Research Protocol

Project Title: **Feasibility Testing of a Randomized Controlled Trial of Acupuncture to Improve Symptoms for Individuals with Stable Angina (AIMS-A)**

a. SIGNIFICANCE

The significance of managing the symptoms of stable angina cannot be overstated given that; 1) heart disease remains the number one killer of individuals in the US, 2) the incidence of stable angina is projected to rise with concomitant increases in comorbid conditions, 3) the direct and indirect costs of angina are high, and 4) the largest generation of Americans, the "Baby Boomers", are reaching retirement. A reduction in the amount and severity of pain and associated symptoms has the potential to contribute to improvements in functional status and quality of life. Camm et al.[1] found that one-third of patients with stable angina have suboptimal management of their disease and concluded that neither clinicians nor patients should accept the idea that symptoms are unavoidable.

b. INNOVATION

This study is innovative in that it will: 1) use a theoretically-based TCM model to test the effect of acupuncture on angina symptoms; 2) test a complementary therapy for individuals with inadequate pain and symptom control; 3) target a population of public health interest, individuals with stable angina whose symptoms are not well controlled with conventional therapy; and 4) the use of McGill Pain Questionnaire[2] which will allow us to better characterize the sensory elements of angina pain location and distribution including intensity, quality, and pattern. This therapy has not been tested in a sample of *American*s with angina, thus there is a significant gap in knowledge of feasibility and efficacy in this population. If found to be effective in a larger trial, the addition of acupuncture therapy has the potential to change the western medicine paradigm of treatment of angina based solely on a model of obstructive coronary artery disease to a complementary therapy approach based on an integrative western medicine/TCM model.

c. APPROACH

c.1. Introduction

Currently 15.5 million Americans have ischemic heart disease (IHD).[3] Ischemic heart disease puts an enormous strain on the health care system, the work-force, caregivers, and afflicted individuals.[4] Ischemic heart disease has a chronic, stable form (angina) signifying partial obstruction of flow[5] or microvascular dysfunction[6] and comes with substantial lifetime consequences including heart failure[7], atrial fibrillation[8], reinfarction[9], and cardiac arrest.[9] Direct and indirect costs of IHD for 2011 were estimated to be $215.6 billion[10,11]. Stable angina is associated with multiple symptoms[12], impaired functional status[13,14], and reduced quality of life (QoL).[5,15] Stable angina is a syndrome induced by transient myocardial ischemia resulting in chest pain and associated symptoms such as shortness of breath and fatigue[16]. Ischemia may be due to obstructed coronary arteries or microvascular coronary dysfunction (MCD)[17].

Sex differences in the clinical presentation of IHD have been reported[18]. Heart disease in men is more often due to occlusions in their main coronary arteries, referred to as obstructive coronary artery disease[19,20]. Humphries et al. found that 7.1% of males vs. 23.3% of females in a large (n=32,856) cohort of Canadians undergoing elective angiography for suspected IHD[18] had angiographically normal coronary arteries. A diagnosis of normal coronary arteries has been reported to be as high as five times more common in women[6]. Women with "normal" coronary arteries are frequently thought to have MCD. To date there has been no clear explication of the pathogenesis of microvascular disease[21] but it is thought to involve damage to the tiny blood vessels in the heart, causing them to narrow, tighten or constrict (spasm). These abnormalities may be caused by vasomotor or metabolic regulators[6]. This reduces blood flow to the myocardium often causing symptoms associated with ischemia[22]. Microvascular coronary dysfunction is more likely to occur in younger women. Women with angiographic evidence of stable angina have poorer outcomes compared to men[17]. In one study, hospital readmissions *for angina* accounted for 45% of adverse outcomes following ACS[17]. Those with stable angina are also at risk for ACS, sudden cardiac death[12], and heart failure[5,15]. Therefore, the examination of sex differences in the efficacy of acupuncture for stable angina is critically needed.

