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D-HH IRB OVERSIGHT:

One of the following must be true in order to submit to the D-HH IRB. Please check all that apply:

☒ The Principal Investigator is employed by D-H
☒ The study will utilize any D-H data or specimens
☒ The study will enroll D-H patients or recruit from D-H sites
☒ The study will utilize any D-H resources, e.g. study procedures will occur at D-H locations and/or use of D-H equipment or shared resources

PROTOCOL TITLE:

Exploring the Dose-Response Effect of Adjunctive Acupuncture on Pulmonary Rehabilitation: A Pilot Study.

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER/DATE:

V4 6/26/2023

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	2/13/23	Changes to consent process for control group, changes to intervention groups	Yes
2	5/23/23	Addition of flyers for recruitment, administrative corrections	No
3	6/26/23	Administrative correction to show group C is voluntary and not randomized. Addition of delegated RAs to assist in consenting.	No
4	12/19/23	Clarification on control arm being SOC pulmonary rehab	

Table of Contents

1.0 Study Summary

Study Title	Exploring the Dose-Response Effect of Adjunctive Acupuncture on Pulmonary Rehabilitation: A Pilot Study
Study Design	Wait time control with varying intervention duration
Primary Objective	Explore Adjunctive acupuncture effect on QOL and quantitative measures for Chronic COPD patient undergoing pulmonary rehab.
Secondary Objective(s)	- Explore the dose response relationship between adjunctive acupuncture and improvement in pulmonary function and/or quality of life. - Explore the effect of EA on inflammatory markers in patients undergoing PR
Research Intervention(s)/ Investigational Agent(s)	Electro-acupuncture
IND/IDE #	
Study Population	Patients with severe COPD
Sample Size	30
Study Duration for individual participants	9 months
Study Specific Abbreviations/ Definitions	EA – electro-acupuncture PR – pulmonary rehabilitation

2.0 Objectives*

- Explore Adjunctive acupuncture effect on QOL and quantitative measures for Chronic COPD patient undergoing pulmonary rehab.
- Explore the dose response relationship between adjunctive acupuncture and improvement in pulmonary function and/or quality of life.
- Explore the effect of EA on inflammatory markers in patients undergoing PR Hypotheses
- EA will: will significantly improve QOL and quantitative measures for Chronic COPD patient undergoing pulmonary rehab.
- There will be a significant dose response relationship between adjunctive acupuncture and improvement in pulmonary function and/or quality of life.
- EA will significantly reduce inflammatory markers in patients undergoing PR

3.0 Background*

Chronic obstructive pulmonary disease (COPD), is the fourth leading cause of death in the US (www.cdc.gov). COPD affects more than 15 million Americans. More than 140,000 Americans die of COPD each year approximately 1 death every 4 minutes.

Though tobacco smoke is the primary cause, 1 in 4 people with COPD have never smoked. Their disease has resulted from air pollutants at home (secondhand smoke), at work (fumes). Symptoms include chronic or smoker's cough, chronic phlegm production, shortness of breath, and wheezing. Early detection and treatment of COPD may change its course. This is usually via pulmonary function tests and chest x-ray often through the patients' primary care.

Treatment requires a careful and thorough evaluation, avoiding tobacco smoke, and removing air pollutants from the home and at work. As the disease progresses symptoms may initially be treated with medication. If the disease continues to worsen occasionally surgery may help, removing emphysematous areas. Another successful approach to severe COPD is pulmonary rehabilitation see below.

In 2015, CDC's Morbidity and Mortality Weekly Report (MMWR), reported that rural US residents experienced higher rates of COPD prevalence, COPD-related Medicare-covered hospitalizations, and deaths than residents living in more urban counties (those with populations of at least 10,000 people): The percentage of adults in rural areas diagnosed with COPD has nearly double the percentage in large metropolitan areas. Approximately 8% in rural areas as compared to 5% in metropolitan areas. Hospitalizations among Medicare enrollees for COPD were about 14 per 1000 enrollees in rural areas compared

with about 11 per 1000 enrollees in large metropolitan centers. Death rates from COPD were also greater among people living in rural areas (55 per 100,000 people) compared with people living in large metropolitan centers (32 per 100,000 people). New Hampshire and Vermont are largely rural states.

