STUDY PROTOCOL

Protocol Title:

Electroacupuncture for the management of symptom clusters in cancer patients and survivors (EAST): A feasibility study

Protocol Version: 2.2

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Protocol:

Electroacupuncture for the management of symptom clusters in cancer patients and survivors (EAST): A feasibility study [Version 2.0, dated August 10th, 2022]

Grantor:

Funding is provided by the California Breast Cancer Research Program (CBCRP) and the UCI Anti-Cancer Challenge.

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: Professor Alexandre Chan

Principal Investigator Signature: _____  _____

Date:

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1. ABSTRACT

Background: Many individuals in the United States (US) with a history of cancer are alive and cured of the disease. However, several cancer survivors frequently experience various physical and psychosocial symptoms after receiving chemotherapy. Introspection into the immune-oncological mechanisms that play a part in these symptoms helps us understand why these symptoms co-occur in cancer patients. Management of these symptom clusters remains challenging within the cancer treatment community. Issues such as the inability of pharmacological therapies to relieve concurrent symptoms remain prevalent as obstacles to discovering more beneficial therapies. There has been substantial headway in incorporating integrative oncology within cancer care in recent years. Particularly, acupuncture holds excellent potential in managing symptom clusters in cancer patients. Previous studies suggest that electro acupuncture, a variation of acupuncture, is more beneficial in symptom relief.

Objectives: To investigate the efficacy, safety, and feasibility of offering EA as an intervention to improve cancer-related symptoms (cognitive impairment, fatigue, psychological distress and insomnia) and quality of life among cancer patients and survivors receiving care at UCI Health.

Methods: Recruited patients will receive EA or sham-EA treatments depending on their randomized placement. For 14 weeks, patients will receive their respective treatments while providing blood samples and completing questionnaires and computerized cognitive tests at designated points in the study. Four weeks after the 10th and final treatment, a follow-up visit will be scheduled where the patients will again have blood drawn and complete the questionnaires and computer test to determine the effects of the study. In addition, they will fill out one final form describing their experience with the study during their last appointment. In a small group of participants, we will perform neuroimaging at baseline and after the final treatment.

2. SPECIFIC AIMS AND STUDY OBJECTIVES

The purpose of this study is to investigate the efficacy, safety, and feasibility of offering EA as an intervention to improve cancer-related symptoms (cognitive impairment, fatigue, psychological distress and insomnia) and quality of life among cancer patients and survivors receiving care at UCI Health. In addition, changes in biomarkers (plasma BDNF, pro-inflammatory cytokines and mitochondrial DNA) known to be associated with cancer-related symptoms. We hypothesize that EA is an effective, safe, and feasible intervention for cancer patients and survivors.

Our specific aims are as follows:

1. To compare the efficacy of EA versus sham-EA control in reducing cognitive toxicity, fatigue, psychological distress, insomnia, and to improve quality of life.

2. To evaluate the impact of EA versus sham-EA control on biomarkers, including circulating BDNF, pro-inflammatory cytokines (IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-alpha), mitochondrial DNA (oxidative stress indicator).

3. To compare the reduction of structural (brain gray matter) and functional connectivity at the prefrontal, medial temporal, and parietal brain regions pre- and post-EA treatment.

4. To assess the safety and feasibility of administering EA to manage symptom clusters in cancer patients and survivors.

5. As the UCI MINDS C2C registry (UCI IRB Approval #: HS# 2015-2494) will be leveraged to recruit some patients, we will quantify the characteristics associated with non-response to our study advertisement among C2C registrants using C2C-collected data.

3. INTRODUCTION

3.1 Background

In 2019, it was estimated that approximately 16.9 million US individuals with a history of cancer are alive and cured of cancer. With the advent of therapeutics in cancer and improved early detection of first malignancies, the number of cancer survivors is predicted to increase drastically over the next decade. Unfortunately, many survivors of cancer often experience a range of physical symptoms and psychosocial burden throughout and after chemotherapy treatment, of which fatigue, cognitive impairment, insomnia, and psychological distress are often the most prevalent. For example, **up to 49% of all breast cancer patients experience co-occurring symptoms, a phenomenon known as 'symptom clustering', implying the great overlaps of cognitive, affective, and somatic symptoms.** There is a large amount of evidence in the literature describing how these symptoms co-occur in cancer survivors. For example, there is strong evidence to support determinants of psychological distress (anxiety and depression) and cancer-related fatigue as predictors for perceived cognitive functioning. Similarly, somatic symptoms of fatigue and sleep disturbance can lead to mood disturbance, which may also contribute to cognitive disturbances.

The novel insights into the immune-oncological mechanisms underlying symptom clusters allow us to understand why these symptoms often co-occur in cancer patients. Biologically, stress, mood changes, fatigue and cognitive changes are part of the "cytokine-induced sickness behavior" observed in cancer patients. **Pro-inflammatory cytokine irregularities and mitochondria dysfunction are associated with cognitive complaints, depression, anxiety, and fatigue.** Particularly, high IL-6 is associated with poor executive function, whereas IL-6, IL-1RA, and TNF-α levels relate to fatigue ratings. Recent work has also suggested that chemotherapy leads to dysregulation of cytokines, which may provoke a neuroimmunoendocrine response that affects patients' mood and cognitive performance.

Management of symptom clusters remains a significant challenge within the cancer care community. Firstly, none of the current pharmacological therapies are capable to tackle multiple symptoms that patients are experiencing concurrently. For example, current pharmacological therapies to treat anxiety (such as benzodiazepines) are very specific to target a symptom and are unlikely to provide benefits for co-occurring symptoms such as fatigue and cognitive impairment. Likewise, although hypnotics (such as diphenhydramine or melatonin) are frequently prescribed to cancer patients and provide rapid relief to insomnia, however, they can also lead to other symptoms such as fatigue and cognitive impairment. Non-pharmacological modalities, such as exercise, have been routinely recommended by guidelines to manage symptoms such as cancer-related fatigue in cancer patients. However, the most ideal exercise regimen to recommend is currently unknown, and the needed potency in order to provide adequate symptomatic relief is unclear at this time.

Over the past few years, there is a significant growth of integrative oncology within cancer care. Integrative oncology is a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, including acupuncture, alongside conventional cancer treatments. **To address the current gaps in managing symptom clusters within cancer patients, integrative health practices such as acupuncture hold great potential.** Currently, guidelines are recommending the use of acupuncture to manage individual symptoms such as mood disturbances, fatigue, and pain. An improved variation of acupuncture, namely electroacupuncture (EA), is gaining traction within integrative health practices.

Current literature suggests that EA is more beneficial than traditional acupuncture to provide symptom relief. The clinical benefits associated with EA are likely to span across multiple symptom domains with synergistic effect. **However, there is a lack of clinical studies to evaluate whether EA is beneficial for managing multiple co-occurring symptoms in cancer patients.** Hence, we designed this pilot trial to study whether it is feasible to administer EA as an intervention for symptom clusters in our cancer population, and to evaluate the degree that EA could reduce symptom clusters and the possible underlying mechanisms through examining its influence on biomarkers that are linked with the symptoms.

