CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE:
A randomized controlled trial of electroacupuncture in the management of patients with axial Spondyloarthritis in Singapore (E-AcuSpA)

PROTOCOL VERSION: 2.0
PROTOCOL DATE: 17 November 2020

PRINCIPAL INVESTIGATOR:
Dr Warren Fong, Consultant, Singapore General Hospital

CO-INVESTIGATORS:
A/Prof Koh Hwee Ling, Associate Professor, National University of Singapore
Prof Truls Ostbye, Professor, Duke-NUS Medical School
A/Prof Tai Bee Choo, Associate Professor, National University of Singapore
Dr Tan Chuen Seng, Assistant Professor, National University of Singapore
Dr Stanley Angkodjojo, Associate Consultant, Singapore General Hospital
Ms Ang Xiang Ling, TCM Physician, Singapore Thong Chai Medical Institution
Ms Quek Su-An, TCM Physician, Singapore Thong Chai Medical Institution
Dr Huang Youyi, Resident, Singapore General Hospital
Dr Kwan Yu Heng, MD-PhD Candidate, Duke-NUS Medical School

Table of Contents

PROTOCOL SIGNATURE PAGE

Protocol Title: A randomized controlled trial of electroacupuncture in the management of patients with axial Spondyloarthritis in Singapore (E-AcuSpA)

Protocol Number:

Protocol Version/ Date: 2.0, 17 November 2020

Sponsor Name:

Declaration of Investigator

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

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

1 BACKGROUND AND RATIONALE

1.1 General Introduction

Axial Spondyloarthritis (AxSpA) is a chronic debilitating disease which often results in severe disability and poor quality of life. Till date, there is no cure for AxSpA and the pathophysiology of the disease is still unclear. Based on current treatment guidelines, the first line treatment involves nonsteroidal anti-inflammatory drugs (NSAIDs), but this is only effective in about one-third of the patients. For patients with persistently active disease despite NSAIDs, the next recommended treatment is biologics which cost around $15,000 per year and is only efficacious in 60% of biologic treated patients. Of these, majority of patients will suffer a relapse upon discontinuation of the biologics. NSAIDs and biologics are also not without side effects, which includes risk of developing renal impairment and peptic ulcer disease, increased risk of cardiovascular disease or increased risk of infection.

In Traditional Chinese Medicine (TCM), AxSpA disease can be classified under Bi Syndrome. Acupuncture is commonly used to treat Bi Syndrome in TCM. Acupuncture treatment theories include Acupuncture along the 12 Tendon Meridians and Acupuncture along the 12 Meridians. The Meridian Tendon is part of the twelve meridians, and it is also the system that gather and connect the muscles and joints. The movement of vertebrae along the spine creates tension in the muscles, forming lesions or meridian tendon points on the back. These tendon points are tangible and detectable signs produced under pathological conditions, so it is also called "positive reaction point", and a small lesion can cause a wide range of pain, thus removal of this lesion can cure a wide range of pain. During disease development, corresponding positive reaction point (lesion point) will be formed, and they can be felt as painful nodules or cords under the finger.

1.2 Rationale and Justification for the Study

There are anecdotal reports that electroacupuncture provides faster and more sustained pain relief compared to manual acupuncture, but there are no randomized trials performed thus far comparing the two modes of acupuncture. Previous small studies have shown that electroacupuncture might be beneficial in patients with rheumatoid arthritis. Till date, there are no trials looking at the effectiveness of electroacupuncture in patients with AxSpA.

1.2.1 Rationale for the Study Purpose

TCM is one of the most commonly used complementary and alternative medicine modalities. TCM, especially acupuncture, has shown promising results in the management of pain, possibly by releasing encephalin. Acupuncture has frequently been promoted for lower back pain and osteoarthritis, and rheumatic diseases are, according to survey data, frequently treated by acupuncturists. Previous studies have demonstrated efficacy of acupuncture in pain relief for various rheumatic diseases, especially osteoarthritis, with minimal side effects. For patients with irritable bowel syndrome, acupuncture plus usual care can provide additional benefit over usual care alone, and the magnitude of the effect is sustained. Hence, acupuncture may be a safe and effective intervention to relieve pain.

Electroacupuncture is a modification of manual acupuncture in which electrical stimulation is administered through acupuncture needles, and it has been shown to have better local analgesic effects as compared to manual acupuncture. In animal models, electroacupuncture has further been shown to down-regulate levels of tumour necrosis factor alpha (TNFα) and interleukin-17 (IL-17), both of which are important mediators of inflammation in AxSpA. Continuous waves below 30Hz are known as sparse waves, whereas continuous waves above 30Hz are called dense waves. The dense-sparse wave is a combination of both, alternating between each about every 1.5 seconds, which makes the body less prone to adaptive response, thereby resulting in rhythmic tensing and relaxation of the muscles, better blood and lymph circulation, improved nutrient uptake of tissues and reduction in inflammation and edema. In addition, it can regulate the excitation and inhibition of the cerebral cortex, as well as the function of the subcortical autonomic nervous system. Therefore, when the endogenous analgesic system or the endogenous pain modulation system in the brain is activated, the analgesic effect can be exerted more effectively.