Costs
In 2010, costs attributable to having COPD were $32.1 billion and were projected to increase to $49.0 billion by 2020. Medicare paid 51% of those costs with 25% paid by Medicaid and 18% paid by private insurance in 2010. Total absenteeism costs were $3.9 billion in 2010 with an estimated 16.4 million days of work lost because of COPD.

Dyspnea is a cardinal symptom of chronic obstructive pulmonary disease (COPD), and its severity and magnitude increase as the disease progresses. This can lead to significant disability and reduction on quality of life. Refractory dyspnea is a common and difficult symptom to treat in patients with advanced COPD.

Evidence supports the benefits of oral opioids, neuromuscular electrical stimulation, chest wall vibration, walking aids and pursed-lip breathing in the management of dyspnea in the individual patient with advanced COPD. Oxygen is recommended for COPD patients with resting hypoxemia, though should be reserved for patients who receive symptomatic benefit. Up until the present the evidence has been mixed to support the routine use of anxiolytic medications, nebulized opioids, acupuncture, acupressure, distractive auditory stimuli (music), relaxation, handheld fans, counselling programs or psychotherapy(1).

What is Pulmonary Rehabilitation?
Pulmonary rehabilitation is a program of education and exercise that teach patients with severe COPD how to manage breathing, increase exercise tolerance and decrease dyspnea or breathlessness. The education part of the program teaches patient how to control their breathing to pace breathing with activities, how to take medicines optimally and how best to work with your health care team. The exercise sessions are supervised by a pulmonary rehabilitation staff that prepares a personalized exercise program. Typically, exercise start at the highest tolerable level for the patient, either sitting or standing. The amount of time spent exercising and the difficulty of the exercises are slowly increased with time. As you get stronger, and develop more endurance, breathlessness reduces.

Most Pulmonary Rehabilitation programs meet two to three times a week and programs can last 4 to 12 weeks or more. Program staff constantly monitor patient progress adjusting and increasing exercise as patients are able.

What is Acupuncture?
Acupuncture is a method of encouraging the body to promote natural healing and to improve functioning through the application of needles and heat or other forms of energy such as electricity at specific points on the body.

Acupuncture is one of the oldest, most commonly used medical procedures in the world. Though most familiar as an East Asian practice being documented in China for at least 2000 yrs. its origins are probably much older as evidenced by the acupuncture points tattooed on Ötzi the Bronze Age traveler thawed out of the Austrian Alps (1991). It first came to general attention in the US in 1971 when New York Times reporter James Reston wrote about how doctors in Beijing, China, used needles to ease his abdominal pain after surgery.

Acupuncture research has shown its benefit in treating a wide variety of conditions. It has grown rapidly in uses. In 1993, the U.S. Food and Drug Administration (FDA) estimated that Americans made 9 to 12 million visits per year to acupuncture practitioners and spent as much as $500 million on acupuncture treatments.1 In 1995, an estimated 10,000 nationally certified acupuncturists were practicing in the United States. By the year 2000, that number is expected to double. Currently, an estimated one-third of certified acupuncturists in the United States are medical doctors.

The National Institutes of Health (NIH) has funded a variety of research projects on acupuncture that have been awarded by its National Center for Complementary and Alternative Medicine (NCCAM), National Institute on Alcohol Abuse and Alcoholism, National Institute of Dental Research, National Institute of Neurological Disorders and Stroke.

Mechanisms of Action
From the western frame, several processes have been proposed to explain acupuncture's effects, primarily those on pain. Acupuncture is believed to:

•*Stimulate the central nervous system* (the brain and spinal cord) to release chemicals into the muscles, spinal cord, and brain. These chemicals either change the experience of pain or release other chemicals, such as hormones, that influence the body's self-regulating systems. The biochemical changes may stimulate the body's natural healing abilities and promote physical and emotional well-being.

•*Conduct electromagnetic signals*. Scientists have found evidence that acupuncture points are strategic conductors of electromagnetic signals. Stimulating points along these pathways through acupuncture enables electromagnetic signals to be relayed at a greater

rate than under normal conditions. These signals may start the flow of pain-killing biochemicals such as endorphins and of immune system cells to specific sites that are injured or vulnerable to disease.

