TITLE: EACH STUDY: Ear Acupuncture During Chemotherapy Infusion for Breast Cancer, a Feasibility Study Protocol (NCT03170648)

Protocol version date: September 28, 2017

Protocol #: 17-065 (NCT03170648)

Principal Investigator: Weidong Lu, MB, MPH, PhD
Dana-Farber Cancer Institute
Ph: 617-632-4350
Weidong_Lu@dfci.harvard.edu

Co-Investigator: Jennifer Ligibel, MD
Dana-Farber Cancer Institute
Ph: 617-632-3800
Jennifer_Ligibel@dfci.harvard.edu

Biostatistician: Anita Giobbie-Hurder, MS
Dana-Farber Cancer Institute
Ph: 617-632-2193
Agiohur@jimmy.harvard.edu

Research Assistant: Roxanne Quinn
Dana-Farber Cancer Institute
Ph: 617-632-5408
Roxanne_Quinn@dfci.harvard.edu

SCHEMA

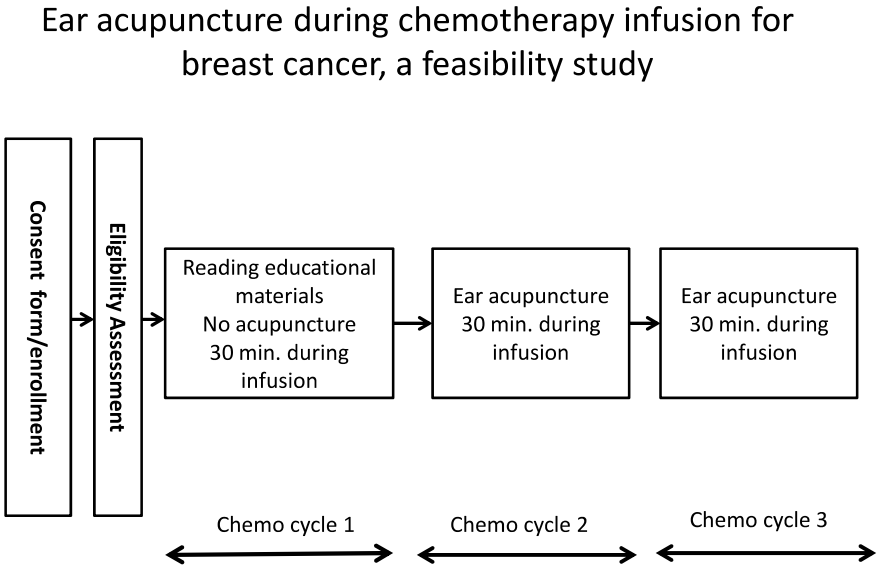

Ear acupuncture during chemotherapy infusion for breast cancer, a feasibility study
Consent form/enrollment
Eligibility Assessment
Reading educational materials
No acupuncture
30 min. during infusion
Ear acupuncture
30 min. during infusion
Ear acupuncture
30 min. during infusion
Chemo cycle 1
Chemo cycle 2
Chemo cycle 3

TABLE OF CONTENTS

1. ABSTRACT

It is well recognized that breast cancer patients experience significant symptoms during chemotherapy, including anxiety, nausea and vomiting, and appetite loss. Management of the multiple symptoms patients experience typically requires an array of pharmacologic interventions, but patients still often experience residual symptoms despite aggressive symptom management. Although clinical evidence suggests that acupuncture is an effective therapy for reducing chemotherapy-induced nausea and vomiting, as well as other symptoms such as anxiety, acupuncture generally requires additional appointments and a time commitment which is not feasible for many patients.

Preliminary data suggest that ear acupuncture, a subset of acupuncture that involves stimulation of points on the external ear (ear auricles), could provide relief of symptoms without an added time commitment. However, scientific investigation of ear acupuncture to reduce symptoms burden during chemotherapy infusion in breast cancer patients has not been reported.

We will conduct a single arm, pilot feasibility study of ear acupuncture for breast cancer patients during chemotherapy infusions in the Breast Oncology Center. This study will assess the feasibility of recruiting and retaining breast cancer patients, as well as of administering the ear acupuncture protocol. Additional outcomes will include evaluating the impact of ear acupuncture on symptom burden during infusions and health-related quality of life (QOL).

This study will enroll 26 patients receiving chemotherapy infusion for stage I-III breast cancer, for 3 consecutive chemotherapy cycles. During the first cycle of chemotherapy infusion, participants will receive an educational reading booklet. During cycles 2 and 3 of chemotherapy infusions, participants will receive a standardized ear acupuncture protocol. Measurements will be collected at 4 time points in each chemotherapy cycle: Pre-intervention on the Day 1 of infusions, post-intervention on the Day 1 of infusions, on the day after the chemotherapy infusion (Day 2), and on Day 5. Patient-reported outcomes including Edmonton Symptom Assessment System (ESAS), State-Trait Anxiety Inventory (STAI), The MASCC Antiemesis Tool (MAT), will be collected. Safety data will be measured using NCI-CTCAE v.4.023.

Data collected from this study will provide important data for a future randomized controlled trial to evaluate the efficacy of ear acupuncture in reducing symptom burden during chemotherapy infusion for breast cancer.

2. BACKGROUND AND RATIONALE

Acupuncture has been practiced in Asia and other parts of world for thousands of years. Experimental and clinical evidence over past forty years suggest that acupuncture is effective for various conditions, including pain management. However, the use of acupuncture as a therapy for symptom management in cancer patients during stages of cancer journey presents a completely new challenge. In the past 15 years, emerging clinical evidence, largely from randomized clinical trials, suggests that acupuncture be recommended for symptom relief during cancer treatment [1-4]. Given these data, the National Comprehensive Cancer Network (NCCN), an alliance of the world's leading cancer centers, has recommended acupuncture in its guidelines for the following conditions: adult cancer pain, chemotherapy-induced nausea and vomiting (CINV), cancer-related fatigue, and palliative care[5]. However, acupuncture generally requires one-to-one service as well as additional appointments and time commitment.

2.1 Symptom Burden during Chemotherapy Overview

Symptom burden is the sum of the severity and impact of symptoms reported by patients with a given disease or treatment[6]. Symptoms can be caused by disease itself as well cancer treatment. Multiple symptoms are additive and can significantly affect functions and quality of life of cancer patients. It is well recognized that breast cancer patients experience a significant number of symptoms during chemotherapy, including anxiety[7, 8], appetite loss[9, 10], depression, and pain.

One study found that patients with early stage breast cancer who received chemotherapy experienced significantly more pain, tiredness, depression and diminished well-being compared to those who did not receive chemotherapy[11]. In another study, 13.2% and 21.1% breast cancer patients reported moderate to severe nausea and loss of appetite respectively[12]. Despite the use of advanced antiemetic medications, chemotherapy induced nausea and vomiting (CINV) is still a significant side effect of cancer therapy, particularly delayed nausea. Adriamycin–cyclophosphamide (AC) is a standard chemotherapy regimen for breast cancer patients. With this regimen, one study reported an acute vomiting rate of 15% and delayed nausea rates of 73%-82% during chemotherapy in breast cancer patients[13, 14]. Another study reported that 37% of breast cancer patients had nausea and 13% had vomiting during the first 24 hours of chemotherapy while 70% and 15% developed nausea and vomiting during 2nd to 5th day after chemotherapy[15].

Anxiety is another common symptom among breast cancer patients. One study of 913 patients with newly-diagnosed breast cancer found that 77% of patients reported anxiety during the 2 years following diagnosis[16]. Another study found that approximately a fourth to over half of breast cancer patients undergoing or who had undergone breast cancer treatment experienced anxiety, particularly during chemotherapy infusions[8].