Electroacupuncture has also been shown to provide a stronger and more continuous level of stimulation than traditional acupuncture, and produce more rapid and prolonged treatment effects. This may be because electrical stimulation of a tissue triggers an increase in the movement, especially potassium and sodium ions along the axon of the nerve cell. This accelerates the neuronal depolarization, which is responsible for nerve conduction. A previous study had shown that electroacupuncture is more effective in alleviating tender joints among patients with rheumatoid arthritis as compared to manual acupuncture. With electroacupuncture at the corresponding acupoints, we hope to deliver faster and more sustained relief of pain compared to manual acupuncture, thus improving the overall quality of life of patients with AxSpA. Currently, there are no published studies investigating the effectiveness of electroacupuncture for patients with AxSpA, and this study will help to address this gap in knowledge.

In this proposal, we aim to assess the clinical effectiveness, safety and cost-effectiveness of electroacupuncture as compared to manual acupuncture. We hope the research findings from this study will inform policy makers of the impact of a collaborative model of care involving electroacupuncture on healthcare delivery in rheumatology. The results of this study will provide a robust, real world-based evidence to understand the clinical effectiveness, safety and cost-effectiveness of electroacupuncture. For the TCM community, this trial can provide stakeholders greater evidence base towards implementation of electroacupuncture into the current healthcare system. For rheumatology community, a successful implementation of this model of care involving electroacupuncture will allow better management of AxSpA and also other chronic diseases such as chronic back pain and osteoarthritis. The long-term implications of a successful outcome of this project will provide clinicians in other specialties and policy makers confidence to explore electroacupuncture in management of patients with other chronic diseases such as diabetes, cancer care and cardiovascular diseases.

1.2.2 Rationale for Study Population

AxSpA is a chronic debilitating disease which often results in severe disability and poor quality of life. Till date, there is no cure for AxSpA and the pathophysiology of the disease is still unclear. Based on current treatment guidelines, the first line treatment involves NSAIDs, but this is only effective in about one-third of the patients. For patients with

persistently active disease despite NSAIDs, the next recommended treatment is biologics which cost around $15,000 per year and is only efficacious in 60% of biologic treated patients. Of these, 75-90% of patients will suffer a relapse upon discontinuation of the biologics. NSAIDs and biologics are also not without side effects, which includes risk of developing renal impairment and peptic ulcer disease, increased risk of cardiovascular disease or increased risk of infection.

1.2.3 Rationale for Study Design

This proposed project is a randomized controlled trial anchored closely using the Consolidated Standards of Reporting Trials (CONSORT) guidelines as well as the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) statement for acupuncture. This design can provide evidence of effectiveness, which may be important for policy- and decision-makers considering TCM as a treatment option for patients with AxSpA.

2 HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

Our primary hypothesis is that electroacupuncture may result in better control of disease activity in patients with AxSpA as compared to manual acupuncture over 12 weeks. The secondary hypothesis is that electroacupuncture may result in greater improvements in other clinical and quality of life outcomes as compared to those receiving manual acupuncture over 24 weeks. The clinical, quality of life, and economic outcomes over 52 weeks serve as exploratory outcomes. We also hypothesize that there is no difference in safety between both arms.

2.2 Objectives

The objective of this study is to determine the clinical effectiveness, safety and cost-effectiveness of electroacupuncture as compared to manual acupuncture in the management of Axial Spondyloarthritis (AxSpA) with the following outcomes in Table 1.

Table 1: Type of outcomes and time point

Types of Outcomes	**Descriptions**
Primary outcome	BASDAI score over 12 weeks (as assessed at weeks 0, 3, 6, 9, and 12)
Secondary outcomes	**Clinical** BASDAI score over 24 weeks (as assessed at weeks 0, 3, 6, 9, 12 and 24) BASFI, BASG, ASAS HI over 12 and 24 weeks (as assessed at weeks 0, 6, 12, and 24) **Quality of life** Quality of life – ASQoL and EQ-5D over 12 and 24 weeks (as assessed at weeks 0, 6, 12, and 24) **Economic Outcomes** *Healthcare resource use* Rheumatologist's consultation fees, TCM physician time and salary, costs of acupuncture needles and equipment, costs of electroacupuncture unit, costs of imaging, costs of laboratory and procedures, AxSpA-related drug costs, AxSpA-related device costs, AxSpA-related physiotherapy costs, costs of other outpatient visits, costs of other drugs, costs of inpatient visits, costs of emergency department visits over 12 and 24 weeks (as assessed at weeks 0, 6, 12, and 24) *Indirect costs* Patient income and salary, number of days of work missed due to illness (when applicable), travel costs, work status (active, inactive, retired) over 12 and 24 weeks (as assessed at weeks 0, 6, 12, and 24) WPAI over 12 and 24 weeks (as assessed at weeks 0, 6, 12, and 24)
Exploratory outcomes	**Clinical** BASDAI score over 52 weeks (as assessed at weeks 0, 3, 6, 9, 12, 24 and 52) BASFI, BASG, ASAS HI over 52 weeks (as assessed at weeks 0, 6, 12, 24 and 52) TCM syndrome score over 12 weeks (as assessed at weeks 0, 3, 6, 9, and 12) **Quality of life** Quality of life – ASQoL and EQ-5D over 52 weeks (as assessed at weeks 0, 6, 12, 24 and 52) **Economic Outcomes** *Healthcare resource use* Rheumatologist's consultation fees, TCM physician time and salary, costs of acupuncture needles and equipment, costs of electroacupuncture unit, costs of imaging, costs of laboratory and procedures, AxSpA-related drug costs, AxSpA-related device costs, AxSpA-related physiotherapy costs, costs of other outpatient visits, costs of other drugs,

	costs of inpatient visits, costs of emergency department visits over 52 weeks (as assessed at weeks 0, 6, 12, 24 and 52) *Indirect costs* Patient income and salary, number of days of work missed due to illness (when applicable), travel costs, work status (active, inactive, retired) over 52 weeks (as assessed at weeks 0, 6, 12, 24 and 52) WPAI over 52 weeks (as assessed at weeks 0, 6, 12, 24 and 52)