•*Activate the opioid systems*: research has found that several types of opioids may be released into the central nervous system during acupuncture treatment, thereby reducing pain. Potentially also alleviating dyspnea through beta endorphin induction(2).

•*Change the release of neurotransmitters and neurohormones*

•*Change the parts of the central nervous system related to sensation and involuntary body functions*, such as immune reactions and processes whereby a person's blood pressure, blood flow, and body temperature are regulated.

Innovation

There are several challenges in doing acupuncture research(3). The challenges we will focus on here are that of dose, response and control. The control issue is probably the best known of these issues. Essentially, is it possible to find a nonfunctional point on a person and is a sham needle truly inactive. There have been ample studies showing similar effects of sham needles to true or verum needles in clinical outcome at least in studies where the intervention and follow up are short in duration. The challenges here boil down to time, place and whether is there such a thing as a placebo. The time question is driven by the placebo effect. Almost all active clinical acts result in some improvement. If I give sugar pill to controls and a known anti-hypertensive to subjects, some portion of both arms will reduce their blood pressure and some will not, independent of the chemical itself. The mind is our most potent pharmacopeia we have. That said after the initial excitement promoting the placebo, this mind-body phenomenon tends to wane, and the placebo effect fades, especially if there is no further reinforcement. As a result, if one follows studies out long enough the placebo effect often fades while the verum treatment persists.

The second concern is placement. In the past, it was assumed that acupoints were precise with a variance within the range of a millimeter or 2 and anything placed further out would have no effect. Mouse models and clinical experience have shown this not to be true. That while acupoints may be the most effective locations for treatment there are often areas and zones along pathways and meridians that retain some activity even quite far from the target point, such as in the tendino-muscular meridians. As a result, there may be no part of the body that reaction free or inert.

The third concern is the nature of the placebo effect itself. It is unclear whether any substance or activity that can be sensed is truly inert. Some feel the placebo effect is present in every medical intervention. Sugar pills have taste and texture and all activities touching upon the mind and body convey information and have some form of meaning. Meaning evokes response which can be aligned or counter the portrayed intended purpose of the intervention.

Our innovation, in addition to promoting improved pulmonary function with the aid of acupuncture. Is to explore the dose response curve of acupuncture and use a counter or non-inert but skew control to maximize effect size. In this case, with frail patients we do not wish to sedate the lung channel, which in theory could create the greatest spread in the acupuncture effect size. Neither do we wish to choose to be near but within the same tendino-muscular plane.

Therefore, our acupuncture intervention will be EA with Lung Mu-Shu (B13, Lu2) and St 36.

Preliminary Data

Mind body medicine and acupuncture

Acupuncture by engaging in TCM and working with mind body and spirit may be consider one branch of mind body medicine. Mind-body intervention have been shown to dramatically improve health outcomes in the cardiac arena and been shown to improve both metabolic as well as immune responses. (4)

Mouse/Rat models

There has been a substantial body of research into acupuncture using mouse and rat models. Electro-acupuncture (EA) has been noted to have a variety of effects on the pulmonary function, immune response, vagal system, hormone system in these murine models of COPD.

Inflammation:

- EA intervention can improve the pulmonary function in COPD rats, which may be related to its effects in inhibiting inflammatory reaction, and MIF/CD 74-CD 44/p 38 MAPK signaling pathway(5). This latter is an angiogenic pathway driven by macrophage inhibitory factors (MIF).
- EA is associated with reducing pulmonary monocytes and lymphocytes and serum TNF-α, IL-6 and IL-1 β contents of bronchoalveolar fluid, suggesting an enhancement of immunoregulation(6)
- EA can effectively suppress the increased expression of pulmonary Matrix metallopeptidase 9 (MMP-9), and TIMP-1, classes of enzymes that belong to the

zinc-metalloproteinases family involved in the degradation of the extracellular matrix, in COPD rats, which may contribute to its effect in improving pathological changes induced by COPD(7)