Guideline-directed therapy for the treatment of stable angina include nitrates, beta-blockers, calcium channel blockers, and angiotension converting enzyme (ACE) inhibitors[16]. These drugs can have side effects such as headache, flushing, fatigue, and cough which can lead to non-adherence and lack of symptom control. Acupuncture has been recommended as a potential complementary or alternative treatment for hypertension[23], hyperlipidemia[24], and smoking cessation[25] but has not been proposed for the treatment of stable angina in the US[16]. The National Institutes of Health (NIH) has recommended acupuncture as an alternative or complementary therapy for a number of conditions[26].

c.2. Importance of the Problem

The number one cause of death for individuals in the United States is IHD[3]. As noted, IHD is associated with poor outcomes including heart failure[7], atrial fibrillation[8], reinfarction[9], and cardiac arrest [9] and women have poorer outcomes compared to men with IHD[27]. We have demonstrated in our prior studies that angina symptoms are not as well controlled for women as for men[28]. We have quantified the burden of symptoms and found that women experience a higher number of symptoms and more distress from symptoms despite receiving standard care following an episode of ACS[29]. Our short term goal is to determine, in a rigorously controlled trial, if acupuncture is an effective complementary treatment for stable angina. The continued growth in the number of older adults and the preponderance of elder females in the population further warrants research into symptom management. Symptoms that are well-controlled result in better functional status[30] and QoL[31]. Managing heart disease in women is a vital health issue if aging women are to maintain a high QoL.

c.2.1 Side Effects of Anti-anginal Medications and Lack of Symptom Control for Indivduals with Angina

Standard guideline-directed therapy for the treatment of stable angina relies on pharmacologic therapies including anti-platelet agents[32,33], statins[34], and anti-ischemic agents[35]. Xu et al. found patients undergoing acupuncture complained of side effects from anti-anginal drugs including nitroglycerin related headaches; isosorbide related dizziness and nausea/vomiting; and propranolol related chest pain and depression[36].

c.2.2. Physiologic Mechanisms of Acupuncture and their Effect on the Cardiovascular System

Acupuncture regulates the autonomic nervous system and reduces sympathetic stimulation to the heart and vasculature by modulating the midbrain, releasing endorphins and dynorphins, with a resultant decrease in production of norepinephrine and epinephrine. These processes impact the CV system by reducing blood pressure, heart rate, and centrally mediated arrhythmias[37]. Acupuncture helps relieve pain by: 1) deactivating the limbic-paralimbic-neocorticol network system[38]; 2) activating mu opioid receptors[39]; 3) increasing serum β endorphins[40]; 4) increasing ACTH release from the anterior pituitary[41]; and 5) downregulating M1 macrophages, Interleukin-1β, Interleukin-6, Interleukin-18 and Tumor Necrosis Factor (TNF)[42].

c.2.3. Theory of Traditional Chinese Medicine

TCM is based on the theory of *Yin* and *Yang*: 1) *yin* and *yang* are relative opposites to one another (e.g., hot/cold, night/day) but are perpetually undergoing transformation (night becomes dawn, dawn becomes day etc.); 2) *yin* and *yang* are interdependent and nothing can be all *yin* or all *yang*; and 3) an imbalance of either *yin* or *yang* eventually weakens both. When *yin* and *yang* are in balance health is sustained[43]. Disease and/or pain ensues when *yin* and *yang* are out of balance. When *yang* (warming) is weak, *yin* predominates and the body is cold, the hands and feet are cold, the skin is pale, and the person is lethargic. *Qi* is the vital energy flowing within and surrounding the body. *Qi* can be *yin* or *yang*[44]. Disorders of *qi* or blood can result in pain; they can be deficient, or result in excess (stagnant or obstructed). The channels through which *qi* and *blood* flow in the body are called meridians[45]. Acupuncture needles are inserted into acupuncture points which access the meridians and promote the circulation of *qi* and blood[43]. Deficient *qi* and/or blood is strengthened (tonified); excess *qi* and/or blood is moved to reduce stagnation or obstruction[46,47]. *Thus the yin and yang of the body become balanced and pain and other symptoms are reduced[43,46].* In the TCM model, it is theorized that the pain, shortness of breath, and fatigue of stable angina results when there is an excess (stagnant or obstructed) or a deficiency in qi and/or blood in the meridians that flow through and around the heart[47].