2.2 Ear Acupuncture and Clinical Trials

Ear acupuncture (EA) or auricular acupuncture is a subset of acupuncture that involves the stimulation of points on the external ear (ear auricles). Ear acupuncture has been studied for a number of clinical conditions including pain[17], epilepsy[18], substance dependence[19], anxiety[20], insomnia[21], and obesity[22]. Ear acupuncture has also been studied for pre-operative and dental procedure-related anxiety[23-25]. One randomized controlled trial of ear acupuncture in 182 patients undergoing dental procedures demonstrated a significant reduction of state anxiety by 7.3 points in a group that received acupuncture prior to the procedure versus a 3.7 point reduction in the group that did not receive acupuncture[23].

Ear acupuncture has also been studied for the treatment of chemotherapy-induced nausea and vomiting. A recent published systematic review of 21 randomized clinical trials with 1713 patients revealed that the effect rate of auricular therapy, including ear acupressure and ear acupuncture, for CINV ranges from 44% to 93%[26]. The average sample size of these trials was 81. The majority of these trials used acupressure as the intervention. One study (n=80) evaluated the additional of auricular acupuncture to antiemetic drugs in a breast cancer population and reported. It reported an effective rate (the proportion of grade 0-2 toxicity) of 87.5% in the acupuncture arm versus 45% in the control arm[27], as defined by the World Health Organization (WHO) Recommendations for Grading Acute and Subacute Toxicity[28]. Further study is needed.

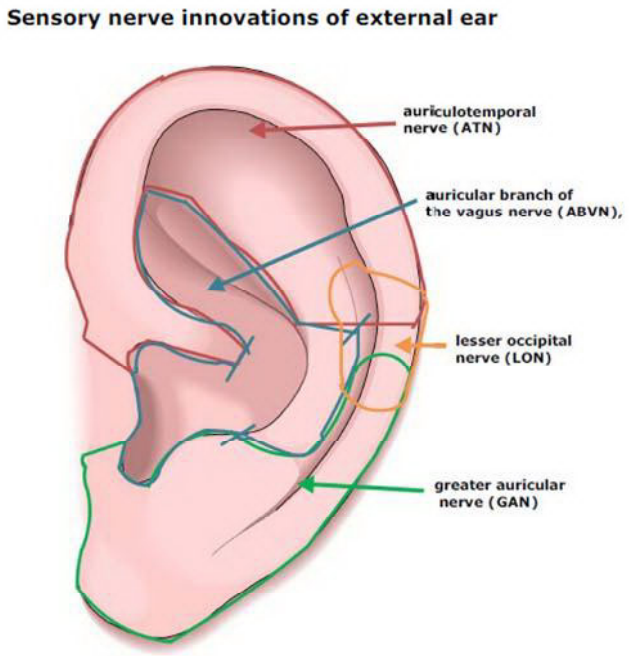
In 2016, we piloted an ear acupuncture service for breast cancer patients at DFCI. Our initial data indicated that about 43% of patients reported nausea and 79% of patients reported anxiety during infusion time. Anecdotal reports suggested that patients reported reductions in both nausea and anxiety immediately after receiving an ear acupuncture treatment.

2.3 Mechanisms of Ear Acupuncture

The mechanisms of ear acupuncture are believed to be mediated through the autonomic nervous system, specifically through stimulation of auricular branches of the vagus nerve (ABVN) in the outer ear[29]. Figure 1 presents the sensory nerve innovations of external ear. Animal studies found that afferent projections from ABVN to the nucleus of the solitary tract (NTS) form the anatomical basis for the vagal regulation of auricular acupuncture. A so-called “auriculovagal afferent pathway” (AVAP) has been suggested in which both the autonomic and the central nervous system could be modified by auricular vagal stimulation[30]. Another animal study found that auricular vagal stimulation improves burn-induced delay in gastric emptying, possibly mediated via the sympathetic-COX-2 pathway[31]. In addition, auricular stimulation have been found to affect autonomic functions of cardiovascular, respiratory, and gastrointestinal systems[30] Other factors such as the neuroendocrine system, neuroimmunological factors, neuroinflammation, and neural reflex, as well as antioxidation have also been suggested[29].

General or body acupuncture has been effectively used in clinical practice for CINV and other symptoms, however, given that breast cancer patients are often required to spend hours of infusion time during which patients experience a variety of psychological and physical symptoms, ear acupuncture could provide relief of symptoms without an added time commitment. However, scientific investigation of ear acupuncture to reduce symptoms burden (SB) during chemotherapy infusion in breast cancer patients has not been well-studied.

Figure 1: Sensory nerve innovations of external ear



3. OBJECTIVES

1. To evaluate the safety and feasibility of recruiting and retaining breast cancer patients (n = 26), during 3 cycles of adjuvant or neoadjuvant chemotherapy, as measured by rate of recruitment, ear acupuncture compliance, measure collection, and incidences of acupuncture-related side effects during the trial.
2. To collect preliminary efficacy data on ear acupuncture for the reduction of symptom burden (SB) including chemotherapy-induced CINV and anxiety in breast cancer patients, as measured by the *Edmonton Symptom Assessment System* **(***ESAS***)**, *State-Trait Anxiety Inventory (STAI)*, *the MASCC*[1] *Antiemesis Tool (MAT),* the usage of antinausea medications as well as the ER visits and the hospital admission rate during the trial.

[1] The Multinational Association of Supportive Care in Cancer (MASCC)

4. ELIGIBILITY

4.1 Inclusion

Inclusion Criteria:

1. History of histologically or cytologically proven Stage I-III breast cancer receiving intravenous chemotherapy on an every 14 days or every 21 days schedule
2. Age ≥ 18 years
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
4. Signed informed consent

4.2 Exclusion

Exclusion Criteria:

1. Receiving weekly chemotherapy
2. Unstable cardiac disease or myocardial infarction within 6 months prior to study entry
3. Uncontrolled seizure disorder
4. Active clinically significant uncontrolled infection
5. Prior use of acupuncture within 3 months prior to the study entry
6. Uncontrolled major psychiatric disorders, such as major depression or psychosis
7. Metastatic breast or other cancer

4.3 Inclusion of Women, Minorities and Other Underrepresented Populations

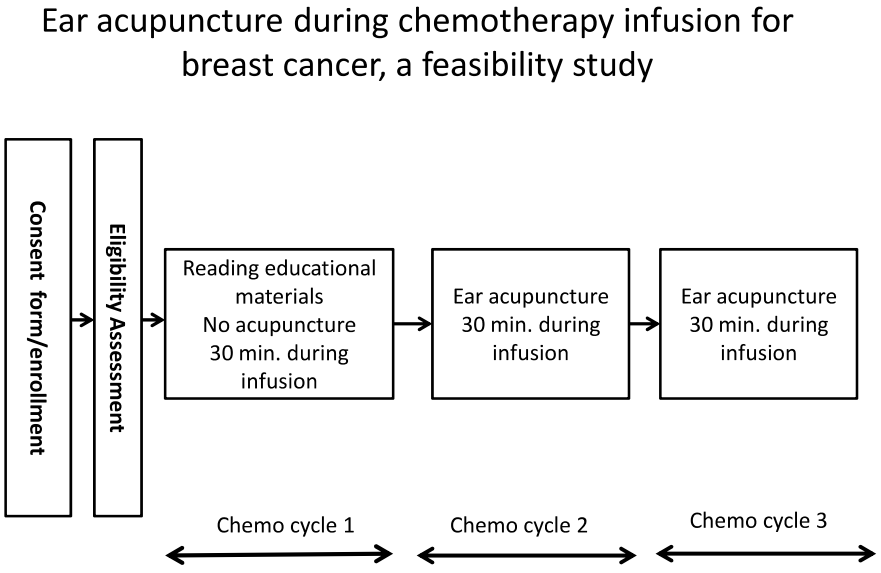
This protocol will be open to women and minorities. Women comprise approximately 98% of the breast cancer patients at Dana-Farber Cancer Institute.

