We hypothesize that both treatment groups will have decreased headaches, but that 10 treatments will greater alleviate headaches when compared to 5 treatments.
Specific Aims:	Specific Aim 1: To determine the effect of a low versus high dose acupuncture treatment on number of headache days for individuals suffering from CPTH. Specific Aim 2: To determine the safety and tolerability of acupuncture on CPTH in individuals with mTBI. Specific Aim 3: To explore the effects of acupuncture on sleep, quality of life (QOL), headache outcomes, and medications in individuals with mTBI who suffer from CPTH.
Endpoints:	Primary Endpoint: Number of headache days over 4 weeks Secondary Endpoints: 1) Adverse or Serious Adverse Events and 2) Completion of treatment durations and sessions Exploratory Endpoints: 1) Sleep, 2) Quality of life, 3) Headache Outcomes, and 4) Medications
Study Population:	40 individuals aged 18-70 with a diagnosis of mTBI suffering from CPTH will be recruited for this study.
Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled at HealthPartners Neuroscience Center, and will be treated at the Neuroscience Center, HealthPartners Clinic St. Paul Como, or Healing Response Acupuncture & Functional Neurology.
Description of Study Intervention/Experimental Manipulation:	Acupuncture treatment will be administered by a licensed acupuncturist for a duration of 5 weeks. One treatment group will receive 5 treatments and the other will receive 10 treatments.
Study Duration:	The duration of this study is 2 years.
Participant Duration:	Participants should complete all study-related tasks within 176 days (approximately 6 months).

1.2 SCHEMA


Pre-screening Phone Call
Pre-screen potential participants by inclusion and exclusion criteria.
Schedule Pre-treatment Visit.
Visit 1 (Day 1)
Pre-treatment Visit
Conduct informed consent process. Perform baseline assessments:
Pittsburgh Sleep Quality Index (PSQI)
Traumatic Brain Injury-Quality of Life (TBI-QOL) short forms
Medication Review
Randomize N = 36
Arm 1 N = 18
Arm 2 N = 18
Visits 2-6 [Arm 1] Visits 2-11 [Arm 2] (Days 29 + 14 to 64 + 14)
Study intervention (Low Dose)
Acupuncture treatment 1x/week for 5 weeks (5 total)
Completed Headache Diary
Adverse Events Reporting
Medication Review
Treatment Adherence
Study intervention (High Dose)
Acupuncture treatment 2x/week for 5 weeks (10 total)
Completed Headache Diary
Adverse Events Reporting
Medication Review
Treatment Adherence
Visit 7 [Arm 1] Visit 12 [Arm 2] (Day 71-106 + 7)
4-week Post-treatment Visit
Perform assessments:
Completed Headache Diary
Adverse Events Reporting
Medication Review
PSQI
TBI-QOL short forms
Visit 8 [Arm 1] Visit 13 [Arm 2] (Day 127-169 + 7)
12-week Post-treatment Visit
Perform final assessments:
Completed Headache Diary
Adverse Events Reporting
Medication Review
PSQI
TBI-QOL short forms

1.3 SCHEDULE OF ACTIVITIES

	Pre-screening Phone Call	Pre-treatment Visit	Study Intervention	4-week Post-treatment Visit	12-week Post-treatment Visit
Arm 1: 5 Treatments	*Visit 0*	*Visit 1*	*Visit 2-6*	*Visit 7*	*Visit 8*
Arm 2: 10 Treatments			*Visit 2-11*	*Visit 12*	*Visit 13*
Review Eligibility	X				
Informed Consent		X			
Demographics		X			
Randomization		X			
Medication Review		X	X	X	X
Completed Headache Diary			X	X	X
Pittsburgh Sleep Quality Index (PSQI)		X		X	X
Traumatic Brain Injury-Quality of Life (TBI-QOL) short forms		X		X	X
Adverse Events (AE) Reporting			X	X	X
Treatment Adherence			X		

VISIT SCHEUDULE DESCRIPTION

All in-person visits will take place at: **HealthPartners Neuroscience Center, 295 Phalen Boulevard, St. Paul, MN, 55130, or HealthPartners Clinic St. Paul Como, 2500 Como Ave, St. Paul, MN 55108, or Healing Response Acupuncture & Functional Neurology, 1940 Greeley St. S, Suite 108, Stillwater, MN 55082.**

1. Pre-screening Phone Call

- Duration: Approximately 30 minutes
- Research staff will:
  - Provide potential participants information about the study and ask whether they are interested in participating.
  - Determine whether they meet the inclusion/exclusion criteria for the study.
  - Ask participants for permission to communicate through e-mail for the study (e.g. send them study documents and surveys to complete).

- Assist participants with setting up an e-mail account, if they do not have one.
- Schedule Pre-treatment Visit if the person is eligible for the study and e-mail the person the Informed Consent, Health Insurance Portability and Accountability Act (HIPAA), and HealthPartners non-discrimination forms.

2. Pre-treatment Visit

- Duration: Approximately 1 hour via phone
- Research staff will:
  - Review the Informed Consent and HIPAA documents with potential participants.
  - Answer any questions of potential participants and ensure they understand the expectations of the study.
  - Ask participants to electronically sign the Informed Consent and HIPAA documents via REDCap and provide them electronic copies for their records.
  - Complete the Demographics and Medication Reviewshort forms in the relevant electronic case report forms (eCRFs) in Research Electronic Data Capture (REDCap), a secure web-based system.
  - E-mail the Pittsburgh Sleep Quality Index (PSQI) and Traumatic Brain Injury-Quality of Life (TBI-QOL) surveys to the patient for completion. Ask patients to complete the surveys prior to their first acupuncture visit. During the reminder call for the acupuncture visit, patients will be reminded to complete the surveys if they have not yet completed them.
  - Provide participants instructions regarding the Headache Diary REDCap survey (example script below):
    1. "You will receive a Headache Diary survey via e-mail once a week for the next 4 weeks. Each survey will ask questions about your headaches over the last week. What is most important for you to remember is the number of headaches you had. The rest of the information is also helpful."
    2. Provide participants a paper diary and ask them to use it to keep track of their headaches during the week. Instruct participants that they should use it to fill out the weekly e-mail survey.
    3. Show participants an example of the REDCap survey.