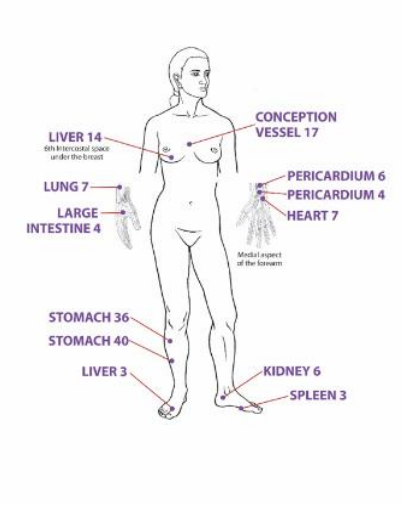
c.2.4. Acupuncture for the Treatment of Angina

A recent systematic review of 25 RCTs[48] and a meta-analysis of 8 RCTs[49] of acupuncture for the treatment of stable angina in China showed improvements in relief of angina symptoms for the acupuncture treated

participants compared to controls. However there was no reduction in ischemia as measured by ECG or reduction in nitroglycerin use. All but two studies (Scandinavian) were performed in China.[50,51] The authors noted limitations to the studies including heterogeneous samples, lack of adjustment for potential confounders, lack of standardization of acupuncture point prescriptions, varying medication prescriptions, and different outcome measures. Only one study, conducted in Sweden, addressed duration of acupuncture effect[51]. This study used a randomized crossover design and included 21 individuals (2 women) with angina. Patients in the acupuncture group reported a mean reduction in angina episodes from 10.6 to 6.1/week during the 4 weeks of therapy and 2 weeks of washout. Duration of effect beyond 2 weeks remains unknown. We will test this in our R21 study. Based on available, low quality evidence, an AHA writing group concluded that acupuncture has not been studied sufficiently to warrant recommendation as a treatment option for relief of angina symptoms for patients with stable IHD[52].

c.2.5. Acupuncture Use in the United States

Acupuncture use is on the rise in the United States. In 2012, Americans received 3,484,000 acupuncture sessions which was a significant increase from the years 2002 to 2007[53]. Overall 34% of American adults in 2012 used some form of complimentary alternative medicine (CAM)[53]. In 2007 a total of $33.9 billion dollars was spent on CAM[54,55]. Most Americans use CAM to supplement western medical treatments as opposed to replace them[56-58] and/or treat symptoms of chronic disease or side effects from medications[54,59,60]. Almost 8% of those using CAM did not tell their physicians[61]. Since women with symptoms of stable angina are seeking acupuncture and other CAM therapies for amelioration of symptoms, it is imperative to begin to evaluate the feasibility of using acupuncture to treat the pain and symptoms of stable angina. In addition, determination of sex differences in response to acupuncture is important.



Figure

c.2.6. Lack of a Standardized Acupuncture Protocol for Stable Angina.