- EA at Zusanli and Feishu improved lung function of rats with COPD and had an anti-inflammatory effect, which may be related to down-regulation of orexins and their receptors(8). Orexins [orexin-A (OXA) and orexin-B (OXB)] are two isoforms of neuropeptides produced by the hypothalamus. The main biological actions of orexins, focus on the central nervous system, controlling the sleep/wake process, appetite and feeding, energy homeostasis, drug addiction, and cognitive processes. Orexins also have neuroprotective and immuno-regulatory (i.e., anti-inflammatory) properties.
- In one study rats with COPD given EA, not only improved lung function ($P<0.05$) but were noted to have notable decreases in TNF-α and IL-1β levels ($P<0.05$ and <0.01, respectively). Orexin A, but not Orexin B, levels in lung tissue also decreased ($P<0.01$), as did mRNA expression of OX1R and OX2R in lung tissue ($P<0.05$ and $P<0.01$, respectively). Receptor IODs were also reduced after EA treatment ($P<0.05$). Furthermore, orexin A levels and ratio of forced expiratory volume in 0.3 s to forced vital capacity were strongly negatively correlated ($P<0.01$), and orexin A was positively correlated with TNF-α and IL-1β ($P<0.001$ and $P<0.05$, respectively).
- In another study, EA resulted in a change in the balance of Thelper1/Thelper2 cells and creating and anti-inflammatory effect as well as reducing Leukotriene B4 (LTB4) and NO(9).
- In a study by Zhang et al, compared with the model rats, the rats that received acupuncture had higher levels of TNF-α and IL-1β, A/t and BALF cell counts, and lung function (FEV50/FVC, FEV100/FVC, RL, Cdyn) ($P<0.05$). The effects of acupuncture were superior on the ST-36 points compared with the non-points. Significant correlations between lung function (FRC, RL, Cdyn) and inflammatory factors (TNF-α, IL-1β, IL-6, IL-8) were found ($P<0.001$) . TLC was correlated with IL-8, IL-1β and A/t ($P<0.05$). Plasma dopamine was correlated with FRC, TLC, FEV50/FVC, FEV100/FVC ($P<0.05$).(10)

Vagal function:

Another pathway in which EA may help COPD is through the regulation of cholinergic anti-inflammatory pathway (CAP). Compared with normal rats, there were a significant decline in lung function and discharge of the vagus nerve ($P < 0.01$), a sign of lung inflammation and an increase of ACh, AChE, IL-6 and TNF-α level in BALF or lung tissue ($P < 0.05$, $P < 0.01$) and higher expression of α7nAChR, JAK2, STAT3 and NF-κB ($P < 0.05$, $P < 0.01$) in the COPD rats. In rats receiving EA, the lung function and vagal

discharge were enhanced ($P < 0.01$), lung inflammation was improved and the levels of ACh, AChE, IL-6 and TNF-α were decreased ($P < 0.01$). Further, the expression of α7nAChR, JAK2, STAT3 and NF-κB was downregulated ($P < 0.05$, $P < 0.01$). The above effects of EA could be blocked in rats injected with α-BGT ($P < 0.01$)(11)
Hormonal:

The positive effect of EA on pulmonary function in COPD rats may also be related to downregulation of orexins and their receptors in the medulla(12)

Clinical trials

PFTs
In 2011, a RCT was conducted using acupuncture as an adjunct to pulmonary rehabilitation. There were 19 controls, 25 who underwent pulmonary rehabilitation, and 16 who had both acupuncture and PR. The primary outcome measure was a change in measures of systemic inflammation at the end of pulmonary rehabilitation and at 3 month follow up. Lung function, including maximum inspiratory pressure (PiMax), quality-of-life scores, functional capacity including steps taken, dyspnea scores, and exercise capacity, were secondary endpoints. There were no differences in most of the outcome measures between the 2 treatment groups except that subjects who had both acupuncture and PR remained less breathless for a longer period(13).

In a separate studies, adding transcutaneous electrical nerve stimulation therapy to pharmacotherapy in patients with acute exacerbation of chronic obstructive pulmonary disease provided clinical improvement in forced expiratory volume in 1 seconds and add benefit in exercise capacity (14). Acu-TENS over acupoints of bilateral EX-B-1 (Dingchuan), BL-13 (Feishu), BL-23 (Shenshu), and ST-36 (Zusanli) improved FEV(1)% predicted and reduced DVAS and CAT scores on patients with stable COPD. (15, 16). In one study the improvement in FEV1 and dyspnea score at the end of Acu-TENS treatment was associated with a concurrent increase in b-endorphin level in patients with COPD.(17)

