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Clinical Intervention Project Protocol: **Predicting Analgesic Response to Acupuncture – A Practical Approach**

Predicting Analgesic Response to Acupuncture:

**A randomized, placebo-controlled, subject and assessor
blinded, 100-subject Clinical Trial of Electro-
Acupuncture In the Treatment of
Chronic Low Back Pain**

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Study Intervention Provided by:

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N/A

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35 **Tool Revision History**

36 Version Number: 1.0

37 Version Date: Dec 8, 2015

38 *Summary of Revisions Made:*

39 Version Number: 2.0

40 Version Date: 2/15/2016

41 *Summary of Revisions Made:*

- 42 1. Addition of acupuncturists to the program
- 43 2. Clarification of study timeline
- 44 3. Revision and clarification of inclusion and exclusion criteria
- 45 4. Revision of treatment protocol to clarify difference between current protocol and P01 Project
- 46 3
- 47 5. Revision of study consents to clarify difference between current protocol and P01 Project 3
- 48 6. Clarification on procedures of trial monitoring

49 Version Number: 3.0

50 Version Date: 05/18/2016

51 *Summary of Revisions Made:*

52 *Personnel*

- 53 1. Revision of **protocol personnel** (full list of acupuncturists and research coordinator)

54 *Inclusion/Exclusion*

- 55 2. Revision of **inclusion criteria** such that filling out 50% of baseline daily questionnaires
- 56 and a mean daily pain of 4 or above on the baseline daily questionnaire are no longer
- 57 required for entry into study (4.1 and 4.2).
- 58 3. Due to change #2, it is no longer necessary to perform 2-step consent, which is replaced
- 59 with **a single step consent** at the screening visit (4.3 and 6.2).
- 60 4. Changed **exclusion criteria** from ASA classification IV and above to ASA classification
- 61 III and above to minimize risk to participants (4.2).
- 62 5. Replaced Beck's depression index with **MINI** (in the discretionary exclusion list) to better
- 63 identify and assess psychiatric conditions that may interfere with the proper receipt of
- 64 the study interventions. (4.2, 6.2)

65 *Participant Recruitment*

- 66 6. Added an **online screening form** so we can direct those who learned about our study
- 67 online to visit our study immediately and know relatively soon if he/she is eligible (4.3.1).
- 68 7. Added **rescreen window of 4 weeks** to screening eligibility section (4.3.1).

69 *Study Procedures*

- 70 8. Revision of the **schedule of evaluations** to include personnel responsible to fill out
- 71 each questionnaire/CRF (6.1), and revision of **study procedures** (6.2) to reflect

72 changes due to the transition **from 2-step to 1-step consent**, and to reflect the most up
73 to date changes in each study visit.

74 9. Revised language when referencing **actigraphy** measures (6.1) by emphasizing the
75 word "optional." This test may be excluded from the protocol.

76 *Randomization*

77 10. Revised **randomization plan** from simple randomization to randomization stratified to
78 each acupuncturist/site with a block size of 4, to account for the increased number of
79 acupuncturists in the study to cover the greater Bay Area (6.2.2).

80 11. Added more **details on procedure of randomization** (6.2.2) to a) streamline the
81 process; b) ensure blinding of the research team (the PI and research coordinator [RC]).

82 *QA plan (deviations and AE's).*

83 Established standard procedure to QA the study: the PI and RC will perform **monthly**
84 **QA checks** on: informed consents, participant surveys, research team CRF's,
85 acupuncturist's CRF's and treatment audiotapes. For each participant, protocol
86 deviations and all forms of AE's will be logged accordingly at a monthly basis on Excel
87 spread sheet (7.4, and 10.3.5).
88

89 Version Number: 4.0

90 Version Date: 8/29/2016

91 Summary of Revisions Made:

92 In this revision, we widened both the inclusion criteria and the rescreening window in an effort to
93 boost recruitment and maximize participant retention with minimal impact to the study quality.

94 Inclusion criteria (page 15): 1) decreased pain level from 5 or above to 4 or above out an 11-
95 point (0-10) numerical rating scale (section 4.1); 2) decreased acupuncture-free period from the
96 last decade to the last 5 years (section 4.2).

97 Participant rescreening (page 16 & 17): Currently many of our acupuncturists are at full capacity
98 due to active engagement with the P01. Participants in this K23 study may need to wait for 6-10
99 weeks between the time of their screening visit and the first acupuncture treatment. It is thus of
100 interest to expand the rescreening window to allow this waiting period. We increased the
101 rescreening window from 1 to 3 months with following policy to facilitate the waiting period while
102 being careful to ensure that the participant remains eligible (section 4.3.1).

- 103 a. Participant returns for pre-treatment (ie baseline) visit within 1 month after the screening visit:
104 no additional screening necessary.
- 105 b. Participant returns between 1 and 3 months after the screening visit: rechecking mean pain
106 score over 30 days, and medication list.
- 107 c. Participant returns between 3-6 months after the screening visit: rechecking mean pain score,
108 medication list, PH-9, perform inclusion/exclusion CRF and screening physical exam.
- 109 d. Participant returns > 6 months after the screening visit, repeat the entire screening visit (all of
110 the tests in step C, plus questionnaires, QST and HRV tests).

111 Version Number: 4.1

112 Version Date: 9/20/2017

113 Summary of Revisions Made:

114 This revision was made to correct minor errors identified by the WESTAT mid-trial visit from
115 August 2017. The majority of the changes take place in section 6.1 (page 33) to reflect minor
116 errors on the schedule of surveys/CRF's outlined in the table.

117 Additionally, for the inclusion criteria, both our communications with NCCIH and our IRB listed a
118 minimum of 3 years since the most recent acupuncture treatment, but we mistakenly wrote
119 down 5 years in version 4.0. This error was corrected in section 4.2 of this revision.

120 For participants who missed filling out more than 50% of the daily surveys, we will mark this as
121 a protocol deviation (section 6.2.2) per suggestion by WESTAT.

122 Finally, one of the acupuncturists (AF) passed away this year and our administrative assistant
123 (CD) is replaced by a new one (KH).

124

125 Version Number: 4.2

126 Version Date: 10/3/2017

127 Summary of Revisions Made:

128 This revision is a follow up to address TWO concerns raised by OCRA regarding two issues
129 from version 4.1.

130 **First**, we would like to clarify on a mistaken assumption we've made regarding **our primary**
131 **outcome, the PROMIS pain intensity instrument (PPII)**, which is collected at pre-treatment
132 and post-treatment visits. We assumed it contained an **11-point numerical rating scale (NRS)**
133 measure of mean pain intensity. However, in fact, it consists of 3 questions, assessing the
134 mean, most and least pain intensity over the last 7 days, ALL on a **5-point Likert Scale** (no
135 pain=1, mild pain=2, moderate pain=3, severe pain=4, very severe pain=5). The PPII is scored
136 by adding the patient's response to all 3 questions (ranging from 3-15) and convert the raw
137 score to a T-score (0-100) where 50 represents population mean and 10 represents standard
138 deviation.

139 Because of the above change in the exact measure of our primary outcome (from 11-point NRS
140 to 100 point T-score), we need to make the **following adjustment to the definition of a**
141 **responder**. Previously, based on established literature (Farrar, Young et al, Pain, 2001), we
142 defined a responder as those with $\geq 30\%$ or ≥ 2 points of pain reduction (pre-treatment minus
143 post-treatment) using the NRS. With the PPII, there isn't a universally agreed upon minimally
144 significant difference (MID). However, Yost and Eton estimated the MID's of several PROMIS
145 instruments in cancer patients (Yost, Eton et al, J Clin Epidemiol, 2011). These included MID of
146 T-scores between 4.2 and 4.5 for pain measures. Thissen and Liu estimated the MID of

147 pediatric PROMIS instruments for depression, pain, fatigue and mobility, and found that the MID
148 for these tend to cluster around a T-score of 2 for pediatric patients, and around 3 (2.4 to 3.5)
149 for adolescents and parents (Thissen, Liu et al, Qual Life Res, 2016). Taken together, with
150 limited available data, we feel that a T-score of 5 is a reasonable choice for MID for the PPII.
151 Alternatively, a 1-point deduction on the 5-point Likert scale (1-5) for the MEAN pain intensity
152 subscale (single question) will be used to replace the 2-point reduction on the 11-point NRS (0-
153 10). **In summary, with the PPII, we define the primary outcome as the change in T-score
154 of the full 3-item instrument. A responder is defined as a completer who showed \geq 5-
155 point reduction in the T-score of the full instrument, OR, \geq 1-point reduction in the 5-point
156 mean pain intensity sub-scale.** For good measure, from here on, we will be adding the 11-
157 point NRS to the PROMIS packet at both the pre- and post- treatment visits for ALL future
158 participants. The above clarification/changes of primary outcome, responder definition and
159 additional of the NRS scale will be reflected throughout this protocol, including the Precis
160 section, and sections 1.2, 3, 6.1, and 9.5.1.

161 Last but not least, **we confirmed that our power calculation and statistical methods remain
162 the same despite the slight adjustment in the measure of the primary outcome (pain).**
163 Specifically, the power calculation does not change, because it is estimated using TS as our
164 primary predictor for a moderate change in pain, measured either in NRS or the T-score from
165 the PPII. Furthermore, there also will not be changes in our statistical methods, as the outcome
166 measure remains to be percentage changes from pre-treatment, measured at post-treatment,
167 regardless of the actual measure (0-10 in NRS or 0-100 in T-score).

168 **Second**, per OCRA's suggestion, we removed all languages related to Actigraphy. If units
169 become available later in our study, we will add back Actigraphy with detailed plans of use.

170

171 Version Number: 4.3

172 Version Date: 10/19/2018

173 Summary of Revisions Made:

174 This revision was made to correct issues identified by the WESTAT interim monitoring visit from
175 August 2018. Most of these changes involve following up on previously missed details and/or
176 clarification of research procedures. These protocol revision will not result in any major changes
177 in the conduct of this study.

178 1. Eliminate languages involving the MINI (pg 18 and 37). Due to a clerical oversight, we
179 included MINI in some of our language, yet, we have NEVER used the MINI as our psychiatric
180 screener. MINI had been only considered during our earlier planning phase and we had rejected
181 it due to its cost and the time needed for its administration. Previous studies have used PH-9
182 successfully in the screening of suicidality and major depression. We have been using PH-9
183 since the start of our study.

184 2. Clarification on long-term follow up (pg 42, under “online follow-up.”) We have clarified on the
185 exact timing of the 3, 6, and 12 month follow-up surveys, measured from the day of the last
186 study treatment, and the windows for the follow up surveys, per suggestions from WESTAT.

187 3. Clarification on weekly surveys (pg 36 and 38). We have clarified that all weekly surveys
188 during the study period have the same exact content. They are administered after the
189 completion of the baseline (pre-treatment) visit on a weekly basis until the completion of the
190 post-treatment visit. Greater than 50% missing of weekly surveys in an individual will be
191 considered a protocol deviation.

192 4. Clarification on assessment of radicular pain symptoms on pg 18, section 4.2. One of the
193 exclusion criteria in our study is the presence of radicular pain. Per discussion with WESTAT,
194 we have the clarified the research procedures to rule out radicular pain.

195 5. Clarification on physical exam (top of pg 42). We have never performed physical exam at the
196 post-treatment visit. Our protocol was accurate in the overall assessment table on page 36 but
197 there was an error on the list of tasks for the post-treatment visit on p42. This error is now
198 corrected.

199 6. Clarification – QI of acupuncture treatment audios (pg 32 and 33). Per request from
200 WESTAT, we clarified that we will listen to 1 to 3 audio records from 20 randomly selected
201 participants to ensure adherence to protocol.

202 7. Personnel update – see page 11 for changes in RC and in acupuncturist roster.
203

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278 *II. Informed Consent Form Template*

279 *III. Other (add as many appendices as necessary)*

280

STUDY TEAM

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PARTICIPATING STUDY SITES

286 Stanford Systems Neuroscience and Pain Laboratory (SNAPL)
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 288 Palo Alto, CA 94304
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 290 Community Acupuncture clinics in the Peninsula/San Francisco Bay Area.

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293

PRÉCIS

Study Title

Predicting Analgesic Response to Acupuncture – A Pragmatic Approach.

A randomized, placebo-controlled, subject and assessor blinded, 100-subject clinical trial of electro-acupuncture in the treatment of chronic low back pain

Objectives

Aim 1. Explore the predictive relationship and the association between ascending sensitization measures and clinical response to acupuncture.

300
301

302 **Aim 2.** Explore the predictive relationship and the association between
303 descending pain modulatory measures and clinical response to acupuncture.

304 **Aim 3.** Exploratory model building for predicting pain reduction by
305 acupuncture.

306 **Design and Outcomes**

307 The current design is a randomized control trial in which 100 participants with
308 chronic low back pain will be randomized with equal probability to verum (electro)
309 acupuncture (VA) or sham/placebo ('electro') acupuncture (PA). Participants and
310 researchers will be masked to treatment assignment; treatment providers will not (and
311 cannot) be masked to treatment assignment.

312 **Primary Outcome:** Change in Pain Intensity score (T-score) measured by the
313 PROMIS Pain Intensity Instrument administered at the pre-treatment and post-
314 treatment visit.

315 **Primary Predictors:** temporal summation, conditioned pain modulation, pressure pain
316 threshold, degree of widespread pain, pain catastrophizing, expectations, coping and
317 pain self-efficacy.

318 **Secondary Predictors:** history of trauma, PTSD symptoms, illness-perception
319 questionnaire, treatment appraisal questionnaire, depression, anxiety, fear-avoidance
320 beliefs, heart-rate variability, heat pain threshold and tolerance.

321 **Interventions and Duration**

322 One hundred adult male and female participants with chronic, non-radiating low back
323 pain (CLBP) will be randomly assigned to receiving either verum (VA) or
324 sham/placebo (PA) electroacupuncture treatment with equal probability. The
325 treatments will be delivered by 7 senior acupuncturists at 7 treatment centers in the
326 San Francisco Bay Area, within 60 miles from Stanford Hospital and Clinics. Each
327 treatment will be around 45 minutes long, delivered twice per week, for a total of 12
328 sessions.

329 Participants will be assessed at screening, pre-treatment baseline visits, post-treatment
330 visits, and at 3, 6, and 12 month follow-ups. Additionally, during the active treatment
331 period, participants will be assessed daily for pain, sleep and function, twice per week
332 at treatment, and weekly for treatment side effects.

333 **Sample Size and Population**

334 This project will recruit men and women with axial chronic lower back pain (greater
335 than 3 months) and no radicular symptoms. Participants must be within the age range
336 of 21 to 65. A total of 100 participants will be enrolled in the project.

337 1. STUDY OBJECTIVES

338 1.1 Primary Objective

339 *Aim 1. Explore the predictive relationship and the association between **ascending***
340 ***sensitization** measures and clinical response to acupuncture.*

341 *Hypothesis 1: augmented temporal summation (TS), and more wide-spread pain*
342 *(WSP) (quantified by number of painful areas marked by the participant on a*
343 *standardized body map) will be associated with greater pain reduction in the verum*
344 *arm than in the placebo arm; decreased pressure pain threshold (PPT_r) will be*
345 *associated with greater pain reduction in the placebo arm than the verum arm.*

346 *Aim 2. Explore the predictive relationship and the association between **descending***
347 ***modulatory** measures and clinical response to acupuncture.*

348 *Hypothesis 2: decreased conditioned pain modulation (CPM), and more favorable*
349 *psychological state, measured by less pain catastrophizing, better self-efficacy in*
350 *copng and in pain management, will be associated with greater pain reduction in the*
351 *verum than the placebo arm; expectation of positive treatment outcome will be*
352 *associated with pain reduction in both the verum and the placebo arm.*

353 *Aim 3. **Exploratory model building** to predict pain reduction by electroacupuncture.*

354 *Hypothesis 3. A mathematical model relating key baseline characteristics to percent*
355 *pain reduction will be developed using advanced techniques, and this model will be*
356 *tested using cross-validation within the proposed pilot.*

357 1.2 Secondary Objectives

358 **1. Alternative outcome measures:** pain intensity measured by an 11-point NRS;
359 physical functioning, measured by the PROMIS physical functioning scale will be
360 assessed before and after the intervention, and the immediate percent change in
361 physical functioning measured by the Roland Morris Disability Questionnaire, will be
362 used as a secondary outcome. Furthermore, long-term relief, measured in both pain
363 and physical functioning will be used as additional outcome measures in the analyses
364 performed in Aims 1, 2 and 3.