Abbreviation
ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASQoL: Ankylosing Spondylitis Quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BAS-G: Bath Ankylosing Spondylitis Global score; TCM: Traditional Chinese Medicine; WPAI: Work Productivity and Activity Impairment

Outcome Measurement

The type of outcome measures and time of assessment are summarized in Table 2 below. Patient demographics, past medical history, and current medication use will be collected at enrolment and randomisation, which is also the date when patients have their baseline visit with the attending rheumatologist. Follow-up at week 3 is selected after the first 5 sessions of acupuncture as the pain-relieving effects of electroacupuncture are postulated to be of faster onset and better as compared to manual acupuncture at this time point and is of clinical relevance to the patient. The week 6 and 12 visits are selected because participants would have completed their 10 and 20 sessions of acupuncture respectively, and most trials in this field assessed the outcomes at this time point. Follow-up at week 9 is selected to allow the trending of the trajectory of pain relief. Outcomes at week 24 and 52 can be used to assess long term effectiveness of electroacupuncture, which matter most to patients.

Primary outcome

The mean difference in BASDAI score between the 2 groups over 12 weeks (as assessed at weeks 0, 3, 6, 9, and 12) adjusted for baseline covariate and other potential confounders (as appropriate) is the primary outcome in this study. It measures severity of fatigue, spinal and peripheral joint pain, localized tenderness and morning stiffness (both qualitative and quantitative).The 0-10 pain numerical rating scale (NRS) will be used and it is widely used and validated across many settings to assess the disease activity of AxSpA, and has been endorsed by Assessment of SpondyloArthritis International Society (ASAS) for the measurement of disease activity. This was selected, as the pain-relieving effects of the two different modes of acupuncture will be captured by the BASDAI. BASDAI (ranges from 0 to 10) is an English, self-administered disease-specific questionnaire to measure disease activity, with higher values indicating more active disease.

Secondary clinical outcomes

The mean difference in BASDAI score between the 2 groups over 24 weeks (as assessed at weeks 0, 3, 6, 9, 12 and 24) adjusted for baseline covariate and other potential confounders (as appropriate) will serve as one of the secondary clinical outcomes.

The mean difference in clinical parameters including BASFI, BAS-G and ASAS HI between the 2 groups over 12 and 24 weeks (as assessed at weeks 0, 6, 12, and 24) adjusted for baseline covariate and other potential confounders (as appropriate) will serve as the other clinical outcomes for this study. These are clinically relevant outcomes measures used in daily practice in the management of AxSpA patients and endorsed by ASAS. These patient-reported outcomes will be collected via interviews by our research assistant.

BASFI (ranges from 0 to 10) is a disease-specific questionnaire used to measure physical functioning, with higher values indicating worse functioning. BAS-G (ranges from 0 to 100) is a disease-specific questionnaire to give a global assessment of well-being, with higher score reflecting poorer well-being. ASAS HI is a disease-specific questionnaire, with 17 dichotomous items (dichotomous response option: “I agree” and “I do not agree”) to assess health status in patients with all forms of SpA. The total sum of the ASAS HI ranges from 0-17, with lower scores indicating better health status.

Secondary and exploratory quality of life outcomes

The mean difference in the ASQoL and EQ-5D score between the 2 groups over 12 and 24 weeks (as assessed at weeks 0, 6, 12, and 24) adjusted for baseline covariate and other potential

confounders (as appropriate) will serve as the secondary quality of life outcomes for this study.

ASQoL is a self-administered patient-derived and disease-specific measure of QoL for AS. It consists of 18 items with a "yes" (scored as 1) or "no" (scored as 0) response to each item. All item scores are summed to a total score ranging from 0 to 18, with higher scores indicating worse QoL. The English version of ASQoL has been shown to be a valid and reliable measure for use in patients with axSpA, also in Singapore.

The EQ-5D comprises a descriptive system and a visual analogue scale (VAS). The former assesses five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with five possible answers for each item (1= "no", 2= "slight", 3= "moderate", 4= "severe" and 5= "unable"/"extreme"). EQ-5D utility scores will then be computed with 0 representing death and 1 representing full health, using time trade-off valuations from the Singaporean value set. The VAS is a vertical "ruler" that records the patient's self-rated health and extends from 0 ("worst imaginable health state") to 100 points ("best imaginable health state") for respondents to rate their overall health.

Secondary economic outcomes
AxSpA-related and non-AxSpa-related health care costs will include rheumatologist's consultation fees, TCM physician time and salary, costs of imaging, laboratory and procedures, drug costs, assistive devices cost, costs of other outpatient visits, AxSpA-related physiotherapy costs, costs of inpatient visits, and costs of visits to emergency departments. Healthcare use and costs will be obtained through questionnaires administered to patients. In addition, this information will be supplemented by a review of medical records and data retrieval from the electronic databases at SGH. Non-health care financial consequences will be captured in the questionnaires by recording self-reported travel costs incurred by the patients to receive treatment, patient income and salary, the number of days patients missed work due to illness, and work status (active, inactive, retired). The mean difference in the healthcare use and costs over 12 and 24 weeks (as assessed at weeks 0, 6, 12, and 24) adjusted for baseline covariate and other potential confounders (as appropriate) will serve as the secondary economic outcomes for this study.