3.2 Relevant Preliminary Data

1. **Using patient-reported outcome tools to assess symptom clusters in cancer patients**: We have optimized the numerous tools that will be used in our proposed study to describe the various cancer-related symptoms. Moving forward, these robust tools will be incorporated into the proposed study to ensure that we are accurately capturing the symptoms. This includes the Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog) v.3.0, Multidimensional *Fatigue* Syndrome Inventory-Short Form (*MFSI*-SF)[4] and Rotterdam Symptom Checklist (RSCL). Psychometrics and minimally clinical differences were established for all the tools.

2. **Symptom clustering and employment interference in breast cancer patients and survivors:** To study how cancer-related symptoms co-occur in patients, we have

conducted 2 studies. In a longitudinal cohort study of 131 breast cancer patients receiving chemotherapy, self-reported cognitive impairment was strongly associated with anxiety, fatigue, and biomarkers. More importantly, when we trended the trajectory of the four symptoms (cognition, fatigue, anxiety, and insomnia) over 15 months, we reported that the symptom profiles were very similar, suggesting that these symptoms are likely to co-occur, confirming the characteristics of symptom clustering. In another study, higher sleep disturbance scores were associated with both initial and ongoing employment interference in breast cancer patients. Survivors of breast cancer experience difficulty returning to normalcy as they are affected by poorly managed symptoms.

3. **Evaluating symptom-related biomarkers:** We have conducted numerous translational studies to evaluate the associations between various biomarkers and cancer-related symptoms in patients, providing us potential targets for our EA intervention.

Biomarker	**Findings**
Proinflammatory Cytokines	Elevation of TNF-α is associated with cognitive impairment and cancer-related fatigue during chemotherapy[4], while elevation of IL-6 and IL-8 was associated with persistent cognitive impairment post-chemotherapy in survivors.
Brain-derived neurotropic factor (BDNF)	Patients with higher plasma BDNF levels at the end of chemotherapy had lower odds of developing persistent overall subjective CRCI (OR = 0.74; 95% CI = 0.57–0.97) and persistent CRCI in the functional interference domain (OR = 0.62; 95% CI = 0.39–0.98).
Mitochondria DNA	Reduction of mtDNA level was associated with 4% increased risk for worsening of CRF.

Based on our previous prospective cohort study (Ng et al. 2017) which characterized the long-term trajectory of self-perceived cognitive impairment among early-stage breast cancer patients, we observed that approximately half of the breast cancer patients reported cognitive impairments during and post-chemotherapy, and up to one-third experienced deficits at 15 months post-treatment. In another study that interviewed breast cancer patients via focus group discussions (Cheung et al. 2012), many of them experienced memory loss, difficulty in decision making and speech problems after chemotherapy which had affected their quality of life. In another cohort study, we have observed that 1 out of 4 (23.8%) of the cancer patients experienced clinically significant fatigue after chemotherapy. (Toh et al., 2019) CRCI, CRF and insomnia are real but insidious complications of cancer and chemotherapy that need to be managed during cancer treatment and survivorship care.

3.3 Importance

The findings of this study will inform us the preliminary efficacy of EA at ameliorating cognitive impairment, fatigue, psychological distress and insomnia in cancer and provide preliminary data required for the conduct of a larger multi-centered clinical trial. Ultimately, we aim to develop an intervention that can address cancer-related symptoms that, for the longest time, do not have evidence-based interventions for treatment.

4. METHODOLOGY

4.1 Study Design

This is a randomized sham-controlled, patient and assessor-blinded pilot trial. Participants will be stratified by recruitment sites [UCI (n=34) or CHOC (n=30)] and randomized in random blocks of 4 or 6 to receive either weekly EA (treatment arm) or weekly sham-EA (control arm).

A research assistant who is not involved in the study will perform the allocation to either arm using the computer-generated randomization sequence in a double-blind manner. The participants and outcome assessors are blinded to the treatment allocation, only the acupuncturist will be aware of treatment allocation the randomization codes.

4.2 Study Definitions

Cognitive function – cognitive function will be measured using two types of cognitive assessments.

- Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog v.3.0) – FACT-Cog assesses subjective cognitive impairment. This validated questionnaire contains 33 items in the domains of concentration, functional interference, mental acuity, memory, multitasking and verbal fluency. there are four other scoring subscales: perceived cognitive impairments (PCI; 18 items); perceived cognitive abilities (7 items); impact of perceived cognitive impairment on QOL (4 items); and comments from others on cognitive function (4 items). Both total and PCI scores will be calculated in this study. Total score is calculated by summing scores from all the items and ranges from 0-148, and higher scores represent better subjective cognitive functioning. Similarly, PCI score is calculated by summing responses of all relevant items and ranges from 0 to 72. Overall impairment in self-perceived cognitive function is defined by a reduction of ≥10.6 points in the global score prior to study initiation. In addition, a PCI score of less than 60 will also be used to identify CRCI cases.

- CANTAB® – CANTAB® is a computerized objective assessment containing five tests: reaction time, paired associates learning, spatial working memory, attention switching task, and rapid visual information processing that assesses response speed, learning and memory, working memory, multitasking, and sustained attention. Using

International Cognition and Cancer Task Force (ICCTF criteria), overall cognitive impairment is defined as ≥ 2 standard deviations below normative mean on at least 1 cognitive test or ≥ 1.5 standard deviations below normative mean on 2 or more tests. Impairment of each individual CANTAB® domains will be defined as ≥ 1.5 standard deviations below the normative mean. Further, the reliable change index (RCI) score will be calculated using test–retest reliability and the standard error of the difference to control for practice effect in repeated objective cognitive assessments.

Fatigue - Multidimensional Fatigue Syndrome Inventory-Short Form (MFSI-SF) – This validated questionnaire consists of 30 items and has 5 subscales, each with 6 items: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigour. The total score is obtained by subtracting the vigour subscale from the sum of all the dimensions (total score range from 24 to 96), with a higher score indicating higher fatigue level.

Psychological distress and insomnia - The Rotterdam Symptom Checklist (RSCL) will be used to measure the symptoms that may confound with cognition (such as psychological distress and fatigue). It covers 4 domains: physical symptom distress (23 items), psychological distress (7 items), activity level (8 items) and overall global life quality (single item). Each response is given a 4-point Likert scale. The scores are transformed on a 100-point scale for comparison using the formula: [(raw score-minimum raw score) / (maximum-minimum score) x 100]. Psychological distress is indicated by a score of >16 in the psychological domain. Insomnia is measured by a single item in the checklist.

Quality of Life (QOL)

- EORTC QLQ-C30 – This validated questionnaire was developed to assess cancer patients' health-related QoL. It incorporates 5 functional scales (cognitive, emotional, physical, role, and social), symptom scales (eg. pain, fatigue, insomnia), and a global health scale. Higher functional, and global health scores, and lower symptom scores represent better quality of life.

- EQ-5D comprises a visual analog scale of general health status ranging from 0 (worst imaginable) to 100 (best imaginable) and a descriptive system based on five dimensions of health status: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D descriptive index responses were mapped into a single dimension health utility index (UI) ranging from death (0) to full health (1), with health states worse than death being possible (<0), by using utility weights for the US population.