Minorities represent 10-20% of the breast cancer patients at Dana-Farber. Previous trials have demonstrated that 7-25% of patients enrolled on clinical trials are minorities.

5. STUDY DESIGN AND PROTOCOL OVERVIEW

This single arm feasibility study will enroll 26 patients receiving chemotherapy for stage I-III breast cancer. Patients will be enrolled into a single ear acupuncture arm for 3 consecutive chemotherapy cycles. During the first cycle of chemotherapy infusion, participants will receive an educational reading booklet (*Chemotherapy and You* by National Center Institute[32]). During cycles 2 and 3 of chemotherapy infusions, participants will receive a standardized ear acupuncture protocol. Each ear acupuncture session lasts for 30 minutes (Figure 1). The study patients will have an option to continue ear acupuncture treatments with their subsequent chemotherapy infusions but no additional data will be collected. Measurements will be collected at 4 time points in each chemotherapy cycle: Pre-infusion on the Day 1 of chemotherapy, post-intervention on the Day 1 of infusions, on the day after the chemotherapy infusion (Day 2), and on Day 5. Patient-reported outcomes including ***Edmonton Symptom Assessment System*** (***ESAS***), ***State-Trait Anxiety Inventory (STAI)***, ***The MASCC[2] Antiemesis Tool (MAT)***, anti-nausea medication usage and emergency events diary will be collected. Safety data will be measured using NCI-CTCAE v.4.023[33] (Figure 2). Measures will be compared between chemotherapy cycles.

Figure 2: Study Schema



[2] The Multinational Association of Supportive Care in Cancer (MASCC)

6. SUBJECT RECRUITMENT AND ENROLLMENT

Patients will be recruited from the Breast Oncology Center at the Dana-Farber Cancer Institute.

We will utilize multiple active recruitment techniques to maximize participation and generalizability. We will use the following strategies to identify potential participants:

- Review of clinic schedules and patient lists for medical oncologists at Dana-Farber Cancer Institute to identify patients with Stage I-III breast cancer who are scheduled to initiate intravenous chemotherapy on every 14 days or every 21 days schedule, such as dose-dense AC followed by paclitaxel regimen or AC followed by paclitaxel with trastuzumab. A HIPAA waiver will be obtained from the DF/HCC IRB to review these patient lists.
- Advertisements in patient areas (see Appendix IX)

For potential participants identified through patient lists, we will contact providers (medical oncologists) and request permission to contact their patients. Providers will be asked to indicate any patients who should not be approached regarding participation in this study. Once potential participants are identified, they will be contacted during a clinic visit or through mailings. For patients with upcoming clinic visits, the research coordinator will approach potential patients in clinic. For patients without an upcoming clinic visit, invitation letters will be mailed with a reply card to indicate interest and an opt-out card (see Appendix VIII). For patients who are self-identified through advertisements in clinic, we will obtain permission from their treating physician before participation in the study.

Interested subjects identified through these recruitment strategies will be screened by the research study staff either in person or by phone initially and if potentially eligible, he or she will schedule a visit with a member of the study staff to review the protocol and sign informed consent.

6.1 Registration Procedures

General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of the protocol intervention. Any participant not registered to the protocol before protocol intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin the protocol intervention. Issues that would cause delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive the protocol intervention following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

6.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

7. SPECIMEN/DATA COLLECTION PROCEDURES

The pre-infusion assessments will be collected before patients are given educational materials (cycle 1) or receive acupuncture (cycles 2 and 3) on Day 1 of cycles 1-3. The post-intervention assessments will be repeated after the completion of reading educational material or acupuncture on Day 1, Day 2 and Day 5 of cycles 1-3.

Study measures will be collected according to the following schedule (Table 1):

Table 1. Schedule of Study Measures

	Tracking Log	Consent Form	Educational Booklet	ESAS	STAI	MAT	Medication Log	Event Log	AES	Acupuncture Tx Form
Recruitment	X	X					X			
Cycle 1										
Day 1 Pre-Intervention			X	X	X				X	
Day 1 Post-Intervention				X	X					
Day 2				X	X	X				
Day 5				X	X	X	X	X		
Cycle 2										
Day 1 Pre-Intervention				X	X					X
Day 1 Post-Intervention				X	X					
Day 2				X	X	X				
Day 5				X	X	X	X	X		
Cycle 3										
Day 1 Pre-Intervention				X	X					X
Day 1 Post-Intervention				X	X					
Day 2				X	X	X				
Day 5				X	X	X	X	X		

Study measures will be collected by the study CRC (cycle 1) and/or by the study acupuncturists (cycle 2 and 3). The post-acupuncture assessments will be collected by the study acupuncturists. Assessments will be coordinated with ear acupuncture visits when possible, so that patient convenience is maximized. Day 2 and Day 5 assessments will be filled out by the patients at home and returned to the study CRC at the next visit. The home assessments will be put in an envelope to keep the confidentiality. To facilitate completion, patients will be reminded by phone and by email to complete the home assessments. Patients may also choose to complete the home assessments over the phone with the study coordinator.

The following measures will be collected:

7.1 The Edmonton Symptom Assessment System (ESAS)

Our primary outcome is symptom burden (SB) as measured with the Edmonton Symptom Assessment System (ESAS). ESAS is a validated symptom battery that assesses the average intensity of 9 symptoms (pain, fatigue, drowsiness, nausea, appetite, shortness of breath, depression, anxiety, feelings of well-being), each with an 11-point numerical rating scale that ranges from 0 (no symptom) to 10 (worst intensity). In clinical trial settings, symptom burden based on ESAS is generally use the physical score, the emotional score and the total symptoms score. The physical score ranges between 0 and 60, representing the sum of ESAS pain, fatigue, nausea, drowsiness, dyspnea, and loss of appetite. The emotional score consists of both anxiety and depression (total 0-20). The total symptom score represents the combination of physical and emotional scores as well as well-being (total 0-90)[34]. Higher scores indicate higher symptom burden. The ESAS is a self-administered questionnaire that was developed and validated to rapidly assesses patients' symptoms burden. The reliability by test–retest with the ESAS and within 1 day is generally high, exceeding 0.8. Correlations between individual ESAS items and scores with other alternative similar tools are good, particularly for physical symptoms. For example, ESAS symptoms correlate strongly with Memorial Symptom Assessment Scales such as shortness of breath (0.85), appetite (0.75), nausea (0.62), nervous (0.45), and depression (0.44). ESAS symptoms correlate strongly with items in the Symptom Distress Scale as well. Correlation with the Brief Pain Inventory and pain was reported to 0.61. ESAS has been used in breast cancer population to assess symptom burden and quality of life[11, 35]. ESAS will be collected 4 times during each cycle[36, 37].

7.2 State-Trait Anxiety Inventory (STAI)

State-Trait Anxiety Inventory (STAI) is a validated questionnaire measuring the presence and severity of current symptoms of anxiety and a generalized propensity to be anxious. It has 2 subscales: the State Anxiety Scale (S-Anxiety) evaluates the current state of anxiety and the Trait Anxiety Scale (T-Anxiety) evaluates relatively stable aspects of "anxiety proneness," each having 20 items. The State Anxiety Scale is scored on four levels of anxiety intensity from1= 'not at all' to 4= 'very much' and with a sum score between 20 and 80. Higher scores indicate greater anxiety[38-40]. The State Anxiety Scale has been previously used in several acupuncture trials for anxiety[20, 23, 41, 42]. In our present study, the State Anxiety Scale will be used. STAI will be collected 4 times during each cycle.