There has been no attempt to standardize a set of acupuncture points used to treat chest pain or stable angina. Clinical practice guidelines cannot be developed until standardized study protocols are devised which offer investigators an algorithm for implementing consistent repeatable acupuncture interventions that can be tested in future trials. To overcome this gap, co-PI Schlaeger has developed an acupuncture point prescription (a set of standardized acupuncture points to determine needle insertion site) for treating the symptoms associated with a diagnosis of chest pain or stable angina. The point prescription includes the following points: Conception Vessel (CV)17, Pericardium (PC)4 and Pericardium (PC)6, Stomach (ST)36, Stomach (ST)40, Spleen (SP)3, Large Intestine (LI)4, Liver (LV)3, Liver (LV)14, Heart (HT)7, Lung (LU)7, and Kidney (KD)6. See Figure for exact needling locations.

c.3. Study Design. We will conduct a pilot randomized attention control trial. This design will be used to calculate the effect sizes for intra-individual and group differences in pain and symptoms. This design is superior to either *placebo* or *sham* acupuncture interventions. A placebo control design is not possible since neither the clinician nor participant can be blinded to the acupuncture treatment without the use of double-blind acupuncture needles, which are being tested in small studies and not yet commercially available[62]. Sham acupuncture, whereby needles are inserted into non acupuncture points on the body, is inferior to RCT with attention control design because needle punctures anywhere on the skin may be considered an *ashi* point; i.e. an active acupuncture point that may have therapeutic effects[63,64]. Following consent and upon admission to the study participants will be randomized 1:1 to the acupuncture or the attention control group.

c.4. Study Team. Our study has a high probability of success because our well-qualified team has expertise in all facets of this study including: ischemic heart disease (Dr. DeVon), acupuncture (Dr. Schlaeger), stable angina, and (Dr. Shroff). Dr. DeVon has been conducting rigorous multi-site clinical research with heart disease populations for more than 15 years. Dr. Schlaeger is an early stage investigator with a track record of success in clinical trials and acupuncture studies.

c.5. Preliminary Studies. This is a feasibility study so no preliminary data for this protocol have been collected. Dr. Schlaeger has recently successfully developed and tested a standardized acupuncture protocol for the treatment of women with vulvodynia[65]. Dr. DeVon, has extensive expertise in symptoms, gender, and measurement and has received substantial extramural (F31, T32, R15, R01) and intramural funding for her cardiovascular research. She has developed a validated symptom checklist for patients with acute coronary syndrome and has been funded on several studies to examine the acute and chronic symptoms of IHD[66-68].

c.6. Methods

c.6.1. Sample & Setting. Sixty-nine women and men, with a confirmed diagnosis of chest pain or stable angina will be included. We will recruit women from the Chicago metropolitan area including the UIC campus community. Inclusion criteria are: provision of a verified diagnosis from a care provider, individual, ≥21 years of age (since IHD presenting as angina has not been reported in children), chest pain or intermittent angina symptoms (pain, pressure, or discomfort in the chest or other areas of the upper body), and medical confirmation of a diagnosis of stable angina. Exclusion criteria include pregnancy, , COPD causing pain or associated symptoms, autoimmune dysfunction, use of steroid medications, and concomitant, biofeedback, or additional acupuncture. Participants will be instructed to continue medications to treat their chest pain or angina, as well as other health conditions, as prescribed. Etiology of chest pain or angina (i.e. occlusive coronary artery disease, microvascular disease, or vasospastic ischemia) is not an inclusion criteria. Menopausal status will be adjusted for in statistical analyses.

The study will be conducted at the University of Illinois, College of Nursing (UIC CON) in clinical research exam rooms on the fourth floor. One Illinois licensed acupuncturist, Jun Fu, whose qualifications are described in the budget justification will be administering all 10 acupuncture treatments to 35 experimental participants (and up to 34 control group participants upon study completion) there. The exam rooms will also be utilized to obtain informed consent and for research data collection. The UIC CON is accessible by public transportation and has parking available nearby.

c.6.2. Power Analysis. This feasibility pilot study is not powered to detect significant effects for improvement in symptom outcome measures. However, In order to achieve 80% power to detect a large effect size using Cohen's classification (EF=.80), 52 patients randomized and completing the final symptoms assessments will be needed. Based on our sample of 26 participants, we will be able to detect a Cohen's d effect size of 1.10 as statistically significant. While a large effect size is not anticipated in this pilot feasibility study, an expanded trial will be adequately powered to explore the threshold for a clinically meaningful effect.