The WPAI assesses absenteeism, presenteeism, daily activity impairment and work productivity. The mean difference in the WPAI outcomes over 12 and 24 weeks (as assessed at weeks 0, 6, 12, and 24) adjusted for baseline covariate and other potential confounders (as appropriate) will serve as the secondary economic outcomes for this study.

Exploratory outcomes
The BASDAI, BASFI, BAS-G, ASAS HI, ASQoL, EQ-5D, WPAI outcomes, total AxSpA-related and non-AxSpA-related costs over 52 weeks will serve as exploratory outcomes.

TCM syndrome score between the 2 groups over 12 weeks (as assessed at weeks 0, 3, 6, 9, and 12) adjusted for baseline covariate and other potential confounders (as appropriate) is one of the exploratory outcomes in this study. The score will be calculated based on the severity of symptoms observed. Guidelines of symptom differentiation and severity rating are according to the "Guiding principles for clinical research of new Traditional Chinese Medicine" (中药新药临床研究指导原则). All patients are evaluated holistically, and other areas of discomfort, in addition to pain, also contribute to the severity of their condition and impact their quality of life. These symptoms can be treated by acupuncture and changes in the severity will also serve as an indication on the

effectiveness of the different forms of acupuncture in improving their overall condition.

Table 2: Summary of primary, secondary and exploratory outcome measures

Outcomes	**Time**						
	Baseline	**Week 3**	**Week 6**	**Week 9**	**Week 12**	**Week 24**	**Week 52**
1. Primary outcome							
1.1 **BASDAI**	✓	✓	✓	✓	✓		
2. Secondary outcomes							
2.1 Clinical outcomes							
2.1.1 **BASDAI**	✓	✓	✓	✓	✓	✓	
2.1.2 **BASFI**	✓		✓		✓	✓	
2.1.3 **BAS-G**	✓		✓		✓	✓	
2.1.3 **ASAS HI**	✓		✓		✓	✓	
2.2 Quality of life outcomes							
2.2.1 **ASQoL**	✓		✓		✓	✓	
2.2.2 **EQ-5D**	✓		✓		✓	✓	
2.3 Economic outcomes							
2.3.1 **Costs**	✓		✓		✓	✓	
2.3.2 **WPAI**	✓		✓		✓	✓	
3. Exploratory outcomes							
3.1 Clinical outcomes							
3.1.1 **BASDAI**							✓
3.1.2 **BASFI**							✓
3.1.3 **BAS-G**							✓
3.1.4 **ASAS HI**							✓
3.1.5 **TCM syndrome**	✓	✓	✓	✓	✓		
3.2 Quality of life outcomes							
3.2.1 **ASQoL**							✓
3.2.2 **EQ-5D**							✓
3.3 Economic outcomes							
3.3.1 **Costs**							✓
3.3.2 **WPAI**							✓

Abbreviation
ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASQoL: Ankylosing Spondylitis Quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BAS-G: Bath Ankylosing Spondylitis Global score; TCM: Traditional Chinese Medicine; WPAI: Work Productivity and Activity Impairment

2.3 Potential Risks and Benefits:

2.3.1 Potential Risks

Potential adverse effects of acupuncture and electroacupuncture include fainting, bent or broken needle, local pain, slight bleeding and skin infections. If any of these symptoms occur, they will be advised to contact study personnel. These symptoms will be evaluated and reviewed by the PI who will determine if these symptoms are related to acupuncture.

2.3.2 Potential Benefits

There is no assurance that participants will benefit from this study. However, their participation may contribute to the medical knowledge about the use of TCM in particular electroacupuncture in the management of AxSpA.

3 STUDY POPULATION

3.1 List the Number and Nature of Subjects to be Enrolled

A total of 100 patients with 50 patients per group will be recruited. There is no subject restriction based on race or gender of the subject.

3.2 Criteria for Recruitment and Recruitment Process

Patients with a clinical diagnosis of AxSpA and fulfil the inclusion criteria will be recruited from outpatient clinics by the attending rheumatologist. In the case whereby the PI is also the attending physician, he will directly make first contact and ask for informed consent. If not, a study team member will ask for informed consent. The study will be performed in accordance with the guidelines and with the approval of the SingHealth Centralised Institutional Review Board.

3.3 Inclusion Criteria

We aim to recruit adult patients with AxSpA who have spinal pain and active disease despite standard medical therapy. Patients are eligible for the study if they are 21 years of age or older; have AxSpA, diagnosed according to the 2009 Assessment of Spondyloarthritis International Society (ASAS) criteria; have active disease based on Bath AS Disease Activity Index (BASDAI) score ≥4 on a 11-point Numerical Rating Scale (NRS); have failed 2 sequential NSAIDs (including COX-2 inhibitor) at maximal tolerated doses for ≥ 4 weeks in total. Patients who are on current treatment with concomitant biological therapy (e.g. tumour necrosis factor inhibitor therapy, anti-interleukin 17) or non-biologic disease-modifying antirheumatic drugs (DMARDs) (e.g. methotrexate (MTX) or sulfasalazine (SSZ) or leflunomide (LEF)) at study entry must be on the drug for ≥12 weeks and at stable dose for ≥4 weeks prior to randomisation. Patients taking systemic corticosteroids have to be on stable dose of ≤ 10mg/day prednisolone or equivalent for at least two weeks before randomisation.