7.3 The MASCC Antiemesis Tool (MAT)

The MASCC Antiemesis Tool (MAT) is a validated questionnaire developed by the Multinational Association of Supportive Care in Cancer (MASCC). MAT assesses the domains of nausea and vomiting through the acute and delayed phases of CINV. Each phase is assessed by four items that measure the occurrence of CINV, duration of nausea (10-point scale), and frequency of vomiting (number of episodes)[43-45]. MAT will be collected on Day 2 and Day 5 during each cycle of chemotherapy.

7.4 Patient Medication Log

A patient medication log will be kept and administered to track the usage and dose of support medications as well as dietary supplements. Support medications include, but are not limited to: antiemetics: Compazine (prochlorperazine), Lorazepam (Ativan), Ondansetron (Zofran), Dexamethasone and Metoclopramide (Reglan). Laxatives: Senokot, Colace, or Miralax; opioid analgesics: tramadol and other narcotics; and NSAIDs. Dietary supplements include, but are not limited to: glutamine, glutathione, vitamin E and vitamin B12. Data for the medication log will be collected at each scheduled visit.

7.5 Acupuncture Expectancy Scale (AES)

The AES consists of four items measuring the expectation of improvement of illness (symptom), enhanced coping, increased vitality, and symptom alleviation due to acupuncture therapy. Patients are asked to endorse their expectancy of acupuncture for specific symptoms (e.g., joint pain for breast cancer survivors, and fatigue for patients undergoing radiation therapy). Subjects are asked to rate from 1 to 5 on a five-point Likert scale, with 1 indicating “Not at all agree” and 5 indicating “Completely agree” with the expected improvement as result of acupuncture. Possible scores range from 4 to 20, with higher scores indicating greater expectancy. The AES has been validated with an acceptable reliability coefficient. Additionally, the score on the AES was positively correlated with both the perceived effectiveness of acupuncture treatment and the confidence in acupuncture care. The AES will be administered once before the randomization process[46, 47].

7.6 Acupuncture Treatment Form

An acupuncture treatment form will be generated by the treating acupuncturist at each ear acupuncture treatment. The form will document the following items: acupuncture points used, patient-reported acupuncture intensity, and any acupuncture-related adverse events.

8. ACUPUNCTURE PROCEDURE

All treatments will take place at DFCI and be administered by experienced, licensed and credentialed staff oncology acupuncturists who have also been specifically trained to administer this study protocol. All acupuncture staff members have a minimum of 10 years of experience. The study PI, Dr. Lu will train all acupuncturists and periodically observe the treatment technique being performed to ensure the quality of the treatment.

8.1 Ear Acupuncture Protocol

At the infusion during the 1st cycle, the study patients will receive an educational booklet developed by National Cancer Institute. This booklet includes facts about chemotherapy and its side effects. It highlights ways that a patient can care for herself before, during, and after treatment. No acupuncture will be performed during the first infusion cycle. The patient will be encouraged to read the booklet during the infusion. During the second and third infusion cycles, the study patients will receive a 30-minute session of a standardized ear acupuncture treatment.

At each visit, the study patient will be sitting in an infusion chair either reading the booklet (cycle 1) or receiving ear acupuncture treatment (cycles 2 and 3). For each ear acupuncture session, the patient will have ear acupuncture therapy administered to each ear. After the skin of the ear is cleaned with alcohol, six acupuncture needles (SEIRIN®, No. 1., 30 mm x 0.16 mm) will be inserted into acupuncture points bilaterally. The depth of needle insertions is around 2-3 millimeters. Then, acupuncture needles will be gently manipulated to increase stimulation. The patient will be asked to orally report the needling intensity level on a scale from 0-10 (0 being feeling nothing at all and 10 being the strongest one can imagine). Then, the needles will remain in the sites for 30 minutes while receiving IV infusion. After 30 minutes, another round of gentle manual manipulation will be performed prior to the removal of the needles. Figure 3 and Table 2 presents the names and locations of ear acupuncture points.

If a study patient misses an acupuncture treatment, the patient will be asked to make up the missed treatment session during the next chemotherapy infusion, so that a total of 2 consecutive sessions of acupuncture will be provided. The total number of acupuncture sessions received will be recorded for each participant. Any side effects related to the acupuncture will be collected by treating acupuncturists.

An outline of the acupuncture protocol and a summary of acupuncture points to be used are presented below in Figure 3 and Table 2, respectively.

8.2 Adverse Events

Individuals receiving the ear acupuncture will be asked about acupuncture-related adverse events at each acupuncture treatment. Any acupuncture-related injuries will be reported to study investigators. Any reported events will be evaluated for the likelihood that they occurred as a result of acupuncture (very likely to be related, likely to be related, possibly related, or unlikely to be related). Patients will also be provided a phone number to contact study staff at DFCI to report potential acupuncture-related adverse events.

Figure 3: Ear acupuncture points

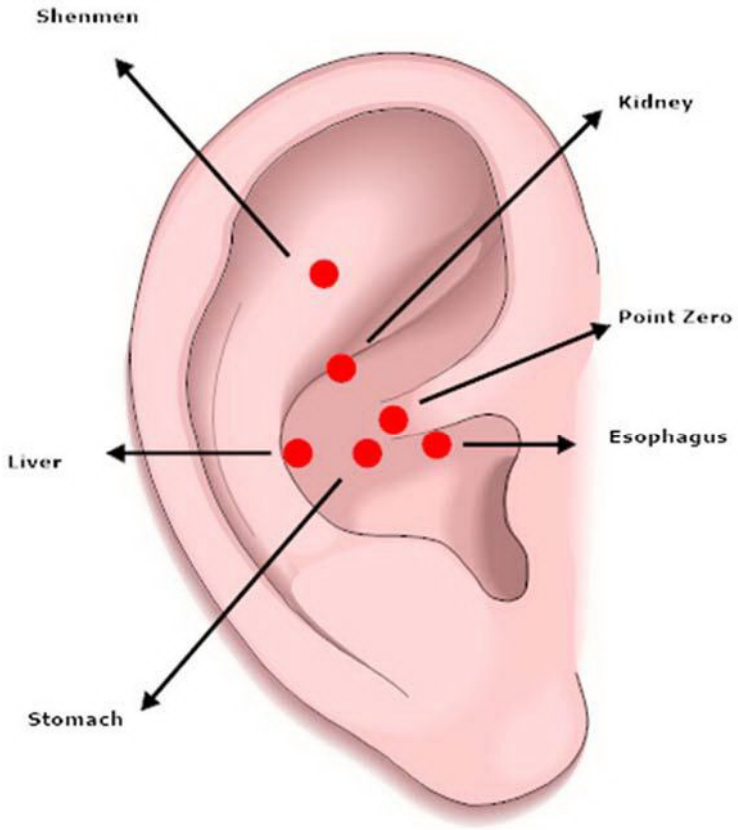


Table 2: Ear Acupuncture Points and Locations

Name	Location
Shen men	Superior and central to the tip of the triangular fossa, between the junction of the superior crus and inferior crus of antihelix. It is not at the tip of the triangular fossa, but slightly inward and slightly upward from where the triangular fossa descends from the superior crus toward deeper regions of the triangular fossa.
Point Zero	Notch on the helix root at LM0 (ear center), just as the vertically ascending helix rises from the more horizontal concha ridge.
Kidney	Superior concha, below LM16 (antihelix notch) and superior to the Stomach point. It is often difficult to view this point because it is hidden by the overhanging ledge of the inferior crus.
Liver	Peripheral concha ridge and concha wall, peripheral to the Stomach point.
Stomach	Medial concha ridge, just peripheral to LM0 (ear center) and the central concha ridge.
Esophagus	Inferior concha, peripheral to the Mouth point.