3. Study Intervention

- Duration: Each visit approximately 1 hour
- A study acupuncturist will:
  - Complete the Adverse Events (AE) Reporting, Medication Review, and Treatment Adherence in the relevant eCRFs in REDCap.
  - Perform the acupuncture treatment.
- Only at the *LAST* acupuncture visit, a study acupuncturist will:
  - Provide participants instructions regarding the Headache Diary REDCap survey (example script below):
    1. "Like you experienced before, you will receive a Headache Diary survey via e-mail once a week for the next 4 weeks. Each survey will ask questions about your headaches over the last week. What is most important for you to remember is the number of headaches you had. The rest of the information is also helpful."

2. Provide participants a paper diary and ask them to use it to keep track of their headaches during the week. Instruct participants that they should use it to fill out the weekly e-mail survey.
3. Show participants an example of the REDCap survey.

4. 4-week Post-treatment Visit

- Duration: Approximately 30 minutes via phone
- Research staff will:
  - Complete the AE Reporting and Medication Review forms in the relevant eCRFs in REDCap.
  - E-mail the PSQI and TBI-QOL surveys to the patient for completion. Ask patients to complete the surveys within one week. Five days after the visit, patients will receive a reminder call if they have not yet completed the surveys.
  - Provide participants instructions regarding the Headache Diary REDCap survey (example script below):
    1. "Like you experienced before, you will receive a Headache Diary survey via e-mail once a week for the next 4 weeks. Each survey will ask questions about your headaches over the last week. What is most important for you to remember is the number of headaches you had. The rest of the information is also helpful."
    2. Provide participants a paper diary and ask them to use it to keep track of their headaches during the week. Instruct participants that they should use it to fill out the weekly e-mail survey.
    3. Show participants an example of the REDCap survey.

5. 12-week Post-treatment Visit

- Duration: Approximately 30 minutes via phone
- Research staff will:
  - Complete the AE Reporting and Medication Review forms in the relevant eCRFs in REDCap.
  - E-mail the PSQI and TBI-QOL surveys to the patient for completion. Ask patients to complete the surveys within one week. Five days after the visit, patients will receive a reminder call if they have not yet completed the surveys.

2 INTRODUCTION

2.1 BACKGROUND & STUDY RATIONALE

Chronic post-traumatic headache (CPTH) after a mild traumatic brain injury (mTBI) is extremely debilitating, dramatically impacts function and quality of life, and is the most frequent type of chronic pain reported after injury.[1] It has been estimated that approximately 17.1 million Americans suffer a traumatic brain injury (TBI) each year,[2] with CPTH estimated to occur in 57.8% of these individuals.[3] CPTH presents as: 1) tension-like (mild-moderate dull pain), 2) migraine headache (moderate-severe throbbing pain), or 3) combined tension-like and migraine headache.[1] On average, the number of reported headache days each month for individuals suffering from CPTH is 26,[4] which is almost daily. Individuals suffering from CPTH are more likely to have post-traumatic stress disorder, cognitive symptoms, and somatic symptoms.[4] They are also more likely to perceive difficulties in their physical and social function.[4] Consequently, it is not surprising that CPTH is extremely agonizing and frustrating for individuals with mTBI.

There are currently no FDA approved pharmacological treatments specifically for CPTH and the long-term effects of pharmacologic treatments on recovery after TBI are unclear.[5] Thus, individuals are typically prescribed medications that target the particular type of headache (e.g. triptan for a migraine headache).[5] Non-narcotic analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and triptans are often prescribed for headache and migraine treatment and have been recommended to be coupled with non-pharmacological treatments, such as physical therapy, biofeedback, and relaxation training.[6] However, because the long-term effects of pharmacologic treatments on recovery after TBI are unclear, non-pharmacologic or behavioral treatments for CPTH are very appealing.[5]

As an alternative, acupuncture is a non-pharmacologic treatment that has been explored for CPTH. Acupuncture has been practiced in Chinese medicine for over 4,000 years.[7] It is a technique where fine needles are inserted into specific areas of the body to achieve a therapeutic benefit.[7] Historically, acupuncture is based on a Chinese/East Asian medical theory that acupuncture restores normal function to the body by balancing Qi.[7] Although the mechanism of acupuncture is not fully understood, previous research has shown that it has a regulating effect on the nervous system[8] and it has been effective for treating a wide range of chronic pain conditions, including headaches and migraines.[9]

Acupuncture has been shown to be safe and effective treatment for individuals suffering from headaches and migraines. Acupuncture has been used and reported by physicians in the United States as early as the 1600s and has been researched since the 1800s. Most of the early reports were of individual patient cases, whereas the first randomized controlled trial of acupuncture treatment was published in 1975.[10] While there are still many theories regarding the mechanism of acupuncture, research has provided evidence for the benefits of acupuncture in several medical indications, including for migraine and tension headache. Acupuncture has been shown to be efficacious for both acute migraine treatment, migraine prophylaxis, and tension headache treatment.[11] In addition, acupuncture has been shown to be more effective than, or as effective as pharmacotherapy with fewer side effects.[11-13] It has also been shown to decrease migraine[11,12] and tension headache[11] frequency, reduce pain intensity,[11,12,14] decrease the use of acute medication,[14] and improve quality of life.[12] Importantly, the safety of acupuncture has been well documented. Although both minor and serious adverse events (AEs) have been reported, serious complications related to acupuncture are rare.[15]

While acupuncture is currently well-accepted as a behavioral treatment for individuals with chronic pain, headaches, and migraines,[9] it has not been extensively examined in individuals with CPTH. Although there have been studies as early as the 1980s that have shown improvements in headache symptoms with acupuncture for individuals who have suffered from mTBI,[16,17] there have been a limited number of studies since. In two recent case reports, acupuncture combined improved acute post-traumatic headache symptoms in an individual who suffered a mTBI.[18,19] In another recent study, acupuncture improved headache-related quality of life and reduced overall pain in adult service members with mild-to-moderate TBI suffering from CPTH.[20] Therefore, although there is a paucity of research examining acupuncture for CPTH, it has shown efficacy in patients with chronic headaches and migraines,[11] and researchers have suggested that it be investigated and considered for treatment of CPTH.[21] In addition, while they did not examine CPTH specifically, four randomized controlled trials investigated acupuncture treatment in individuals with TBI and reported no AEs.[22] Thus, acupuncture could potentially be a safe and viable alternative to medication for individuals with mTBI suffering from CPTH.