3.4 Exclusion Criteria

We will exclude patients who are pregnant or breastfeeding, have bleeding disorders, have blood-borne communicable diseases (e.g. hepatitis B, hepatitis C, human immunodeficiency

virus, etc), have implantable electrical device (e.g. pacemaker), as well as patients suffering from impaired skin sensation or serious skin lesions along the vertebrae.

3.5 Subject Replacement

Subjects who drop out will not be replaced.

4 STUDY DESIGN

4.1 Randomisation and Blinding

Patients will be randomly allocated to receive electroacupuncture or manual acupuncture on a 1:1 basis via random permuted block randomization.

4.2 Study Visits and Procedures

4.2.1 Screening Visits and Procedures

As BASDAI and spinal pain score are routinely used during outpatient sessions to measure patient disease activity and pain level, there will be no specific screening visits and procedures for this study. The PI will assess the eligibility for each participant before enrolment.

4.2.2 Study Visits and Procedures

Usual rheumatological care, which will be given to all patients in this trial, comprises of medications (e.g. NSAIDs, DMARDs or biologics) and regular monitoring for other complications that may arise from AxSpA such as cardiac events and maintenance of bone health. In this trial, the attending rheumatologist will see each patient at regular time points (Figure 1) from the start of randomization till trial termination at week 52. Extra visits will be arranged if needed e.g. for titration of medications or to address monitoring of complications of disease. The attending rheumatologist will prescribe a variety of treatments inclusive of medications such as NSAIDs and physiotherapy. At each session, the attending rheumatologist will monitor the disease activity through a validated patient-reported outcome instrument. Further investigations such as imaging or laboratory tests will be ordered depending on the clinical judgment of the attending rheumatologist and the guidelines stipulated. The rheumatologist will be allowed to prescribe the full range of treatment usually used, including biologics, as per treatment guidelines.