9. ADVERSE EVENT REPORTING REQUIREMENTS

9.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:

  http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

9.2 Expedited Adverse Event Reporting

9.2.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

9.2.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

9.2.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades determined to be related to chemotherapy treatment or the disease under study (i.e. breast cancer) and not the study intervention (ear acupuncture) do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

9.3 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

9.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB) must also be reported in routine study data submissions.**

10. STATISTICAL CONSIDERATIONS

10.1 Accrual

In this feasibility pilot study, the target sample size is 26 patients enrolled during a 3-month period.

10.2 Endpoints

Enrolled patients will receive an educational reading material during the first cycle of chemotherapy and ear acupuncture during cycles 2 and 3. The primary feasibility endpoint consists of three parts. The intervention will be deemed feasible if: (a) at least 20 patients (80%) are enrolled by September 2017; (b) all 20 patients complete at least 75% of the acupuncture sessions; and (c) all 20 patients complete at least 9 out of 12 (75%) assessments. Secondary endpoints will investigate changes in patient-reported outcomes relative to baseline (T1) for the following time points: after the intervention (T2), Day 2, and Day 5 after chemotherapy infusion (T3 and T4). Changes will be compared between cycle 1 (no acupuncture) and cycles 2 and 3 (acupuncture).

For the secondary endpoints, we are primarily interested in the effect of acupuncture therapy compared with no acupuncture; therefore, comparisons will be based on the

averages of the assessment change scores over a time interval during acupuncture (cycles 2 and 3) compared with the change during the same time interval of cycle 1.

For example, if Tij is the score at time i (i = 1 to 4) during cycle j (j = 1 to 3), then three pairwise differences will be of interest:

PD1: Change between T_2 and baseline: $[(T_{22} - T_{12}) + (T_{23} - T_{13})]/2$ vs. $(T_{21} - T_{11})$
PD2: Change between T_3 and baseline: $[(T_{32} - T_{12}) + (T_{33} - T_{13})]/2$ vs. $(T_{31} - T_{11})$
PD3: Change between T_4 and baseline: $[(T_{42} - T_{12}) + (T_{43} - T_{13})]/2$ vs. $(T_{41} - T_{11})$

10.3 Sample Size

Sample size considerations for the secondary endpoints are based on a one-sample t-tests, 80% power, and an overall type-I error of 0.1 (two-sided), which will be divided equally between the three pairwise comparisons (0.033 for each). The detectable effect size based on these operating characteristics is 0.625.

For our main secondary endpoint of ESAS Total Score, it has been reported that the minimal clinically important difference (MCID) for improvement, based on within-patient change, is 5.7 points (SD=11.6, N=105)[48]. For the purposes of this protocol, a clinically significant improvement in ESAS Total Score will be defined as a 6-point decrease.

If the within-patient correlation of change scores between T2 and baseline is 0.6, then the estimated standard deviation of the pairwise difference (PD1, above) would be 9.4. There would be 80% power to detect a difference in change scores of 5.9 points. The table following summarizes detectable differences in ESAS Total Score for varying within-patient correlations.

Detectable Differences in ESAS Total Score based on one-sample t-tests, two-sided alpha = 0.033, and 80% power

Within-patient Correlation	Estimated Standard Deviation	Detectable Difference
0.6	9.4	5.9
0.7	8.3	5.2
0.8	7.0	4.4
0.85	6.3	3.9
0.9	5.5	3.4

Therefore, for a sample of 26 patients, we would have at least 80% power to detect the ESAS Total Score MCID, for within-patient correlations of at least 0.6.

10.4 Data Analysis

Baseline demographic, disease characteristics, prior treatment, and comorbidities will be compared using the relevant descriptive methods for continuous and categorical variables.

For the primary, feasibility endpoint, the proportion of patients who satisfy the definition of feasibility will be summarized with a 90%, exact binomial confidence interval. For samples of size 20 and 26, the confidence interval will be no wider than 0.4 and 0.35, respectively.

Pairwise differences (PD1-PD3, above) of the ESAS Total Score will be analyzed using one-sample t-tests and a comparison-wide error rate of 0.1, which will be divided equally among the three pairwise comparisons. Model-based approaches will also be used to investigate changes over time. We will also present the proportion of patients who had at least a 6-point decrease on ESAS Total Score from T1 at each time point with exact confidence intervals. Comparable analyses will be conducted for ESAS Physical Score, ESAS Emotional Score, the individual symptom scores, State Anxiety Scale scores, and MET nausea scores at each time point between cycle 1 and cycles 2 and 3.

Patient-reported outcomes will also be presented graphically over time by chemotherapy cycle. Safety data will be reported for all patients according to CTCAE Version 4.0.

11. DATA AND SAFETY MONITORING PLAN

11.1 Data Reporting

The Office of Data Quality (ODQ) will collect, manage, and monitor data for this study.

11.2 Responsibility for Data Submission

Investigative sites within DF/HCC are responsible for submitting data forms to the ODQ in accordance with DF/HCC SOPs.

12. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the statistical section. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

13. REFERENCES

1. Mao JJ, Bowman MA, Xie SX, Bruner D, DeMichele A, Farrar JT. Electroacupuncture Versus Gabapentin for Hot Flashes Among Breast Cancer Survivors: A Randomized Placebo-Controlled Trial. J Clin Oncol. 2015;33: 3615-3620.
2. Crew K, Capodice J, Greenlee H, et al. Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer. J Clin Oncol. 2010;28: 1154-1160.
3. Shen J, Wenger N, Glaspy J, et al. Electroacupuncture for control of myeloablative chemotherapy-induced emesis: A randomized controlled trial. JAMA. 2000;284: 2755-2761.
4. Molassiotis A, Bardy J, Finnegan-John J, et al. Acupuncture for cancer-related fatigue in patients with breast cancer: a pragmatic randomized controlled trial. J Clin Oncol. 2012;30: 4470-4476.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Available from URL: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#supportive [accessed Oct. 25, 2016, 2916].
6. Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. J Natl Cancer Inst Monogr. 2007: 16-21.
7. Schneider A, Kotronoulas G, Papadopoulou C, et al. Trajectories and predictors of state and trait anxiety in patients receiving chemotherapy for breast and colorectal cancer: Results from a longitudinal study. Eur J Oncol Nurs. 2016;24: 1-7.
8. Lim CC, Devi MK, Ang E. Anxiety in women with breast cancer undergoing treatment: a systematic review. Int J Evid Based Healthc. 2011;9: 215-235.
9. Boltong A, Aranda S, Keast R, et al. A prospective cohort study of the effects of adjuvant breast cancer chemotherapy on taste function, food liking, appetite and associated nutritional outcomes. PLoS One. 2014;9: e103512.
10. Boltong A, Keast R. The influence of chemotherapy on taste perception and food hedonics: a systematic review. Cancer Treat Rev. 2012;38: 152-163.
11. Hamer J, McDonald R, Zhang L, et al. Quality of life (QOL) and symptom burden (SB) in patients with breast cancer. Support Care Cancer. 2016.
12. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer. 2000;89: 1634-1646.
13. Dibble SL, Isreal J, Nussey B, Casey K, Luce J. Delayed chemotherapy-induced nausea in women treated for breast cancer. Oncol Nurs Forum. 2003;30: E40-47.
14. Dibble SL, Casey K, Nussey B, Israel J, Luce J. Chemotherapy-induced vomiting in women treated for breast cancer. Oncol Nurs Forum. 2004;31: E1-8.
15. Booth CM, Clemons M, Dranitsaris G, et al. Chemotherapy-induced nausea and vomiting in breast cancer patients: a prospective observational study. J Support Oncol. 2007;5: 374-380.
16. Ashbury FD, Findlay H, Reynolds B, McKerracher K. A Canadian survey of cancer patients' experiences: are their needs being met? J Pain Symptom Manage. 1998;16: 298-306.
17. Kindberg S, Klünder L, Strøm J, Henriksen TB. Ear acupuncture or local anaesthetics as pain relief during postpartum surgical repair: a randomised controlled trial. BJOG. 2009;116: 569-576.
18. Cheuk DK, Wong V. Acupuncture for epilepsy. Cochrane Database Syst Rev. 2014:

CD005062.
19. Ahlberg R, Skarberg K, Brus O, Kjellin L. Auricular acupuncture for substance use: a randomized controlled trial of effects on anxiety, sleep, drug use and use of addiction treatment services. Subst Abuse Treat Prev Policy. 2016;11: 24.
20. Klausenitz C, Hesse T, Hacker H, Hahnenkamp K, Usichenko T. Auricular acupuncture for pre-exam anxiety in medical students: a prospective observational pilot investigation. Acupunct Med. 2016;34: 90-94.
21. King HC, Spence DL, Hickey AH, Sargent P, Elesh R, Connelly CD. Auricular acupuncture for sleep disturbance in veterans with post-traumatic stress disorder: a feasibility study. Mil Med. 2015;180: 582-590.
22. Set T, Cayir Y, Pirim AB. Effects of ear acupuncture therapy for obesity on the depression of obese women. Acupunct Med. 2014;32: 427-429.
23. Michalek-Sauberer A, Gusenleitner E, Gleiss A, Tepper G, Deusch E. Auricular acupuncture effectively reduces state anxiety before dental treatment--a randomised controlled trial. Clin Oral Investig. 2012;16: 1517-1522.
24. Karst M, Winterhalter M, Münte S, et al. Auricular acupuncture for dental anxiety: a randomized controlled trial. Anesth Analg. 2007;104: 295-300.
25. Wu S, Liang J, Zhu X, Liu X, Miao D. Comparing the treatment effectiveness of body acupuncture and auricular acupuncture in preoperative anxiety treatment. J Res Med Sci. 2011;16: 39-42.
26. Tan JY, Molassiotis A, Wang T, Suen LK. Current evidence on auricular therapy for chemotherapy-induced nausea and vomiting in cancer patients: a systematic review of randomized controlled trials. Evid Based Complement Alternat Med. 2014;2014: 430796.
27. Zhang YM, Ji FQ, Sun L, Jin LH. Effect of auricular acupuncture for chemotherapy induced nausea and vomting in breast cancer patients: clinical analysis of 40 cases. Chinese Journal of Traditional Medical Science and Technology. 2013;20: 134.
28. Organization WH. WHO handbook for reporting results of cancer treatment1979.
29. Hou PW, Hsu HC, Lin YW, Tang NY, Cheng CY, Hsieh CL. The History, Mechanism, and Clinical Application of Auricular Therapy in Traditional Chinese Medicine. Evid Based Complement Alternat Med. 2015;2015: 495684.
30. He W, Wang X, Shi H, et al. Auricular acupuncture and vagal regulation. Evid Based Complement Alternat Med. 2012;2012: 786839.
31. Li H, Yin J, Zhang Z, Winston JH, Shi XZ, Chen JD. Auricular vagal nerve stimulation ameliorates burn-induced gastric dysmotility via sympathetic-COX-2 pathways in rats. Neurogastroenterol Motil. 2016;28: 36-42.
32. National Cancer Institute. Chemotherapy and You: Support for People With Cancer - National Cancer Institute. Available from URL: https://www.cancer.gov/publications/patient-education/chemo-and-you [accessed Oct. 25, 2016, 2016].
33. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Available from URL: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 [accessed Oct. 25, 2016, 2016].
34. Hui D, Shamieh O, Paiva CE, et al. Minimal Clinically Important Difference in the Physical, Emotional, and Total Symptom Distress Scores of the Edmonton Symptom Assessment System. J Pain Symptom Manage. 2016;51: 262-269.

35. Ecclestone C, Chow R, Pulenzas N, et al. Quality of life and symptom burden in patients with metastatic breast cancer. Support Care Cancer. 2016;24: 4035-4043.
36. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care. 1991;7: 6-9.
37. Watanabe SM, Nekolaichuk C, Beaumont C, Johnson L, Myers J, Strasser F. A multicenter study comparing two numerical versions of the Edmonton Symptom Assessment System in palliative care patients. J Pain Symptom Manage. 2011;41: 456-468.
38. Nixon GF, Steffeck JC. Reliability of the state-trait anxiety inventory. Psychol Rep. 1977;40: 357-358.
39. Kendall PC, Finch AJ, Auerbach SM, Hooke JF, Mikulka PJ. The State-Trait Anxiety Inventory: a systematic evaluation. J Consult Clin Psychol. 1976;44: 406-412.
40. Spielberger CD. STATE-TRAIT ANXIETY INVENTORY. Consulting Psychologists Press, 1970.
41. Karst M, Passie T, Friedrich S, Wiese B, Schneider U. Acupuncture in the treatment of alcohol withdrawal symptoms: a randomized, placebo-controlled inpatient study. Addict Biol. 2002;7: 415-419.
42. Reilly PM, Buchanan TM, Vafides C, Breakey S, Dykes P. Auricular acupuncture to relieve health care workers' stress and anxiety: impact on caring. Dimens Crit Care Nurs. 2014;33: 151-159.
43. Matsuda Y, Okita K, Furuhata T, et al. Evaluation of the validity of chemotherapy-induced nausea and vomiting assessment in outpatients using the Japanese version of the MASCC antiemesis tool. Support Care Cancer. 2015;23: 3331-3339.
44. Molassiotis A, Coventry PA, Stricker CT, et al. Validation and psychometric assessment of a short clinical scale to measure chemotherapy-induced nausea and vomiting: the MASCC antiemesis tool. J Pain Symptom Manage. 2007;34: 148-159.
45. Molassiotis A, Saunders MP, Valle J, et al. A prospective observational study of chemotherapy-related nausea and vomiting in routine practice in a UK cancer centre. Support Care Cancer. 2008;16: 201-208.
46. Mao JJ, Armstrong K, Farrar JT, Bowman MA. Acupuncture expectancy scale: development and preliminary validation in China. Explore (NY). 2007;3: 372-377.
47. Mao JJ, Xie SX, Bowman MA. Uncovering the expectancy effect: the validation of the acupuncture expectancy scale. Altern Ther Health Med. 2011;16: 22-27.
48. Cheifetz O, Packham TL, Macdermid JC. Rasch analysis of the Edmonton Symptom Assessment System and research implications. Curr Oncol. 2014;21: e186-194.

14. APPENDICES

14.1 Appendix I. Edmonton Symptom Assessment System (ESAS-R)

Please circle the number that best describes how you feel NOW:

No Pain	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Drowsiness
No Nausea	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Nausea
No Lack of Appetite	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Lack of Appetite
No Shortness of Breath	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Anxiety

Best Wellbeing *(Wellbeing = how you feel overall)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Wellbeing
No _____ Other Problem *(for example, sleep disturbance or constipation)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible _____

Patient's Name _____

Date _____ Time _____

Completed by (check one):

- ☐ Patient
- ☐ Family caregiver
- ☐ Health care professional caregiver
- ☐ Caregiver-assisted

14.2 Appendix II. State-Trait Anxiety Inventory (STAI)

A number of statements which people have used to describe themselves are given below Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel right now, that is, at this moment There are no right or wrong answers Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best

		NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1.	I feel calm	1	2	3	4
2.	I feel secure	1	2	3	4
3.	I am tense	1	2	3	4
4.	I feel strained	1	2	3	4
5.	I feel at ease	1	2	3	4
6.	I feel upset	1	2	3	4
7.	I am presently worrying over possible misfortunes	1	2	3	4
8.	I feel satisfied	1	2	3	4
9.	I feel frightened	1	2	3	4
10.	I feel comfortable	1	2	3	4
11.	I feel self-confident	1	2	3	4
12.	I feel nervous	1	2	3	4
13.	I am jittery	1	2	3	4
14.	I feel indecisive	1	2	3	4
15.	I am relaxed	1	2	3	4
16.	I feel content	1	2	3	4
17.	I am worried	1	2	3	4
18.	I feel confused	1	2	3	4
19.	I feel steady	1	2	3	4
20.	I feel pleasant	1	2	3	4