365 **2. Exploring objective markers:** heart rate variability is sometimes associated with
366 wellness. For example, increased variability in the low frequency spectrum is
367 considered a measure of robust parasympathetic system and good health.¹ A few
368 small studies has shown effects of acupuncture on improving heart-rate variability.²⁻⁴
369 HRV will be captured prior to and immediately after the interventions.

370 **3. Characterizing response to acupuncture at high resolution:** the daily symptom
371 capture tool included in this project will allow characterization of clinical response
372 (pain and symptom improvement) at a higher granular level than previously possible,
373 to the best of our knowledge.

376 2. BACKGROUND AND RATIONALE

377 2.1 Background on Condition, Disease, or Other Primary Study Focus

378 100 million Americans suffer from chronic pain.⁶ Conventional treatments are often
379 inadequate.⁶ Acupuncture reduces pain better than conventional care (ie medications,
380 physician and physiotherapy visits) for several pain conditions.⁷ However, not all
381 patients respond to acupuncture,⁸ and it often takes multiple sessions to determine if

382 acupuncture is effective. Thus, there is a great need in capturing and understanding
383 factors that may predict clinical response to acupuncture analgesia.

384 The characteristics that differentiate responders from non-responders to acupuncture
385 analgesia remain elusive. Although acupuncture studies have evaluated patient
386 demographics, comorbidities, and expectations, most of these turned out to be
387 insignificant predictors,⁹⁻¹⁴ except for expectation which yielded mixed results.^{10,15,16}

388 Researchers have rarely explored predictive factors that are unique to chronic pain.
389 Pain is influenced by the integration of both ascending nociceptive signals and
390 descending cognitive-emotional modulation at key relay centers.^{17,18} In chronic pain,
391 the ascending transmission of pain is often augmented, which may be considered as
392 ascending sensitization.¹⁹ In contrast, descending inhibition of pain is often reduced.²⁰
393 Standardized quantitative sensory testing (QST) can measure changes in both the
394 ascending and descending pain pathways,²¹ whereas psychological processes mainly
395 contribute to the descending regulation of pain.²² Although both QST and
396 psychological assessments are common diagnostics in pain research, they have not
397 been systematically examined in the context of predicting acupuncture analgesia.

398 Taking advantage of the latest studies in personalizing pain medicine where select
399 QST and relevant psychological measures were found to be potential predictors of
400 long term outcome in chronic low back pain (see section 2.2 below), we will explore
401 the associations between these factors, and the outcomes to electroacupuncture in
402 treating back pain patients.

403 2.2 Study Rationale

404 1. Pressure Pain Threshold Predicted Pain Reduction by Sham Acupuncture in 405 Patients with Fibromyalgia (Harte et al 2013 Medical acupuncture).²³

406 Rationale: to determine if experimental pressure pain assessment and chemical
407 neuroimaging can identify differential responsiveness to sham vs traditional
408 acupuncture

409 Study: Fifty patients with fibromyalgia were randomized to either 9 traditional (TA)
410 or sham (SA) acupuncture treatments over 4 weeks. Both participants and assessors
411 were blinded.

412 Results: Patients with low pain sensitivity (LPS), but not with high pain sensitivity
413 (HPS), had a significantly reduced clinical pain response to SA (change in mean
414 [standard deviation (SD)]: HPS - 8.65 [7.91]; LPS - 2.14 [6.68]; $p = 0.03$). This
415 relationship was not the case for TA (HPS - 6.90 [4.51]; LPS - 6.41 [9.25]; $p = 0.88$).
416 SA-treated patients who were more sensitive also had greater baseline levels of
417 insular Glx than patients who were less sensitive (Glx mean [SD]: HPS 11.3 [1.18];
418 LPS 10.2 [0.54]; $p = 0.04$).

419 Relevance: this study demonstrates the potential for pressure pain sensitivity, a
420 measure that will be captured in our study, in differentially predicting response to
421 sham vs verum acupuncture in patients with chronic pain.

422 2. Conditioned Pain Modulation Predicted Response to Duloxetine in Patients with 423 Diabetes Peripheral Neuropathy (Yarnitsky 2012 Pain).²⁴

424 Rationale: to determine if pain modulation patterns as assessed by temporal
425 summation (TS) and conditioned pain modulation (CPM) may predict clinical
426 response to Duloxetine, a serotonin-norepinephrine reuptake inhibitor

427 Study: Thirty patients with painful diabetic neuropathy received 1 week of placebo, 1
428 week of 30 mg/d duloxetine, and 4 weeks of 60 mg/d duloxetine. Pain modulation
429 was assessed psychophysically, both before and at the end of treatment. Patient
430 assessment of drug efficacy, assessed weekly, was the study's primary outcome.
431 Results: Baseline CPM was found to be correlated with duloxetine efficacy ($r=0.628$,
432 $P<.001$, efficient CPM is marked negative), such that less efficient CPM predicted
433 efficacious use of duloxetine. Regression analysis ($R^2=0.673$; $P=.012$) showed that
434 drug efficacy was predicted only by CPM ($P=.001$) and not by pretreatment pain
435 levels, neuropathy severity, depression level, or patient assessment of improvement
436 by placebo. Furthermore, beyond its predictive value, the treatment-induced
437 improvement in CPM was correlated with drug efficacy ($r=-0.411$, $P=.033$).
438 However, this improvement occurred only in patients with less efficient CPM
439 (16.8 ± 16.0 to -1.1 ± 15.5 , $P<.050$). No predictive role was found for TS.

440 Relevance: the coupling of CPM and duloxetine efficacy highlights the importance of
441 pain pathophysiology in clinical decision making. CPM and TS will also be examined
442 in the current study. We hypothesize that because electroacupuncture will influence
443 both descending pain modulation (measured by CPM) and ascending pain facilitation
444 (measured by TS), both measures will be predictive of pain reduction by acupuncture.

445

446 3. Degree of widespread pain was associated with clinical outcome to acupuncture:
447 An Observational Pilot.

448 Rationale: to determine if widespread pain at baseline may predict pain reduction by
449 acupuncture

450 Study: In collaboration with the NIH Pain Consortium, we recently began an open
451 source platform to capture real-world, patient-reported outcomes (PROs) at the
452 Stanford Pain Management Center. This platform includes an interactive BodyMap
453 for patient to indicate the locations of their pain. This BodyMap can be used as a
454 surrogate measure of widespread pain. The more areas marked off by a patient as
455 painful, the more widely spread is his/her pain. We define an acupuncture course as
456 consecutive sessions no more than two weeks apart. We used Fisher's exact test to
457 evaluate whether increase areas in BodyMap marked by the patient predicted clinical
458 response to acupuncture ($\geq 30\%$ pain reduction).

459 Results: Our system captured 34 patients with pain rating and BodyMap data within
460 30 days prior and 30 days following the acupuncture course. About 40% of the 34
461 patients responded by reporting at least 30% reduction of pre-acupuncture pain.
462 Importantly, we found a trend that widespread pain defined by ≥ 6 BodyMap areas
463 predicted pain reduction by acupuncture with an odds ratio of 3.4 (p-value 0.33 by
464 Fisher's exact test).

465 Relevance: the preliminary results in this pilot suggests the possibility that
466 widespread pain may potentially predict responsiveness to real-world acupuncture

467 treatments. Recognizing the low sample size at this stage, we will be pursuing similar
468 type of analysis in a larger sample size both in a real-world setting at our clinic to
469 improve patient care, and, in the current clinical trial to be initiated soon.

470 4. Multiple psychological factors are associated with long term outcome in back pain
471 patients receiving acupuncture (Bishop 2015, Clin J Pain).²⁵

472 Rationale: To identify psychological covariates of longitudinal changes in back-
473 related disability in patients undergoing acupuncture.

474 Study: A longitudinal postal questionnaire study was conducted with data collection
475 at baseline (pretreatment), 2 weeks, 3, and 6 months later. A total of 485 patients
476 were recruited from 83 acupuncturists before commencing acupuncture for back pain.
477 Questionnaires measured variables from 4 theories (fear-avoidance model, common-
478 sense model, expectancy theory, social-cognitive theory), clinical and
479 sociodemographic characteristics, and disability. Longitudinal multilevel models
480 were constructed with disability over time as the outcome.

481 Results: Within individuals, reductions in disability (compared with the person's
482 individual mean) were associated with reductions in: fear-avoidance beliefs about
483 physical activity ($\beta=0.11$, $P<0.01$) and work ($\beta=0.03$, $P<0.05$), catastrophizing
484 ($\beta=0.28$, $P<0.05$), consequences ($\beta=0.28$, $P<0.01$), concerns ($\beta=0.17$, $P<0.05$),
485 emotions ($\beta=0.16$, $P<0.05$), and pain identity ($\beta=0.43$, $P<0.01$). Within-person
486 reductions in disability were associated with increases in: personal control ($\beta=-0.17$,
487 $P<0.01$), comprehension ($\beta=-0.11$, $P<0.05$) and self-efficacy for coping ($\beta=-0.04$,
488 $P<0.01$). Between individuals, people who were less disabled had weaker fear-
489 avoidance beliefs about physical activity ($\beta=0.12$, $P<0.01$), had more self-efficacy for
490 coping ($\beta=-0.07$, $P<0.01$), perceived less severe consequences of back pain ($\beta=0.87$,
491 $P<0.01$), had more positive outcome expectancies ($\beta=-0.30$, $P<0.05$), and appraised
492 acupuncture appointments as less convenient ($\beta=0.92$, $P<0.05$).

493 Relevance: this study demonstrated the importance of psychological factors and
494 beliefs in influencing the long term outcomes in patients with chronic back pain who
495 also received acupuncture. Note this is an uncontrolled association study. Our current
496 study will re-examine the key predictors uncovered in this paper in a controlled,
497 blinded trial.

498 3. STUDY DESIGN

499 This is a randomized placebo-controlled trial in which 100 consented adults with
500 chronic low back pain (CLBP) will be randomized to 6 weeks of twice a week
501 sessions with verum acupuncture (VA) or sham/placebo-acupuncture (PA).
502 Participants and researchers will be blind to treatment assignment. Treatment
503 providers will not (and cannot) be masked to treatment assignment.

504 Timeline: Eligible participants will be invited for a baseline visit. Since the focus of
505 this study is prediction, extensive collection of baseline characteristics, including
506 physical (vital signs and heart rate variability, physical exam), psychological
507 (questionnaires), and QST measures will be collected around and at the time of the
508 baseline visit. Approximately 1 week after the baseline visit, the participant will enter

509 a 6-week treatment phase, during which they will be randomized to VA or PA. (See
510 Section 4.3.2. for details of randomization). The Post-Treatment Visit will take place
511 1 to 2 weeks after the last treatment visit. Participants will then be followed up and
512 assessed at 3, 6 and 12 months after treatment ends. Thus, participants will be in the
513 project for a total of approximately 12 months.

514 Location: The treatments will be provided at 7 sites: our laboratory (SNAPL) where
515 our main acupuncturist (Camille Langlois Loveman) will be providing services to
516 patients located on and near the Peninsula; as well as 6 other acupuncture clinics
517 located in the greater San Francisco Bay Area (SF, South and East Bay). The baseline
518 and post-treatment visit will take place at our laboratory, SNAPL (Systems
519 Neuroscience and Pain Laboratory) at the Stanford Division of Pain.

520 Interventions: The interventions, verum (electro) acupuncture (VA) and sham/placebo
521 ('electro') acupuncture (PA), are described in detailed in Section 5 (Project
522 Interventions). Interventions will be provided at no charge to participants.

523 Primary outcomes: a) Change in Pain Intensity measured by the PROMIS Pain
524 Intensity Instrument administered at the pre-treatment and post-treatment visit. . b) a
525 responder is defined as one who experiences $\geq 10\%$ reduction in the T-score (1
526 standard deviation) of the full instrument, or ≥ 1 point decrease in the 5-point Likert
527 Scale of the mean pain intensity question in the PROMIS Pain Intensity Instrument.

528 Secondary outcomes: Pain ratings from an 11-point numerical rating scale (NRS),
529 functional capacity measured by the Roland Morris Disability Questionnaire and the
530 physical function instrument from NIH PROMIS.

531 4. SELECTION AND ENROLLMENT OF PARTICIPANTS

532 *A total of 100 participants, age 21-65, with chronic axial low back pain for at least 6 months,*
533 *will be enrolled.*

534 4.1 Inclusion Criteria

535 Participants must meet all of the following inclusion criteria in order to be enrolled in the project.

- 536 • Males and females, ages 21-65
- 537 • English fluency
- 538 • Have had chronic low back pain for at least 6 months:

539 Definition of Chronic Low Back Pain (CLBP)—criteria from the NIH Task Force for CLBP

- 540 ○ Chronicity: CLBP “defined as a back pain problem that has persisted at least 3 months
541 and has resulted in pain on at least half the days in the past 6 months.”
- 542 ○ Location: “between the lower posterior margin of the rib cage and the horizontal gluteal
543 fold.”
- 544 • Average pain over the last month $\geq 4/10$ for initial eligibility

545 4.2 Exclusion Criteria

546 All candidates meeting any of the exclusion criteria at screening will be excluded from the project.

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- Radicular low back pain: defined as sharp (or burning) pain, with a defined territory, radiating down the limb, beyond the knee. Diagnosing radicular pain in the absence of an electromyogram (EMG) or MRI is a challenging problem, because referred pain from axial structures (such as the ligamentum flavum and lumbar facets) may involve the legs or even the feet, thus mimicking radicular pain. In order to accurately identify radicular pain while minimizing false positives, we use the following criteria: 1-the participant must report frequent symptoms of spontaneous radicular pain as defined above (at least once a week) accounting for at least 30% of his/her total pain complaint; AND, 2- the participant must demonstrate a positive response to a dorsiflexion test during the screening physical exam. A dorsiflexion test is a clinical exam performed in the supine position. While keeping one leg flat, the experimenter raises the other leg of the participant (with a straight knee) to near the flexibility limit, at which point the experimenter dorsiflexes the foot of the participant’s raised leg. This test is deemed positive if the participant reports true radicular pain (sharp, well-demarcated, shooting pain that travels beyond the knee) upon dorsiflexion. Given the challenging nature of this exam, we have provided extensive training of our RC’s via clinical papers, videos and multiple practice sessions. In addition, we allow the RC’s to consult the PI (MD) if ambiguities arise from the history and the physical exam. Ultimately, for ambiguous cases, the PI will make a final decision on the presence of radicular pain/symptoms based on clinical judgment.
 - Pending litigation or Worker’s compensation related to the low back pain.
 - Currently pregnant or planning to become pregnant
 - American Society of Anesthesiologist (ASA) class III or above physical status. ASA class III is defined as “a patient with severe systemic disease.” Examples would include poorly controlled diabetes, hypertension, COPD or morbid obesity (BMI ≥ 40).
 - Mental health conditions or treatment for mental health problems that would interfere with study procedures, at the discretion of the study team. For example, psychosis, untreated major depression, ongoing substance abuse, suicidal ideation. These will be assessed by the PH-9.
 - Medications: opioids ≥60mg morphine equivalent units/day, benzodiazapenes, corticosteroids.
 - Prohibited interventions: during the study period, the following are not permitted
 - Back surgeries
 - Injections with local anesthetics or steroids to the back
 - New chiropractic maneuvers
 - New physical therapy programs
 - New medications for back pain
 - Bleeding disorders at the discretion of the study team.
 - Previous acupuncture treatment in the past 3 years.
 - Medical conditions that would interfere with study procedures (eg. Heart disease or pacemaker, active infection), per discretion of the team

584 **4.3 Study Enrollment Procedures**

585 **4.3.1 Recruitment**

586 **Stanford Pain Clinic:** About 50% patients at the Stanford Pain Center who are referred to
587 acupuncture were denied by their insurance to receive this service. The clinic admin (M. Preciado)
588 will provide these patients information on the K23 study (she will have IRB approved study
589 brochures at the clinic to provide to patients upon request), and keep a list of the patient who
590 expressed interest and consented to be contacted by the research team. The research team will
591 access this list regularly (once every 1-4 weeks) and reach out to these patients.