Plasma BDNF and cytokine levels - Plasma BDNF and cytokines (IL-1β, IL-4, IL-6, IL_8, IL-10, TNF-alpha) levels will be quantified using commercially available ELISA kits.

Mitochondrial DNA quantification - Mitochondrial DNA, a biomarker for fatigue and oxidative stress will be quantified using the quantitative PCR method.

Neuroimaging – Gray matter and white matter volumes, diffusional tensor imaging (DTI) measures (mean diffusivity, fractional anisotropy, and radial and axial diffusivities) and resting state functional connectivities of different neural networks.

Recruitment – Recruitment will be evaluated as the number of participants recruited (% of target recruitment) and rate of recruitment per month. Reasons for declining the participation will also be documented.

Compliance – Compliance is measured as the number of acupuncture sessions successfully completed, and proportion (%) of participants completing the acupuncture sessions.

Safety monitoring – Participants will be monitored for adverse events including bruising, pain or discomfort, bleeding and possible infections. Severity of symptoms are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V5.

Blinding and patient acceptance – After completion of 10 weeks of EA/sham-EA, all study participants will complete a questionnaire evaluating their perceptions towards the EA treatment. Participants will be asked whether they believe that they received EA or sham-EA, if they are satisfied and benefited from the treatment and whether they would consider undergoing treatment again outside of a trial setting.

Non-response to study advertisement (C2C) – C2C registrants who reply that they are not interested with our EA study or did not reply regarding their interest will be considered as non-responders to our study advertisement.

Patient characteristics (C2C) – Characteristics that may be associated research participation include demographics, medical history, cancer history, psychiatric history, neurological history, and lifestyle (exercise, diet and sleep).

Types of interested studies (C2C) – C2C registrants were asked about whether they are interested to hear about studies involving approved medication, investigational medication, altering diet or lifestyle, blood draws, cognitive testing, magnetic resonance imaging, Positron Emission Tomography, lumbar puncture, and autopsy after death.

Perception towards medical research (C2C) – C2C registry responses to questions regarding their view of medical research, between cancer and non-cancer participants, will be assessed. A summary score that ranges from 7 to 35 will be computed, with higher scores representing more positive research attitudes.

4.3 Study Location

Administration of treatment will be conducted at one of the following sites:

- Susan Samueli Integrative Health Clinic
- UCI Health – Yorba Linda
- UCI Health – Newport Beach

- UCI Health Pacific Breast Center

Participants who are also eligible for and agreed to join the neuroimaging substudy will also proceed to the Facility for Imaging & Brain Research (FIBRE) at UCI (Director: Dr. Craig Stark) at baseline and after the end of treatment.

4.4 Research Procedures

1. Following completion of informed consent, study participants will be asked to complete a baseline data collection form. Clinical information regarding cancer diagnosis and treatment will be extracted from the patient's medical record by approved study personnel.

2. Participants will be stratified by recruitment sites [UCI (n=34) or CHOC (n=30)] and randomized in random blocks of 4 or 6 to receive either twice weekly EA (treatment arm) or weekly sham-EA (control arm). Only the acupuncturist will be aware of the treatment allocation, both participants and assessors will remain blinded.

3. Each participant will attend a total of 10 treatment visits (one visit per week), over the course of 10 weeks. Each EA or sham-EA session will be approximately 1 hour. Participants in the treatment arm will receive EA at 13 standardized acu-points that were chosen for their therapeutic effects. Participants in the control arm will receive electrical stimulation at non-disease related acu-points. This strategy will overcome the issue that sham-control may elicit placebo therapeutic effects. Table 1 displays more information about the acu-points and procedures of EA and sham-EA. During their visit, patients will be monitored for adverse events such as bruising, pain or discomfort, bleeding, and possible infections. Severity is graded according to the Common Terminology Criteria for Adverse Events V5. Any unanticipated problems will be submitted to the IRB via the unanticipated problems (UP) report as well as to the CFCCC within 5 business days upon the Lead Researcher's knowledge of the event.

Table 1: Treatment procedures and acu-points of EA and sham-EA

Intervention (EA)	**Control (Sham-EA)**
With electrical stimulation	*Non-disease related points with electrical stimulation*
Shenting (GV24), Baihui (DU20), Sinshencong (EX-HN1), Zhongwan (CV12), Guanyuan (CV4), Neiguan (PC6) bilateral, Shenmen (HT7) bilateral, Zusanli (ST36) bilateral, Sanyinjiao (SP6) bilateral, Taixi (KI3) bilateral, Zhaohai (KI6) bilateral, Hegu (LI4) bilateral, Taichong (LIV3) bilateral	Pianli (LI6) bilateral, Wenliu (LI7) bilateral, Fuyang (BL59) bilateral, Kunlun (BL60) bilateral, Sanyangluo (TE8), Sidu (TE9) bilateral, Daheng (SP15) bilateral

The selection of acupoints is based on the experience of experts and previous basic and clinical research. Baihui (DU20), with or without Shenting (GV24), alleviates cognitive impairment by increased antioxidant and anti-inflammatory effects, inhibits NF-κB mediated neuronal cell apoptosis, and enhances expression of BDNF. Baihui (DU20) in combination with Renzhong (GV26), Hegu (LI4), and Zusanli (ST36) can promote the recovery of neurological impairment after traumatic brain injury by activating BDNF/TrkB signaling pathway. Baihui (DU20), Shenting (DU24), Hegu (LI4), Zusanli (ST36) and other acupoints applied in this study including Sishencong (EX-HN1), Taixi (K13), Neiguan (PC6), Taichong (LR3) have shown effectiveness in improving CRCI in several clinical research studies. Zhongwan (CV12) and Guanyuan (CV4) may relieve the degree of fatigue in patients undergo chemotherapy. Zusanli (ST36) in combination with Hegu (LI4), and Sanyingjiao (SP6) or Neiguan (PC6) may effectively improve fatigue. Sanyinjiao (SP6) and Shenmen (HT7) reduce insomnia level through increased GABA and GABA(A)R expression or by reducing the hormones associated with the HPA axis. Zhaohai (KI6) in combination with Sishencong (EX-HN1), Neiguan (PC6), Shenmen (HT7), Zusanli (ST36), Sanyinjiao (SP6), Taichong (LR3) improve depression in cancer patients.

4. Four data collection time points are planned for each participant:(1) baseline, (2) mid-treatment (5 weeks from baseline), (3) end of treatment (10 weeks from baseline), and (4) 4 weeks after end of treatment (14 weeks from baseline). At each time point, 10mL of peripheral blood will be collected for blood biomarkers assessment. Additionally, each participant will complete five questionnaires (FACT-Cog Version 3, MFSI-SF, RSCL, EORTC QLQ-C30, and EQ-5D) and one computerized cognitive test (CANTAB) to evaluate cognitive function, fatigue level, sleep quality, psychological distress, and quality of life. Figure 1 summarizes the study design and assessment time points for the planned study. Completion of these questionnaires and blood draw will take approximately 45 minutes.