A number of statements which people have used to describe themselves are given below Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel right now, that is, at this moment There are no right or wrong answers Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best

		ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21.	I feel pleasant	1	2	3	4
22.	I feel nervous and restless	1	2	3	4
23.	I feel satisfied with myself	1	2	3	4
24.	I wish I could be as happy as others seem to be	1	2	3	4
25.	I feel like a failure	1	2	3	4
26.	I feel rested	1	2	3	4
27.	I am "calm, cool, and collected"	1	2	3	4
28.	I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29.	I worry too much over something that doesn't really matter	1	2	3	4
30.	I am happy	1	2	3	4
31.	I have disturbing thoughts	1	2	3	4
32.	I lack self-confidence	1	2	3	4
33.	I feel secure	1	2	3	4
34.	I make decisions easily	1	2	3	4
35.	I feel inadequate	1	2	3	4
36.	I am content	1	2	3	4
37.	Some unimportant thought runs through my mind and bothers me	1	2	3	4
38.	I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39.	I am a steady person	1	2	3	4
40.	I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

14.3 Appendix III. The MASCC Antiemesis Tool (MAT)

MASCC Antiemesis Tool: Instructions

Date of Chemotherapy *(this cycle)*:

Day	Month	Day of the Week

Information about this brief form:

The MASCC Antiemesis Tool (MAT) is a way to help your doctors and nurses be sure you get the best care there is to prevent nausea and vomiting from chemotherapy. By filling out this form, you can help us make sure that you are having the best control of these possible side effects.

Here are the definitions used on this form:

Vomiting: The bringing up of stomach contents.

Nausea: The feeling that you might vomit.

Please answer all questions. There are no right or wrong answers, only your impression.
If you have any concerns about how or when to complete this form, please ask!

Please notice that Question #4 and Question #8 have a different style. These questions are scales.
For this type of question, just circle the number from 0 to 10 that most closely resembles your experience with your nausea and vomiting and write the number in the box to the right. An example of this form of question (but dealing with parking) is given below. Feel free to practice with this example or ask one of us to go over it with you.

How much difficulty did you have parking your car today?

0 1 2 3 4 5 6 7 8 9 10

None — As much as possible

(Write the number in this box)

MASCC Antiemesis Tool

Please fill this out the day after chemotherapy on:

Day ☐ Month ☐ Day of the Week ☐

Nausea and Vomiting during the first 24 hours after chemotherapy:

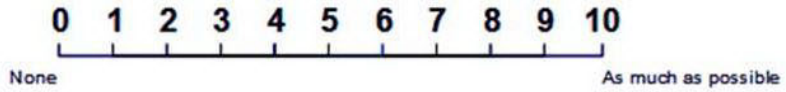
(This page refers to the first 24 hours following chemotherapy):

1) In the 24 hours since chemotherapy, did you have any **vomiting?** **Yes** ☐ **No** ☐ (Select one)

2) If you vomited in the 24 hours since chemotherapy, how many **times** did it happen? ☐ (Write the number of times in this box)

3) In the 24 hours since chemotherapy, did you have any **nausea?** **Yes** ☐ **No** ☐ (Select one)

4) If you had nausea, please circle or enter the number that most closely resembles your experience.
How much nausea did you have in the last 24 hours? ☐ (Write the number in this box)



MASCC Antiemesis Tool

This page asks about the period from the day after to 4 days after chemotherapy.
So it asks about the time after the first 24 hours.

Please fill this out four days after chemotherapy on:

Day	Month	Day of the Week

Delayed Nausea and Vomiting

5) Did you **vomit** 24 hours or more after chemotherapy? **Yes** ☐ **No** ☐ (Select one)

6) If you vomited during this period, how many **times** did it happen? ☐ (Write the number of times in this box)

7) Did you have any **nausea** 24 hours or more after chemotherapy? **Yes** ☐ **No** ☐ (Select one)

8) If you had nausea, please circle or enter the number that most closely resembles your experience.
How much nausea did you have over this time period?

0 1 2 3 4 5 6 7 8 9 10

None — As much as possible

☐ (Write the number in this box)

14.4 Appendix IV. Acupuncture Expectation Scale

Name of participant: _____ Hospital Number:_____

Date: _____

ACUPUNCTURE EXPECTATION SCALE

Every individual may have different expectations for the effects of acupuncture. If we use the following sentences to describe your expectation of acupuncture's effect on your chemotherapy related symptoms after the entire course of acupuncture therapy, how much do you agree? For each statement, please choose the closest answer.

	Not at all agree	A little agree	Moderately agree	Mostly agree	Completely agree
My chemotherapy related symptoms will improve a lot	1	2	3	4	5
I will be able to cope with my chemotherapy related symptoms better	1	2	3	4	5
My chemotherapy related symptoms will disappear	1	2	3	4	5
My energy level will increase	1	2	3	4	5

14.5 Appendix V. Acupuncture Treatment Form

Name of patient:_____ **Hospital ID# :**_____**Date of Visit :**_____

1. **Time: Needle Insertions: ____AM/PM_____ minutes. Needles Out: _____AM/PM_____ minutes**
2. Please make X below to indicate the ear acupuncture points used at today's session, and the points that *De Qi* sensation was obtained.

Points	L	R	**Points**	L	R	*De Qi?*		Note
Shenmen			Kidney			Y	N	
Liver			Point Zero					
Stomach			Esophagus					

3. Please ask the study patient when you have <u>just completed the adjustment</u> of during the treatment session today and make a "X" below:

"Please tell me, on a scale from 0 to 10, the intensity of the needling sensation you are experiencing right now; 0 is that you do not feel anything at all and 10 is the strongest sensation you could imagine."

Intensity Score	0	1	2	3	4	5	6	7	8	9	10
X											

4. At the end of the session, please make "X" below on the patient's immediate responses for today's treatment:

	Question Items	**Yes**	**No**	**Unknown**
a	Did the patient appear to be relaxed?			
b	Was the patient dozed off during the treatment?			
c	Was the pulse/heart rate of the patient slower than the beginning of the session?			
d	Has the patient's skin temperature of hands noticeably changed (either warmed up or cooled down)?			
e	Other observations?			

5. Did the patient report any adverse event per CTCAE v4.0 at this visit?

NO YES, If " YES" is answered, please describe the details here:

Adverse Event	**Start Date**	**Stop Date**	**Grade (1-5)** Mild, Moderate, Severe, Life Threatening, Fatal	**Attribution** unrelated, unlikely, possible, probable, definite	**Comments**
Skin bruise					
Hematoma					
Skin infection					
Presyncope					
Syncope					
Nausea					

6. Was today's session <u>completely</u> followed the study protocol requirement?

Question Item	YES	NO	If "no", please explain here
Was today's session <u>completely</u> followed the study protocol requirement?			

Signature of acupuncturist

14.6 Appendix VI. Medication Log

Name of Patient: _____Hospital ID#:_____Today's Date:_____

Date of Chemotherapy:_____Please circle the time period: Before chemo; Chemo cycle: 1 2 3

The followings are possible medications or supplements you might be using at home after chemotherapy. You might be taking medications that are not in the list as well. Please indicate ALL prescription medications AND over-the-counter medications you have taken at home **in past 5 days since last cycle of chemotherapy**. If you have not yet started chemotherapy, please list medications and supplements you are currently taking.