592 **Stanford CAM Center for Back Pain (database sharing with NCCIH P01 trial):** The Stanford CAM
593 back pain center has a large database of patients with back pain. Because the P01 trial is a
594 mechanistic study and has stringent inclusion criteria, the majority of the individuals from the P01
595 database are ineligible for P01 because of comorbid medical conditions, medication use, or MRI
596 contra-indications. Our research team has access to a log on the eligibility details of patients on this
597 data base and will be able to rapidly screen these patients for the K23 study, which has much less
598 stringent inclusion criteria than the P01 study.

599 **Clinicaltrials.gov posting:** The research team will register the K23 study on both the Stanford Clinical
600 Trial site and clinicaltrials.gov. Interested patients may contact the team at the contact information
601 provided.

602 **Craigslist ads:** Monthly Craigslist ads will be placed to advertise for the project. These ads will
603 include basic details about the project and contact information for the project Recruiter.

604 **Flyers, recruitment cards, and brochures in the community:** We will be distributing project flyers,
605 recruitment cards, and brochures throughout the community at locations such as cafes, restaurants,
606 yoga studios, gyms, YMCAs, libraries, et cetera.

607 **Community clinics:** The PI (JT Kong) will send emails to colleagues in the community pain clinics as
608 well in the primary care colleagues in the Peninsula and SF Bay area to solicit appropriate patients
609 for the study.

610 **Online Screening Form (OSF):** Interested participants from all of the above sources will be directed
611 to a secure, online screening form that gathers basic contact info and back pain info. The research
612 team will manually review entries from this REDCAP form on a minimally weekly basis, and contact
613 those who are eligible from this online form.

614 **Phone Screening and Screening Logs**

615 Participants who have passed the OSF will be screened over the phone to further determine
616 eligibility by the research coordinator (RC). A record of all phone screens will be kept in the
617 Screening Log including phone screen result, reason for ineligibility, and reason of lack of interest by
618 the participant. All phone screens conducted will also be entered into the SNAPL Central Database,
619 from which it will be possible to retrieve this data to assess why callers are ineligible.

620 **Eligible and Interested Participants**

621 Eligible and interested participants will be invited to our site for a Screening Visit. At this visit, if
622 participants are eligible, they will be consented for the entire study. They will be explained the
623 details of the study objectives, interventions as well as all necessary assessments.

624 After the initial screening visit, the participant will be asked to fill out brief daily questionnaires on
625 their back pain symptoms for 1-2 weeks before they come in for a baseline visit which will take place
626 immediately before initiation of treatments. Between the screening visit and the baseline visit, if
627 participants indicate that they have developed an illness, have travel plans or may not complete the
628 baseline and treatment visits as outlined, their participation will be put on hold and they will be
629 invited to participate in the study again after the resolution of the issues.

630 Rescreening window: in addition to participant side issues, our acupuncturists sometimes
631 experience full capacity from another study (P01, AT006651). As such, participants may need to wait
632 for up to 6-10 weeks before slots open up. To accommodate such waiting time, we've expanded our
633 rescreening window (defined as time between the screening and the pre-treatment visit), from 1
634 month to 3 months, with the following policy to ensure that the participant remains eligible after
635 waiting:

- 636 1. Participant returns within 1 month after the initial screening visit: no additional testing needed
637 at the pre-treatment visit.
 - 638 2. Participant returns between 1 to 3 months after the screening visit: At the beginning of the pre-
639 treatment visit, confirm eligibility by repeating question on mean-pain over the last 30 days, and
640 re-check medication list. If new or increased dose in pain meds, repeat inclusion/exclusion CRF
641 (by the RC) and physical exam. If new or increase dose in psychiatric meds, repeat PH-9
642 questionnaire.
 - 643 3. Participant returns between 3 to 6 months after the screening visit: At the beginning of the pre-
644 treatment visit, confirm eligibility by repeating mean-pain over 30 days and PH-9 questionnaires
645 (by participant), repeat medication and inclusion/exclusion CRF (by RC), repeat physical exam.
 - 646 4. Participant returns more than 6 months after the screening visit: repeat the entire screening
647 visit. Proceed to pre-treatment visit per protocol (ie 1-2 weeks later, and ONLY IF participant
648 passes the repeat screening visit).
- 649

650 **Participants not Interested or Ineligible**

651 Participants who are not interested or ineligible will be asked if they want their information to be
652 included in the SNAPL Central Database so that they may be contacted for future projects that are of
653 interest to them.

654 **Database Registration**

655 The Research Staff will register all consented participants into the SNAPL Central Database with their
656 unique project ID number and demographic information.

657 **Recruitment Contingency Plan**

658 We have a recruitment plan in place to ensure steady enrollment. This includes recurring
659 advertisements on Craigslist, local newspapers, direct mailers, and a presence on the social media

660 (the research team will consider a Youtube video). The research team will be contacting community
661 clinics, primary care physicians, free clinics, yoga studios, gymnasiums, and other such facilities to
662 give talks on the Center for community outreach and to educate and build relationships with
663 practitioners who can refer participants to us.

664 4.3.2 Randomization

665 When a new participant has passed the initial screening and baseline visit, he/she will be randomized to
666 receiving either VA or PA with equal chance. An R program for randomization will be used. We will
667 randomize patients within each of the 7 acupuncture sites with equal chance of receiving either VA or
668 PA. Our lab manager or his associates (who are NOT immediately related to the proposed project) will
669 run the randomization program and inform the treatment assignments to each provider via secure
670 emails. Note that the participant will be able to pick the acupuncturist based on ease of access
671 (commute time). Lastly, block randomization will be employed within each of the 7 acupuncturists to
672 minimize chance imbalance in the number of verum vs sham assignments for each provider in case
673 there is a large difference in the number of patients assigned to a provider (we observed this situation in
674 the current P01 trial).

675 4.3.3 Consent

676 **Consent Process:** Prior to conducting any study procedures, designated and trained research staff will
677 review the IRB-approved Consent and HIPAA forms with the participant in a private area, answer any
678 questions, witness informed consent and the date obtained, and verify by signing as the research team
679 member that obtained consent. Each participant will receive a signed and dated copy of their Consent
680 Form and HIPAA documents.

681 The consenting process will take place at the screening visit. At the beginning of the screening visit, the
682 participant will be consented for the research project. The consent process will include explanation of
683 the details of the study, including interventions, visits, assessments as well as the timeline.
684 Furthermore, participants will also learn about our HIPAA compliant information collection procedures
685 and sign the HIPAA form. Research staff will answer all project-related questions and make sure that
686 the participant fully understands all procedures, tests, and visits for the project. Participants will be
687 given all the time necessary to comprehend the research project and procedures and all of their
688 questions will be answered prior to them signing and dating the consent and HIPAA form. They will also
689 be given the opportunity to receive a signed copy of their consent forms.

690

691 **Storage of Consent Forms:** Consent and HIPAA forms will be stored in a dated binder labeled "PHI and
692 Consent Forms for Acupuncture Predictor Study". The binder(s) will be stored in locked cabinets in Dr.
693 Kong's lab at 1070 Arastradero Road, Suite 200, Palo Alto, CA 94304. Only research staff will have access
694 to study documents. Each consent form will be labeled in the bottom left corner with subject ID
695 number.

696 5. STUDY INTERVENTIONS

697 5.1 Interventions, Administration, and Duration

698 5.1.1 General Concerns

699 **Verum acupuncture (VA):** to be administered by private licensed acupuncturists in their respective
700 private offices. Each acupuncturist has over 3 years of practice experience. The treatment sessions will
701 be around 45 minutes long out of which 20-25 minutes will involve active electrical stimulation of the
702 needles. Within each session, in addition to body acupuncture, each participant will also receive
703 standardized heat and auricular acupuncture therapy. The treatments will be delivered twice a week for
704 6 weeks, making a total of 12 treatments. We allow up to 3 missed sessions total (25%), two of which
705 may be consecutive.

706 **Sham/placebo acupuncture (PA):** will also be administered by the same acupuncturists who deliver the
707 verum acupuncture. PA treatments will follow the same exact time course as the VA treatments (around
708 45 min per session with 20-25 min under sham stimulation, 2 sessions per week for 6 weeks) and subject
709 to the same rules for missing sessions. As with VA, participants assigned to the PA arm will also receive
710 heat and auricular acupuncture therapy (both simulated, see detail in section 5.1.3) in each treatment
711 session. Table 1 below summarizes the key parameters of each treatment. We designed these protocols
712 to balance between increasing credibility of the PA and optimizing the therapeutic effect of the VA.

713 Table 1 Contrasting the Key Elements of the VA and PA Treatment Protocols

TREATMENT PARAMETER	VERUM (SUN) ARM	PLACEBO (MOON) ARM
Number of sessions	12	12
Frequency of sessions	2 / week	2 / week
Session Duration	45min	45min
Number of needles used	20	8
Flexibility of point selection	Yes. (Section 5.1.2.B) Based on anatomy (at baseline) and response (after 4 sessions);	Not flexible (Section 5.1.3.B)
% of points penetrated	100%	0% (all non-specific)
% of points hooked to wires	50% (all intact electrical wires)	100% (all broken wires for shamming)
Titration of the intensity of electrical stimulation	Real (see Section 5.1.2.C)	Simulated (see Section 5.1.3.C)

Heat Therapy	Standardized, to back, 30-40min	Standardized, away from back, 10-15min
Auricular acupuncture	4, fixed, pain specific points, with penetrating needles	2, fixed, pain NON-specific points, with non-penetrating tapes
Communication between acupuncturist and participant	Minimized and standardized	Minimized and standardized
Moxibustion	No	No
Music	No	No
Massage	No	No
Aromatherapy	No	No

714

715 5.1.2 Details of VA Administration

716 **A. Rationale and Treatment Modules**

717 The VA treatment protocol aims to treat low back pain with both local (anatomy driven) and distal
718 (energetic, meridian driven) approaches. It has two principal modules (1 local, 1 distal) and two optional
719 modules (also 1 local, 1 distal).

720 The principal modules consist of Module #1 and #2, as shown below in Figure 5 and Figure 6,
721 respectively. Both are activated in ALL treatment sessions. Module #1 represents the local approach. It is
722 a modified PENS (percutaneous electrical nerve stimulation), where key Bladder back Shu points in the
723 affected dermatomes are needled and electrically stimulated (see “Ghonomie EA, Craig WF, White PF, et
724 al. *JAMA* 1999; 281(9): 818-23” for details of the original protocol).²⁶ Module #2, the distal approach,
725 aims to tonify Shaoyin-Taiyang meridians by needling the following points: KI-3, KI-7, HR-3, SI-3, BL-40.
726 Out of these, KI-3 (negative) and KI-7 (positive) are electrically stimulated as a pair. Two additional
727 points, GV-3 and GV-20 will be needled to tonify Governor’s Vessel meridian.

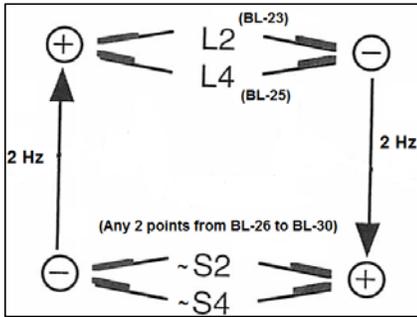


Figure 5 - Module 1: Modified PENS (obligatory)

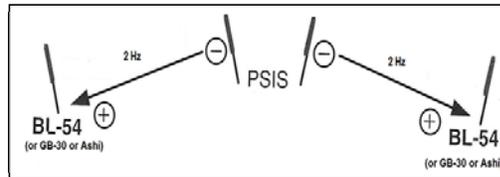


Figure 6 - Module 3: Periosteal (optional)

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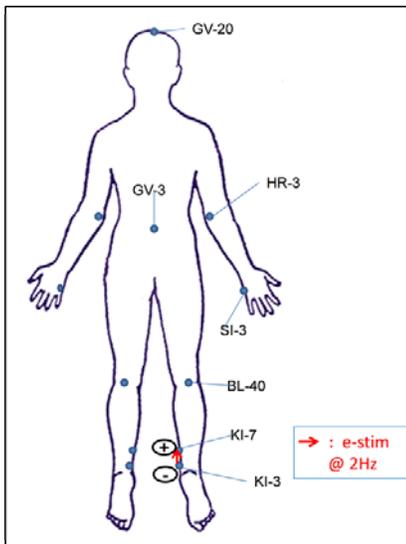


Figure 7 - Module 2: Principle Meridians (Obligatory)

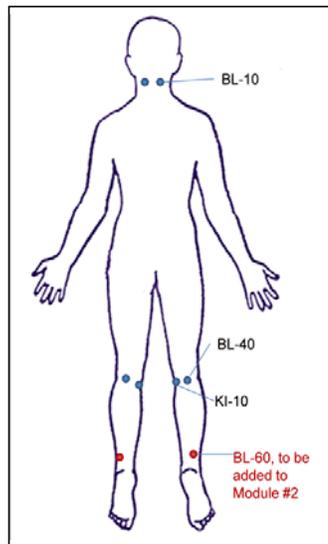


Figure 8 - Module 4: Distinct Meridian Activation (optional)

729 The optional modules are #3 (local) and #4 (distal). First, at baseline, if the back pain radiates to the
 730 buttocks and hips, we will activate module #3, the periosteal protocol for all session. It involves needling
 731 and paired stimulation of the posterior superior iliac spine (PSIS) and a deep muscular point in the
 732 affected gluteal region.¹⁹ The posterior superior iliac spine is identified by palpating the posterior
 733 termination of the iliac crest (Figure 9). Second, if, after four treatments, the participant does not
 734 respond (see Section B below for criteria of clinical response), the kidney-bladder distinct meridian
 735 (module #4) will be activated for sessions 5-16. Distinct meridians are often needed to activate deep
 736 meridian energy in treating refractory conditions. The kidney-bladder distinct meridian consists of
 737 bilateral KI-10, BL-10, and BL-40 (which is activated in the principle treatment). Since BL-40 will be taken

738 out from Module #2 to complete Module #4, BL-60 will be added to complete Module #2. The activation
739 of Module #4 does not involve electrical stimulation.

740 Last but not least, in addition to the above main building blocks, the VA protocol also includes 2
741 standardized elements in each treatment session: heat and auricular acupuncture. We made the
742 decision to include standardize heat and auricular therapies to both mimic real-life practice of



Figure 9 - Surface and bony landmarks of the posterior superior iliac spine (PSIS)

743 acupuncture and optimize the treatment effects.