Because acupuncture for CPTH has not been extensively examined, there is also no consensus on the number of acupuncture sessions that are necessary for improvement. In the study of service members with mild-to-moderate TBI suffering from CPTH, 10 sessions of acupuncture were administered over 6 weeks.[20] Because the two case studies were examining acupuncture for acute post-traumatic headache,[18,19] the specific treatment methods may not be applicable for CPTH. In a recent review of acupuncture for chronic headaches and migraines, 6-10 weekly or twice-weekly acupuncture sessions were reported to be most effective.[21] However, the amount of acupuncture necessary for improvement in individuals suffering from CPTH is unclear. Thus, the primary goal of this study is to determine the effect of a low versus high dose of acupuncture treatment on number of headache days for individuals suffering from CPTH.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

Acupuncture Treatment
Reported Side Effects[23]:

Common **1-10 out of 100 people**	**Uncommon** **1-10 out of 1,000 people**	**Rare** **1-10 out of 10,000 people**	**Very Rare** **<1 out of 10,000 people**
Bleeding	Inflammation/swelling	Local infection	Palpitations
Hematoma (bleeding outside of vessels)	Bruising	Redness	Constipation
	Pain during needling	Itching	Diarrhea
	Local muscle pain	Sweating	Gastrospasm (stomach spasm)
	Nerve irritation or injury	Decrease/increase of blood pressure	Enterospasm (spasm of the intestine)
	Headache	Unconsciousness	Weight loss
	Fatigue	Tachycardia	Circulatory disturbance
	Dizziness	Breathing difficulties	Lesion of blood vessels
	Nausea	Vomiting	Systemic infection

	Exacerbation of symptoms that led to treatment	Worsening health state	Euphoria
		Generalized muscle pain	Nightmares
		Restricted movement	Poor concentration
		Joint problems	Imbalance
		Feeling of coldness	Disturbance of speech
		Menstrual problems	Disorientation
		Depressive mood	Shivering
		Anxiety	Eye irritation
		Sleep disturbance	Broken (retained) needles
		Restlessness/nervousness	Organ puncture/ Pneumothorax
		Disturbed vision	Injury of the central nervous system
		Tinnitus	Injury of the pericardium

Additional potential risks specific to electroacupunture treatment and minimization of these risks

Potential risks[24]:

- Increased depth and altered angulation of needles to ensure needles can support the weight of the leads and clips.
    - We plan to use microclips, which are much lighter than alligator clips, so this risk will be dramatically minimized.
- Vigorous muscle contraction causing needle movement (e.g. need drawn deeper into the body).
    - The goal of acupuncture treatment in this study is not to illicit a muscle twitch. The goal is to induce a mild level of sensation, which typically does not cause muscle contraction. Thus, we do not anticipate vigorous muscle contractions or unsafe needle movement.
- Minor risks have been reported for acupuncture treatment of the abdominal muscles, over the rib cage, the carotid sinus, the laryngeal muscles, and the vagus nerve.
    - For this study, we will not be performing acupuncture treatment in any of these areas, so we do not anticipate these risks.
- Risk of cardiac arrest with excessive current (risks reported around 50mA).
    - The Pantheon Research 8c.Pro stimulator we will use for this study has a current range of 0-15 mA, therefore we will be simulating with a current that is much lower than the range for this risk.
    - There is also a risk of excessive current if electrostimulation devices are plugged into the main electrical supply. The Pantheon Research 8c.Pro stimulator that we will use for this study is battery operated, therefore we do not anticipate this risk.
- Interference with implantable cardioverter defibrillators, pacemakers, or other implantable devices.
    - We have minimized this risk for our study by excluding anyone with a history of cardiac arrhythmia or current pacemaker, neurostimulator, or other implanted stimulation device.
- Seizures
    - We have minimized this risk for our study by excluding anyone with a history of seizures.

- In addition, there have not been any reports linking electroacupuncture to seizures.

Assessments/Questionnaires (Headache Diary, PSQI, & TBI-QOL)
Participants will be asked to complete a headache diary 3 times, each time for a duration of 4-weeks. This may be difficult or tiring for participants. The PSQI and the Traumatic Brain Injury-Quality of Life (TBI-QOL) are standardized questionnaires that will measure personal perception of life and sleep quality. The questions on these assessments may make participants feel uncomfortable because some parts may be easy to answer, while some parts may be difficult or tiring. Filling out the questionnaires may also cause individuals to feel uncomfortable or upset.

Loss of Confidentiality
There may be a slight possibility of breach of confidential information that was collected. However, the following procedures will be implemented to reduce this risk:

- Data collection and reporting tools will be developed and stored internally.
- Data collected and stored electronically will remain confidential and secure (e.g. secured server and password protected files [REDCap]).
- Study binders will be stored in a locked file cabinet within a locked office.
- After the study is closed, all subject identifiers will be destroyed.