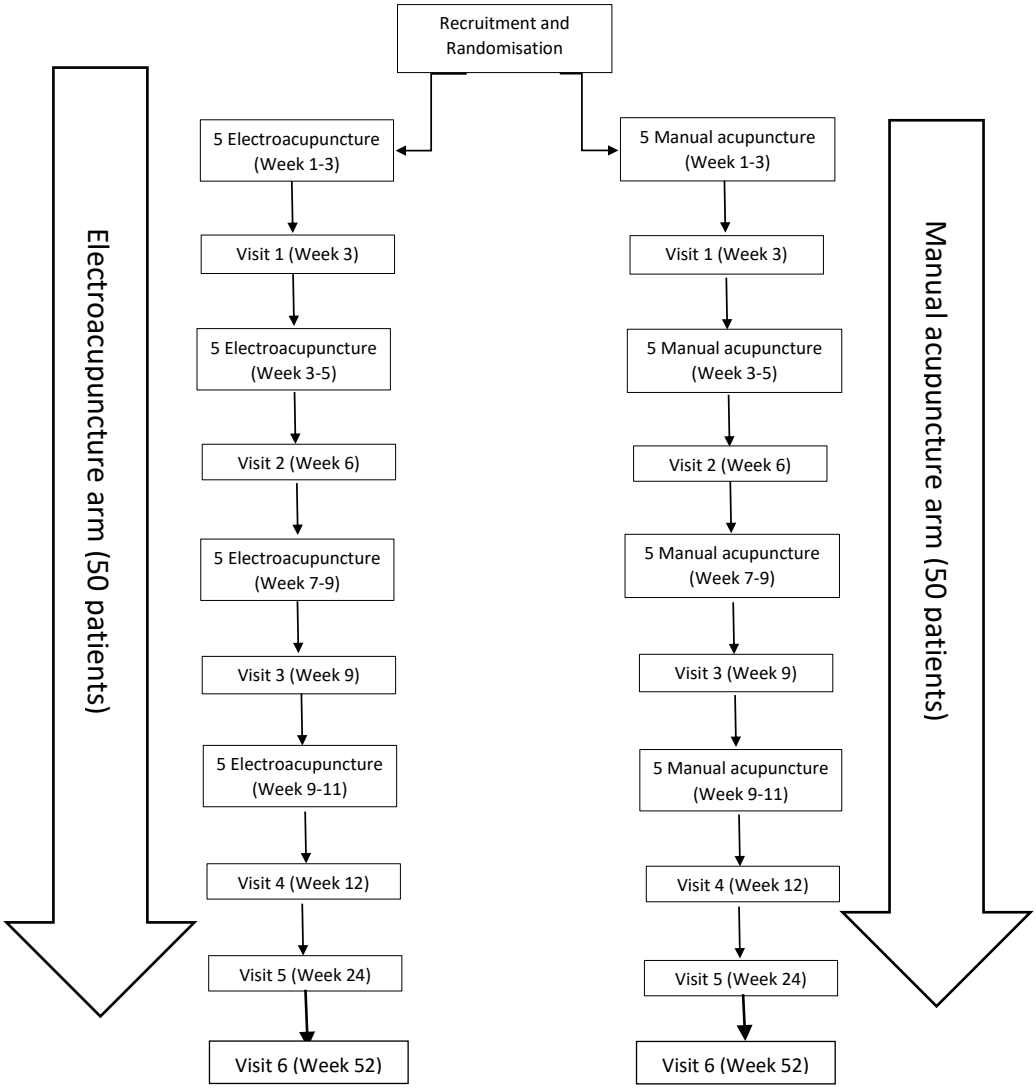

Figure 1: Flowchart to illustrate research methodology and timelines

Both arms will involve the TCM physician in the management of patients with AxSpA in addition to the usual rheumatological care. The clinical interventions carried out by the TCM physicians include, but is not limited to, counselling of patients regarding their illness from the TCM perspective, diagnosing based on TCM clinical syndromes and prescribing acupuncture treatment (electroacupuncture or manual acupuncture) accordingly. The recommended acupuncture treatment will consist of a total of 20 sessions (or 2 courses) in total. Each course of treatment will consist of 10 acupuncture sessions held over 5 weeks. The patient will take a break of 5-7 days in between each course of acupuncture. The TCM physicians will be allowed to make minor adjustment to the acupuncture points in view of the differing constitution of the patients as per the holistic treatment philosophy of TCM.

<u>Manual acupuncture</u>

Patients will receive usual rheumatologic care. In this study, the main acupoints will be Jingjin points (meridian sinews) along the Bladder meridian of Foot – Taiyang (足太阳经筋

筋病灶点), such as Shenshuci (肾俞次), as well as Jingjin points (meridian sinews) at transverse process from L2 to L4 (腰 2 至腰 4 横突), iliac crest (髂嵴) and spinous process from S1 to S4 (骶 1 至骶 4 棘突). Secondary acupoints for the various syndromes and symptoms are listed below.

Secondary acupoints for syndromes:
1. Blockage due to dampness and heat (湿热痹阻证): Main acupoints PLUS Quchi (LI11 曲池), Yinlingquan (SP9 阴陵泉) acupoints would also be chosen.
2. Blockage due to dampness and coldness (寒湿痹阻证): Main acupoints PLUS Yaoyangguan (DU3 腰阳关)，Yinlingquan (SP9 阴陵泉)acupoints would also be chosen.
3. Blockage due to stagnated blood (瘀血痹阻证): Main acupoints PLUS Sanyinjiao (SP6 三阴交), Geshu (BL 17 膈俞) acupoints would also be chosen.
4. "Yang" deficiency in kidneys and "Du" meridian (肾督阳虚证): Main acupoints PLUS Mingmen (DU4 命门), Yaoyangguan (DU3 腰阳关) acupoints would also be chosen.
5. Deficiency in the liver and kidneys (肝肾不足证): Main acupoints PLUS Ganshu (BL18 肝俞), Sanyinjiao (SP6 三阴交) acupoints would also be chosen.

Secondary acupoints for symptoms:
1. Neck pain: Main points PLUS secondary points PLUS Fengchi (GB20 风池), Jianjing (GB21 肩井), Dazhui (DU14 大椎)
2. Thoracic pain: Main points PLUS secondary points PLUS Dazhu (BL11 大杼), Shenzhu (DU12 身柱), Zhiyang (DU9 至阳)
3. Lumbar pain: Main points PLUS secondary points PLUS Dachangshu (BL25 大肠俞), Yaoyan(EX-B7 腰眼) , Weizhong (BL40 委中)
4. Sacrum pain: Main points PLUS secondary points PLUS Ciliao (BL32 次髎)
5. Knee paint: Main points PLUS secondary points PLUS Yinlingquan (SP9 阴陵泉), Yanglingquan (GB34 阳陵泉), Weizhong (BL40 委中)
6. Ankle Pain: Main points PLUS secondary points PLUS Taixi (KI3 太溪), Kunlun (BL60 昆仑), Qiuxu (GB40 丘墟)

Acupuncture will be performed after disinfecting the acupuncture points. Depending on the acupuncture points, 0.25-0.30 mm × 25-75 mm sterile acupuncture needle will be used, with patient lying prone. Depending on the acupuncture points, we will insert the needles 10-50 mm, and will use rotating manipulation or lifting-thrusting manipulation to achieve de qi (a compositional sensation including soreness, numbness, distention and heaviness).

<u>Electroacupuncture</u>
In addition to the procedures described in the manual acupuncture group, for patients in the electroacupuncture group, the electroacupuncture unit will be connected to 1-3 pairs of acupoints on the same side of body after "de qi" is obtained. At the beginning, all adjustment dials and knobs of the electroacupuncture unit are to be set at 0 (no stimulation). The dense-sparse wave is selected before the power switched on. Paired electrodes are to be connected to points on the same side of the body and should not cross the spine to prevent current from reaching the heart. Current will be applied to acupuncture points in order of top to bottom (superior to inferior), medial to lateral. After connecting the electrodes to the needle, current

intensity will be increased slowly to avoid sudden shock to the patients. The current used is based on the tolerance of each patient, with the intensity at a range from 2 to 5. For patients who report weak or no sensation at the point of stimulation, the electrical flow can be increased gradually, or the apparatus switched off for 1-2 minutes and then restarted. Needles with electrical stimulation will be retained for 30 min.

4.2.3 Final Study Visit

The final study visit will be at 52 weeks after baseline visit.

4.2.4 Post Study Follow up and Procedures

There will be no post study follow up and procedures. However, subjects will be advised to contact study personnel if there is occurrence of adverse event.

4.3 Discontinuation/Withdrawal

4.3.1 Discontinuation Criteria

Study treatment will be discontinued and the subjects withdrawn from the trial if the investigator determines that continuing it would result in significant safety risk for the subject. The following circumstances require study treatment discontinuation:

- Withdrawal of informed consent.
- Study closure.