744 **B. Treatment flexibility and decision algorithms**

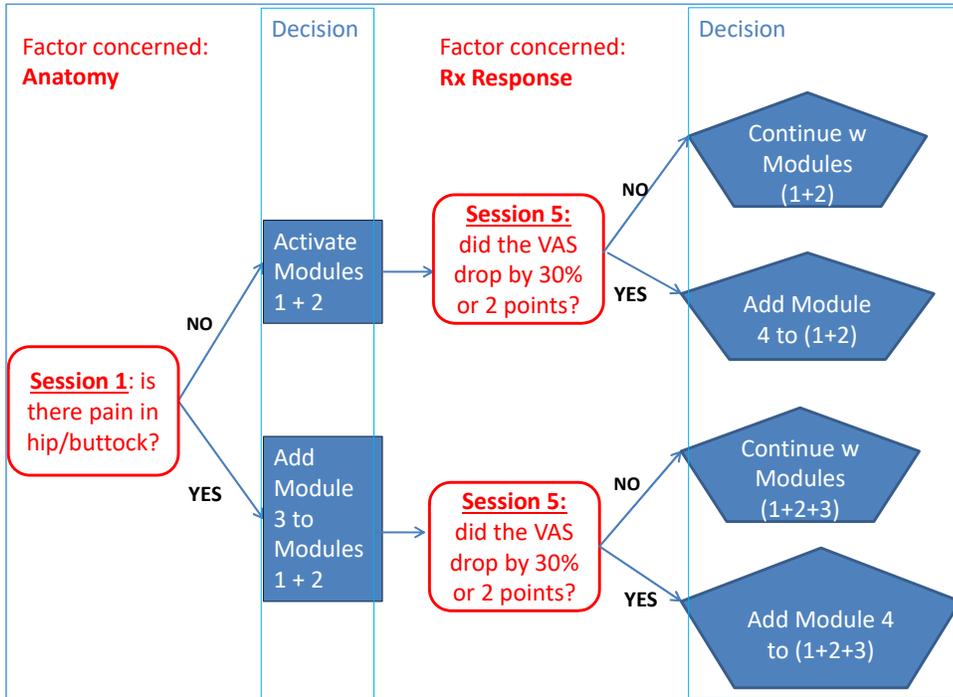
745 **Flexibility in VA**

746 We will allow very little flexibility in the treatment for the proposed clinical trial because of three
747 reasons. First, in contrast to many other clinical trials, our primary interest is in the mechanism of
748 electroacupuncture (EA). As such, the more unified the treatment approach, the easier it will be to identify
749 a common mechanism underlying electroacupuncture. Second, Helm's approach to EA allows very little
750 variation because: 1) the modified PENS uses a standard protocol; 2) the protocol assumes most
751 CHRONIC low back pain is due to a combination of blockage of Qi in the bladder meridian and vacuity in
752 the Kidney organ, further limiting the TCM choice points. Third, previous studies have shown, at least in
753 the case of low back pain, the choice of points may not matter as long as local and distal points from the
754 bladder and kidney meridians are stimulated.²⁰

755 **Decision algorithms**

756 Although minimal flexibility is permitted, there are still TWO specific times during the treatment period
757 that the acupuncturist will make a decision regarding WHICH TREATMENT MODULES to activate for
758 subsequent sessions (Figure 10). Modules #1 and #2 will be activated in ALL treatment sessions. On
759 session 1, depending on whether or not the pain radiates to buttocks and hips, Module #3 may be
760 activated. On session #5, we will assess if the participant has responded clinically to the first four
761 treatments. A response is defined as either $\geq 30\%$ reduction of original pain rating or > 2 out of 10 points
762 on the visual analog scale (VAS) of pain. If there is a response, the previous regimen will be continued. If
763 not, we will activate Module #4 for the remainder of the treatment sessions (sessions 5 to 16).

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Figure 10. Decision algorithms within the VA protocol (made by acupuncturist). Module 1 = modified PENS (local); Module 2 = KD-BL meridian tonification (distal); Module 3 = periosteal (local); Module 4 = distinct meridian (distal). In addition to these main treatment modules, standardized heat and auricular therapy are applied at the beginning of all verum sessions.

Finally, we do not expect the treatment algorithm above to unblind the participants in the verum arm because: A) At the initial evaluation with the acupuncturist, all participants will be informed that they will receive treatments which may or may not vary from time to time depending on their specific conditions; B) BOTH VA and PA participants will be filling out STANDARDIZED questionnaires assessing their treatment response as part of the trial data collection; C) The additional module (module 4) is based on TCM principles, and does NOT involve electrical stimulation NOR additional points in the back. As such, unless the patients are well-versed in TCM, these 3 additional points should NOT draw extra attention from the participants leading to unblinding; D) On the other hand, the PA patients will be subject to the same rigorous evaluations, rituals, except they won't have the extra mystery points. Again, unless the patient is well versed in TCM theory and practice, the chance of unblinding the PA folks should be also minimal.

C. Stimulation parameters

Frequency

784 Ghoname et al showed previously that even though low frequency (2-4 Hz) for the PENS stimulation was
785 sufficient to produce clinically significant pain relief,{Ghoname, 1999 #36} an alternating frequency of
786 15/30Hz produced even better results.{Helms, 1995 #37} On the other hand, stimulation of distal points
787 (KI-3 and KI-7) has been traditionally carried out at lower frequencies (2Hz) to maximize
788 tonification{Chen, 1992 #38} and to induce increase in CNS endorphin level.{Han, 2004 #39;Thomas,
789 1994 #40} Given this is a mechanistic protocol, the fewer variables we include the easier it would be to
790 identify a mechanism. As such, we will use **2Hz for ALL stimulated pairs.**

791 **Intensity**

792 Several lines of evidence contributed to our decision to titrate the intensity of stimulation to “**visible**
793 **muscular twitching at a level that the participant can comfortably tolerate.**” First, the studies by
794 Thomus¹⁴ and Chu¹⁵ identified muscular twitching as a predictive factor of response to treatment.
795 Second, we ran a preliminary best practice survey on treating CLBP by EA in a select group of senior
796 teaching acupuncturists. Out of the 27 respondents, all mentioned they would titrate to the participant’s
797 comfort level and about half described objective confirmation of muscular twitching. Third, the Helms
798 method also calls for such combination of subject comfort and objective muscle twitching. If it is not
799 possible to achieve muscular twitching, we titrate to the maximum stimulation intensity that the
800 participant can comfortably tolerate for 25 minutes.

801 **Stimulator and needle specifications**

802 A direct current, square-wave electro-stimulator from Ito Co Ltd (Tokyo, Japan), model IC-1107+ will be
803 used. It has three bipolar channels, with frequencies ranging from 1Hz to 100Hz, and delivers squared
804 pulse waves with a width of 100 µsec. The maximum current output is 14mA +/- 20%.

805 For all points except for the deep muscular point in Module #3, all needles should be identical.
806 Specifically, these will be Spring Ten sterile needles from DBC™. They are 30mm long and 0.2mm in
807 diameter. Deqi sensation should be elicited for EVERY needle with or without electrical stimulation.

808 **C. Additional Therapies**

809 As indicated in Figure 10 above, each verum treatment is consisted of both individualized treatment
810 modules (major) and standardized heat and auricular therapy (minor). In real life practice,
811 acupuncturist often use simple adjuncts to augment their treatment effects. The Helm’s protocol calls
812 for the addition of both heat to low back and simple auricular needling which are applied at the
813 beginning and maintained throughout each treatment session. In order to mimic real life practice and
814 ensure maximum treatment effect, we opted to include these two modalities per the Helms protocol.

815 Heat: To ensure adequate heat is applied to the back for at least 30min, we will turn on the heat lamp as
816 soon as participant is positioned in the prone position, before any needle placement. We will keep the
817 heat about 30-40cm away from the skin to ensure close heating yet minimize chance of burning.

818 Auricular acupuncture: we will use 40G auricular needles to the follow points shown in Figure 11:
819 Shenmen, Point Zero, Thalamus, and lumbar spine. We will place ear needles immediately after the heat
820 lamp is on, before placing the first main needle, GV-20.

821

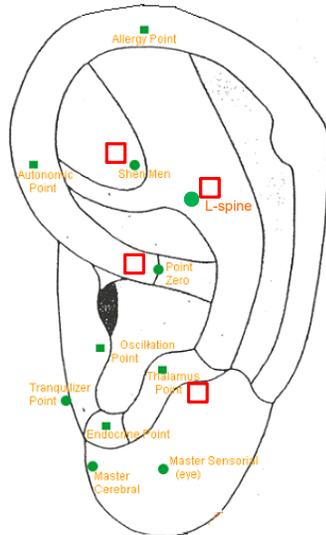


Figure 11 - Obligatory Auricular Points

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D. Order of tasks for each VA session

824 After the patient is placed in the prone position, the heat and auricular modules (minor) are activated,
825 the placement of the body needles should then start. The goal is to allow the PENS module (and the
826 periosteal module, if included) to be stimulated for 20-25 minutes and the principle meridian (KI 3 to KI-
827 7) to be stimulated for 15 minutes. Furthermore, GV-20 should be placed first (immediately after
828 auricular needles are placed) to help with sedation.

829 Therefore, the order of actions should be:

830 Prone positioning, heat application, placing auricular needles,

831 GV-20, PENS, periosteal, start e-stim for both PENS and periosteal,

832 Shaoying-Taiyang circuit +/- distinct meridian circuit (if included), finally start e-stim for KI-3 to
833 KI-7.

834 5.1.3 Details of PA Administration:

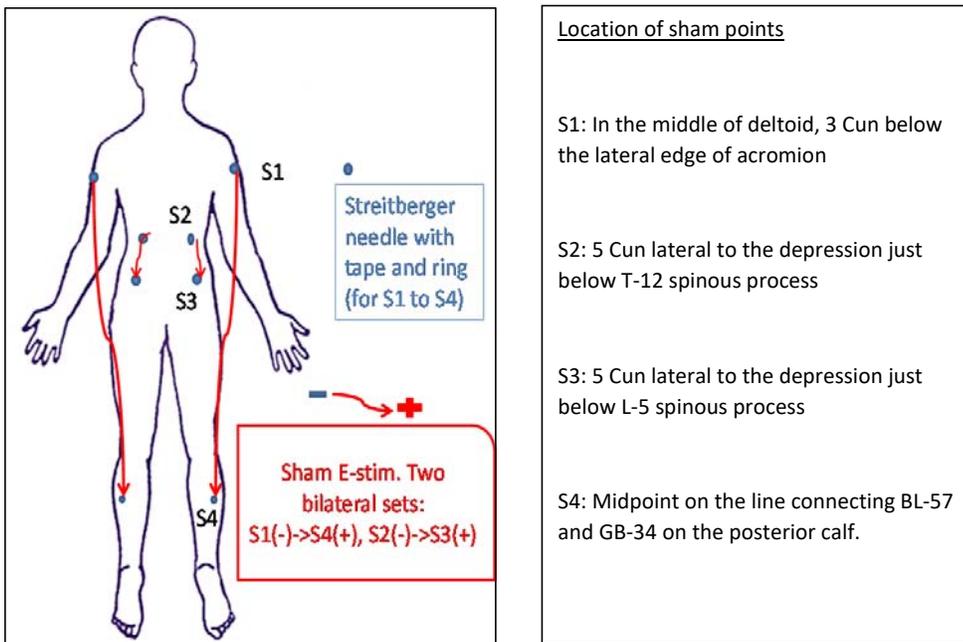
835 **A. Rationale for design and point selection**

836 In designing the sham treatment (PA), we balanced 2 objectives: a) to maximize credibility of PA; and b)
837 to simultaneously minimize possible specific therapeutic effect from tactile stimulation of relevant areas
838 on the body. To achieve the first objective, we used a generous number of needles (8 Streitberger
839 needles), ensured the length and frequency of the treatment sessions in PA are equal to VA, and
840 followed the same rituals in PA as those in VA, including titration of the sham electrical stimulation and
841 the inclusion of heat and auricular therapy (both shammed in PA). To achieve the second objective, we
842 used non-penetrating, Streitberger needles only, applied no electricity to the Streitberger needles by

843 intentionally breaking the wires to the electrical stimulator, and ensured the sham points are off-
844 meridian and away from the focus of the patients' maximum pain.

845 As shown in Figure 12, the sham treatment consists of 8 sham points (bilateral S1 to S4) away from all
846 meridians onto which the Streitberger apparatus will stand. To ensure the credibility of our treatment,
847 we included both truncal (S2, S3) and extremity (S1, S4) sham points, all at least 2cm away from known
848 meridians. Furthermore, S2 and S3 are away from patient's indicated area of maximum pain and away
849 from the center of low back.

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Figure 12- Points Used in the PA Treatment

854 B. Treatment flexibility

855 The PA treatment should be identical for ALL participants assigned to the PA arm. There will be no
856 treatment flexibility for PA. We are not concerned that lack of treatment flexibility might unblind the
857 participant as acupuncturists in real life may use fixed points in multiple sessions after a thorough initial
858 evaluation.

859 C. Sham equipment and procedures to carry out sham stimulation

860 **Equipment:** Streitberger needles x 8, with plastic rings + tape to secure their secure placement over the
861 skin. ITO electro acupuncture stimulator x 2 (with intentionally broken wires). Sham needling is
862 achieved by placing non-penetrating Streitberger needles at bilateral S1-S4 sham points. Sham electrical

863 stimulation is achieved by connecting the Streitberger needles to respective leads on the ITO e-stim
864 machine, with intentionally broken wire, such that no electricity will go through.

865 **No Deqi:** During PA administration, the acupuncturist will not attempt Deqi or ask about Deqi while
866 inserting both the Streitberger and the verum needles. Directing the participant's attention to the lack
867 of Deqi on the Streitberger needles will increase the chance of unblinding. Furthermore, none of the
868 needles will be manipulated after insertion throughout the session.

869 Obviously, the participant may feel different sensations with the Streitberger vs the real needle at GB-
870 21. The different sensations will be pre-emptively addressed by informing the participant that different
871 types of needles (leading to different sensory experiences) will be used for each treatment.

872 **Fake electrical connections:** After all needles (sham and verum) are placed, the acupuncturist will
873 connect the sham needles to the fake wires. As shown in Figure 12, the set up will include two circuits
874 carried out by two Ito stimulators. The central circuit (S2, S3) will be connected first, then the peripheral
875 circuit (S1, S4).

876 Stimulator 1 (central circuit): bilateral S2 to S3 (connect negative lead to S2 on one side and positive lead
877 from the same pair to S3 on the same side, then do the same for the other side using the second pair of
878 leads from the same stimulator).

879 Stimulator 2 (peripheral circuit): bilateral S1 to S4 (connect negative lead to S1 on one side and positive
880 lead from the same pair to S4 on the same side, then do the same for the other side using the second
881 pair of leads from the same stimulator).

882 **Ritual of intensity titration:** Since the stimulator wires are broken, the participant will not feel ANY
883 stimulation. However, we ask the acupuncturist to still turn on the stimulator, adjust the frequency to
884 2Hz, and bring the intensity dial to 50%. Furthermore, the acupuncturist will carefully perform a mock
885 intensity titration to best mimic the verum scenario, with the following steps:

- 886 1) connect the needle handles to the wire leads,
- 887 2) inform the participant that the provider will be dialing up the intensity of stimulation,
- 888 3) dialing up the stimulator to 50% intensity,
- 889 4) inquire of the participant if he/she is comfortable and will be able tolerate the intervention
890 for 20-25 minutes.
- 891 5) If the participant questions the lack of sensation, the acupuncturist may reassure the
892 participant that for "this particular type of acupuncture," the stimulation may sometimes be
893 below detection threshold.

894 **D. Additional sham therapies**

895 To best mimic the verum rituals, we will also perform standardized sham heat therapy and sham
896 auricular acupuncture for each PA session.

