CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE:
A pragmatic randomized controlled trial of a novel TCM physician-involved collaborative care model in the management of patients with axial Spondyloarthritis in Singapore (AcuSpA)

PROTOCOL NUMBER:

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Table of Contents

PROTOCOL SIGNATURE PAGE

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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 heterogeneous group of chronic disease of various subsets of diagnoses such as ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disease related arthritis. AxSpA results in severe disability and morbidity and severely affected the quality of life of patients. Till date, there is no cure for AxSpA and the pathophysiology of the disease is still unclear. The treatment for AxSpA usually involved biologics which cost more than SGD$30,000 per year and only provided short-term relief to their symptoms. Treatment such as NSAIDs and biologics although provide symptomatic pain relief but may not be able to stop the progression of disease.

The management of AxSpA and its associated complications and comorbidities can be complex and often require multiple interventions. Since AxSpA is life long and without cure, together with limited patient-physician contact, this results in suboptimal care as different aspects of AxSpA care such as subjective data from a thorough patient interview, monitoring of objective data trend, drug optimization, medication tolerability, lifestyle modifications such as morning stretching exercises, accuracy in the use of medications and other assistive devices, and management of psychological state cannot be well addressed. Such situations may give rise to therapeutic failures but also result in potential complications such as depressions, which is very common in rheumatologic setting.

1.2 Rationale and Justification for the Study

TCM modalities especially acupuncture had shown promising results in the management of symptoms such as pain. A systematic review in the prototype disease of AxSpA (Ankylosing Spondylitis) had shown that acupuncture resulted in improvement in inflammatory markers and mobility of patients. However, till date there is no study in the broader umbrella AxSpA disease that involved patients with similar symptoms but no radiologic features. Also, these trials did not examine the treatment modalities with the aim of implementation into the healthcare system. After an average of 17 years, only 14% of clinical trials were implemented. Although clinical trials that are explanatory provided good internal validity, the studies did not give stakeholders of the healthcare system sufficient confidence due to the extremely homogenous population and its aim was to further scientific knowledge and not implementation. Therefore, there is a need to consider the usage of pragmatic trials to allow the implementation of the results of the intervention should the trial provided evidence for it. Pragmatic trial aims to measure a wide spectrum of outcomes, mostly patient-centred and the research question under investigation is whether an intervention actually works in real life.

In this proposal we aim to assess the effectiveness, safety and cost effectiveness of TCM physician collaborative model of care. We hope that our research outcome from this study, we will be able to provide policy makers evidence to understand the impact of TCM physician collaboration on healthcare delivery in rheumatology. The results of this study will provide a robust, real world base to understand the safety, efficacy and synergistic effect TCM can provide. For the TCM community, this pragmatic trial can provide greater confidence to embed other modalities into the model of care, giving stakeholders a greater evidence base towards implementation of TCM into the current healthcare system. The long term implications of a successful outcome of this project will provide other clinicians, TCM physicians and policy makers in other chronic diseases such as diabetes, cancer care and cardiovascular diseases confidence to initiate collaboration with their TCM physician counterpart. For rheumatology, a successful implementation of this model of care will allow expansion of this novel model of care, thus allowing better management of other diseases such as rheumatoid arthritis and systemic lupus erythematous and provide patients with an alternative model of care that has similar or even better efficacy, safety and cost-effectiveness profile.

1.2.1 Rationale for the Study Purpose

Patients with AxSpA often look to Traditional Chinese Medicine (TCM) for complementary and

alternative therapies. TCM provides these chronic disease patients a second hope and a more holistic approach to treatment. TCM is the most commonly used complementary and alternative medicine used in the world. Although not reported, our internal research through a qualitative study found that more than 80% of patients were on TCM and most of them do not report to their primary physician. A study that is being done on a close disease of SpA, rheumatoid arthritis, found that 70% of the patients were on TCM and only 40% reported to their primary physicians. This may results in significant drug-herb interactions and may result in severe adverse drug reactions and reduced efficacy of drugs.

1.2.2 Rationale for Study Population

Axial Spondyloarthritis (AxSpA) is a chronic debilitating disease and often results in severe disability and morbidity and adversely affected the quality of life of patients. Till date, there is no cure for AxSpA and the pathophysiology of the disease is still unclear. The treatment for AxSpA usually involves biologics which cost more than SGD$30,000 per year and only provides short-term relief to their symptoms. While NSAIDs and biologics provide symptomatic pain relief, they do not stop the progression of disease.

1.2.3 Rationale for Study Design

The proposed methodology makes use of the most prevalent and commonly utilized methods found in the studies that intend to achieve similar objectives. While most of these similar studies that explored novel model of care with TCM were conducted retrospectively, a prospectively randomized controlled study will allow the effectiveness of the interventions to be captured without relying on past records, which are often incomplete and prone to inaccuracy. The administration of the quality of life outcomes forms at baseline, after the course of acupuncture (6-week), and at 12-week, 24-week and 52-week intervals will allow the investigators to capture changes. The intervals of data collection mirror that of current clinical practice whereby data will be collected are of importance and relevance to clinical practice. Furthermore, with the design of pragmatic trial anchored with the PRECIS-2 criteria, extended CONSORT guidelines for pragmatic trials and STRICTA statement of acupuncture, we aim to provide definitive evidence of this novel model in the current healthcare system.