4.3.2 Discontinuation Visit and Procedures

Subjects may withdraw voluntarily from participation in the study at any time. Subjects may also withdraw voluntarily from receiving the study intervention for any reason.

If voluntary withdrawal occurs, the subject will be asked to continue scheduled evaluations, complete an end of study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable. In addition, the investigators must determine the primary reason for a subject's withdrawal and record this information on the medical record.

5 TRIAL MATERIALS

The TCM modality for treatment used here will be electroacupuncture and manual acupuncture, which is specially implemented by our experienced collaborators at Thong Chai Medical Institution. The recommended acupuncture treatment will consist of a total of 20 sessions (or 2 courses) in total. Each course of treatment will consist of 10 acupuncture sessions held over 5 weeks of 30 minutes each. Special queues will be set up with the TCM partner to reduce dropout rates due to long queues at the TCM site. To avoid potential contamination of the study results, the rheumatologist, nurses and allied health professionals will be reminded to treat the patients in both interventional and control arms in a consistent manner. All adverse reactions as shown will be entered in a registry by a panel of experts consisting of rheumatologists and TCM physician with regards to its severity. All research-related electronic data will be password locked and stored together with the study survey or paper documents in a locked cabinet in the PI's office at SGH. All patient information will be kept strictly confidential, following policies in SingHealth.

6 TREATMENT

6.1 Specific Restrictions / Requirements

The rheumatologist will see these patients at baseline, week 6, week 12, week 24 and week 52, and whenever required. Patients will not visit any other TCM physician nor seek alternative therapy for the first 24-week of the study. As per usual medication-dispensing advice, we will counsel on the importance of medication adherence. As it is likely that the patients will not be upfront about their visit to the TCM physicians from previous data, the research assistant will also query about their use of other TCM at specified data collection points. We will analyze as per intention to treat (ITT) protocol to minimize the potential bias associated with not following assigned treatment.

6.2 Blinding

The Principal Investigator is blinded to the treatment allocation in the first 12 weeks. There will be no blinding of study participants nor other study staff.

6.3 Concomitant therapy

All medications (prescription and over the counter), vitamin and mineral supplements, and / or herbs taken by the participant will be documented.

7 SAFETY MEASUREMENTS

7.1 Definitions

An adverse event (AE) refers to any untoward event or medical occurrence in a patient or clinical investigation subject that:

- does not necessarily have a causal relationship with the treatment
- reveals any defect in any medical device
- concerns any adverse effect arising from the use of thereof

Adverse effect refers to any debilitating, harmful, toxic or detrimental effect that the medical device has been found to have or to be likely to have on the body or health of humans when such a medical device is used by or administered to humans.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the intervention or use of a medical device, whether or not related to the intervention or medical device.

A serious adverse event (SAE) is any untoward medical occurrence as a result of human biomedical research which:

- results in or contributes to death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity
- results in or contributes to a congenital anomaly/birth defect

- results in the transmission of a communicable disease
- results in any misidentification or mix-up of any type of human biological material, gamete or embryo
- results in such other events as may be prescribed

7.2 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to Centralised Institutional Review Board (CIRB)

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB, in accordance with the reporting requirement and timeline stated on CIRB website. Related SAEs are SAEs with a reasonable possibility that they may have been caused by participation in the research.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Related AEs will not be reported to CIRB. However, the investigator will keep record of such AEs cases at the Study Site File.

7.3 Collecting, Recording and Reporting of Adverse Events (AEs) to the Health Sciences Authority (HSA)

The occurrence of any AE that is associated with use of the medical device, which led to one of the following outcomes, will be reported to HSA, in accordance with the reporting requirement and timeline stated on HSA website:

- caused a serious threat to public health
- death of a patient, user or other person
- serious deterioration in state of health, user or other person
- no death or serious injury, but might lead to death or serious injury of a patient, user or other person if the event recurs

Any event or other occurrence relating to a medical device represents a serious threat to public health if one or more of the following occur:

- the event or other occurrence is a hazard arising from a systematic failure of the medical device that becomes known to the manufacturer, importer or wholesaler of the medical device
- the event or other occurrence may lead to death of, or a serious injury to, a patient, a user of the medical device or any other person
- the probable rate of occurrence of or degree of severity of harm caused by the hazard was not previously known or anticipated by the product owner of the medical device
- it becomes necessary for the product owner of the medical device to take prompt action (including the recall of the medical device) to eliminate or reduce the risk of the hazard

A serious deterioration in state of health can include:

- life-threatening illness or injury
- permanent impairment of a body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

7.4 Safety Monitoring Plan

The data and safety review will be conducted every twelve months. All AEs such as skin injuries and infections will be monitored for safety.

All study AEs will be recorded on the Adverse Event data collection form with the following information:

1. AE term
2. Severity grade (mild, moderate, severe)
3. Its relationship to the study intervention
4. Its duration (start and end dates or if continuing at final examination)
5. Description of AE and subsequent treatment, if any
6. Whether it constitutes as SAE
7. Outcome
8. Date which Site Principal Investigator or project team members were aware of AE

The study will be stopped if any SAE occurs. The IRB and HSA will be consulted, and if it is determined that the SAE was not related to study intervention, the study may be continued.

If the adverse event is determined to be related to study intervention, the nature of the relationship between the adverse event and the medical device will be elucidated. IRB and HSA will be consulted regarding further enrolment.