2.2.2 KNOWN POTENTIAL BENEFITS

Acupuncture has been shown to be a safe and effective treatment for individuals suffering from headache and migraines. Although there is less evidence for individuals with mTBI suffering from CPTH, acupuncture treatment may provide headache relief to patients.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We believe the potential risks to the participants in this study are minimal and that the benefit of understanding how much acupuncture treatment is needed for headache relief in individuals with CPTH outweighs the potential risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To determine the effect of a low versus high dose of acupuncture on number of headache days per month in individuals with mTBI suffering from CPTH.	Number of headache days over 4 weeks
Secondary	
To determine the safety and tolerability of acupuncture on CPTH in individuals with mTBI.	1. Adverse or Serious Adverse Events 2. Completion of treatment durations and sessions
Exploratory	
To explore the effects of acupuncture on sleep, quality of life, headache outcomes, and	1. Pittsburgh Sleep Quality Index 2. Traumatic Brain Injury-Quality of Life

OBJECTIVES	ENDPOINTS
medications in individuals with mTBI who suffer from CPTH.	3. Headache Outcomes 4. Medications

4 STUDY DESIGN

4.1 OVERALL DESIGN

Study Design:
This study is an unblinded, uncontrolled randomized, 2-arm clinical trial.

Hypotheses:
Primary Hypothesis: We hypothesize that both treatment groups will have decreased headaches.
Secondary Hypothesis: We hypothesize that acupuncture will be safe and tolerated in both groups.

Randomization:
Prior to the first acupuncture treatment visit, participants will be randomized into two treatment groups. Randomization is explained in **Section 6.3**.

Acupuncture Treatment Groups:

Group 1: 18 participants will receive acupuncture treatment 1x per week for 5 weeks = 5 total.
Group 2: 18 participants will receive acupuncture treatment 2x per week for 5 weeks = 10 total.

Study Intervention:
Acupuncture treatment will consist of a standardized treatment protocol designed for this study. Specifically, 18 needles will be inserted into specific areas of the body for a duration of 30 minutes. Additional details of the treatment are discussed in **Section 6.1**.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Justification for an unblinded study: Because it will be clear to both study personnel and participants who is receiving 5 vs. 10 treatments, neither will be blinded in this study. This will be reported as a limitation of the study.

Justification for an uncontrolled study with no control group: Because there is already evidence that acupuncture treatment improved headache-related quality of life and reduced headache pain in individuals suffering from CPTH[20], the goal of this study was to provide treatment to both groups and to determine whether a low or high dose of treatment is more effective.

4.3 JUSTIFICATION FOR INTERVENTION

Acupuncture is a treatment that has been practiced for over 4,000 years and is well-accepted by many cultures. Although the mechanism is not well understood, acupuncture has been shown to be safe and effective at treating headaches and migraines. The number of treatments will be examined to determine whether 5 or 10 treatments is more effective at treating CPTH. The 30-minute treatment duration was based on clinical practice guidelines for acupuncture treatment.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed study/treatment visits and assessments. Study withdrawals are described in **Section 7**. The end of the study is defined as completion of the 12-week post-treatment visit shown in the Schedule of Activities, **Section 0**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Ability to provide and provision of signed and dated informed consent form
- Age 18-70
- Diagnosis of mTBI (as defined by ICHD-3; a. Either no loss of consciousness, or loss of consciousness of <30 minutes duration, b. Glascow Coma Scale (GCS) ≥ 13, and c. Symptoms and/or signs diagnostic of concussion)[25]
- Diagnosis of mTBI ≥3 months and ≤2 years at the time of study enrollment
- Suffering from CPTH of any etiology (e.g. tension or migraine), with chronic defined as developed within 7 days after injury and lasting ≥3 months from the time of injury[25]

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Non-English speaking
- Participation in acupuncture treatment outside of the study, while enrolled
- History of pre-existing primary headache, defined as more than 12 days of tension-type headache annually and/or more than one migraine attacks per month in the last year[4]
- History of any other serious neurological, psychiatric, chronic pain disorders, or seizures
- History of bleeding diathesis, other bleeding disorders, or syncope with needle puncture
- History of cardiac arrhythmia or current pacemaker, neurostimulator, or other implanted stimulation device
- Recent or active substance use disorder
- Women who are currently pregnant, lactating, or planning to become pregnant during the study
- Any other medical conditions that could affect their ability to participate in acupuncture treatments for the study duration (as determined by study investigators)
- Active participation or past participation ≤3 months in any other interventional study.
- Unwilling to participate in all study related activites

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Pre-screening Phone Call:

All potential participants will undergo a pre-screening phone call to determine whether they meet the inclusion/exclusion criteria. Patients will be considered ineligible if they do not meet one or more of the inclusion/exclusion criteria during pre-screening. We will collect information on why participants are ineligible or decide not to move forward with the trial.

Pre-treatment Visit:
Screen failures are defined as participants who are considered eligible during the pre-screening phone call, but it was subsequently determined that they do not meet one or more of the inclusion/exclusion criteria at or after the Pre-treatment (baseline) visit. We will collect information on why participants screen fail or decide not to move forward with the trial.

Rescreening Patients:
Individuals who do not meet the criteria for participation in this trial (ineligible or screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened up to one time. Examples include: successful treatment for a substance use disorder; women who are no longer pregnant, lactating, or planning to become pregnant; or participation in an interventional study ≥3 months prior. Rescreened participants will be assigned a new participant number.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment: Individuals with mTBI suffering from CPTH will be recruited by physician and therapist referrals from HealthPartners' clinics. We will also advertise our research study by distributing flyers to HealthPartners' physicians and throughout HealthPartners' clinics. Recruitment flyers will also be provided to our community partners for example, the Minnesota Brain Injury Alliance, TRIA, and Allina Health. If we encounter difficulties with recruitment, we plan to submit an amendment to the IRB to contact HealthPartners patients and members and invite them to participate.

To reach our target enrollment, we anticipate that we will need to screen 100 people, of those 50 individuals will sign the informed consent, and of those 40 individuals will be randomized to treatment groups. We expect that we will enroll approximately 35% (~13) women and 65% (~23) men, primarily between the ages of 41-84, and approximately 80% will be white. Values are based on our Regions Hospital Rehabilitation census data.

Remuneration: Participants will be provided gift cards totaling $50 per person for completing certain time points of the research study. Specifically, after completing all acupuncture treatment visits, participants will receive a $25 gift card. After completion of the 12-week post-treatment visit (end of study visit) participants will receive another $25 gift card.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The study intervention for both groups is acupuncture treatment. Acupuncture is a treatment where fine needles are inserted into specific areas of the body to achieve a therapeutic benefit. The treatment regimen is described next in more detail.