5. Neuroimaging will be optional for all participants and for participants who met the additional neuroimaging exclusion criteria. Neuroimaging will only be acquired at baseline (T1) and at the end of treatment (T3). All neuroimaging studies described below will be performed using a 3T Siemens Prisma scanner at FIBRE at UCI (Director: Dr. Craig Stark). We will perform rsfMRI, FLAIR, diffusion weighed, T1-weighted and T2-weighted sequences as per the ADNI-3 MRI protocol, to evaluate structural quantification, white matter integrity (mean diffusivity, fractional anisotropy, radial and axial diffusivities) and functional connectivity of the neural networks. In addition, we will perform CEST MRI a technique that has been widely used to study brain metabolism to assess potential changes in metabolites. Data pre-processing and analyses will follow standardized techniques in the field in the use of the Stark Lab and the FIBRE center. Participants will be notified if there are any incidental findings.

6. Additionally, upon 10 weeks of EA/sham-EA, participants will be asked to complete an additional form evaluating their acceptance towards EA and to verify subject blinding maintenance.

7. At the 14-week visit, blood drawing and completion of four questionnaires and CANTAB® will be performed as well.

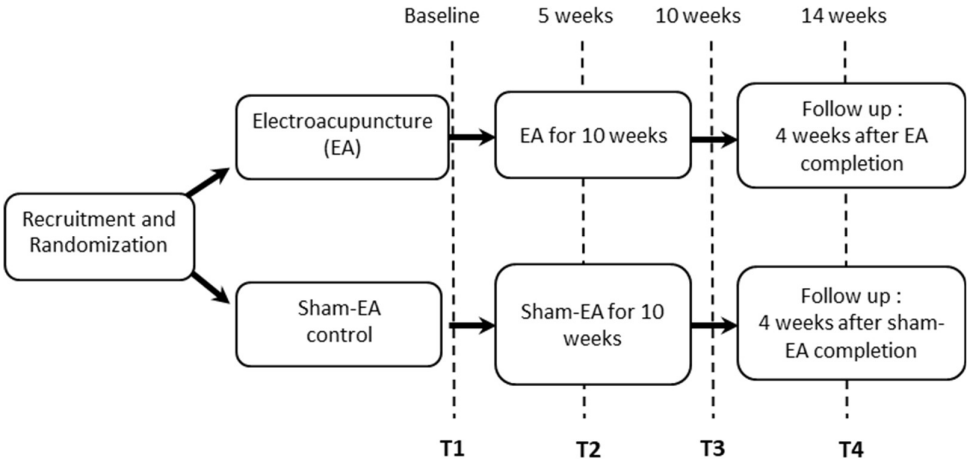

Figure 1: Study assessment time points (T1 denotes time point 1, T2 time point 2 and so on). The duration of this study is approximately 14 weeks, composed of a 10-week treatment period and a study completion visit at 14 weeks.

4.5 Data Collection Instruments

- Baseline demographics and clinical characteristics data collection form
- Patient acceptance and blinding assessment questionnaire
- Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) Version 3
- Multidimensional Fatigue Syndrome Inventory-Short Form (MFSI-SF)
- Rotterdam Symptom Checklist (RSCL)
- European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
- European Quality of Life-5 Dimensions Questionnaire (EQ-5D)
- Cambridge Neuropsychological Test Automated Battery (CANTAB)
- 3T Siemens Prisma scanner

4.6 Outcome Variables

Primary outcome variable:

- **Subjective cognitive function –** All subjects will complete the FACT-Cog version 3 questionnaire to assess self-perceived subjective cognitive function.

Secondary outcome variables

- **Objective cognitive function –** All subjects will complete CANTAB®, to assess objective cognitive functions. CANTAB® is a computerized cognitive testing software to assess various cognitive domains. Both subjective and objective assessments are recommended by the International Cognition and Cancer Task Force (ICCTF).

- **Fatigue –** MFSI-SF is a validated questionnaire that comprises of 30 items and contains 5 subscales, each with 6 items: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor.

- **Psychological distress and insomnia** – The Rotterdam Symptom Checklist (RSCL) will be used to measure the psychological symptoms (anxiety and depression) and insomnia. Psychological distress is indicated by a score of >16 in the psychological domain. Insomnia is measured by a single item in the checklist.

- **Quality of life –** EORTC QLQ-C30 is a validated questionnaire developed to assess cancer patients' health-related quality of life. It incorporates 5 functional scales (cognitive, emotional, physical, role, and social), symptom scales (e.g. pain, fatigue, insomnia), and a global health scale. EQ-5D comprises a visual analog scale of general health status and a descriptive system based on five dimensions of health status: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

- **Safety monitoring** – Participants will be monitored for adverse events such as bruising, pain or discomfort, bleeding and possible infections. Severity are graded according to the Common Terminology Criteria for Adverse Events V5.

- **Biomarkers – <u>Plasma BDNF and cytokines</u>** (IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-alpha) levels will be quantified using commercially available ELISA kits. **<u>Mitochondrial DNA</u>** will be quantified using the quantitative PCR method.

- **Neuroimaging –** Gray matter and white matter volumes, diffusional tensor imaging (DTI) measures (mean diffusivity, fractional anisotropy, and radial and axial diffusivities) and resting state functional connectivities of different neural networks.

- **Feasibility of EA (recruitment, compliance, blinding and patient acceptance)**

    - ***<u>Recruitment:</u>*** Recruitment will be evaluated as the number of participants recruited (% of target recruitment) and rate of recruitment a month. Reasons for declining the participation will also be documented. Additionally, time spent on recruitment will be examined to assess recruitment productivity.

    - ***<u>Compliance:</u>*** Compliance is measured as the number of acupuncture sessions successfully completed, and the proportion of participants completing the scheduled acupuncture sessions.

    - ***<u>Blinding and patient acceptance:</u>*** all study participants will complete a questionnaire evaluating their perceptions towards the EA treatment at the end

of study period. Participants will be asked whether they believe that they have received EA or sham-EA, if they are satisfied and benefited from the treatment, and whether they would consider undergoing treatment again outside of a trial setting.

- **Non-response bias (UCI MINDS C2C)**
    - ***Non-response to study advertisement:*** C2C registrants who reply that they are not interested with our EA study or did not reply regarding their interest will be considered as non-responders to our study advertisement.
    - ***C2C registrant characteristics:*** Registrant characteristics that may be associated with non-response include demographics, medical history, cancer history, psychiatric history, neurological history, lifestyle behaviors (exercise, diet and sleep), interested research procedures (approved medication, investigational medication, altering diet or lifestyle, blood draws, cognitive testing, magnetic resonance imaging, Positron Emission Tomography, lumbar puncture, and autopsy after death), and perception towards medical research.

4.7 Data Analysis

Aim 1: To compare the efficacy of EA versus sham-EA control in reducing cognitive toxicity, fatigue, psychological distress, insomnia, and in improving quality of life.

FACT-Cog, CANTAB, MFSI-SF, RSCL, EORTC QLQ-C30 and EQ-5D scores will be presented as median, mean, standard deviation, minimum and maximum at each assessment time point. Box plots and histograms will be generated for each score. The number of people with overall cognitive impairment based on FACT-Cog and CANTAB scores will be presented in counts, percentages, and confidence intervals. All the descriptive statistics and the graphical displays will be constructed for the entire cohort and stratified by treatment allocation.