Name of Medication	Did you take any of these?		What is the dose of each pill? (5 mg? or 10 mg?)	How MANY pills did you take EACH TIME?	How OFTEN did you take it EACH DAY?	Date Started (MM/DD/YY)	Date Stopped (MM/DD/YY)
Prochlorperazine (Compazine)	Y	N					
Lorazepam (Ativan)	Y	N					
Ondansetron (Zofran)	Y	N					
Metoclopramide (Reglan)	Y	N					
Aprepitant (Emend)	Y	N					
Dexamethasone (Decadron)	Y	N					
Prednisone	Y	N					
Senna(Senokot)	Y	N					
Docusate (Colace)	Y	N					
Polyethylene glycol (Miralax)	Y	N					
loperamide (IMODIUM)	Y	N					
Tramadol (Ultram)	Y	N					
Oxycodone(OxyContin/Percocet)	Y	N					
Hydromorphone (DILAUDID)	Y	N					
Iburpofen(Advil, Motrin)	Y	N					
acetaminophen (TYLENOL)	Y	N					
omeprazole (PRILOSEC)	Y	N					
loratadine (CLARITIN)	Y	N					
Dietary supplements	Y	N					
Others	Y	N					
	Y	N					
	Y	N					
	Y	N					
	Y	N					

Other comments:

14.7 Appendix VII. Study Letter

DANA-FARBER CANCER INSTITUTE
DANA-FARBER / HARVARD CANCER CENTER

Date

Dear,

We are conducting a research study to look at whether ear acupuncture can help reduce the symptoms associated with receiving chemotherapy. Many patients experience nausea, vomiting, fatigue, pain, depression and anxiety after receiving chemotherapy medications for breast cancer. Some prescription medications and supplements can reduce these symptoms in some patients, but these medications often have their own side effects and often do not result in complete resolution of symptoms. Additional strategies are needed to reduce the symptoms related to receiving chemotherapy for breast cancer.

This study is being done to see if ear acupuncture will help reduce the symptoms associated with receiving chemotherapy as a treatment for breast cancer. The study will also explore whether ear acupuncture influences the dosage of medications used to treat the symptoms of chemotherapy, such as medications for pain and nausea.

The ear acupuncture program will take place during chemotherapy infusion appointments in the infusion rooms at the Dana-Farber Cancer Institute. If you decide to participate, you will be involved with the study for about 3 months and receive two ear acupuncture sessions lasting 30 minutes. Participants will also be asked to complete a series of questionnaires. You may change your mind and withdraw from the study at any time.

This study has been approved by the Institutional Review Board of the Dana-Farber Cancer Institute. All individual data will be kept confidential. Group data may be presented or published, but no identifying data would be included.

Please complete the response card and return it in the envelope provided. If you have any questions or would like to discuss study participation, please call Roxanne Quinn at 617-632-5408. Participation is voluntary and your decision will not affect your care at the Dana-Farber Cancer Institute in any way. Thank you for considering this study.

Sincerely,

Dr. Weidong Lu

Principal Investigator

14.8 Appendix VIII. Study Response Card

Study ID#_____

Please check one box below and return this postcard in prepaid envelope provided:

☐ YES, I would like to hear more about this study. You can call me at the numbers and times listed below.

My phone number is _____

The best days/times to reach me are: _____

☐ NO, thank you. I am not interested in participating.

Please contact Roxanne Quinn at 617-632-5408 with questions.

14.9 Appendix IX. Study Brochure

Symptoms such as nausea, fatigue, and pain are common in women who receive Chemotherapy for Breast Cancer.

This study is being done to see if ear acupuncture treatments reduce the symptoms associated with receiving chemotherapy.

Talk to your doctor about whether this study is a good fit for you.

The Ear Acupuncture Study

(EACH Study)

DANA-FARBER CANCER INSTITUTE

SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

www.dana-farber.org

For more information, contact:

Roxanne Quinn

(617) 632-5408

Roxanne_Quinn@dfci.harvard.edu

Principal Investigator:

Weidong Lu, MB, MPH, PhD

(Dana-Farber)

Are you receiving chemotherapy & experiencing nausea, fatigue, pain, or other symptoms?

-Or-

Are you about to receive chemotherapy?

Ask your oncologist about

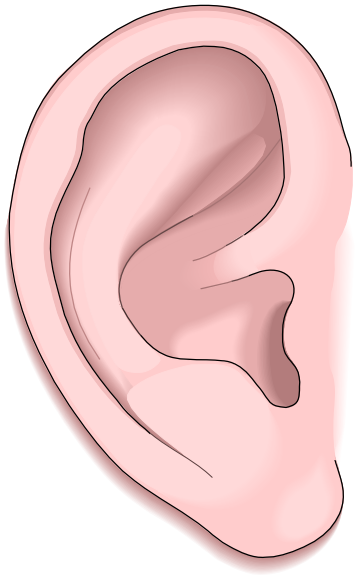
The Ear Acupuncture Study

(EACH Study)

A Dana-Farber study for symptoms associated with receiving chemotherapy

YOU MAY BE ABLE TO JOIN THIS STUDY IF:

- ✓ You are currently receiving chemotherapy every 2-3 weeks for breast cancer
- ✓ You are experiencing nausea, fatigue, pain, or other symptoms associated with receiving chemotherapy



ALL STUDY PARTCIPANTS WILL RECEIVE THE FOLLOWING ACUPUNCTURE SCHEDULE:

Cycle 1

- No Ear Acupuncture, Participants will receive an educational reading booklet

Cycle 2

- Ear Acupuncture for 30 minutes during chemotherapy infusion

Cycle 3

- Ear Acupuncture for 30 minutes during chemotherapy infusion

FREQUENTLY ASKED QUESTIONS

WHAT IS EAR ACUPUNCTURE?

- Ear Acupuncture is a complementary therapy in which thin, sterile, disposable needles are inserted into various spots on the external ear with the goal of improving symptoms associated with receiving chemotherapy

IF I JOIN, HOW LONG WILL I BE INVOLVED IN THE STUDY?

- If you are eligible to join the study you will be involved in the study for about 3 months

IF I JOIN, WHAT DO I HAVE TO DO?

- ✓ Complete a series of questionnaires
- ✓ Follow the assigned acupuncture schedule

14.10 Appendix X. Study Scripts

Email Reminder Script

Subject: Ear Acupuncture Survey Reminder

Dear [patient name],

This email is a friendly reminder to please complete your [Day 2 or Day 5] experience survey for the ear acupuncture study. It's important that you fill out and mail in the surveys in real-time so that we can better understand your patient experience. If you would like, you can also complete the surveys over the phone by calling [study coordinator's name] at [study coordinator's phone number] or by responding to this email with preferred dates and times. The phone call should take about 10 minutes.

Thank you again for participating and we look forward to hearing from you,

[Study team member]

Phone Reminder Script

Hello [patient name], this is [study coordinator] from the ear acupuncture study calling to remind you about the [Day 2 or Day 5] experience survey. It's important that you fill out and mail in the surveys in real-time so that we can better understand your patient experience. If you prefer, we can set up a time complete the survey over the phone, the survey should take about 10 minutes to complete. If you have any questions or would like to set up a time to complete the survey over the phone, please give me a call back at [study coordinator phone number] or email me at [study coordinator email]. Thank you again for participating and we look forward to hearing from you.

Surveys Conducted by Phone

Day 2 and Day 5 surveys will be conducted over the phone only by patient preference and with patient permission. All phone calls will take place in SW 560 and all answers will be kept confidential. The study measures that will be conducted over the phone are the Edmonton Symptom Assessment Scale (ESAS), the State-Trait Anxiety Inventory (STAI), the MASCC Anti-Emesis Tool (MAT), and the medication log. The study coordinator will read the instructions, followed by question and answer options to the patient. Patients will also be reminded that they can choose to skip any question they don't wish to answer and can stop the survey at any time for any reason.