In a pediatric study, the acupuncture group had significantly different peak expiratory flow variability ($p<0.01$) from the control group as well as, the acupuncture group significantly reduced perceived anxiety (STAIC-S) at program discharge. The other lung function tests did not reach statistical difference(12). Duration seems to matter. In Ngai et al. increasing doses of AcuTENS 20, 40 and 60 min increasingly reduced decline of FEV(1) following exercise training in patients with asthma. (18)

In Maa et al 45 minutes of Acu-TENS in the experimental group increased FEV1 by 0.12 liters (95% CI 0.07 to 0.15) and decreased dyspnea by 10.7 mm (95% CI -13.9 to -7.6) on a VAS more than the control group. The effect on FVC was only small (mean difference 0.05 liters, 95% CI -0.01 to 0.10).(19)

Patients with clinically stable, chronic obstructive asthma experienced clinically significant improvements in quality of life when their standard care was supplemented with acupuncture or acupressure.(8 weeks)(20)

Reduction in weight loss
In Suzuki et al , after 12 weeks, the change in body weight was significantly greater in the real acupuncture group compared with the placebo (mean [SD] difference from baseline: 2.5 [0.4] in RAG vs - 0.5 [1.4] in placebo; mean difference between the groups: 3.00, 95% CI, 2.00 to 4.00 with ANCOVA). Patients receiving real acupuncture also had improvements in the results nutritional markers (RBP, PA, Tf, Hb), Inflammation biomarkers (TNF-α, IL-6, SAA, Hs-CRP, COHb) and the BODE index.(21), Acupuncture combined with aerobic training of bicycle and conventional western medication could prevent the reducing of BMI in patients with COPD at stable phase, improve pulmonary ventilation function, and increase the function of peripheral skeletal muscle to improve its performance.(22)

Immune response
There was a reduction in the concentration of plasma IL-6 associated with an increase in CD4+/CD8+ ratio in both groups, but laser was superior to inspiratory muscle training. IL-6 and CD4+/CD8+ were negatively correlated. Both inspiratory muscle training and low level laser therapy are effective physical therapy modalities in promoting immune disturbances.(23)

Exercise tolerance
In Feng et al, the 6-minute walking distance measurements and health-related quality of life were significantly better in the real acupuncture group than that in the sham acupuncture group.(24) After the treatment, the scores of symptoms, life quality (CAT) were significantly decreased ($P<0.05$), while FEV 1% and FEV 1/FVC levels were considerably increased ($P<0.05$) in both groups. The effects of the test group were significantly superior to those of the control group in down-regulating symptom score and life quality score and raising FEV 1% and FEV 1/FVC levels ($P<0.05$). In addition, of the two 30 cases in the control and test groups, 10 and 18 patients experienced marked improvement, 16 and 10 were effective, 4 and 2 failed in the treatment, with the effective rates being 86.66% and 93.33%, respectively. The effective rate of acupuncture+acupoint application was superior medication along ($P<0.05$)(25)

Exercise tolerance: the differences of 6-MWD and exercise time were statistically significant between groups, which were more superior in the treatment group (both P<0.01); the VO2max was significantly increased after treatment in the treatment group (P<0.05), but there was no difference between two groups (P>0.05). (2) Pulmonary ventilation function: the differences of FEV1%, FEV1/FVC and MVV% were statistically significant between groups, which were more superior in the treatment group (P<0.05, P<0.01); (3) SGRQ: the SGRQ was significantly improved after treatment in the treatment group (P<0.05), but there was no difference between two groups (P>0.05)(26)

Dyspnea
In the Suzuki RCT, it was clearly demonstrated that acupuncture is a useful adjunctive therapy in reducing DOE in patients with COPD. The acupuncture group had significantly better results on the Borg scale than the control group after 10 weeks (2.2 +/- 2.7 versus 6.4 +/- 3.4, p = 0.0001, 95% confidence interval, -5.10 to -2.35, paired t-test). The 6-minute walk distance and oxygen saturation at the minimum rate improved significantly in the acupuncture group compared with the control group.(27) After three weeks' treatment a traditional-acupuncture group showed significantly greater benefit in terms of subjective scores of breathlessness and six-minute walking distance(28),(29)