All the mean scores will be compared before and 5, 10 and 14 weeks after acupuncture therapy for EA and sham-EA control groups. The mean score changes will also be compared between the EA and sham-EA control groups at 5, 10 and 14 weeks after baseline. Biomarkers (BDNF, cytokines and mitochondrial DNA level) changes will be compared between treatment groups.

Mixed effects model, with random intercepts for individual patient, will be generated to evaluate the changes in of symptoms and biomarkers overtime, and its association with the treatment allocation (EA or sham-EA). The covariates of interest will include a treatment indicator (EA vs sham-EA), the duration between the beginning of the latest chemotherapy cycle and the start of EA/sham-EA treatment, the indicator of the EA intervention time point (timept) and the interaction terms which include treatment X duration, treatment X timept, and duration X timept. Patients who have yet to complete their chemotherapy treatment will be imputed with zero for the variable time from end of chemotherapy. Both intention-to-treat and per-protocol analyses will be conducted.

Aim 2: To evaluate the impact of EA versus sham-EA control on biomarkers, including circulating BDNF, pro-inflammatory cytokines (IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-alpha), mitochondrial DNA (oxidative stress indicator).

Scatter plots of BDNF, cytokines and mitochondrial DNA levels will be plotted against FACT-Cog, CANTAB, MFSI-SF, RSCL, EORTC QLQ-C30, and EQ-5D scores. All the descriptive statistics and the graphical displays will be constructed for the entire cohort and stratified by treatment allocation. Mixed effects model, with random intercepts for individual patient, will be generated to evaluate the changes in of symptoms and biomarkers overtime, and its association with the treatment allocation (EA or sham-EA). The covariates of interest will include a treatment indicator (EA vs sham-EA), the duration between the beginning of the latest chemotherapy cycle and the start of EA/sham-EA treatment, the indicator of the EA intervention time point (timept) and the interaction terms which include treatment X duration, treatment X timept, and duration X timept. Patients who have yet to complete their chemotherapy treatment will be imputed with zero for the variable time from end of chemotherapy. Both intention-to-treat and per-protocol analyses will be conducted. All the descriptive statistics will be constructed for the entire cohort and stratified by the treatment allocation.

Aim 3: To compare the reduction of structural (brain gray matter) and functional connectivity at the prefrontal, medial temporal, and parietal brain regions pre- and post-EA treatment.

To determine the structural alterations associated with chemotherapy, group comparisons of pre-post differences in gray matter and white matter volumes, DTI measures (mean diffusivity, fractional anisotropy, and radial and axial diffusivities), and resting state functional connectivity of different neural networks will be performed both in a priori regions of interest based on prior research and in whole-brain analyses (correcting for multiple comparisons).

Aim 4: To assess the safety and feasibility of administering EA to manage symptom clusters in cancer patients.

Descriptive statistics, presented as counts, percentages, and confidence intervals will be used to analyze the safety outcomes. Descriptive statistics will be used to analyze the feasibility outcomes. Categorical variables (participants recruited, acupuncture sessions completed, participants completing all sessions, adverse events, patient responses to acceptability questionnaire) will be analyzed using descriptive statistics and will be presented as counts, percentages, and confidence intervals. All the descriptive statistics will be constructed for the entire cohort and stratified by the treatment allocation.

Aim 5: As the UCI MINDS C2C registry (UCI IRB Approval #: HS# 2015-2494) will be leveraged to recruit some patients, we will quantify the characteristics associated with non-response to our study advertisement among C2C registrants using C2C-collected data.

Using the C2C registry, cancer patients and survivors will be identified, and regression models will be generated to identify predictors associated with response and non-response to our study. AIC and BIC will be used to guide model building and selection. The performance metrics of the final model, as well as coefficients, 95% confidence intervals and p-values of the selected predictors will be presented.

The significance level of 0.05 will be used, and all statistical analyses will be performed using Stata v. 16 and R v. 4.1.3.

4.8 Anticipated Risks and Benefits

EA and Sham-EA Treatment Risks:

The current and frequency used are very low and participants will likely only experience a slight tingling feeling. Electroacupuncture has a very low incidence of side effects. This is, in part, because the diameter of acupuncture needles is very small (0.20-0.25 mm, which is equivalent to 32 gauge). The needles used in the acupuncture are new, sterile needles so there is no chance of contracting a disease, such as AIDS or hepatitis as a result of this study.

Foreseeable risks and discomforts include:

Likely

- Very mild discomfort might occur during removal of the electrodes stuck to the skin.
- Mild discomfort including a feeling of heaviness, swelling, soreness, or numbness
- The presence of <1-2 drops of blood following needle removal

Less Likely

- Slight pain, bruising, bleeding or discomfort may occur from needle insertion and removal.

Rare

- Infection at needle insertion site

Severity of adverse events will be graded according to the Common Terminology Criteria for Adverse Events V5, as follows:

Bruising – A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.

- Grade 1: Localized or in a dependent area
- Grade 2: Generalized

Pain - A disorder characterized by the sensation of marked discomfort, distress or agony.

- Grade 1: Mild pain
- Grade 2: Moderate pain; limiting instrumental activities of daily living
- Grade 3: Severe pain; limiting self care activities of daily living

Skin Infection - A disorder characterized by an infectious process involving the skin such as cellulitis.

- Grade 1: Localized, local intervention indicated
- Grade 2: Oral intervention indicated (e.g. antibiotic, antifungal, or antiviral)
- Grade 3: IV antibiotic, antifungal, or antiviral intervention indicated
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death

Randomization: Study participants will be allocated randomly to either the EA or sham-EA arm. The sham-EA is chosen as control to account for potential biases and placebo effects. A research assistant who is not involved in the study will perform the allocation to either arm using the computer-generated randomization sequence in a double-blind manner. The participants and outcome assessors are blinded to the treatment allocation, only the acupuncturist will be aware of treatment allocation the randomization codes.

Control: During this study there is a 50% chance that participants will receive sham-EA treatments. This could lengthen the amount of time before they receive a treatment that may be effective. During this time participants may experience worsening of their condition, including increased symptoms such as cognitive issues. The researchers will carefully monitor participants' condition. If participants' symptoms worsen and make them uncomfortable, they can withdraw from the study.

Blood draw: Removing blood by a needle may cause temporary pain, bruising, bleeding, swelling, dizziness, and on rare instances fainting or infection.

Psychological discomforts: Some of the procedures may cause embarrassment or anxiety, or the questions the researchers ask participants may be upsetting or make them uncomfortable. If participants do not wish to answer a question, they can skip it and go to the next question. If participants do not wish to participate you can stop.

MRI: The MRI procedure uses a powerful magnetic field to generate detailed images of the body. The magnet could move objects within the participant's body that contain metal, such as implants, clips and pacemakers.