897 For the sham heat, we use the same heat lamp, but at a different location (calves), shorter time (10min),
898 and lower intensity (≥ 1 foot distance). Also in contrast to verum heat which is turned on before needle
899 placement, in sham, we will turn on the heat as the LAST step in treatment (after needles are placed and
900 sham e-stim is titrated).

901 For sham auricular acupuncture, in order to minimize potential specific effects, we will NOT be using any
902 penetrating needles. Instead, we will be placing two tiny (3mm X 3mm) square tapes at locations
903 specified in Figure 13 below. Neither location is known to have any specific, therapeutic effects. There
904 will be no seeds buried under the tapes, which will be removed at the end of each treatment session.

905 **E. Order of procedures performed in each PA session**

906 The task list and order for a PA session is largely similar to that of a VA session, except for the heat lamp
907 is turned on AFTER all needles are placed in PA and that the protocols involved to place and secure the
908 Streitberger needles are slightly more involved than the verum needle. Furthermore, to re-iterate, in a
909 PA session, NO Deqi sensation will be attempted during all needle placement and no needle
910 manipulation is allowed once the needle is secured. The action orders are summarized below:

911 Place patient in prone position, place AURICULAR tapes at sham locations.

912 Place tape and ring on each of the bilateral sham BODY points (S1 to S2, S3, then S4), with
913 minimal palpation of the back. Position and secure Streitberger needles on all eight points.

914 Connect Streitberger needles to the electrical stimulators and start sham stimulation one
915 stimulator at a time.

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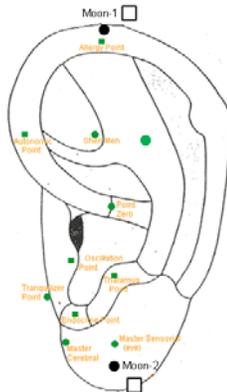


Figure 13 - Sham Auricular Points (Moon1 and Moon 2)

929

930 **5.2 Handling of Study Interventions**

931 **5.2.1 Intervention Accountability Records**

932 The acupuncture interventions will be accounted for in three ways. First, from a materials
933 perspective, about 20-30 needles will be used for each treatment depending which modules are
934 activated by the acupuncturist at the two decision juncture points. Therefore, progress can be
935 tracked by assessing the consumption of needles. Second, from a record-keeping standpoint, the

936 acupuncturist will record each point she/he needed, as well as level of stimulation by hand and by
937 electrical stimulator in details using a Case Report Form (CRF) which is to be submitted within the
938 same day the treatment is delivered. Third, all treatment sessions will be audio-recorded and the
939 research team will listen to between 1 to 3 randomly selected audio sessions from 20 randomly
940 selected participants.

941 5.2.2 Insurance of Blinding

942 This project will involve a parallel arm design including a placebo arm. Similar parallel design of
943 verum electrical and placebo acupuncture treatments were successfully carried out with minimal
944 unblinding by Wayne et al (Arch Phy Med Rehabil Vol 86, Dec 2005). With help from Dr. Rosa
945 Schnyer, a key consultant in the Wayne 2005 trial, we will use a PA design very similar to Wayne as
946 detailed below.

947 First, Streitberger needles, which are visibly similar to verum needles, will be used (stage-dagger
948 type of device). A thin 1cm diameter plastic ring, secured on skin by paper surgical tape will support
949 the needle and hold it in a perpendicular position.

950 Second, we will use a standardized script to guide communication between participants and
951 providers for both the verum and placebo arm.

952 Finally, the effectiveness of blinding will be assessed at the post-treatment assessment visit. We will
953 administer a questionnaire to the participants to ask if they believe they received the more effective
954 or the less effective treatment.

955 5.3 Concomitant Interventions

956 5.3.1 Allowed Interventions

957 Participants may continue their current medication/intervention regimen throughout the project if
958 there are no changes in dosage and the regimen does not include any medications listed in
959 “Prohibited interventions” below. Specific medications that are not exclusionary include:

- 960 • Antidepressants
- 961 • Antihypertensives
- 962 • Inhalers
- 963 • Ophthalmic drops
- 964 • Thyroid medications
- 965 • Opioids < 60mg morphine equivalent units/day

966 5.3.2 Required Interventions

967 N/A

968 5.3.3 Prohibited Interventions

- 969 • Benzodiazepines
- 970 • Opioid ≥ 60mg daily

- 971 • Oral or other systemic steroids
- 972 • None of the following interventions are allowed during the trial period
- 973 ○ Back surgeries
- 974 ○ Cortisone shots to the back
- 975 ○ New chiropractic care / maneuvers
- 976 ○ New physical therapy routines

977 5.4 Adherence Assessment

978 5.4.1 Protocol Adherence

979 Provider's adherence: Based on the geographic distribution of participant in our current P01 study,
980 we found that the majority of our participants are from within 20-mile radius of Palo Alto. The rest
981 are from South Bay (San Jose/Los Gatos), San Francisco and East Bay (Oakland/Berkeley). As such,
982 we decided to hire a main acupuncturist who will be spending two full working days at our facility to
983 provide treatments to the majority of our patients what live around Palo Alto. We hired one
984 acupuncturist from South Bay, SF and East Bay respectively to provide treatments to patients who
985 live far from Stanford/Palo Alto. The names and contact info of the acupuncturists are listed at the
986 beginning of this protocol. The following steps are taken to enhance fidelity of delivery of the
987 interventions.

988 **1. Providers' qualifications:** The acupuncturists are licensed and have been in practice for ≥ 3 years.
989 With help from American College of Traditional Chinese Medicine, we were able to advertise our
990 positions to a broad audience of experienced acupuncturists. The providers are competitively
991 selected based on their experience, education, interest and commitment to acupuncture research.

992 **2. Standardization of treatment protocol:** Our treatment protocols are standardized for both verum
993 and sham treatments. This will facilitate fidelity and decrease the likelihood of drift over time.
994 Please refer to Provider's Manual for details of the VA and PA treatment protocols.

995 3. Training of providers:

996 **a. Initial training:** each provider will receive 1.5-2 days of training prior to seeing any participant.
997 During day 1, the provider will meet with the PI and the study team, pick up supplies, learn about
998 the study and the rationale behind the treatment protocols, as well as observe and practice the VA
999 and SA protocol at least once. On day 2, the PI will visit the provider's clinic, observe the provider
1000 independently perform the VA, PA treatments and independently document the procedures. PI will
1001 then provide feedback and answer additional questions. We will schedule Day 2 of the training such
1002 that it is within 1-2 weeks of the first participant that the provider is assigned to treat.

1003 **b. Regular feedback and support meetings:** the PI will review the documentation and audio
1004 records of the providers' treatments from 20% of the participants (1-3 randomly selected sessions
1005 from 20 randomly selected participants) and provide feedback as issues arise. The feedback will be
1006 provided within 1 week of the issue. Additionally, given the challenges of performing clinical trial
1007 protocols, PI will hold optional meetings for providers to obtain general feedback and provide
1008 support.

1009 **4. Adherence monitoring:** As suggested by NCCIH, to monitor providers' adherence, we will audio-
1010 record ALL sessions from beginning to end. Two aspects of adherence will be monitored, adherence
1011 to the general guidelines on communication with participants and adherence with point selection
1012 and intensity of stimulation.

1013 a. Fidelity to communication guidelines will be monitored via review of audio-taped sessions. This
1014 review will be conducted by the PI and will allow for frequent corrective feedback, should issues
1015 with fidelity be detected. The schedule of tape review will be as follows: The initial four sessions
1016 from each provider will be reviewed immediately. Subsequently 20% of each acupuncturist's
1017 sessions will be reviewed every three months (using the Ceiling function).

1018 b. Fidelity to point selection and stimulation guidelines will be based on review of case report
1019 forms. These forms will be filled out by the acupuncturist at the end of each treatment session,
1020 electronically and securely, via REDCAP. The schedule of CRF review will be as follows: The CRFs
1021 from the initial four sessions of each provider will be reviewed immediately for accuracy,
1022 completion, and adherence. Subsequently CRFs from 20% of each acupuncturist's sessions will
1023 be reviewed every three months (using the Ceiling function). This review will also be conducted
1024 by the PI.

1025 **5.4.2 Daily Questions**

1026 One secondary objective of the study is to delineate the time to response to electroacupuncture.
1027 Though not able to obtain hourly ratings of pain after the treatment, we will be able to collect daily
1028 measures of average pain and physical function electronically via REDCAP. The patient will be
1029 reminded to fill out this very brief questionnaire (2 questions) daily via a text to their smart phone or
1030 an email if the patient does not have access to a smart phone. Additionally, we will collect
1031 information weekly via another brief questionnaire on the side effects from the study interventions
1032 as well as other treatments obtained by the patient for back pain. This weekly questionnaire will be
1033 administered in a similar fashion as the brief daily questionnaire.

1034 **5.4.3 Treatment Session Check-in Twice Per Week**

1035 Participant attendance at each acupuncture session will be recorded by the acupuncturist and
1036 monitored by the PI and the study team.

1037 **5.4.4 Measures to Promote Adherence**

1038 Measures to promote adherence to treatment protocols by acupuncturists are discussed in Section
1039 5.4.1 above.

1040 Ensuring participant understanding of project expectations

- 1041 • Knowledgeable and receptive staff: PI and lab managers will train research staff on
1042 appropriate languages for consenting as well as setting appropriate expectations for study
1043 participants.
- 1044 • Provide a Welcome Packet with project information and easily found contact information
1045 for project staff.

- 1046
- Develop a personal relationship with the participant
- 1047
- Continued outreach: After enrollment, PI will write letter to participant thanking him/her for their work/participation and outline/remind participant of study timeline. Birthday and holiday cards may also be sent to the participant periodically.
- 1048
- 1049

1050 **5.4.5 Specific Triggers and Stopping Rules**

1051 All analyses performed in this project will be intent-to-treat.

1052 If participants miss more than 3 treatment sessions, their participation will be considered
1053 incomplete. Out of the 3 missed sessions allowed, only two may be consecutive. All non-completers
1054 will have the opportunity to resume treatment even if their data is considered incomplete.

1055 Post-treatment data will be collected on non-completers identically as on the completers. In
1056 addition to ITT, we will also run a per-protocol analysis where the non-completers will not be
1057 included.

1058

1059 **6. STUDY PROCEDURES**

1060

1061 [6.1 Schedule of Evaluations \(see next page\)](#)

1062

Who Completes	Assessment	Screening Visit	Baseline Tracking	Pre-Tx Visit	Tx #1	Tx #2	Tx 3,4, 6-11	Tx #5	Tx #12	Post-Tx Visit	Follow up 3,6,12 mo
Participant	Informed Consent	X									
	Demographics	X									
	Pain Intensity (30 d) (NRS)	X									X
	Pain Intensity (7 d) (NRS) – to be added			X						X	
	BodyMap	X		X						X	X
	NIH Dataset	X									
	STartBACk Tool	X									
	Medical History	X									
	Medication List	X									
	Questionnaire Packet #1	X									
	Daily Symptom Tracking		X	X	X	X	X	X	X	X	X
	Weekly AE, BodyMap, Med tracking		X	X	X	X	X	X	X	X	X
	RMDQ				X						X
	PROMIS Packet				X						X
	Questionnaire Packet #2				X						X
	Expectation					X					
Vincent Credibility						X					
Blinding Assessment								X			
Acupuncturist	Acupuncturist Intake Form				X						
	Tx Record				X	X	X	X	X		
	Adverse Events				X	X	X	X	X		
	treatment appraisal questionnaire							X			
	Session 5 Form							X			
Research Team	PH-9	X									
	Incl/Excl CRF	X									
	IC CRF	X									
	Physical Exam	X									
	QST	X		X						X	
	Vitals/HRV	X		X						X	
	Screening Visit CRF	X									
	Pre-Tx Visit CRF			X							
	Enrollment	X									
	Randomization			X							
	Post-Tx Visit CRF									X	
	Completion CRF									X	
	Protocol deviation log									X	
Cumulative AE log									X		
Monthly QA CRF		Monthly on consents, all data entry, timing compliance / protocol deviations, AE's and audio tapes									

Comment [p1]: Please note that all weekly surveys are identical. We start administering them at the completion of the baseline visit and continue until the completion of the post-treatment visit. What is shown in this table represents a typical timeline. The total number of weekly questionnaires administered may vary due to the difference in the time lag between the assessment visits and the start and end of the treatment period.

1063

1064 Questionnaire Packet 1: Fear-avoidance behavior questionnaire (FABQ), coping skills questionnaire-revised (CSQ-
 1065 R), PTSD checklist-civilian, PTSD history questionnaire,

1066 Questionnaire packet 2: pain catastrophizing scale (PCS), illness perception questionnaire (IPQ), , caffeine intake
1067 questionnaire, pain self-efficacy questionnaire (P-SEQ)
1068 PROMIS packet (CAT version): **pain intensity**, pain interference, physical function, depression, anxiety, anger, sleep
1069 related impairment, sleep quality, fatigue.

1070 6.2 Description of Evaluations

1071 *Refer to Appendix A for schedule of events.*

1072 6.2.1 Screening Visit and Enrollment

1073 These evaluations occur to determine if the candidate is eligible for the project, and to collect initial
1074 assessments for the study after the participant is determined eligible and consented.

1075 *Pre- Screening*

1076 Initial eligibility will be assessed via an online platform with basic eligibility questions. Further eligibility
1077 will be assessed via a telephone screen based on the inclusion/exclusion criteria. Individuals who meet
1078 preliminary criteria will be scheduled for their Screening Visit.

1079 *The Screening Visit*

1080 The screening process may last 1-4 weeks from the time the participant is screened over the phone to
1081 the time of enrollment (ie screening visit) depending on the mutual availability of the participant and
1082 the research team. On this visit, informed consent will be obtained, followed by eligibility
1083 determination, enrollment, additional evaluations and scheduling of the subsequent, baseline visit.

1084 *Informed Consent*

1085 At the beginning of the screening visit, a member of the research team will consent the patient for the
1086 procedures of the study (evaluations, treatment, timeline, follow up, HIPAA) etc. For details on the
1087 consenting process, please refer to section 4.3.3. All participants will be provided with a Welcome
1088 Packet which may include: copies of their consent forms, brochures on the research project, study
1089 appointment information, a timeline of participation, and relevant contact numbers.

1090 *Assessing for Eligibility*

1091 After the informed consent is obtained, the eligibility assessment will include the following evaluations:

- 1092 • Mean Pain Intensity Over 30 days
- 1093 • Medical History questionnaire
- 1094 • Prior and Concomitant Medications
- 1095 • Demographics
- 1096 • Brief physical exam
- 1097 • PH-9 (patient health questionnaire)
- 1098 • Confirmation of meeting inclusion/exclusion criteria

1099

1100 *Eligibility Determination and Enrollment*

1101 *Eligibility determination:* The patient will undergo the evaluations above and the research team will
1102 check the patient's eligibility against an inclusion/exclusion checklist. Once the patient passes the
1103 checklist, he/she will be deemed eligible for the study and will be enrolled (see below). If the patient is

1104 not eligible, we will ask his/her permission to be included in the database so we can contact him/her for
1105 future studies which may be suitable.

1106 **Enrollment procedure:** Once the patient is deemed eligible, he/she will be enrolled for the project and
1107 assigned a project ID. The enrollment date will be the date of the screening visit and will be recorded in
1108 the SNAPL Central Database. Enrollment date and future visit dates will also be recorded in the project
1109 database on REDCAP for tracking purposes.

1110 **Additional evaluations**

- 1111 • **Questionnaires:** key assessment tools of chronic low back pain (NIH minimum dataset, Start Back
1112 Tool, BodyMap) will be collected at the visit. For the sake of time, a packet of additional
1113 questionnaires (#1) will be emailed to the participant who will be reminded to fill these out during
1114 the subsequent week.
- 1115 • **Additional Physical Assessments:** In addition to the physical exam (which was part of the screening
1116 procedure) we will collect data on QST and vital signs, including measures of heart rate variability
1117 [HRV].