Meta-analyses
Of the 922 articles, 12 studies were included with attesting a total of 798 participants. The result obtained indicated a significant improvement that favored the BAT + M group over the M group in CAT scores (MD: -4.77; 95% CI: -6.53 to -3.01; p < 0.00001). Acupuncture improved breathlessness severity in patients with advanced diseases. Acupuncture therapies may result in clinically important improvements in QoL and dyspnea(29). The methodological heterogeneity, low power, and potential morphine-sparing effects of acupuncture as add-on should be further addressed in future trials.(31)

4.0 Study Endpoints*

Pulmonary function as measured by:
- PFTs: FEV1, FEV1%, FVC, FVC%

Inflammation as measured by:
- Blood Eosinophils, Neutrophil, CRP

Quality of life as measured by:
- Dyspnea scores (31): Borg
- HRQOL
    - St George's Respiratory Questionnaire
    - PH Q9
- 6-minute walk distance

- The incidence of Acute Exacerbations (AE)

5.0 Study Intervention/Investigational Agent

Acupuncture is one of the oldest, most commonly used medical procedures in the world. Acupuncture is a method of encouraging the body to promote natural healing and to improve functioning through the application of needles and heat or other forms of energy such as electricity at specific points on the body. Electro acupuncture uses mA electricity at varying frequencies for its energy input.

There are 361 defined points in traditional acupuncture. Most are described by a combination of their affiliated organ, position on the traditional meridian and their set of functions. The points being used in the intervention are the Lung Mu-Shu points and St36 which are related to lung function and general function. The control group will undergo the standard pulmonary rehab program.

The EA will be applied just prior to the patients scheduled pulmonary rehab session. The EA generator will be placed on these points and amperage will be adjusted with feedback from the patient to just below the ability of the patient to sense the electricity. The ES intervention will be applied for 20 minutes.

All acupuncture needles are surgical grade steel, sterile, single use and disposable.

The EA unit is the ITO ES 130. It is compliant with FDA regulations (Approved by FDA 2008, re K081943). This device is currently in regular use treating patients in the DHMC GIM Acupuncture clinic.

This protocol does not deviate from standard of care options available to DH patients. DH patients will be receiving the highest standard of care in both pulmonary rehab and in acupuncture.

6.0 Procedures Involved*

The study will use a wait-time control design with varying intervention durations, i.e., dose.

Group	
A	**INTERVENTION-** 8 weeks acupuncture
B	**INTERVENTION-** 4 week acupuncture
C	**SOC CONTROL-** standard of care for the study duration

Patients will be recruited from the DHMC pulmonary rehab program. They will be randomized to start in group A or B with groups A and B to the EA intervention of 4 or 8 weeks or will volunteer to be a control subject in group C.

Current practice at the DHMC pulmonary rehabilitation unit is 6 - 12 patient per rehab cohort. Their program is applied in 4- or 8- week increments.

As this is a pilot, part of the study is to evaluate the facilitators and barriers to recruitment. For example, this protocol can be extended in time if recruitment is slow. We will be aiming for at least 10 participants per arm. If recruitment is robust, we will cap each arm at 30 participants.

Intervention: DHMC pulmonary rehabilitation program + EA Lung Mu-Shu+ St36
Control: DHMC pulmonary rehabilitation program

EA intervention will be applied sitting for 20 minutes prior to pulmonary rehab session.

Analysis

The blinded data will be submitted to Dartmouth Synergy Clinical and Translational Science Institute, Biostatistics Consultation core for independent statistical analysis.

Descriptive analysis of continuous variables will include median and interquartile range (IQR), or mean and standard deviation (SD) as appropriate. Categorical variables will be reported as counts and percentages. Baseline characteristics will be compared across all 3 groups using Chi-square test or Fisher's exact test where appropriate for categorical variables and t-test for continuous variables for all enrolled participants.

Predictors of change in scores compared with baseline for outcomes each follow-up will be selected via stepwise general linear models with an inclusion criterion of $P < 0.1$ to enter and $P > 0.05$ to exit, while age and gender will be forced in the models. In addition, age, gender, and baseline outcomes will be included in all longitudinal outcome models. Outcomes analyses using changes from baseline at each follow-up, with a mixed-effects longitudinal regression model including a random individual effect to account for correlation between repeated measurements within individuals. Computations will be performed using SAS procedure PROC MIXED (SAS version 9.4, SAS Institute Inc., Cary, NC) or its equivalent. Statistical significance was defined as $p < 0.05$ based on a two-sided hypothesis test with no adjustments made for multiple comparisons.