MRI scanning is painless, but participants might experience discomfort in the machine. Participants may be bothered by feelings of claustrophobia when placed inside the MRI, or by lying in one position for a long time. In addition, loud noises occur during the study when the scanner is collecting measurements. These noises are beeping and hammering sounds and may bother the participants. Temporary hearing loss has been reported from this loud noise when ear protection is not used. Therefore, participants will be asked to wear ear plugs.

Reproductive Risks: Participants should not get pregnant while in this study. The EA/sham-EA used in this study could harm an unborn baby. Participants should also not breastfeed a baby while in this study.

4.9 Measures to minimize risks/discomforts

If a patient becomes pregnant during the study, there may be unknown risks to the unborn child. By signing the consent form, the patient confirms to the best of her knowledge that she is not pregnant now, nor does she intend to become pregnant (or nurse an infant) during involvement in the study. Women of childbearing potential should use a medically acceptable form of birth control during her participation in the study. The acting physician and the patient will discuss available methods.

During explanation of the study procedures to study participants, clear instructions will be provided regarding all aspects of the study, including the randomization procedure, the EA and sham-EA treatment, blood drawing and questionnaires. The acupuncturist will show the participant the small acupuncture needles and will explain the procedures of the study, including the low current stimulation, and the feelings that they may encounter when needles are inserted into the acupoints, etc. This type of explanation helps to mitigate the psychological stress experienced by some patients.

All questions and concerns raised by participants will also be addressed by the study team member prior to initiation of any study procedures. Furthermore, all study personnel will complete the UCI Human Subjects and HIPAA training required by the IRB of all individuals working on studies that require contact with human subjects. All study personnel will be trained in confidentiality protocol procedures.

To ensure data confidentiality, the CANTAB data set will be coded without subject identifiers and will be stored in secured servers hosted by CANTAB with 2 levels of password protection for access to the iPad itself and the CANTAB application. Only key study personnel will have access to the device that is secured in a locked file cabinet in locked office at the Pharmacy Department. All hardcopy questionnaires will be coded without subject identifiers and stored in the locked office at the Pharmacy Department. Only investigators based in the study sites will have access to the iPad or the questionnaires. The code key will be kept separately and encrypted with password protection and stored electronically in highly secure and HIPAA-compliant servers hosted by UC Irvine with access limited to key study personnel.

4.10 Data and Safety Monitoring Plan

This is a **risk level 3 study**, as defined in the Chao Family Comprehensive Cancer Center (CFCCC) Data and Safety Monitoring Plan (DSMP) because it is an investigator-initiated interventional trial with minimal risk.

The Principal Investigator (PI), co-investigator, clinical research coordinator, and statistician are responsible for monitoring of data and safety for this study. For studies that have stopping rules for safety and efficacy, the PI will be responsible for the implementation and make changes as applicable. The CFCCC Data and Safety Monitoring Board (DSMB) is an independent body responsible for the safety of study subjects as well as the data integrity of the protocol. Data and safety will be reported to the DSMB with submission of progress reports that include aggregated reports of adverse events, serious adverse events, deviations, and violations. In addition, certain adverse events, serious adverse events, deviations, violations, and unanticipated problems will be reported promptly to the DSMB for review according to the tables below.

The CFCCC Stern Center for Cancer Clinical Trials and Research Quality Assurance Unit will conduct monitoring and auditing activities as per the UC Irvine CFCCC Quality Assurance Monitoring and Auditing Plan and at the discretion of the CFCCC DSMB in order to ensure patient safety and data integrity oversight. By conducting internal monitoring and auditing, the CFCCC will ensure compliance with high quality standards and all applicable regulations, guidelines, and institutional policies. Trial monitoring and auditing may be completed remotely or on-site.

Risk Levels

Risk Level	Definition	Monitoring
Level 1	**High Risk** - UCI investigator-initiated interventional trials for which the PI holds Investigational New Drug (IND) or Investigation Device Exemption (IDE). Example: Gene therapy, dendritic cell products from GMP suite, phase I/II development and phase I studies, first in human, etc.	Two months after subject enrollment
Level 2	**Medium Risk** - UCI investigator-initiated interventional trials for which IND/IDE is exempt by FDA. Example: Use of commercially available agents for an unapproved indication.	Six months after subject enrollment

Level 3 .	**Low Risk –** UCI investigator-initiated interventional trials that are minimal risk. Example: Phase III clinical studies, dietary intervention trials, and after-market studies.	Twelve months after subject enrollment
Exempt	Studies that are industry-sponsored, NCTN-sponsored, and/or trials that are monitored by an external DSMB.	N/A

Recording of Events

Adverse events, serious adverse events, deviations, violations, and unanticipated problems must be entered into the clinical trial management system (CTMS), OnCore. Adverse events and serious adverse events will be collected from the time the research patient begins treatment until 4 weeks after the end of treatment. All adverse events/serious adverse events should be followed until resolution or stabilization.

Event Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [Modified from the definition of unexpected adverse drug experience in FDA regulations at 21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Serious Adverse Event (SAE) [21 CFR 312.32] - defined as any expected or unexpected adverse event that result in any of the following outcomes:

- Death
- Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred)

- Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization

- A persistent or significant disability/incapacity

- A congenital anomaly/birth defect

- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) - Any incident, experience or outcome that meets all three of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; AND

2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); AND

3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Protocol Violation - A protocol violation is an accidental or unintentional change to or noncompliance with the IRB-approved protocol that increases risk or decreases benefit and/or affects the subject's rights, safety, welfare, and/or the integrity of the data. Examples of incidents that may be considered violations include: enrolling a participant who does not meet the inclusion criteria; obtaining verbal consent before the initiation of study procedures when the IRB requires signed, written informed consent; and failure to collect screening labs before initiation of study procedures [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

Protocol Deviation - a protocol deviation is an accidental or unintentional change to the research protocol that does not increase risk or decrease benefit or have a significant effect on the participant's rights, safety or welfare, or on the integrity of the data. Deviations may result from the action of the participant, researcher, or staff. Examples: a rescheduled study visit, an omitted routine safety lab for a participant with previously normal values; or failure to collect an ancillary self-report questionnaire data (e.g., quality of life) [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

Reporting Requirements to the CFCCC DSMB

Unanticipated Problems

Event Type	Reporting Timeframe
Unanticipated Problems	5 business days from the date the PI is aware of the event

Adverse Event/Serious Adverse Events

Event Type	Reporting Timeframe
Serious Adverse Events (all attributions) that meet all of the following criteria: ▪ Unexpected ▪ Grades 3-5 ▪ Occurring during treatment or within 30 days of the end of treatment*	5 business days from date the PI is aware of the event
Adverse Events that meet all of the following criteria: ▪ Unexpected ▪ Study related (possibly, probably, or definitely) ▪ Grades 3-4 ▪ Occurring during treatment or within 30 days of the end of treatment*	5 business days from date the PI is aware of the event
All other Adverse Events and Serious Adverse Events should be reported as noted in the 'Recording of Events' section	Prior to each scheduled progress review
** Investigators are not obligated to actively seek information regarding the occurrence of new AEs or SAEs beginning after the 30-day post-treatment period. However, if the investigator learns of such an event and that event is deemed relevant to the study, he/she should promptly document and report the event.*	

Deviations/Violations

Event Type	Reporting Timeframe
Violations as defined above (e.g. wrong dosage of drug administered, safety procedures not being conducted at specific time points)	5 business days from the date the PI is aware of the event
Deviations as defined above, including: ▪ Planned deviations (e.g. rescheduling a visit that will be out of window due to a holiday) ▪ Unplanned deviations (e.g. rescheduled visit, a missed routine safety laboratory test for a participant with previously normal values)	Prior to each scheduled progress review

Reporting Requirements to UCI IRB

Report adverse events, serious adverse events, violations, and deviations within 5 business days if the event/incident met the criteria for an unanticipated problem (UP). The current policy can found at the following link: UCI Office of Research

Recording of Events

- The participating institution must enter the above events into OnCore, according to the reporting requirements of the CFCCC DSMB noted above.