6.1.2 ADMINISTRATION AND/OR DOSING

Acupuncture Treatment Methods:
Group 1 will receive weekly acupuncture and Group 2 will receive twice-weekly acupuncture over five weeks. Acupuncture treatments will be separated by a minimum of 2 days and a maximum of 14 days, unless a participant has an illness, such as COVID-19. In this case, additional time may be allowed, as determined by the investigator. Treatment methods will be identical for both groups and are described below.
Standard, sterile stainless-steel, disposable needles (DongBang™ Corporation, Spring Ten 0.25x30mm; Boryeoung, Republic of Korea) will be inserted in the acupuncture point locations (described below), with a total of 18 needles used for each treatment session. The depth of the needle insertion will be approximately 10-20mm, depending on the region of the body undergoing treatment. Needle reaction (soreness, numbness or distended feeling around the point, also known as a Deqi sensation) will occur during the initial insertion. Following 10 minutes of retention, all needles (except points St36 and LI4 under electrostimulation, and auricular points SM and PtZ) will be rotated in order to maintain Deqi sensation. Maintaining Deqi sensation has been shown to increase the effectiveness of acupuncture.[26,27] All needles will be left in place for a total of 30 minutes, which is a typical duration in acupuncture practice. It also is a common duration of previously reported clinical trials of acupuncture for headaches and migraines.[11,12,28]

Acupuncture points were selected for their classical indications, anatomical locations, effect on pain networks[29,30] and influence on cerebral blood flow.[31] The anatomical location for each point will be based on the World Health Organization's acupuncture point guideline.[32] Electroacupuncture will be administered with Pantheon Research electrostimulation 8c pro machines (Pantheon Research Inc; Huntington Beach, CA), with a continuous milliampere wavelength of 2Hz at stomach 36 (ST36) and large intestine 4 (LI4). The intensity will be gradually increased to a comfortable level that participants can tolerate, without the sensation of pain. Traditional Chinese manual acupuncture will be used at eight acupuncture points: yin tang (YT) and Du20 and bilateral acupuncture of liver 3 (LV3), urinary bladder 2 (UB2), small intestine 19 (SI19), extra point Anmian (EX-22), and two auricular points Shen Men (SM) and point zero (PtZ). During treatment, acupuncture needles or electrical stimulation can be removed due to extreme pain or discomfort, so as not to exceed the removal of more than 2 of the 18 needles.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Acupuncturists:
Acupuncture treatments will be administered by MN licensed acupuncturists with a Master's degree level of training in acupuncture (or higher) from accredited institutions, and five or more years of clinical experience. Prior to enrolling participants, the acupuncturists will complete practice sessions together of the treatment protocol and methods of administration to ensure consistency between providers

Training:

Following IRB approval and prior to recruitment and enrollment, the study acupuncturists will complete 10 practice sessions. For the training, we will seek 12 volunteers who will sign a volunteer consent form prior to participating. The purpose of training will be to ensure consistency in intervention procedures and further standardized treatment methods. This includes, but is not limited to: needle location (18 points), needle depth, time of first and last needle placement, total treatment duration, and pre-defined electro-acupuncture settings.

Tracking:
All practice sessions will be documented on a training log. This will include dates and times of the trainings, names of the volunteers, and printed names and signatures of the study acupuncturists. We will also keep a record of the volunteers' signed treatment release forms.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization:
Randomization will be performed with a 1:1 allocation ratio. Balanced treatment assignments will be achieved using permuted block randomization with random block sizes stratified by gender. This decision was based on evidence that females in this population reported higher rates of headaches.[33] The study biostatistician will generate a randomization schedule using the SURVERYSELECT procedure in SAS. Assignments will not be seen by other study personnel in advance and will not be changed after randomization.

Blinding:
Study personnel will be unblinded to the randomization, as it will be clear the number of participants who receive 5 acupuncture treatments versus those that receive 10. In addition, it will be clear to participants which treatment group they are in and it will be impossible to blind them from this information.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participants will be asked to adhere to study visits and to complete study assessments. Participants will remain active unless withdrawn from the study (see **Section 7**). We will track participants' adherence to study visits, as well as completion of the assessments. These will be documented in the relevant eCRF.

6.5 CONCOMITANT THERAPY

For this protocol, participants may use non-opioid analgesics for pain control, including over-the-counter medications and dietary supplements, and prescribed medications. This includes use for rescue therapy in the event of exacerbation of symptoms due to acupuncture treatment. Medication usage will be assessed at each study visit and documented in the relevant eCRF.

6.5.1 RESCUE THERAPY

Any medications used for rescue therapy will be recorded in the Headache Diary.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a participant who signed the consent form chooses to discontinue participation in the study or study intervention, or if the principal investigator and co-investigators determine that a participant should discontinue participation, they will be withdrawn from the study. A withdrawal will either be defined as 'Patient Withdrawal' or 'Principal Investigator Withdrawal'. The participant will be asked to complete an early withdrawal phone call 7-14 days from the date the intervention was discontinued. The purpose of the phone call will be to record any AEs or serious adverse events (SAEs) that may have occurred after the discontinuation of treatment. Research staff will attempt to call the participant up to 3 times.

The data that will be collected at the time of study withdrawal will include the following:

- The reason(s) for discontinuation of the study intervention

The data that will be collected during the early withdrawal phone call will include the following:

- AEs or SAEs that occurred since the time of withdrawal

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

1. Participant has not completed an acupuncture treatment for > 14 days, unless a participant has an illness, such as COVID-19. In this case, additional time may be allowed, as determined by the investigator.
2. Significant study intervention non-compliance
3. Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
4. Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
5. The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the relevant eCRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to attend any scheduled study visit and study staff are unable to contact the participant after at least 5 attempts, while maintaining the 14 day maximum between visits.