1118 **Daily and weekly symptom tracking:** Throughout the study, starting at enrollment, the patient will be emailed a
1119 brief set of **daily** questions assessing his/her back pain and related symptoms. The importance of answering these
1120 questions will be stressed with the patient. In addition, a **weekly** survey will be emailed to each participant,
1121 assessing for presence of adverse event, locations of pain via the BodyMap, and any new treatments (meds or
1122 procedures) started for back pain. All weekly surveys are identical. We start administering them at the completion
1123 of the baseline visit and continue until the completion of the post-treatment visit. What is shown in the table
1124 above represents a typical timeline. The total number of weekly questionnaires administered to each individual
1125 may vary due to the difference in the time lag between the assessment visits and the start and end of the
1126 treatment period. If a participant misses >50% of the weekly surveys, it will be considered a protocol deviation.

1127

1128 **6.2.2 Pre-treatment visit and Randomization**

1129 One to 2 weeks after the screening visit, the participant returns to SNAPL for a baseline (aka pre-
1130 treatment) visit.

1131 *Pre-treatment/Baseline Assessments*

- 1132 • **Questionnaires:**
 - 1133 ○ A second set of **questionnaires (packet #2)**, known to be highly predictive of response
1134 to acupuncture, will be administered to the participant during the baseline visit. These
1135 questionnaires include: pain catastrophizing scale (PCS), illness perception questionnaire
1136 (IPQ), treatment appraisal questionnaire, caffeine intake questionnaire, pain self-
1137 efficacy questionnaire (P-SEQ).
 - 1138 ○ State-measures assessing back pain and associated symptoms via the **NIH PROMIS**
1139 **instruments** (depression, anxiety, pain intensity, physical function, pain interference,
1140 sleep quality, sleep-related impairment, fatigue, anger) will be administered. To
1141 minimize participant burden, all PROMIS instruments will be administered in the
1142 computer adaptive (CAT) format, which should not take 4-6 questions per instrument.

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- **Physical Assessment:** Data will be collected on **vitals, HRV**, as well as a select set of **QST** measures (should be shorter than the initial, screening visit as no optimization steps will need to be repeated). We will NOT be repeating the physical assessment on the baseline visit.
 - **Checking on completion of daily and weekly questionnaires:** While the completion of the daily (and weekly) questionnaires are no longer required for enrollment into the study, it is still important that participants fill out these questionnaires to provide accurate data on baseline symptoms as well as during and immediately after the study intervention. We will check the completion of the questionnaires. If a significant portion is not filled out (>50%) we will inquire the reasons for the lack of completion and work with each participant to improve the completion rate (identify barriers, consider reminders via phone 1-2x per week etc). We will also document any participants that complete less than 50% of their daily questionnaires as a protocol deviation.

1156 Randomization

1157 Randomization to a specific treatment arm will take place after the baseline visit, before the first
1158 treatment session. The study intervention will begin as soon as possible (within 1 week ideally) after the
1159 Baseline Visit. The randomization procedure is detailed below:

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- 1165
- 1166
- 1167
- 1168
- 1169
- 1170
- 1171
- 1172
- 1173
- Participant becomes ready for treatment after completion of baseline visit
 - Research team assign participant to an acupuncturist based on participant's location preference.
 - Research team provide participant the acupuncturist's contact info and the acupuncturist participant's contact info.
 - Acupuncturist and participant reach out to each other and schedule first treatment appointment.
 - Once the appointment is made, acupuncturist alert research team, who then alert an outside party (another RC from or lab not related to our project) who then performs randomization by entering the participant ID and acupuncturist ID into the randomization program.
 - The randomization program is written in R, and we will stratify randomization per acupuncturist with a block of 4 within each acupuncturist, to ensure balanced treatment assignment within each provider.
 - The unrelated RC will then securely email the treatment assignment (participant ID and treatment arm) to the acupuncturist.

1174 6.2.3 Blinding

1175 Blinding of the participant will be ensured by strict controls in the communications between the
1176 acupuncturist and the participant. The acupuncturists will receive one day of hands-on training as well
1177 as written materials, and they will attend a refresher workshop 1-2 weeks before seeing their first
1178 participants. Strict guidelines on communication with the participant will be provided and will be
1179 reinforced during regular provider meetings with the PI (JT Kong).

1180 Blinding of the assessor. The PI and the research assistant will be the assessors. Only the acupuncturists
1181 (treatment providers) will be unblinded. The randomizer will deliver the randomization assignment to
1182 the acupuncture provider via secure email.

1183 Individuals authorized to break the blind. The members from the DSMB will meet and assess side
1184 effects from both treatment arms and decide if there is a need to unblind and to possibly terminate or
1185 modify the problematic treatment.

1186 Circumstances for breaking the blind: We do not anticipate that we will need to break the blind unless
1187 we see clear harm (>50% worse from baseline for one group, or >30% participants experience prolonged
1188 side effects, e.g. severe pain, persistent hematoma, nausea etc) lasting over two weeks.

1189 Procedures for breaking the blind. We stress that we do not anticipate breaking the blind except for
1190 extenuating circumstances where significant harm is caused by the VA or PA treatment. Such
1191 circumstances will always be reported to the DSMB and a decision regarding how to proceed will come
1192 from the DSMB. Such examples include a) large bleeding and bruising (over three sessions) due possibly
1193 to an undiagnosed clotting disorder; b) severe pain due to the treatment as recorded on the participants
1194 weekly adverse event report form lasting more than two weeks; c) unresolved nausea, dizziness
1195 persistent for more than two weeks.

1196 In terms of procedures for breaking the blind, we will use the following steps.

1197 **Level 1:** The research assistant will be responsible for monitoring the participant's adverse event data
1198 gathered via the Android device; additionally, the acupuncturist will monitor and report on side effects
1199 from treatment. If any of the above mentioned severe reactions to acupuncture occur (extremely rare),
1200 the RC and/or the acupuncturist will report to the PI.

1201 **Level 2:** The PI will report the event(s) to the DSMB.

1202 **Level 3:** The DSMB will decide, based on the severity and time course of the reported adverse, whether
1203 or not to terminate the participation of the participant and at the same time to break the blind. The
1204 information of treatment delivered and settings where the adverse event occurred would be important
1205 to minimize such events from happening again in the future.

1206 **6.2.4 Treatment Visits**

1207 Treatment Visits. Each participant will receive 12 treatment sessions. For each session, the participant
1208 fills out adverse event form at the beginning of the session (except for the first session), the
1209 acupuncturist fills out the treatment CRF near the end of the session. Sessions 1, 2, 5 and 12 will contain
1210 specific assessments, as outlined below.

1211 Treatment Session 1: 60 minutes

- 1212
- 1213 • Acupuncturist will perform initial history and physical. History will include similar information as
1214 original baseline visit (pain location, duration, character, intensity, medication list, past medical
1215 and surgical history, previous allopathic and CAM treatment for back pain; as well as at TCM
1216 related question. Physical exam will include pulses, tongue exam according to TCM, as well as
1217 lumbar and low extremity palpation, range of motion, as well as anything else can be
1218 comfortably performed by the acupuncturist. These details will be recorded in the **Acupuncture
Intake CRF**.
 - 1219 • Most importantly, the acupuncturist will record a) if the participant experiences pain in
1220 hips/upper thighs; b) rating of back pain over the last 7 days using an 11-point (0-10) numerical
1221 rating scale (NRS).

- 1222 • Treatment will be administered per protocol (see Section 5.1)
- 1223 • Participant will complete **Stanford Expectancy of Treatment** BEFORE and AFTER the 1st
- 1224 treatment
- 1225 • Acupuncturist will complete session record on Visit Notes CRF
- 1226 • Acupuncturist will schedule/confirm next treatment session(s)
- 1227 Treatment sessions 2: 45 minutes
- 1228 • Participant will complete adverse event form before session starts.
- 1229 • Treatment will be administered per protocol (see Section 5.1)
- 1230 • Participant will complete **Vincent Credibility Scale** after the 2nd session.
- 1231 • Acupuncturist will complete session record on Visit Notes CRF
- 1232 • Acupuncturist will schedule/confirm next treatment session(s)
- 1233 Treatment session 5: 45 minutes
- 1234 • Participant will complete adverse event form before session starts
- 1235 • Acupuncturist will fill out pretreatment **assessment of reduction in pain**, and determine if
- 1236 additional treatment module will be used for this and upcoming sessions in the verum arm
- 1237 (sham arm does not change protocol but will perform identical assessment). Refer to 5.1.2.B and
- 1238 5.1.3.B for details.
- 1239 • Treatment will be administered per protocol (see Section 5.1)
- 1240 • Acupuncturist will complete session record on Visit Notes CRF
- 1241 • Acupuncturist will schedule/confirm next treatment session(s)
- 1242 Treatment sessions 3, 4, 6-11: 45 minutes
- 1243 • Participant will complete adverse event form before session starts
- 1244 • Treatment will be administered per protocol (see Section 5.1)
- 1245 • Acupuncturist will complete session record on Visit Notes CRF
- 1246 • Acupuncturist will schedule/confirm next treatment session(s)
- 1247 Treatment sessions 12: 45 minutes
- 1248 • Participant will complete adverse event form before session starts.
- 1249 • Treatment will be administered per protocol (see Section 5.1)
- 1250 • Participant will complete the simple **blinding assessment questionnaire** at the end of the
- 1251 treatment.
- 1252 • Acupuncturist will complete session record on Visit Notes CRF
- 1253
- 1254 **6.2.5 Post-Treatment Visits & Follow-up**
- 1255 Post-Treatment Follow-Up Visit. The Post-Treatment Visit will be conducted approximately 1-2 weeks
- 1256 after the last (12th) treatment session. Similar assessments to the baseline visits will be performed.
- 1257 • **Questionnaires:** All questionnaires will be administered via REDCap. See Table 1 for details.

- 1258 • **Physical Assessment:** We will record vital signs and HRV of the participants.
 1259 • **Quantitative Sensory Testing (QST):** Participants will undergo QST. See Appendix 2 – QST
 1260 Manual for complete description of tests, devices, and safety parameters.

1261 Online Follow-Up. Participants will complete online assessments at 3, and 6 and 12 months post-
 1262 treatment. These assessments will include a limited dataset out of the questionnaires that the
 1263 participant completed at their Baseline Visit (RMDQ and mean pain intensity). Specifically, these
 1264 questionnaires are scheduled to reach the participant at 3, 6, and 12 months measured from the LAST
 1265 day of intervention. Our automatic survey invitation is programmed such that, if the participant has not
 1266 responded, the questionnaire will be sent 3 more times weekly until a response is entered.

1267 In order to increase the capture of long-range data, the research team will also reach out via email or
 1268 phone to the participants who have missed all 4 email reminders. The windows for completions are: up
 1269 to 6 months for the 12-month survey, up to 3 months for the 6-month survey and up to 1 month for the
 1270 3 month survey. In order to find the balance between maximizing data capture and accuracy of recall,
 1271 for the participants who are outside their window, we ask them to recall the approximate average back
 1272 pain intensity at 3, 6 or 12 months after their last study intervention.

1273 Debriefing. On the post-treatment assessment visit, all participants will be debriefed by RC the research
 1274 team. The PI or the RC will only unblind the participant AFTER all assessments are completed at the
 1275 post-treatment visit.

1276 The table below summarizes the visits for the project.

Week Number*	Visit	Events
Week -1	Screening Visit	Informed consent, eligibility determination/enrollment, questionnaires, physical exam, HRV/QST, daily and weekly tracking
Week 0	Pre-treatment/baseline assessment	More questionnaires, HRV/QST, randomization
Week 1	Treatment sessions 1 and 2	Treatment per protocol
Week 2	Treatment sessions 3 and 4	Treatment per protocol
Week 3	Treatment sessions 5 and 6	Treatment per protocol
Week 4	Treatment sessions 7 and 8	Treatment per protocol
Week 5	Treatment sessions 9 and 10	Treatment per protocol
Week 6	Treatment sessions 11 and 12	Treatment per protocol
Week 8	Post-Treatment Follow-Up Visit	Questionnaires, QST, HRV, physical exam, Debriefing.
~ Week 18	Online/Telephone Follow-up 1	Questionnaires at 3 months post-treatment
~ Week 32	Online/Telephone Follow-up 2	Questionnaires at 6 months post-treatment
~ Week 58	Online/Telephone Follow-up 3	Questionnaires at 12 months post-treatment

1277 *This table assumes the most ideal situation: 1 week between screening and baseline and between
 1278 baseline visit and treatment initiation, and 1-2 week period between end of intervention and post-
 1279 treatment visit.

1280 **6.2.6 Study Completion**

1281 **Study Stop Point CRF**

1282 Research staff will complete the first half of the study stop point CRF indicating the completion of the
1283 participant's study visits. There will be a separate section on the Study Stop Point CRF, which will be
1284 completed after the participant completes their last online follow-up. At this point, it will be indicated
1285 on the CRF that all follow-up visits are complete and the participant's record will be closed.

1286 *Handling of Early Termination:*

- 1287 • List of possible reasons: scheduling conflicts, intolerable adverse events, no longer interested,
1288 lack of benefits (analgesia), pregnancy, development of significant medical/psychiatric
1289 comorbidity or additional pain foci.
- 1290 • Necessary evaluations: Most importantly, we will collect the daily monitoring data and use the
1291 average pain score from the last 7 days prior to termination to calculate the final primary
1292 outcome (pain reduction). Depending on the severity of side effects, we will bring the
1293 participant in for a visit with one of our MD staff, provide appropriate treatments, and monitor
1294 the participant until the side effects resolve. For details of the type of side effects and
1295 prospective treatments, please refer to Section 7.3 under "adverse effects."
1296

1297 **7. SAFETY ASSESSMENTS**

1298 Overall, acupuncture is a generally safe procedure with essentially negligible risk for serious
1299 complications in practiced hands (which is true in our case as all our acupuncturist have >3 years of
1300 practice experience).

1301 **Potential adverse events:** acupuncture is an extremely safe intervention. For each of the **four**
1302 **categories of complications**, we have specific ways to handling them as below.

- 1303 • **First**, the most common side effects are minor pain and bruising at the needle insertion sites
1304 and they typically go away within 2-3 days.
- 1305 • **Second**, some individuals may experience mild vasovagal reaction near the beginning of the
1306 treatment. If it happens, we will immediately lay the participant supine and monitor. Only if
1307 these symptoms do not resolve after the participant is laid supine for 5 minutes, we plan to
1308 vigorously stimulate Du-26 and select Ting points at the toes which are indicated to treat
1309 vasovagal reactions. If within 2 minutes the symptoms do not subside, we will take the needles
1310 out, and offer hydration. Most cases resolve with these maneuvers.
- 1311 • **Third**, nausea and dizziness may also occasionally occur but are short-lived. If they do occur, we
1312 will immediately lay the participant supine and monitor. Only if these symptoms do not resolve
1313 after the participant is laid supine for 5 minutes, we will insert needles to bilateral MH-6, ST-41
1314 (indicated to treat nausea), and GV-20 (indicated for dizziness) in the subsequent sessions. If
1315 the symptoms do not improve after 3 sessions and the participant feels significantly bothered,
1316 we will terminate the participant's enrollment.
- 1317 • **Fourth**, complications such as infection, nerve injury and pneumothorax are extremely rare (less
1318 than one in 10,000). If they do occur, treatment will be terminated, DSMB will be alerted, and
1319 the participants will be followed and treated by an MD until the symptoms resolve following

1320 standard of care (e.g. antibiotics for infection, x-rays and possibly needle decompression for
1321 pneumothorax).