Quality Assurance

- The coordinating center PI (sponsor) is primarily responsible for ensuring the study is conducted according to the investigational plan and protocol.
- Quality Assurance activities (QA monitoring and auditing) will be conducted as per UC Irvine Chao Family Comprehensive Cancer Center Quality Assurance Monitoring and Auditing Plan in order to ensure patient safety and data integrity oversight.
- The participating institution should follow their own internal quality assurance policies in order to monitor patient safety and data integrity oversight.
- The participating institution must permit study-related monitoring and auditing and provide access to study-related materials. Trial monitoring and auditing will be

performed by the UC Irvine CFCCC Stern Center for Cancer Clinical Trials and Research Quality Assurance Unit.

Trial monitoring and auditing may be completed remotely or on-site

Potential Benefits

If participants are randomized to the group that receives EA and it proves to treat their condition more effectively than the sham-EA, they may benefit from participating in the study, but this cannot be guaranteed.

This study will help researchers learn more about EA, and it is hoped that this information will help in the treatment of future cancer patients with complex cancer symptoms.

5. ADDITIONAL INFORMATION ON METHODOLOGY

5.1 Alternatives to Participation

There are no standard of care alternatives available that study participation would preclude participants from utilizing, however, individuals may have the option to participate in another experimental clinical study if one is available.

5.2 Subject Costs

This study involves interaction/intervention with research subjects; however there are no costs to subjects/insurers.

5.3 Compensation

Compensation will be provided to subjects in the form of cash/gift certificate.

Subjects will be compensated with the following schedule and amounts:

Participants will be paid $20 at 5 weeks into the treatment, $20 for completion of the treatment and $10 after the final study visit at 4 weeks after the end of the treatment. Total compensation for participation in the entire study is $50. For subjects who participated in neuroimaging, they will be given an additional $50 upon the completion of the neuroimaging procedures for travel expenses. If the subject decides to withdraw from the study or is withdrawn by the research team, they will receive compensation for the visits and/or procedures that they have completed.

5.4 Data Security, Storage and Confidentiality

All data will be stored electronically and maintained on the highly secure and HIPAA-compliant servers hosted by UC Irvine. All data will be coded, and subject identifiers will be kept separately from the data. These data files will be encrypted with password protection with access limited to key study personnel.

In order to administer our questionnaires electronically, we must use the REDCap Mobile Application. REDCap can be installed on the study team's iPad so that data may be collected in an offline fashion and temporarily stored locally on that device. REDCap employs encryption-at-rest on the mobile device's hard drive so that all important data and information stored on the device is properly protected from unauthorized or malicious users. Immediately following survey administration on the study iPad, the study team will navigate to the pharmacy area, connect to the internet, and sync the data into the project on the secure REDCap server. All data in the REDCap that is downloaded from or uploaded to a REDCap server is transmitted using the REDCap API, which is a RESTful web service API. Therefore, as with all REDCap API requests, data transmitted to/from the app is done using a secure, encrypted transmission (SSL/HTTPS). No subject identifiers will be collected on the iPad and REDCap.

The iPad is secured with 2 levels of password protection for access to the iPad itself and the REDCap. Only key study personnel will have access to the device that is secured in a locked office at the Pharmacy Department. In terms of administering our computerized cognitive tests, we will be using CANTAB, which provides data security measures such as encrypting data at rest, using HTTPS encryption for all data transfers, only permitting authorized users access to study data, and having secure servers in HIPAA/GDPR compliant private cloud. CANTAB will also be used on the same iPad as REDCap.

5.5 Confidentiality of Research Biospecimens/Data

- Information will be maintained electronically. Information will be password protected and maintained in an encrypted format. *Researchers may access UCI-contracted data sharing and storage tools through UCI OIT.*
- Information will be maintained in hard copy. Information will be stored in a locked area that is not accessible to non-study team members.
- Biospecimens will be stored in a locked lab/refrigerator/freezer that is not accessible to non-study team members.

5.6 Location of Biospecimen Storage

Biospecimens will be stored at the Susan Samueli Integrative Health Institute for 1 month before transportation to Acharya's laboratory on campus.

5.7 Subject Identifiers Retained with Biospecimens Collected for the Research Study

- Dates
- Medical record numbers

A code will be used (i.e. information and/or biospecimens will be coded). **Subject identifiers** will be **kept separately** from the information and/or biospecimens. The code key will be destroyed at the earliest opportunity, consistent with the conduct of this research.

5.8 Information and/or Biospecimen Access

Authorized UCI personnel such as the research team and appropriate institutional officials, the study sponsor or the sponsor's agents (if applicable), and regulatory entities such as the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), and the National Institutes of Health (NIH).

Subject identifiers will **not** be disclosed. Information and/or de-identified biospecimens may be shared (i.e. research participants cannot be identified by other researchers). Text regarding the information/biospecimens sharing will be included in the consent document, as applicable. No subject identifiers will be retained by the study team beyond initial collection (i.e. information/biospecimens cannot be linked to an individual and a key code does not exist). Requests for de-identified information and/or de-identified biospecimens will be managed by the UCI study team.

5.9 Research Information and/or Biospecimens Retention

Information/biospecimens will be retained for 10 years after the end of the calendar year in which the research is completed.

5.10 Privacy

- Research procedures (including recruitment) are conducted in a private room.
- Only sensitive information directly related to the research is collected about subjects.
- The study team will request specific patient information/data from UCIMC Health Information Management Services.
- The study team will review their UCI patients' records and abstract data directly from those records.
- The study team will access their UCI patients' records and abstract data directly from those records.
- HIPAA authorization will not be obtained for screening/recruitment purposes. However, written (signed) HIPAA research authorization is obtained for further access to personal health information.