The following actions must be taken if a participant fails to attend any required study visit:

- Study staff will attempt to contact the participant, reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, telephone calls or e-mail – if no answer leave a voicemail on the first and last attempt). These contact attempts will be documented.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Demographics: Demographic information will be collected, including: gender, age, race, ethnicity, language, height, weight, marital status, employment status, date of TBI, date of CPTH diagnosis, and e-mail address for Headache Diary surveys (discussed below).

Medication Review: Medication data will be used for exploratory purposes for Specific Aim 3.

Headache Diary: Participants will be sent an e-mail REDCap survey to complete and asked to record headache information for three 4-week time periods. During each 4-week period, they will receive the e-mail once per week. They will be provided paper headache diaries (Appendix 1-3) to keep track of their headaches and will be asked to complete each e-mail survey they receive. The headache diary survey will include: how many headaches occurred each week during the 4-week period, duration, pain intensity (0-10 scale), type (e.g. tension), and name of medication taken and dosage (if applicable). The outcome measure for Specific Aim 1 is number of headache days over 4 weeks; other variables will be exploratory.

Treatment Adherence: The participant's treatment adherence will be measured to determine tolerability of acupuncture. We will record the number of attended acupuncture sessions. We will also record participants' ability to maintain the acupuncture duration of 30 minutes per session.

Sleep: Participants will be asked to complete the Pittsburgh Sleep Quality Index (PSQI), which contains questions about one's usual sleep habits during the past month.

Quality of Life: Participants will be asked to complete the TBI-QOL short forms. The TBI-QOL includes the following domains: ability to participate in social roles and activities, anger, anxiety, attention-concentration, cognition-general concerns, communication, depression, emotional behavior dyscontrol, executive function, fatigue, grief-loss, headache pain, independence, learning-memory, mobility, pain interference, positive affect and well-being, resilience, satisfaction with social roles and activities, self-esteem, stigma, and upper extremity.

8.2 SAFETY ASSESSMENTS

Assessment of Adverse and Serious Adverse Events:

AEs and SAEs will be monitored by acupuncturists during acupuncture treatment sessions, and by study staff during the 4-week and 12-week post-treatment visits. The acupuncturists and research staff will immediately notify the Principal Investigator and utilize the eCRF to record any AEs or SAEs. The PI and the study physician will review and categorize all AEs or SAEs and report them accordingly, as discussed below.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of AE from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

This protocol uses the definition of SAE from 21 CFR 312.32 (a): An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or study clinician, it results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

1. **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
2. **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
3. **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All AEs will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

A clinician with expertise in TBI, CPTH, and acupuncture will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

Study staff will record events with start dates occurring any time after the first acupuncture treatment session until the 12-week post-treatment visit. At each acupuncture treatment visit (after the 1st) and the 4-week and 12-week post-treatment visits, study staff will inquire about the occurrence of AE/SAEs since the last visit. All reported events will be monitored until the 12-week post-treatment visit. Any reported event that is definitely or probably related to the intervention will be followed until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

In consultation with the Principal Investigator (PI) and the study clinician, a trained member of the study team will be responsible for conducting an evaluation of an AE and shall report the results of such evaluation to the reviewing IRB either at the time of continuing review or within 10 working days of becoming aware of the event if the event is considered to be serious or meets the definition of an unanticipated problem involving risks to study subjects or others.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI and the study clinician, a trained member of the study team will be responsible for conducting an evaluation of a SAE and shall report the results of such evaluation to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Following IRB review of any AEs or SAEs, the PI will follow the IRB's recommended actions. This may include, but is not limited to, modifying the informed consent document or process, re-consenting current participants, providing information to past or current participants (e.g. whenever the information may relate to the participant's willingness to continue participants), and modifications to the protocol/research plan.

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

Women who are currently pregnant, lactating, or planning to become pregnant during the study are excluded from this study. This is due to the hormonal changes that may alter headache patterns. If any participant who is still undergoing acupuncture treatment expectedly or unexpectedly becomes pregnant while active in the trial, the participant will be withdrawn from the study by the Principal Investigator. The participant will be asked to complete an early withdrawal phone call in 7-14 days from the date the intervention was discontinued for safety follow-up.

If any participant who has completed all acupuncture treatment sessions expectedly or unexpectedly becomes pregnant, the participant may remain in the study until study completion.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The PI will report unanticipated problems (UPs) to the reviewing IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB as soon as possible, but no later than 10 working days after the investigator first learns of the event

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Following IRB review of any unanticipated problems, the PI will follow the IRB's recommended actions. This may include, but is not limited to, modifying the informed consent document or process, re-consenting current participants, providing information to past or current participants (e.g. whenever the information may relate to the participant's willingness to continue participants), and modifications to the protocol/research plan.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- **Primary Endpoint: Number of headache days over 4 weeks**
  We hypothesize that 10 treatments will greater alleviate headaches when compared to 5 treatments over a 5-week treatment period. We also hypothesize that both treatment groups will have decreased headaches. Alternatively, our null hypothesis is that there will be no difference between 5 and 10 treatments.

- **Secondary Endpoints: 1) Adverse or Serious Adverse Events and 2) Completion of treatment durations and sessions**
  We hypothesize that acupuncture will be safe and tolerated in both groups.

- **Exploratory Endpoints: 1) Sleep, 2) Quality of life, 3) Headache Outcomes, and 4) Medications**

9.2 SAMPLE SIZE DETERMINATION

We require 18 subjects in each study group to achieve 80% power at a 5% significance level for our primary hypothesis (PASS software version 11). The primary analysis is a a two-sided two-sample t-test comparing the mean number of headache days over 4 weeks from a parallel-group design. We hypothesize that, while both groups will have decreased headaches, 10 treatments will greater alleviate headaches when compared to 5 treatments over a 5-week treatment period. For analysis purposes, we will analyze the data such that the opposite could be shown (5 treatments better reduces headaches). The null hypothesis is that there will be no difference between treatment groups. To conduct the power calculation, we assumed an equal standard deviation of 4.47,[33] equivalence limits of ±1 SD, and a true difference between means of 0. No interim analyses are planned. The potential effect on our power if our estimates for the effect size are inaccurate are displayed in the table below.