1322 • **Finally**, adverse reactions will be recorded two ways: by the acupuncturist at the end of each
1323 session and by the participant on their Android device.

1324 **7.1 Specification of Safety Parameters**

1325 The most common risks in acupuncture are local swelling, bruising, and pain, and less commonly
1326 transient nausea and dizziness. In the rare case of persistent light-headedness, blood pressure and
1327 heart rate will be assessed in the office. Most of the monitoring will be done by verbal report by the
1328 participant and visual exam and palpation of the needled sites by the acupuncturist.

1329 **7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters**

1330 The surveillance and detection of adverse effects by acupuncture will be accomplished in three layers.

1331 **Layer 1** – the participant: The acupuncturist will explain the common side effects of acupuncture to the
1332 participant based on a standardized script. Then, the participant will log the presence of any side effects
1333 on the Android device on a weekly basis. Further, presence of immediate side effects to treatment will
1334 be reported to and noted by the acupuncturist on the session record.

1335 **Layer 2** – The acupuncturist: he/she will observe and inquire about immediate side effects after each
1336 treatment, will also note delayed side effects on the session records.

1337 **Layer 3** – The research team (PI and RC) will survey the Android device logs by the participants every 2-4
1338 weeks and review the presence, time course, and severity of side effects, and intervene if necessary.

1339 **7.3 Adverse Events and Serious Adverse Events**

1340 An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign,
1341 syndrome or disease which either occurs during the project, having been absent at baseline, or if
1342 present at baseline, appears to worsen. Adverse events are to be recording regardless of their
1343 relationship to the project intervention.

1344 A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in
1345 death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization,
1346 results in persistent or significant disability/incapacity, or is a congenital anomaly.

1347 The participants will be provided with emergency phone numbers to contact the team in case of serious
1348 side effects.

1349 At each treatment visit, the acupuncturists will record all adverse events in the Adverse Events CRF and
1350 will notify the Clinical Core.

1351 The daily questions completed by participants on Androids will capture participant mood as well as
1352 common side effects. Triggers will be programmed into the application for a negative mood rating,
1353 which will alert the Clinical Core after 5 consecutive reports of greater than 30% negative change in
1354 mood as compared to baseline. The Clinical Core will then follow-up with the participant by phone to
1355 inquire about the negative mood rating and record it in the Adverse Event CRF.

1356 Finally, there will be a short questionnaire programmed into the Android device to ask about side effects
1357 and adverse events at the end of each week. The Clinical Core will monitor these weekly reports and

1358 follow-up with the participant by phone if side effects are reported and an Adverse Event CRF will be
1359 completed for the participant's record.

1360 **7.4 Reporting Procedures**

1361 Note that adverse events are recorded in 1) participant weekly surveys; 2) acupuncturist's CRF's; 3) at
1362 post-treatment visit by research team. The research team will perform QA check on all of the following
1363 data (with particularly focus on safety) on a monthly basis: participant daily/weekly surveys, participant
1364 questionnaires, consent forms, all research team CRF's, acupuncturist's CRF's. Specifically, we will check
1365 for 1) protocol deviations; 2) all adverse events. We will log these for each participant on Excel
1366 Spreadsheets (on our lab's HIPPA compliant server), monthly and report all to NCCIH, DSMB and IRB at
1367 the appropriate time intervals.

1368 Acupuncturists will assess adverse events twice a week at the treatment sessions and will complete the
1369 Adverse Event CRF. Acupuncturists will also notify the RC in case of adverse events and the RC will
1370 follow-up with the participant by phone within 3 business days if the adverse events are acupuncture
1371 treatment related. If adverse events are severe and related to the acupuncture project, DSMB will be
1372 notified immediately, the treatment will be stopped and the PI will have a consultation with the
1373 participant within 3 days of the onset of side effects.

1374 Adverse Events will be reported to NCCIH, DSMB, and Stanford IRB annually. Serious Adverse Events that
1375 are determined to be related to the study will be reported to the IRB by filing a report on the Stanford
1376 IRB website. A copy of this report will be sent to the NCCIH officer. Unexpected fatal or life-threatening
1377 Adverse Events related to the intervention will be reported to the NCCIH Program Officer within 7 days.
1378 Other serious, unexpected, and related Adverse Events will be reported to the NCCIH Program Official
1379 within 15 days and to the Stanford IRB within 10 business days. Anticipated or unrelated Serious
1380 Adverse Events will be handled in a less urgent manner but will be reported to the Independent
1381 Monitor(s), Stanford IRB, and NCCIH in accordance with their requirements. In the annual Adverse Event
1382 summary, the Independent Monitor(s) Report will state that they have reviewed all Adverse Event
1383 reports.

1384 **7.5 Follow-up for Adverse Events**

1385 After Adverse Events are discussed by the RA/PI and participant and a decision is made regarding
1386 continuation of participation, the RC will conduct a 1-month follow-up phone call to the participant. This
1387 phone call will also be recorded in the Adverse Event CRF.

1388 **7.6 Safety Monitoring**

1389 **Data Monitoring and Safety Board (DSMB)**

1390 The CAM Center DSMB has the following members:

1391 Dr. Manisha Desai, PhD (Biostatistics expertise)

1392 Dr. Karen Sherman, PhD (TCM trials expertise)

1393 Dr. Remy Coeytaux, MD/PhD (Clinical expertise)

1394 The DSMB will convene every 3 to 6 months after initial recruitment. Safety will be reviewed and
1395 participant cases will be reported to the members of the DSMB and relevant safety decisions will be

1396 made. The sessions will be open to PI and the mentors. DSMB reports will be sent to NCCIH and Stanford
1397 IRB within 10 business days of the meeting.

1398 **8. INTERVENTION DISCONTINUATION**

1399 Participants will be free to withdraw from the project if they no longer wish to participate. If participants
1400 do not attend more than 3 sessions of PA or VA project arms, their participation will be considered
1401 incomplete. However, they will not be withdrawn from the project and will be given the opportunity to
1402 resume treatments. Since this project is not monitoring any lab values and does not involve drugs, there
1403 are no such values that would warrant intervention discontinuation. As mentioned above, participant
1404 mood rating and side effects will be monitored via the Android devices, and participants will be
1405 withdrawn from the project by the Investigator if it is determined that the intervention is causing the
1406 negative mood ratings, persistent worsening pain, and/or side effects that cannot be resolved.

1407 **9. STATISTICAL CONSIDERATIONS**

1408 **9.1 General Design Issues**

1409 This is a randomized control trial in which 100 adult participants with chronic low back pain (CLBP) will
1410 be randomized to 6 weeks of twice a week sessions with verum acupuncture (VA) or placebo
1411 acupuncture (PA). Participants and researchers will be blind to treatment assignment. Treatment
1412 providers will not (and cannot) be masked to treatment assignment

1413 **Aim 1.** Explore the predictive relationship and the association between **ascending sensitization**
1414 measures and clinical response to acupuncture.

1415 **Hypothesis 1:** augmented temporal summation (TS), and more wide-spread pain (WSP) (quantified by
1416 number of painful areas marked by the participant on a standardized body map) will be associated with
1417 greater pain reduction in the verum arm than in the placebo arm; decreased pressure pain threshold
1418 (PPT_r) will be associated with greater pain reduction in the placebo arm than the verum arm.

1419 **Aim 2.** Explore the predictive relationship and the association between **descending modulatory**
1420 measures and clinical response to acupuncture.

1421 **Hypothesis 2:** decreased conditioned pain modulation (CPM), and more favorable psychological state,
1422 measured by less pain catastrophizing, better self-efficacy in coping and in pain management, will be
1423 associated with greater pain reduction in the verum than the placebo arm; expectation of positive
1424 treatment outcome will be associated with pain reduction in both the verum and the placebo arm.

1425 **Aim 3. Exploratory model building** to predict pain reduction by electroacupuncture.

1426 **Hypothesis 3.** A mathematical model relating key baseline characteristics to percent pain reduction will
1427 be developed using advanced techniques, and this model will be tested using cross-validation within the
1428 proposed pilot.

1429

1430 **9.2 Sample Size and Randomization**

1431 **Participants**

1432 The project will enroll 100 adults (ages 21-65 years) who meet criteria for chronic axial low back pain
1433 without radicular symptoms. Participants with CLBP will be randomly assigned to an equal duration of
1434 acupuncture treatment or placebo.

1435 **Power Analysis**

1436 The objectives of aim 1 are to 1) explore the predictive relationship between ascending factors of
1437 interest and pain reduction due to our interventions; 2) test the association between the ascending
1438 factors and pain reduction. However, because the former is exploratory in nature, we will design our
1439 study to power for the latter objective. Specifically, we compute the number of patients needed to find
1440 an association between key baseline parameters (pressure pain threshold, temporal summation (TS), or
1441 widespread pain) and pain reduction due to verum treatment. With 50 patients per arm, we will be able
1442 to detect a moderate correlation of 0.4 (supported by literature for pressure pain threshold¹¹ and TS⁶⁷)
1443 with approximately 80% power with alpha of 0.05 using Fisher's transformation. Next, to determine if
1444 the association is stronger in the verum than the sham arm, we will test the interaction between
1445 treatment and the baseline parameters. Fifty patients per arm will provide 80% power (with alpha of
1446 0.05) to detect a moderate difference of 0.5 between correlation from the verum arm and that from the
1447 sham arm. Therefore, we are adequately powered to detect a moderate association between baseline
1448 parameters and the clinical response in the verum acupuncture arm and a moderate difference in the
1449 strengths of these associations between the verum and the sham treatment group.

1450 Similar calculation with identical numbers can be found for aim 2 (descending factors). Note prior
1451 literature supports a moderate association around 0.4 between catastrophizing and pain reduction as
1452 well as between self-efficacy and pain reduction in patients suffering from chronic low back pain.

1453 **Randomization**

1454 When a new participant has passed the initial screening and baseline visit, he/she will be randomized to
1455 receiving either VA or PA with equal chance. An R program for variable block randomization will be used.
1456 We will randomize patients in blocks with block sizes randomly selected from 6, 8 and 10. Our lab
1457 manager or his associates (who are NOT immediately related to the proposed project) will run the
1458 randomization program and inform the treatment assignments to each provider via secure emails. Note
1459 that the participant will be able to pick the acupuncturist based on ease of access (commute time).

1460 Details of Blinding can be found in Section 6.2.3 Blinding. Details on randomization can be found in
1461 Section 4.3.2.

1462 **9.3 Definition of Populations**

1463 ITT (Intent to treat) refers to all participants who have completed the baseline assessments and have
1464 been randomized to 1 of 2 arms.

1465 Modified ITT refers to all participants who have attended at least one session and completed the
1466 measure at the screening and baseline visits.

1467 Per treatment refers to participants who have completed (no more than 3 missed sessions) either VA or
1468 PA and the assessments (both baseline and post-treatment visits).

1469 **9.4 Interim Analyses and Stopping Rules**

1470 The most common risks in acupuncture are local swelling, bruising, and pain, and less commonly
1471 transient nausea and dizziness.

1472 We do not anticipate that safety reviews will be necessary unless we see clear harm (>50% worse from
1473 baseline for one group, or >50% participants experience prolonged (>2 weeks) moderate or severe side
1474 effects (eg nerve injury, large hematoma with diameter > 5cm, or increased back symptoms that prevent

1475 the participant from tending to normal work and recreational activities which were not a problem prior
1476 to participating in the study). Such findings will be reported to the PI and the lab manager to review the
1477 events by group to determine whether there are statistical as well as clinical concerns. The research
1478 team will report the findings to NCCIH. The findings are used to determine what steps will be taken,
1479 such as to determine whether the project should continue per protocol, proceed with caution, be
1480 further investigated, be discontinued, or be modified and then proceed.

1481 9.5 Outcomes

1482 9.5.1 Primary Outcome

1483 **Primary outcome:** Change in Pain Intensity measured by the T-scores computed from the full PROMIS
1484 Pain Intensity Instrument administered at the pre-treatment and post-treatment visit.

1485 9.5.2 Secondary Outcomes

1486 **Secondary outcomes:** a) percent pain reduction at 6 and 12 months from baseline; b) percent change in
1487 physical function, measured by RMDQ or the pain interference instrument from PROMIS at the post-
1488 treatment visit, and at 3, 6 and 12months from baseline. C) percent change in pain intensity measured
1489 by the 11-point NRS at both the pre- and post- treatment visit.

1490 9.6 Data Analyses

1491 **Aim 1. Explore the predictive relationship and the association between ascending sensitization**
1492 **measures and clinical response to acupuncture.**

1493 **Planned analysis:** There are two specific goals of the analysis: (1) explore the predictive relationship
1494 between key baseline parameters and treatment response (pain reduction) accordingly by arm; and (2)
1495 examine the associations between baseline predictors and treatment response by arm. The identified
1496 association can help us understand the underlying mechanism of the treatment effect from acupuncture
1497 and, AND assist in building good subsequent prediction models. To this end, taking temporal summation
1498 (TS) first as an example, we will first estimate the correlation coefficients between baseline TS and the
1499 primary outcome (% pain reduction immediately after treatment) and then perform multivariate linear
1500 regression with clinical pain reduction as the continuous dependent variable and TS and potential
1501 confounding factors such as the demographic variables and the baseline pain level as independent
1502 variables in the verum arm. We will estimate the regression coefficients and their 95% confidence
1503 intervals, which will be used to formally test association between TS and pain reduction with or without
1504 adjustment of potential confounders. To evaluate the predictiveness of TS (with other patients'
1505 characteristics) to pain reduction, we will also calculate the mean squared prediction error of the
1506 multivariate regression model. Variable selection method such as lasso may be used to remove
1507 unnecessary predictors from the model and cross-validation will be used to estimate the prediction
1508 accuracy to account for the adaptive model building step. Likewise, we will repeat the analysis in the
1509 sham arm. Specifically, we will test the presence of the association by examining if zero is inside the
1510 interval for confirming the hypothesis that the association is close to null in the sham arm. We will also
1511 estimate the interaction between the treatment group and TS to determine if decreased TS better
1512 predicts treatment response to verum than to sham acupuncture. Note that factors which are equally
1513 predictive to the pain reduction in both arm in general do not have interaction with the treatment.

1514 In summary, the primary objective will be to assess the predictiveness of baseline TS to pain reduction;
1515 and the primary outcome of pain reduction will be the difference in pain between baseline and
1516 immediately after treatments. The primary analyses will be the computation of mean-squared
1517 prediction error from a multivariate regression model, as well as the use of Lasso and cross-validation to
1518 improve and validate the predictive model with TS. The second objective will be to quantify the
1519 association between TS and pain reduction immediately after treatments (ie secondary outcome is the
1520 same as the primary outcome, pain reduction immediately after treatments). The secondary analyses
1521 will be a) computation of the correlation coefficient between baseline TS and pain reduction and b)
1522 estimation of the regression coefficient and 95% confidence intervals between baseline TS and pain
1523 reduction in a multivariate regression model taking TS and other baseline variables into account.

1524 The same analyses will be applied to pressure pain threshold and widespread pain. Realizing that pain
1525 reduction may not be normally distributed and that the assumed linear regression model may not be
1526 appropriate, we will repeat the above analysis using a conservative, semi-parametric transformation
1527 model. We will perform the parallel logistic analysis with dichotomized pain-reduction (responder vs
1528 non-responder) as the binary dependent variable of interest. We will perform similar analyses for
1529 widespread pain. Finally, we will repeat the above using pain reduction at 6 months post-treatment as
1530 our outcome variable.