c.6.3. Retention Strategies. We anticipate an attrition rate of no more than 10%, which means we expect a 90% retention rate for the subjects. These numbers are based on accruals and withdrawals in Dr. Schlaeger's previous 10 session acupuncture trial for which there were 36 accruals and no withdrawals. The following retention strategies will be employed: Participants will be engaged as active partners in the research by addressing possible benefits of acupuncture (experimental group) and non-pain related health education (control group) as well as the importance of their contribution to science. Data collection will be scheduled at convenient times for participants, including weekend and evening appointments. Multiple contact information (e-mail, cell phone, and home phone) will be collected to improve adherence to appointments. We also will offer $10 per visit to cover the cost of travel.

c.6.4. Procedures. The research assistant will screen and consent eligible individuals. The potential participants will be informed that they will either be randomized to the acupuncture group (10-acupuncture session protocol, two treatments per week for five weeks) or the attention control group. Data will be collected on tablet computers before and after each session. Control group members will be offered the acupuncture protocol at study completion.

c.6.5. Research Protocol. The research assistant (RA) will explain the nature of the study, risks and benefits, the voluntary nature of participation, and the ability to discontinue participation at any time without consequences. After informed consent is obtained, participants will be randomized to the acupuncture or attention control group via a computer-generated random numbers table. Each number (1-26) and assigned group, will be written on an index card and placed in a sealed opaque envelope. The participants will select

one envelope from a sealed box. The participant, acupuncturist, and RA cannot be blinded to group assignment. All participants will complete two measures at baseline: the McGill Pain Questionnaireand the Seattle Angina Questionnaire-7.[69] Those in the treatment group will repeat the measures following all 10 acupuncture session. Those in the control group will repeat measures during weeks 1-5 after their attention control sessions. All participants will complete the AHA Angina Log throughout the study (weeks 1-5). Venipuncture will be performed at baseline and study completion for all participants.

c.6.6. Acupuncture Protocol. The acupuncturist will swab each point with alcohol. Needles will be inserted and retained for 30 minutes. Each needle will be rotated 3 times to stimulate the *qi* in the meridian 10 minutes after insertion, at 20 minutes after insertion, and just prior to removal at 30 minutes. Needles will be inserted using the standards of clean needle technique established by the Council of Colleges of Acupuncture and Oriental Medicine[70] One size acupuncture needle, 0.25 diameter × 40 mm length, will be used. All acupuncture needles are sterile, disposable, and made of surgical stainless steel with stainless steel wound heads. Sessions will be repeated twice weekly (with at least 2 off days in between) for 5 weeks (10 sessions).

c.6.7. Acupuncture Point Prescription for Chest Pain or Angina. The standardized point prescription uses acupuncture points on the front of the body to enable individuals, many who are acupuncture naïve, to remain supine. This is aimed at reducing anxiety by enabling the participant to anticipate needle insertions.

c.6.8. Attention Control Health Videos Protocol. Individuals randomized to the attention control group will watch health videos on broad topics not containing content that could potentially improve pain. Videos will be viewed from weeks 1-5 (5 timepoints) and will equate to the time the experimental group receives acupuncture (~10 hrs.)[71]. Topics include *Defeating the superbugs; Can we live forever?; Do you see what I see?; Cracking your genetic code; How smart can we get?; Vaccines, calling the shots; Can I eat that?; and Alive inside (the benefits of music).*The videos will be shown in the College of Nursing clinical laboratory room on the 4th floor. The standardized content has an additional benefit of assuring complete fidelity to the control protocol.

c.7.1. Measures.
c.7.1.a. *Demographic Data Form* (Appendix A). Personal characteristics will be assessed using the demographic data form. Standard measures including age, race/ethnicity, marital status, education, income, employment, and insurance are included.