7.5 Complaint Handling

The PI will review all complaints and discuss with the study team about the follow-up action when there is complaint.

8 DATA ANALYSIS

8.1 Data Quality Assurance

The PI and study team members will perform the data monitoring. The review will be conducted every twelve months. The research coordinator will key in the data into REDCap. Data checks such as data correlation and cross tabulation will be carried out before commencement of data analysis.

8.2 Data Entry and Storage

The research coordinator will key in the data into REDCap. Data will be password encrypted and only anonymised data will be exported for analysis. No identifiable data of the subjects will be shared with another party, nor the third-party sponsor.

9 SAMPLE SIZE AND STATISTICAL METHODS

9.1 Determination of Sample Size

The sample size is estimated based on a repeated measures trial design with one pre- and four post-intervention (3, 6, 9 and 12 weeks) measurements. Assuming a mean difference of 0.75 with a SD of 2, a correlation of 0.6, a power of 80% and a two-sided level of significance of 5%, a minimum sample size of 80 would be required. Further accounting for 20% attrition, the total sample size would be 100 or 50 per group.

9.2 Statistical and Analytical Plans

All patient data will be analyzed using intention-to-treat approach. The demographic and baseline clinical characteristics of participants will be summarized using mean and standard deviation (or median and interquartile range where appropriate) for continuous variables, and count and percentage for categorical variables. Linear mixed effect models will be implemented to determine the effect of intervention on the primary and secondary outcomes, taking into account possible intra-subject correlation between the repeated measures. These models will further be adjusted for the respective baseline covariate and other potential confounders as appropriate. The effect of intervention on the primary and secondary outcomes will be quantified based on the mean difference and its associated 95% confidence interval. All analyses will be conducted based on the principle of intention-to-treat assuming a two-sided test at the 5% level of significance. To analyze safety of the intervention, we will present the adverse events that occurred in frequency and percentages within the one-year period for both intervention and control arms.

Cost-effectiveness analyses (CEA) will be performed from healthcare system and societal perspectives. The outcome of interest for CEA is the incremental cost effectiveness ratio (ICER), calculated by dividing the difference in total costs by the difference in the outcome between the two arms. Costs from the healthcare system perspective will include direct cost of medical care such as the cost of electroacupuncture, drug and physician time. Cost of TCM physician will be estimated based on the salaries of the TCM physicians. Costs from the societal perspective will include direct cost of medical care as well as indirect cost such as loss of work productivity (secondary economic outcomes).

The outcome measure is the cumulative quality-adjusted life years (QALY) over the study period; thus, the ICER for CEA represents the cost per QALY gained. Cumulative QALY for each study arm will be calculated using area under the curve by summing the areas of the geometrical shapes obtained by linearly interpolating between utility scores at the 5 follow-up time points, with adjustment of baseline utility value if baseline differences exist between study arms. Utility scores will be measured using EQ-5D. To generate confidence intervals of the ICERs, non-parametric bootstrapping (random sampling with replacement) will be conducted. Sensitivity analysis will be conducted to evaluate the influence of uncertainties in the variables and assumptions employed on the analysis results.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The PI and study team members will perform the data monitoring. The review will be conducted every twelve months. The research coordinator will key in the data into REDCap. Data checks such as data correlation and cross tabulation will be carried out before commencement of data analysis.

12 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Clinical Trial Protocol, including the final version of the Participant Information Sheet and Consent Form, must be approved in writing by the CIRB, prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

12.1 Informed Consent

Consent process will take place in the clinic consultation room when the potential participant comes for his/her consultation. The consent process will take place in the outpatient clinic consultation room. The place chosen is suitable because it is a closed and private environment with only the PI, potential participant and research coordinator present. When the potential participant is identified, the PI will explain the study to the potential participant and invite him/her to participate in the study. The PI will answer all questions and the participant will be given ample time to consider. He/She need not agree on participation immediately. Participants are informed that participation to the study is voluntary and they have the rights not to participate.

12.2 Confidentiality of Data and Patient Records

The electronic records will be stored in a PC (with password encryption) in REDCap in the locked office in the Department of Rheumatology & Immunology. Paper records will similarly be stored in the locked office in the Department of Rheumatology & Immunology. All data will be decoded from subject's identity. Only the PI, designated coordinator and designated biostatistician will have access to the identifiable data. Data will be password encrypted and only anonymised data will be exported for analysis. No identifiable data of the subjects will be shared with another party, nor the third-party sponsor. Mr Kwan will access the data in the compound of Singapore General Hospital only and data will be de-identified before sharing. Also, only de-identified research data will be sent to Dr Tan Chuen Seng and

Prof Tai Bee Choo for data analysis.

13 PUBLICATIONS

All authors will review publication for study findings. The PI will decide on authorship for publication.

14 RETENTION OF TRIAL DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation will be kept in the locked office in the Department of Rheumatology & Immunology. The records will be accessible for inspection and copying by authorized authorities. When the study is complete, data will be stored for 7 years as per SingHealth guidelines.

15 FUNDING and INSURANCE

This trial is supported by philanthropic funding under the Reverie Rheumatology Research Fund. The Hospital does not make any provisions to compensate study participants for research related injury. However, compensation may be considered on a case-by-case basis for unexpected injuries due to non-negligent causes. These costs will be covered using the insurance for clinical trials (Ministry of Health Clinical Trial Insurance) conducted in SingHealth.