6. STUDY POPULATION

6.1 Target Sample Size

Category/Group	**Age Range**	**Maximum Number to be Consented or Reviewed/Collected** (include withdrawals and screen failures)	**Number Expected to Complete the Study *or Needed to Address the Research Question***
Adult cancer patients	≥ 16	64	58

Neuroimaging sub study	≥ 16	40	34
		Total: 64	

6.2 Total Number of Subjects

Total number of subjects across all sites: 64

6.3 Sample Size Determination

Based on our previous psychometric study of the FACT-Cog questionnaire, a decrease of 6.9-10.6 points (4.7-7.2% of the total score) in the FACT-Cog corresponds to the threshold for clinically significant cognitive deterioration in breast cancer patients. In our previous prospective cohort study, among 131 participants who completed the study, their mean and standard deviation (SD) of FACT-Cog total score at the prior to chemotherapy initiation (T1), 6 weeks following chemotherapy initiation (end of cycle 2; T2), 12 weeks following chemotherapy initiation (end of cycle 4; T3), and approximately 15-months post-chemotherapy initiation (post-chemotherapy evaluation; T4) were estimated to be 132.00 (SD 15.65), 130.23 (19.44), 128.51 (19.93) and 127.53 (21.89), respectively. Assuming the correlation between observations on the same participant across time is 0.2 and a common standard deviation of two groups is 20.5, with 29 evaluable participants per group, a total of 58 evaluable participants, a power of 80% will be achieved to detect the difference of 9.6 in means of FACT-Cog total score between two groups across 4 time points with a significant level of 0.05. After accounting a potential 10% attrition, sixty-four eligible patients will be enrolled into the study.

6.4 Eligibility Criteria

Study team will **screen medical records and conduct patient interviews** to determine subject eligibility.

Patients

Inclusion criteria
Patients diagnosed with cancer that have received anti-cancer treatment
16 years of age or older
Life expectancy ≥ 6 months
Complaints of one or more of the following symptoms: memory impairment/attention deficit, fatigue, insomnia, depression, or anxiety over the past 7 days
Exclusion criteria
Presence of metastasis
Severe needle phobia
Severe psychiatric or medical disorders which would affect cognitive assessments

Known bleeding disorder (e.g. hemophilia, Von Willebrand's disease, thrombocytopenia) Has pacemaker or other electronic metal implants Epilepsy Already receiving acupuncture therapy or received acupuncture treatment in the past 3 months. Breastfeeding, pregnant or are planning get pregnant during the study period
Additional exclusion criteria for neuroimaging substudy Has any contraindications to fMRI including metal fragments/implants in the body, sever claustrophobia, and non-removable metal orthodontic braces, metallic retainers and oral wires.

The risk of EA or sham-EA on a newborn or an unborn child is unknown. As such, we will exclude patient who are breastfeeding, pregnant or are planning to get pregnant during the study period. This study is restricted to patients who are 16 years or older, as younger patients may not be suitable to receive the treatment.

6.5 Informed Consent

Consent will be completed face-to-face using a stamped approved form. As noted above, potential study participants may be approached in both the inpatient and outpatient (clinic or outpatient infusion center) setting. As such, it is expected that the consent discussion will take place in the same location.

There is no limit on the amount of time a potential study participant has to review the consent document. All potential research participants and families will be given the opportunity to ask and answer questions about the research project prior to executing the signed informed consent agreement and authorization to use, create, and disclose health information for research use documents. If a study participant elects to take the consent home, they will be approached during future appointments/admissions (up to three times) to determine their interest in study participation. In the case of a minor participant (i.e. 16-17 years old), this study will require assent and consent of one parent or legally authorized representative (LAR).

The informed consent agreement and authorization to use, create and disclose health information for research use will be prepared and provided to the potential research participant and his/her family in their preferred language (short form may be employed). The documents will be written at a level that is reflective of a sixth to eighth grade reading comprehension level. All potential research participants and families will be given the opportunity to ask and answer questions about the research project prior to executing the signed informed consent agreement and authorization to use, create and disclose health information for research use documents. If there is the appearance of hesitation or confusion, additional time will be taken to further explain the study and its procedures, the voluntary nature of research, the benefits and risks of participation, and any other parts of documentation identified by the participant and his/her family. When appropriate, a teach-back method may be employed.

If the potential study participant's cognitive limits are not clearly identified in their medical record, the following four elements of decision-making capacity will be assessed for the study protocol:

(1) Understanding

(a) What is purpose of the research study?

(b) What will happen to you in this research study?

(2) Appreciation

(a) What are the potential risks of this research study?

(b) What are the potential benefits of this research study?

(3) Reasoning

(a) What alternative is there if you choose not to participate in this study?

(4) Expressing a Choice

(a) Does the individual express a choice about whether or not to participate?

6.6 Recruitment Process

The study will be listed on Clinicaltrials.gov. In addition, the study will be listed on the Center for Clinical Research (CCR) Find a Trial web page and the UC Irvine Health Clinical Trials web page.

HIPAA authorization will not be obtained for screening/recruitment purposes. However, written (signed) HIPAA research authorization is obtained for further access to personal health information.

Location of Recruitment

Subjects will be recruited from the UCI Chao Family Comprehensive Cancer Center (CFCCC) or one of the affiliated treatment sites (such as UCI Health Cancer Center – Newport Beach, UCI Health – Yorba Linda Infusion Center, the UCI Health Pacific Breast Center, Children's Health Orange County (CHOC) as well as the Susan Samueli Integrative Health Clinics.

Referral from colleagues

- Study team will provide colleagues with UCI IRB-approved recruitment materials for distribution to potential subjects (e.g., recruitment flyer, introductory letter);
- An IRB-approved recruitment letter will be sent by the treating physician. The letter will be signed by the treating physician and sent to his/her patients to inform them about how to contact study team members; and/or

- Colleagues obtain permission from interested patient to release contact information to researchers.

- Study team does not have access to patient names and addresses for mailing.

If colleagues will screen their patients' medical records to determine subject eligibility and approach patients directly about study participation

Other Recruitment Methods:

Study team will **screen non-medical records** (i.e., student records) to which they have access to determine subject eligibility. Specify:

C2C Registry

- Study team members will contact potential subjects who have provided permission to be contacted for participation in future research studies.

- Recruitment will also occur through the Consent-to-Contact (C2C) registry (HS# 2015-2494). The study team will request the contact information from subjects who have submitted data to the C2C registry and who have given permission to be contacted regarding participation in research studies.

- Specify database or IRB-approved protocol number (HS#): HS# 2015-2494

Informed Consent for non-English Speakers

The English version of the consent form will be translated into appropriate languages for non-English speaking subjects or their LAR once IRB approval is granted. *The translated consent form must be submitted to the IRB for review prior to use with human subjects. Only IRB approved consent forms (containing the IRB approval stamp) may be used to consent human subjects at UCI.*

Requesting a short form consent process is applicable for all non-English languages except Spanish. The study team has 24-hour access to a translation service with sufficient medical expertise to discuss the research in this study.

7. TIMELINE

7.1 Milestones

Milestones: The EAST study is expected to begin on August 1, 2022, and end on January 31, 2024, for a total duration of 18 months. Important milestones are listed below:

Milestones	Expected date of completion	Month 2	4	6	8	10	12	14	16	18
Recruitment	August 31, 2023									
Data collection	December 7, 2023									
Biomarker quantification	December 31, 2023									
Data analysis and reporting	January 31, 2024									

8. FINANCIAL ASPECTS/CONFLICTS OF INTEREST

8.1 Grantor

Funding is provided by the California Breast Cancer Research Program (CBCRP) and the UCI Anti-Cancer Challenge.

8.2 Conflict of Interest

The study team members declare no conflict of interest.

9. REFERENCES

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