N	δ	Σ	Power	Alpha
36	4	4.5	0.742	0.05
36	4.5	4.5	0.835	0.05
36	5	4.5	0.903	0.05

N = total sample size; δ = treatment effect (change);
σ = standard deviation.

Based on preliminary estimates, we do not anticipate difficulty recruiting 40 subjects. HealthPartners Physical Medicine and Rehabilitation physicians see approximately 25 individuals with CPTH per month at the Neuroscience Center. Therefore we will need a 16% enrollment rate to reach our recruitment goal in the allotted time frame. In addition, we also plan to recruit and enroll from other HealthPartners clinics and within the community. If we see a 20% reduction in sample size due to dropout, withdrawal, or missing data, our power will be 75.8% to detect a similar effect size. This, and other possible changes in power due to attrition, are listed in the table below.

N	μ1	μ2	δ	σ	Power	Alpha
28	26	21.5	4.5	4.5	0.727	0.05

30	26	21.5	4.5	4.5	0.758	0.05
32	26	21.5	4.5	4.5	0.787	0.05
36	26	21.5	4.5	4.5	0.835	0.05

N = total sample size; μ1 = mean of 5 treatment group; μ2 = mean of 10 treatment group; δ = treatment effect (change); σ = standard deviation.

9.3 POPULATIONS FOR ANALYSES

All analyses will be performed on an intention-to-treat basis. If poor attendance at acupuncture treatments is observed, we will perform a per-protocol analysis as a sensitivity analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Discrete variables will be summarized using frequencies and percentages, while continuous variables will be summarized by means and standard deviations. If the continuous variables are found to be skewed, we will instead report medians and interquartile ranges. Statistical significance will be determined using p-values less than 0.05 and 95% confidence intervals, unless otherwise indicated. All inferential tests will be two-sided. For descriptive statistics (means, SDs, proportions) where no inferential statistics were conducted, we will refrain from making confirmative statements. All covariates will be pre-specified in the sections below. Any additional analyses will be described as post-hoc and exploratory.

Distribution of the outcome variables will be assessed prior to conduct of our analyses to determine if the planned tests are appropriate. If variables are found to be non-normally distributed we will explore the use of log-transformations or non-parametric tests such as the Wilcoxon-Rank Tests.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The number of headache days per 4 weeks will be captured via a headache diary. The primary outcome, change in number of headache days per 4 weeks between the pre-treatment assessment and 4-week post treatment assessment, will be compared using a two sample t-test. We will present the mean change by group with corresponding standard deviations. If baseline differences are found between study groups, they will be adjusted for using a linear regression model. In addition, a mixed-model analysis of variance (ANOVA) will be performed with data from all three time points. The outcome will be number of headache days per 4 weeks and it will be adjusted for group, time, and a group*time interaction. If significant interactions exist, line plots and post hoc tests will be used to define the nature of the interaction.

Prior to analysis, we will plot our outcomes to examine their distribution and decide whether we should consider non-parametric analyses. Only subjects with complete data from both pre-treatment assessment and 4-week post treatment assessment will be included in the final analysis. Data will be analyzed per an intent-to-treat approach regardless of actual treatment received. If a large proportion of missing data is noted, we will compare baseline characteristics of subjects who completed the treatment with those who were lost to follow-up.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary analysis are not dependent on results of primary endpoint. All secondary outcomes are measured as a single summary measure.

Frequencies and proportions of each study group with at least one AE/SAE will be presented together with odds ratios and 95% confidence intervals. To assess compliance with the protocol, the amount of acupuncture treatments completed in the two groups will be reported in absolute numbers and percentages of target treatments. We will also report the proportion of participants who were unable to tolerate a 30-minute session of acupuncture in each treatment group. No inferential statistics will be conducted on these secondary outcomes.

9.4.4 SAFETY ANALYSES

AE/SAEs will be reported as described in section 8.3 of this document. They will be classified by severity, relationship to study procedures, and expectedness. No other formal safety analyses will be conducted.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline variables will be compared between groups to ensure randomization achieved balanced treatment assignments. This will include demographics (e.g. gender, age, race) and medical history (e.g. length of stay in hospital after injury, discharge destination). All such variables are listed in section 8.1 of this document. Variables will be summarized using descriptive statistics (e.g. mean and SD, or frequency and proportion) and compared inferentially. Continuous variables will be compared using two-sample t-tests or Wilcoxon rank tests and discrete variables will be compared using chi-square tests for independence or Fisher's exact tests.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Both primary and secondary outcomes will be descriptively summarized based on gender. Our sample size is unlikely to allow for other meaningful sub-group analyses.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

Exploratory outcomes (headache: intensity, duration, type; sleep; and QOL) will be compared between groups with Student's t-test, Chi-square test, and Mann-Whitney-U test and mixed-model ANOVAs, as appropriate. As an exploratory analysis, patients who report post-COVID-19 symptoms will be identified using the additional COVID-19 set of questions. Types and severity of post-COVID-19 symptoms present within the group will be described. The t-test or non-parametric equivalent will be used to determine whether acupuncture had an effect on post-COVID symptoms.