1531 **Aim 2. Explore the predictive relationship and the association between descending pain modulatory**
1532 **measures and clinical response to acupuncture.**

1533 **Planned analysis:** the statistical plan for Aim 2 is almost identical to that of Aim 1 except, we replace
1534 baseline factors of TS, pressure pain threshold and widespread pain, with baseline CPM, pain
1535 catastrophizing, coping effectiveness and self-efficacy. In summary, the primary objective will be to assess
1536 the predictiveness of baseline descending pain modulatory factors (CPM, pain catastrophizing, coping
1537 effectiveness and self-efficacy for pain management) to pain reduction; and the primary outcome of
1538 pain reduction will be the difference in pain between baseline and immediately after treatments. The
1539 primary analyses will be the computation of mean-squared prediction error from a multivariate
1540 regression model, as well as the use of Lasso and cross-validation to improve and validate the predictive
1541 model with each descending pain-modulatory factor of interest. The second objective will be to quantify
1542 the association between each descending pain-modulatory factor of interest and pain reduction
1543 immediately after treatments (ie secondary outcome is the same as the primary outcome, pain
1544 reduction immediately after treatments). The secondary analyses will be a) computation of the
1545 correlation coefficient between each baseline descending factor and pain reduction and b) estimation of
1546 the regression coefficient and 95% confidence intervals for between each baseline descending factor of
1547 interest and pain reduction in a multivariate regression model.

1548 Finally, recognizing the exploratory nature of our study aims, we appreciate the fact any significant
1549 findings from the analyses from both Aim 1 and Aim2 may be due to artifacts of multiple looks at the
1550 data. Therefore, we will a) consider correction for multiple comparisons in our final analysis; b) verify
1551 the significant findings from our pilot exploratory study in subsequent, larger, controlled clinical trials.

1552 **Aim 3. Exploratory model building. I will explore mathematical models relating acupuncture analgesia**
1553 **to baseline characteristics, and test this model within the proposed pilot via cross-validation.**

1554 **Planned analysis: Model-building.** We will train a predictive model based on all factors examined in
1555 Aims 1 and 2, and additional baseline measures including demographics, job status, history of childhood
1556 trauma (PTSD), fear avoidance beliefs, and current symptoms of mood disorders. We will develop
1557 multivariate prediction models for predicting pain-reduction after treatment. Lasso-penalized
1558 logistic/linear regression, regression tree, random forest, boosted CART, and other data mining
1559 techniques will be employed. Using cross-validation, we will check the quality of our models by mean-
1560 squared prediction error for continuous outcome; and by misclassification error and
1561 sensitivity/specificity in the ROC curves for dichotomized outcomes. The prediction model will be trained
1562 in the verum and sham arms separately. In the end, we will balance simplicity, interpretability and the
1563 prediction performance to select the optimal model, where the prediction performance will be
1564 objectively evaluated again with cross-validation. The final constructed models can be used for guiding
1565 and developing personalized delivery of acupuncture.

1566 **Validation.** We will test the performance of the selected prediction model on patients via cross-
1567 validation by comparing the observed and predicted outcome. The performance will be evaluated via
1568 metrics, including mean-squared error, misclassification rate, sensitivity, specificity, and ROC curve,
1569 when appropriate. Importantly we will predict the treatment benefit of each patient using the chosen
1570 models and will identify the subgroup of patients with the highest predicted benefit of verum relative to
1571 sham. Then we will estimate the treatment effect in the identified subgroup of patients. If the actual
1572 pain reduction in verum arm is significantly higher than sham among the selected subgroup of patients,
1573 then the selected model will be deemed successful and may be used for recommending acupuncture in
1574 clinical practice.

1575 10. DATA COLLECTION AND QUALITY ASSURANCE

1576 10.1 Data Collection Forms

1577 All questionnaires will be completed by participants in the REDCap Database. If some questionnaires
1578 have to be collected on paper due to unforeseen circumstances, the forms will be stored as source data
1579 and a member of the research team will enter the data into the REDCap database.

1580 Participants will complete majority of the questionnaires associated with the pre- and post-treatment
1581 visits on-site. To ease participant's burden during their onsite visit, we will send longer questionnaires
1582 and those with relatively less predictive power based on prior studies via weblinks such that participants
1583 can complete them at the comfort of their home. All follow-up questionnaires will be completed online
1584 by the participants at home.

1585 The research team will fill out the majority of the CRF's and keep these along with the Phone Screen as
1586 source data. The acupuncturists will fill out a CRF for initial intake and a CRF for each acupuncture
1587 session to record details of the treatment.

1588 All participants will be identified by a unique project ID number on their corresponding data and case
1589 report forms and will not be identified by their name. All CRFs will be stored in binders identified by the
1590 Participant ID number and stored in locked cabinets. All staff will receive training on completing CRFs
1591 appropriately, reviewing CRFs for completeness, and maintaining participant confidentiality.

1592 **10.2 Data Management**

1593 The PI and the RC will be responsible for collecting data but both will be blinded to treatment
1594 assignment. Most importantly, PRIOR to analysis, the lab manager or his associates who are not involved
1595 with the current study will de-identified key baseline and outcome data and send these to the PI, RC and
1596 steering committee for analyses.

1597 **10.3 Quality Assurance**

1598 **10.3.1 Training**

1599 All research team members will perform the responsibilities as outlined by the delegation of authority
1600 log. Human Subjects Training and HIPAA training will occur as required by Stanford Policy. Additionally,
1601 all team members will receive a copy of this document, the Lab Policy Manual, and will be trained
1602 directly by PI Kong on the purpose of the project and their responsibilities. Research staff will be trained
1603 on Informed Consent, Phone Screening, and Case Report Form Completion by the PI and other senior
1604 lab research staff. The latter will monitor appropriate conduct and form completion on an ongoing
1605 basis, in collaboration with the lab manager (to be hired soon) and the PI (Kong). Research team
1606 meetings will occur frequently with the PI to ensure ongoing understanding by project staff and to
1607 address any concerns.

1608 *Regulatory and Ethical Training Requirements*

1609 The lab manager and the IRB manager will ensure that all research personnel have completed required
1610 federal and institutional training, and will maintain documentation of such. The managers will schedule
1611 annual training workshops, development of training agendas, and preparation of materials to reinforce
1612 ethical research and Good Clinical Practices. Outside speakers, such as those from the IRB, Stanford
1613 Bioethics Consultation Service, and Spectrum will be invited for training workshops.

- 1614
- Human Subjects Protections: Training will include guidelines related to: HIPAA regulations and participant confidentiality, ethical research conduct, and human subject interactions.
 - Conflict of Interest: Compliance with Stanford's conflict of interest policies and ongoing monitoring will also be maintained by the managers and the PI.
- 1616
- 1617

1618 **10.3.2 Quality Control Committee**

1619 All consent forms and CRF's will be monitored by both the research and the IRB manager. Monitoring
1620 results will be provided to the DSMB and the research team at quarterly research meetings.

1621 **10.3.3 Metrics**

1622 The metric for the primary outcome measure is self-reported pain. Daily Android data and participant
1623 questionnaires will be reviewed by the research team on a regular basis, minimally at the Baseline and
1624 Post-treatment Visits and at least once during the treatment course. The managers and the PI will also
1625 perform quality assurance by reviewing these materials on a quarterly basis.

1626 10.3.4 Protocol Deviations

1627 A major protocol deviation or violation includes any procedure that differs from the IRB approved
1628 protocol that was intended to eliminate an immediate hazard to the participant, was harmful, or is
1629 possible serious or continued non-compliance by a research team member.

1630 Major protocol deviations will be communicated to the PI immediately. All events will be communicated
1631 to NCCIH within five days of the PI learning of the event. A description of the event will be included. The
1632 IRB manager will also submit this information to the IRB.

1633 All minor protocol deviations (those that do not meet the definition of a major deviation and do not
1634 affect the interpretation or outcome of the project) will be reported to NCCIH and Stanford IRB annually.

1635 For each participant, a Protocol Deviations Log will be maintained in the participant's data binder. A
1636 comprehensive Protocol Deviations Log will be maintained by the research assistant.

1637 10.3.5 Monitoring

1638 *Trial Monitoring*

1639 Adverse Events, Serious Adverse Events, Unanticipated Problems, and Protocol Deviations will be
1640 monitored on a continual basis and reported per information in the relevant sections. Specifically, QA
1641 monitoring will occur once a month at the first Monday of the month, by the research team who will
1642 complete a QA monitoring CRF on REDCAP for each participant. Documents/CRF QA's will include:
1643 consent forms, patient surveys, research team CRF's, and acupuncturist's CRF's and audios. All AE's,
1644 SAE's, UP's, and PD's will be logged in separate Excel Spreadsheet for study participants. To ensure that
1645 we do not miss any items, a QA monitoring CRF is created on REDCAP for each participant and will be
1646 filled out monthly.

1647 Additional ongoing monitoring will occur as detailed below. Results will be recorded on a monitoring
1648 log. The PI will review and sign-off on the results and any suggested resolutions.

1649 The consent forms of the first 10 participants will be reviewed for accuracy and completion immediately
1650 after enrollment. Subsequently, consent forms will be reviewed for completion every 3 months.

1651 The case report forms for the first four sessions completed by *each* provider will be reviewed
1652 immediately after the visits (within one day) for completeness and accuracy. Subsequently CRFs from
1653 15-20% of each acupuncturist's sessions will be reviewed every 4 months.

1654 The audio recordings for the first four sessions completed by *each* provider will be reviewed
1655 immediately after the visits (within one day) for protocol adherence. Subsequently recordings from 10-
1656 20% of each acupuncturist's sessions will be reviewed every 3 months (using the Ceiling function). We
1657 will review these recordings to examine adherence to communication guidelines between the provider
1658 and the participants and to protocols for intensity of the needle stimulations.

1659 The results of the monitoring will be reported at quarterly research meetings for the project.

1660 *Case Report Form Completion*

1661 Data discrepancies will be compared to any source data and corrections made by drawing a single line
1662 through the original value, providing the correct value, dating, initialing, and providing a reason for the

1663 correction (corrections can be made this way in REDCap). Missing data or data discrepancies that cannot
1664 be resolved by verifying source data will be left as missing. The PI will be the primary person reviewing
1665 these data. For acupuncturist's procedure notes which are standardized, the PI may train the research
1666 assistant to review these data.

1667 *Consent Form Completion*

1668 Consent forms will be evaluated for completeness of all signatures, required initials, and dates. Any
1669 missing signatures will be obtained by mailing the participant a copy of the consent form and requesting
1670 the signature with the current date. Any missing PI signatures will be obtained and dated with the
1671 current date. Participants with missing signatures who are unable, or unwilling, to provide missing
1672 signature will be withdrawn from the project and data will not be used.

1673 **11. PARTICIPANT RIGHTS AND CONFIDENTIALITY**

1674 The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory
1675 inspection(s) by providing direct access to source data/documents.

1676 **11.1 Institutional Review Board (IRB) Review**

1677 This protocol and the informed consent document and any subsequent modifications will be reviewed
1678 and approved by the Stanford IRB and NCCIH.

1679 **11.2 Informed Consent Forms**

1680 A signed consent form will be obtained from each participant. Participants must be able to understand
1681 all the project procedures in order to be successfully consented. Therefore, only English-speakers will be
1682 consented for the project. Individuals under the age of 21 will not be included in the project. The
1683 consent form will describe the purpose of the project, the procedures to be followed, and the risks and
1684 benefits of participation. A signed copy will be given to each participant and this fact will be
1685 documented in the participant's record.

1686 **11.3 Participant Confidentiality**

1687 Any data, specimens, forms, reports, video recordings, and other records that leave the site will be
1688 identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All
1689 records will be kept in a locked file cabinet. All computer entry and networking programs will be done
1690 using PIDs only. Information will not be released without written permission of the participant, except as
1691 necessary for monitoring by IRB, the FDA, the NCCIH, and the OHRP.

1692 **11.4 Project Discontinuation**

1693 The project may be discontinued at any time by the IRB, the NCCIH, the OHRP, the FDA, or other
1694 government agencies as part of their duties to ensure that research participants are protected.

1695 **12. COMMITTEES**

1696 **12.1 The research team**

1697 The research team will be consisted of the following:

- 1698 • The PI (JK): responsible for the overall design and execution of the study, monitoring completion
1699 of CRFS by participants, research assistant and the acupuncturists. Will also serve as a backup to
1700 the research assistant for conducting the screening, baseline and post-treatment visits.
 - 1701 • The Research coordinator (BM): responsible for execution of the study, particularly with
1702 recruitment, conducting the screening, baseline and post-treatment visits; monitoring
1703 questionnaire completion by the participants and the acupuncturists, telephone reminders for
1704 follow up questionnaire completion by the participant.
 - 1705 • Acupuncturists: provide study interventions to participants, fill our CRF's, administer surveys
1706 (expectation, Vincent, blinding assessment) to participant.
 - 1707 • The randomizer (DB): randomize patient to Sun (verum) or Moon (sham) treatment and inform
1708 acupuncturist about assignment vial secure email.
 - 1709 • Project admin (CD): overseeing budget, purchasing, equipment, and facilitate communication
1710 between research team and acupuncturists.
 - 1711 • Pain Clinic MA (MP): help with recruitment by providing study info to patients referred to
1712 acupuncture for back pain but were denied access by their insurance. She will obtain "ok to
1713 contact" from patient and put him/her on a list and provide the study flyer to this patient.
- 1714 The entire research team, particularly the PI, the acupuncturists and the RC will monitor for adverse
1715 event and protocol compliance and meet regularly (at least quarterly) to confirm safety and compliance
1716 and make reports to NCCIH or the IRB if necessary.

1717 12.2 The supervisory committee

1718 The supervisory committee will be consisted of the K23 mentoring team which is headed by Dr. Sean
1719 Mackey.

- 1720 • Sean Mackey, MD/PhD: Dr. Mackey will oversee the timely progression of the project: that it is
1721 meeting the appropriate recruitment goals, with acceptable levels of participant retention
1722 throughout the project, and that data is collected and analyzed in a safe, blinded manner. Also
1723 he will provide critical input on manuscript preparation related to the project and development
1724 of an R01 level proposal by year 3 of the project, based on the current study.
- 1725 • Margaret Chesney, PhD: Dr. Chesney will oversee the appropriate inclusion, use, and analyses of
1726 the psychological instruments used in this study; and provide mentorship to Dr. Kong on the use
1727 and interpretation of these instrument in clinical trials involving acupuncture.
- 1728 • Richard Harris, PhD: Dr. Harris will over the proper inclusion, use and interpretation of the QST
1729 modalities used in this project, and mentor Dr. Kong on the overall utility of involving QST in
1730 personalized medicine involving acupuncture.
- 1731 • Richard Olshen, PhD and Lu Tian PhD: The success of the project critically hinges upon the PI's
1732 ability to recruit adequate patients for each arm, manage data effectively, and analyze data via
1733 advanced statistical modeling. Drs. Olshen and Tian will provide close guidance to the PI and the
1734 research team to ensure all the above are achieved. They will also supervise the PI's training
1735 course in R-programming, machine learning and statistical modeling.

1736 All 5 mentors will receive progress report from the PI and provide feedback on the current study and the
1737 PI's development in QST, TCM clinical trials and interpretation of psychological determinants in clinical
1738 trials involving acupuncture. The mentors will meet annually via Bluejeans and will together ensure the

1739 proposed study is completed successfully within the proposed timeline and the PI is ready for her R-level
1740 propose by the end of year-3.

1741 13. PUBLICATION OF RESEARCH FINDINGS

1742 Publication of the results of this trial will be governed by the policies and procedures developed by the
1743 Executive Committee. Any presentation, abstract, or manuscript will be made available for review by the
1744 sponsor and the NCCIH prior to submission.

1745 14. REFERENCES

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1811 **15. SUPPLEMENTS/APPENDICES**

1812 Appendix 1 – Project Flow Chart

1813 Appendix 2 – QST Instruction Manual

1814 Appendix 3 – Acupuncture Provider’s Manual

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