c.7.1.b. *Protocol Acceptability Scale for Treating Angina with Acupuncture* (Appendix B). The Satisfaction instrument is a 10-item instrument used to measure acceptability of the study processes and protocols. Items are measured on a 0 (negative response, i.e. did not like acupuncture) to 2 (positive response) scale. The protocol will be deemed to have high acceptability and have an acceptability score > 10 (80%).

c.7.1.c. McGill Pain Questionnaire (MPQ) **(Appendix C).** The MPQ[72] is a valid and reliable measure of pain.. The MPQ captures pain location and pain intensity on a 0 to 10 scale, where 0 is no pain and 10 is pain as bad as it can be andleast and worst pain in the past 24 hours.

C.7.1.d. *Seattle Angina Questionnaire-7 (SAQ-7)* (Appendix D). The instrument consists of 7 items in 5 domains (Physical Limitation, Angina Stability, Angina Frequency, and Quality of Life) measuring the impact of angina on participants' health status. Item responses are coded sequentially from worst to best status and range from 1 to 6 except Quality of Life (range 1-5). Scores are generated for each domain and are scaled 0 to 100, with 0 denoting the worst and 100 the best possible status[69]. The SAQ-7 was validated among patients presenting with stable IHD, undergoing percutaneous coronary intervention, and after acute myocardial infarction[73]. High levels of concordance (0.88–1.00) with each original SAQ domain were found. The SAQ-7 demonstrated good construct validity (compared with Canadian Cardiovascular Society class for angina; r=0.38-0.62) for patients with stable CAD.[69]

c.7.1.e. *AHA Angina Log* (Appendix E). *My Angina Log* is a simple 1 page log used to measure each episode of angina. Participants are instructed to record the date and number of times they experienced angina as well as triggers and treatments.[74] Severity of symptoms are measured on a 1-4 scale with 1 representing mild symptoms and 4, very severe symptoms. The instrument was designed as a clinical assessment form so

we will assess the psychometric properties of the Angina Log by comparing results to the SAQ-7 and the McGill Pain Questionnaire ®. See **Table 1** for all variables, measures, and data collection time points.

c.7.1.f. ***Massachussetts General Hospital Acupuncture Sensation Scale (MASS).*** The MASS Scale is a 13-item instrument which measures the intensity of sensations (on a 0-10 scale where 0 is no sensation felt by the patient and 10 is an unbeartable sensation felt by the patient) when acupuncture needles are stationary or manipulated by the acupuncturist. This phenomenon called "***de qi***" is thought by many acupuncturists to be responsible for the therapeutic effect of acupuncture.[75]

c.7.1.g. ***Biomarkers of Inflammation*.** Proinflammatory cytokines IL-1β, IL-2, IL-8, and IL-18; CRP[76,77]; and TNFα, the anti-inflammatory cytokines IL-4, and IL-10,[76] and the dual pro/anti-inflammatory IL-6[78] will be measured to determine if there is a significant change baseline to post study (5 week). Venous blood (4.5 mls) will be collected in a blue-top tube containing 3.2% sodium citrate. Samples will be processed in our clinical lab in the college. Samples will be centrifuged at room temperature for 15 minutes; plasma will be removed into 2 cryovials in 1 ml aliquots and stored in a -80°C freezer immediately. A label with study ID number, date, and time of blood draw will be placed on the cryovials prior to freezing. Samples will be batch analyzed using high-sensitivity multiplex technologies.[79] *See **Table 1** for all variables, measures, and data collection time points.*

c.8. Potential Problems, Alternate Plans, and Limitations based on the Sample Proposed. Rigorous research into complementary and alternative therapies has been hindered by the inability to conduct placebo-controlled trials[80]. Our attention control design is a strong alternative to an intervention that cannot be blinded to participant or interventionalist without potential confounding treatment effects. Recruitment is always a potential problem with clinical research and we will enlist the help of the American Heart Association Chicago Affiliate and *WomenHeart* of Cook County to identify potential participants. Attrition is also a possible problem but Dr. Schlaeger has experienced very little attrition in prior acupuncture studies. We will continue to enroll to retain 24 participants and we will address attrition with an intention to treat analysis. Design limitations were addressed in section c.3.