7.0 Data and Specimen Banking*

- *NA*

8.0 Sharing of Results with Subjects*

After analysis and anonymization, results will be shared with the subjects, their providers and public thought, oral presentations and written publications

9.0 Study Timelines*

The study will use a wait-time control design with varying intervention durations, i.e., dose.

Group	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9
A	ACU	ACU	ACU	ACU	ACU	ACU	ACU	ACU	T7 + 3MOS	T7 + 6MOS
B	WAIT CTRL	WAIT CTRL	WAIT CTRL	WAIT CTRL	ACU	ACU	ACU	ACU		
C	CTRL	CTRL	CTRL	CTRL	CTRL	CTRL	CTRL	CTRL		

T0 will be the project start time. T4 will be 4 weeks later. T8 will be 3 months after the completion of the intervention and T9 6 months after the completion of the intervention. Patients will be assessed at T0, T4, T8, and T9 for functional and quality of life.

Current practice at the DHMC pulmonary rehabilitation unit is 6 - 12 patient per rehab cohort. Their program is applied in 4- or 8- week increments.

As this is a pilot, part of the study's purpose is to evaluate the facilitators and barriers to recruitment. For example, this protocol can be extended in time if recruitment is slow. We will be aiming for at least 10 participants per arm. If recruitment is robust, we will cap each arm at 30 participants.

10.0 Inclusion and Exclusion Criteria*

- **Inclusion Criteria**:
  - Patients must be 21 y.o. of age or older and qualify to participate in the pulmonary rehab program at DHMC
- **Exclusion Criteria**:
  - Severe cognitive impairment
  - Active pulmonary exacerbation
  - Unstable cardiopulmonary disease
  - Actively receiving chemotherapy
  - Adults unable to consent

- Pregnant women
- Prisoners

Patients who are randomized to groups A and B will be asked additional questions in preparation to receive acupuncture safely.

Patients will be randomized to one of two arms.

11.0 Vulnerable Populations*

We will not be recruiting any vulnerable populations.

12.0 Local Number of Subjects

- This is a pilot study so sample size calculation is not relevant
- We will attempt to include up to 30 patients in total. This is a generally accepted number for pilot studies being sufficiently large to generate estimates in the variability in outcomes but small enough to be logistically efficient.

13.0 Recruitment Methods

- Subjects will be recruited from the pulmonary rehabilitation clinic.
- Subjects will be identified and made aware of the study through their pulmonary providers.
- Flyers will be posted in the pulmonary rehabilitation clinical exam rooms to allow for self-referral for the control group as well as encourage conversation with their providers regarding participation in groups A and B.

14.0 Withdrawal of Subjects*

- If subjects might be withdrawn from the study if they engage in disruptive behavior as defined by DHMC. We would follow DHMC guidelines to terminate any relations with said patient.

- If subjects leave the study for any reason, their data will be censored from that point onward.

15.0 Risks to Subjects*

Acupuncture is considered a very low risk procedure. However, there remains a theoretical risk of pneumothorax. Estimated risk is < 1/1,000,000 acupuncture treatments (Acupunct Med 2019 Dec;37(6):332-339). In order to mitigate this risk, all acupuncture will be provided by an experienced acupuncturist under the supervision of the pulmonary rehab staff in the hospital. All procedures will take place on hospital grounds and patients will have access to the full resources of the hospital in case of emergency.

There are several potential benefits associated with program participation. Patient may improve clinical function and improve quality of life.

As with other studies, there is a risk of breach of confidentiality. Confidentiality will be protected by using unique identification alphanumeric codes in lieu of names on the data documents. Also, data will be stored in encrypted files on password-protected databases stored behind computer firewalls. During the study sessions, participants will be reminded to keep the content of group discussions confidential.

Finally, there may be minor discomforts associated the acupuncture procedure itself, such as an occasional pinprick or small local bruise.

16.0 Potential Benefits to Subjects*

- Potential benefits to subjects are improved lung function and improved quality of life.
- They will also have the benefit of knowing they have contributed knowledge to benefit of society as a whole.