As some patients' medication adherence and regimens are expected to change throughout the intervention period, a sensitivity analysis will be performed for all primary and secondary endpoints in which we exclude patients with medication reginmen ammendments. These results will be compared to our main analysis to help contextualize any observed intervention effect. Patients with and without changes to their medications during the trial will be described separately and any differences will be presented. If necessary, we will conduct a sensitivity analysis in which we exclude participants that had protocol deviations (e.g. large delays between treatments) due to illness, for example COVID-19.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol:

- Study Volunteer Informed Consent Form
- Study Participant Informed Consent Form
- Recruitment Brochure
- Recruitment Flyer
- Early Withdrawal Phone Call Script
- Lost to Follow-Up Phone Call Script

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

At the end of the Pre-screening phone call, all eligible patients will be provided a copy of the consent and HIPAA forms via e-mail. Patients will also be provided an electronic copy of HealthPartners' statement of non-discrimination form. During the Pre-Treatment phone call, research staff will review the consent and HIPAA forms with the patients. Patients will be allowed time to review all documents and ask any questions prior to signing electronically. Research staff will confirm that the patients understand the information in the forms and answer any questions. To obtain signature, the e-consent framework in REDCap will be utilized. This framework allows the patient initials, date, time to be stamped in the footer as extra identity as to who is completing the consent and HIPAA documents. Following the consent conversation, the staff member will sign and e-mail the consent and HIPAA electronically to the patient. The patient will electronically sign, certify, and submit the consent and HIPAA in REDCap. A fully executed PDF copy of the consent and HIPAA will be provided electronically to the patient for their records as well as saved via the auto-archiver function in REDCap. Research staff will complete this process during the Pre-Treatment phone call, to ensure completion and assist if there are any questions.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, the funding agency, the IRB and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and the funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

1. Determination of unexpected, significant, or unacceptable risk to participants
2. Demonstration of efficacy that would warrant stopping
3. Insufficient compliance of study staff to the protocol (ie, significant protocol violations)
4. Data that are not sufficiently complete and/or evaluable
5. Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, IRB, or other relevant regulatory or oversight bodies.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

All study regulatory binders will be stored in a locked file cabinet within a secure office. The internal study monitor, representatives of the IRB, or regulatory agencies, may inspect all documents and records required to be maintained by the investigator, for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be password-protected and stored on REDCap, a secure web-based system. Only research study staff will have access to the data. Individual participants and their research data will be assigned a unique study identification number. While the study is active, subject identifiers (e.g. name, MRN) will be stored in REDCap, however, after the study is closed all subject identifiers will be removed.

The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be

thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

After the study is completed, the de-identified data will be and stored in REDCap for use in future research. Permission to keep the de-identified data will be included in the informed consent.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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10.1.6 SAFETY OVERSIGHT

There is no Data Safety Monitoring Board for this study, as acupuncture has been previously shown to be safe and have minimal risks. During team meetings, the PI and study will review a rolling report of adverse events and report them appropriately.

10.1.7 CLINICAL MONITORING

N/A, refer to next section.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Study staff will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process and 10% of the completed consent documents. Feedback will be provided to study staff to ensure proper consenting procedures are followed.

Source documents and the electronic data --- The majority of data will be directly entered into eCRFs in REDCap. To ensure accuracy for data not directly entered in REDCap, study staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review documented protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the research study staff under the supervision of the PI. The PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All data will be entered directly into eCRFs in REDCap. The data system includes password protection and internal quality checks by study staff to identify data that appear inconsistent, incomplete, or inaccurate. Treatment logs from the acupuncture treatment sessions will be scanned into and stored in REDCap.

10.1.9.2 STUDY RECORDS RETENTION

Investigator records will be retained in accordance with regulatory, organizational and sponsor or grantor requirements, but no less than 6 years following the completion of the research. All records will be maintained securely with limited access. Disposal of investigator records will be done in such a manner that no identifying information can be linked to research data.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

It will be the responsibility of the PI to use continuous vigilance to identify, document, and report deviations as soon as possible, but no later than 10 working days after identification of the protocol deviation. Minor deviations, which do not impact participant safety, compromise the integrity of study data and/or affect the participant's willingness to participate in the research are to be reported at the time of continuing review. Protocol deviations will be addressed in study source documents and sent to the reviewing IRB per their policies. The PI will be responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with HealthPartners Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANOVA	Analysis of Variance
CPTH	Chronic Post-traumatic Headache
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Forms
GCP	Good Clinical Practice
ICH	International Council on Harmonisation
IRB	Institutional Review Board
ITT	Intention-To-Treat
mTBI	Mild Traumatic Brain Injury
OHRP	Office for Human Research Protections
PI	Principal Investigator
PSQI	Pittsburgh Sleep Quality Index
QOL	Quality of Life
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
TBI	Traumatic Brain Injury
TBI-QOL	Traumatic Brain Injury-Quality of Life
UP	Unanticipated Problem

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	12/12/2019	Response to initial IRB Review	Response to initial IRB Review
3.0	09/17/2020	Addition of 3 healthy volunteer protocol practice participants, in-person visits changed to phone visits (except acupuncture treatment visits), consent and assessments to be completed electronically, COVID-19 changes (including PPE) will align with NSC clinic policies and procedures.	COVID-19 Pandemic
4.0	02/16/2021	Changes to the inclusion/exclusion critieria. (Changed to: No acupuncture while enrolled in the study and mTBI diagnosis within 2 years.)	COVID-19 Pandemic; slow recruitment/enrollment
5.0	03/30/2021	Change to inclusion criteria. Change upper limit from 65 to 70.	COVID-19 Pandemic; slow recruitment/enrollment
6.0	05/04/2021	Change to acupuncture treatment protocol- allow for removal of needles or e-stim due to extreme pain/discomfort. Also update AE reporting.	Recent minor protocol deviation due to removal of e-stim due to pain/discomfort.
7.0	07/29/2021	Addition of 2 healthy volunteer patients to train Twin City Acupuncture (TCA) acupuncturists on the study protocol.	We are adding a consulting agreement for the study to allow 2 TCA acupuncturists to assist with the study treatments.
8.0	09/07/2021	Remove inclusion criteria: “Stable medication regimen for ≥1 months and agree to adhere to his or her current medication treatment regimen through study participation.”	Throughout enrollment, we learned that participants require more flexibility with prescription medication changes. We plan to continue to record and monitor medications for all patients.
9.0	05/26/22	Update PN Address	Address was incorrect
10.0	02/16/23	Remove PN location and add Como Clinic and Healing Response Acupuncture	Change in locations for acupuncture treatment
11.0	03/03/23	Add 2 healthy volunteers, increase enrollment to 40 (due to withdrawals), Add Ayla & Michael.	Add 2 healthy volunteers, increase enrollment to 40 (due to withdrawals), Add Ayla & Michael.

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