Table 1. Data Collection Variables, Measures, and Time Points (Both Groups)

Variable	Measure/Analyses	Data Collection Points (Baseline)	(10 tx sessions)	(5 wks.)
Aim 1				
Recruitment	Number enrolled/number invited to participate	X		X
Retention	Number retained at study completion/number recruited	X		X
Completion	Number of time points completed/12 (total)	X		X
Acceptability	*Protocol Acceptability Scale for Treating Angina with Acupuncture*			X
Aim 2				
Effect Size	*Intra-individual effect:* mean pre-scores – mean post-scores/pooled s.d. *Group effect:* mean differences in scores between acupuncture and attention control group.	X		X
Demographic Data	*Demographic Data tionsForm*	X		
Exploratory Aim				
Biomarkers	Interleukin 1β, 2, 6, 8, 10 & 18; CRP, TNF-α	X		X
Outcome Measures				
Pain & Symptoms	McGill Pain Questionnaire; *Seattle Angina Questionnaire-7; AHA Angina Log*	X	X	X
Acupuncture Sensations	MASS		X	

Note: TX is treatment. s.d. is standard deviation. AHA is American Heart Association

c.9. Statistical Analysis. Dr. Steffen will supervise data management and data analysis procedures. We will address missing data by intention to treat analyses (ITT), using the full information maximum likelihood (FIML) approach, which has been shown to produce unbiased parameter estimates and standard errors when data are missing at random[8177767676767683]. All data will be exported from RedCap and imported into SAS version 9.4 for cleaning and analysis. All variables will be screened and descriptive statistics (frequencies, means,

standard deviations) will be used to describe the sample participants. Non-normal distributions may be optimally transformed using the Box-Cox method and/or analyzed using a comparable non-parametric test.

c.9.1. Aim 1: To determine the feasibility of study processes (recruitment, retention, completion, acceptability) to inform the design and execution of a future R21 study.

Hypothesis: Acupuncture therapy will be feasible (80% recruitment, retention, completion) and acceptable to individuals with chest pain or stable angina.

For the feasibility assessments descriptive statistics will be used for describing the subject characteristics and recruitment, retention & completion. We will explore patient characteristics that predict attrition and/or poor adherence to the treatment schedule. Data collected at every session will be explored to assess change in pain ratings following a session and if this pattern is consistent over the course of treatment. We are interested in knowing if pain and other symptom relief continues to improve linearly over the 5 weeks and 10 treatments or if a plateau is reached suggesting the need for fewer treatments.

c.9.2. Aim 2: To estimate effect sizes for pre and post intervention scores and between the acupuncture and attention control groups for pain/symptoms, functional status and QoL. We will estimate standardized mean difference effect sizes (Hedges' g) comparing the treatment and control conditions adjusting for baseline differences and the upward bias due to our small sample size. We will also compute a standardized pre-post difference for the treatment group. Effect sizes will be calculated for pain, angina symptoms reported via survey and diary, functional status, and quality of life.

c.10. Timeline. We will prepare study materials and submit an IRB application upon notice of award. Three months is allotted for IRB approval process. The study is anticipated to begin on June 1, 2016 and be completed on August 31, 2017. See Table 2 for study timeline.

Table 2. Study Timeline

Study Phase	(Jun-Aug 16)	(Sept-Nov 16)	(Dec-Feb 17)	(Mar-May 17)	(Jun-Aug 17)
Submit IRB appl.	→ → →				
Recruit/Train RA		→			
Data Collection		→ → →	→ → →	→ → →	
Data Coding/Entry			→ → →	→ → →	
Data Analysis				→ →	
R21 Preparation				→ →	→
Manuscript Prep					→ →

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