17.0 Data Management* and Confidentiality

The blinded data will be submitted to Dartmouth Synergy Clinical and Translational Science Institute, Biostatistics Consultation core for independent statistical analysis.

Descriptive analysis of continuous variables will include median and interquartile range (IQR), or mean and standard deviation (SD) as appropriate. Categorical variables will be reported as counts and percentages. Baseline characteristics will be compared across all 3 groups using Chi-square test or Fisher's exact test where

appropriate for categorical variables and t-test for continuous variables for all enrolled participants.

Predictors of change in scores compared with baseline for outcomes each follow-up will be selected via stepwise general linear models with an inclusion criterion of $P < 0.1$ to enter and $P > 0.05$ to exit, while age and gender will be forced in the models. In addition, age, gender, and baseline outcomes will be included in all longitudinal outcome models. Outcomes analyses using changes from baseline at each follow-up, with a mixed-effects longitudinal regression model including a random individual effect to account for correlation between repeated measurements within individuals. Computations will be performed using SAS procedure PROC MIXED (SAS version 9.4, SAS Institute Inc., Cary, NC) or its equivalent. Statistical significance was defined as $p < 0.05$ based on a two-sided hypothesis test with no adjustments made for multiple comparisons.

This is a pilot study so power analysis is not applicable.

All collected data will be anonymized and stored on password protected hard drives behind the hospitals firewall. Only the PI or his designee will be allowed access to the data. At the end of the study all key tables mapping identifiable data to unique identifiers with be erased. All data will be kep in compliance with DHMC data policies.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

The research team will be in email communication and meet on an as needed basis during the recruitment, enrollment and intervention phases of the study to ensure that recruitment targets are met, to ensure the quality and thoroughness of the data being collected at baseline, and to confer regarding questions or concerns that arise during the program implementation. Following completion of the intervention portion of the study, the team will meet bi-weekly to address issues concerning data entry and analysis, to manage follow-up assessments, and to discuss results and reporting.

This time will also be used to identify any safety issues or untoward events that may arise. Reports will be filed with the IRB in case such an event occurs and we will comply with DHMC and IRB policies, procedures and recommendations in this regard

19.0 Provisions to Protect the Privacy Interests of Subjects

As with other studies, there is a risk of breach of confidentiality. Confidentiality will be protected by using unique identification alphanumeric codes in lieu of names on the data documents. Also, data will be stored in encrypted files on password-protected databases stored behind computer firewalls. During the study sessions, participants will be reminded to keep the content of group discussions confidential. In the case of a privacy breach, all DH policies and procedures will be adhered to.

20.0 Compensation for Research-Related Injury

Not Applicable

21.0 Economic Burden to Subjects

Not Applicable

22.0 Consent Process

- Consent will take place in the exam rooms of the pulmonary rehab clinic or the Clinical Research Unit for groups A and B with Dr. Stahl, delegated RAs or a Clinical Research Unit RN conducting the consent process. Standard operating procedures SOP: Informed Consent Process for Research (HRP-090)" will be followed.
- For Group C a waiver or alteration of consent process will be requested to allow for the option of verbal consent as no intervention will be included, a CRC from the CRU will provide this consent. The consent process will be documented in the EMR the same as written consent.

23.0 Process to Document Consent in Writing

- Standard operating procedures will be followed for obtaining consent. (see "SOP: Written Documentation of Consent (HRP-091))

24.0 Setting

- All procedures will be conducted in the offices and exam rooms of DHMC including the pulmonary rehab clinic at 5C, Clinical Research Unit at 4M, and the Cardiac and Pulmonary Rehab gym. Telehealth visits for the control group will be conducted at the subject's discretion.

25.0 Resources Available

- The research will be conducted by the PI, co-PI and their designees
- Recruitment: see above

- Research plan: see above
- Pulmonary rehab specialist, pulmonary rehab nurse, pulmonary rehab therapist, nutritionist. Exercise equipment
- Acupuncture team- physician acupuncturist.
- Pulmonary rehab classes consist of two sessions per week for 8 weeks, depending on individual needs. Class size: 6 to 10 individuals per class
- All research staff will have had to complete the CITI program

26.0 Multi-Site Research*

Not applicable