2 HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

Our primary hypothesis is that novel TCMCMC in patients with AxSpA will result in better pain control as compared the usual rheumatological care at 6 weeks.

The main secondary hypothesis is that TCMCMC will result in better pain control in patients with AxSpA at 24 weeks. The other secondary hypotheses of this study are that patients with AxSpA under the TCMCMC will have greater improvements in other clinical, quality of life, and economic outcomes as compared with those under the usual rheumatological care at 6 weeks, 12 weeks, 24 weeks and 52 weeks. We also hypothesized that there will be no difference in safety between both arms.

2.2 Objective

The objective of this study is to determine the clinical effectiveness, safety and cost-effectiveness of a new model of care in the management of Spondyloarthritis (AxSpA) using a pragmatic trial approach.

Patient demographics, past medical history, and current medication use will be collected at enrollment, which is also the date when patients in the intervention group have their first visit with the attending physician. Follow-up at the 6-week time point is selected, as patients randomized to the interventional arm will have completed their course of acupuncture. The 12-week visit is selected because most trials in this

field assessed the outcomes at this time point, while 24-week and 52-week outcomes are to assess long term effectiveness which mattered most to patients.

Table 1: Summary of Primary and Secondary Outcome Measures

Outcomes	**Time period**				
	Baseline	**6-week**	**12-week**	**24-week**	**52-week**
1. Primary outcomes					
1.1 Spinal pain score	✓	✓			
2. Main secondary outcome					
2.1 Spinal pain score	✓			✓	
3. Other secondary outcomes					
3.1 Clinical outcomes					
3.1.1 Spinal pain score	✓		✓		✓
3.1.2 BASDAI	✓	✓	✓	✓	✓
3.1.3 BASFI	✓	✓	✓	✓	✓
3.1.4 BASG	✓	✓	✓	✓	✓
3.1.5 HAQ	✓	✓	✓	✓	✓
3.2 Quality of life outcomes					
3.2.1 SF-36	✓	✓	✓	✓	✓
3.2.2 ASQoL	✓	✓	✓	✓	✓
3.3 Economic outcomes					
3.3.1 Costs		✓	✓	✓	✓

Primary outcomes

Spinal pain score at 6 weeks is the primary outcome in this study. The 10-point pain numerical rating scale (NRS) will be used and it is widely used and validated across many setting. This was selected, as this is the time point immediately after the whole 2 courses of intervention and pain is what mattered most to patients with AxSpA.

Main secondary outcomes

Spinal pain score at 24 weeks is the main secondary outcome in this study. This was selected, as this is the time-point where patients are most concerned about sustained long-term efficacy and it is the basis of calculation of our cost-effectiveness of this intervention.

Other secondary outcomes

Spinal pain at 6-week, 12-week, 24-week, 52-week and four clinical parameters which include BASDAI, BASFI, BASG and HAQ will be collected after the course of acupuncture (6-week), 12-week, 24-week and 52-week intervals. These are outcomes measures used in daily practice in the management of AxSpA patients. Because the main symptoms patients with AxSpA faced are pain and fatigue, there are no investigations available except the above patient-reported outcome measures. These patient-reported outcomes will be collected via interviews by our research staff.

Secondary Quality of Life outcomes

Quality of life (QoL) instruments will be administered by the research assistant at baseline, after the course of acupuncture at 6-week, 12-week, 24-week and 52-week intervals. The QoL measures will include one generic (SF-36) and an AxSpA-specific measure, Ankylosing Spondylitis Quality of Life (ASQoL). Both patient-reported outcomes have been validated in the Singapore population.

SF-36

The SF-36 consists of 36 questions that are summarized into 8 domains and 2 summary component score. The 8 domains include different areas of life such as physical functioning, bodily pain, role physical, role emotional, general health, vitality and social functioning. The 8 domains will be further summarized into physical and mental component score respectively. The score will be norm-based according to population references and the SF-36 ranged from 0 to 100 with 100 representing perfect health.

Ankylosing Spondylitis Quality of Life (ASQoL)

The ASQoL is a disease specific quality of life scale containing 18 questions with 2 responses each. Our colleagues in SGH Department of Rheumatology and Immunology validated the scale and the manuscript is currently in peer review.

Secondary economic outcomes

AxSpA-related and non-AxSpa-related health care use will include rheumatologist's consultation fees, TCM physician time, costs of imaging, laboratory and procedures, drug costs, assistive devices cost, number of other outpatient visits, number of physiotherapy costs, number of inpatient days, and number of visits to emergency departments. Healthcare use will be obtained through questionnaires administered to patients in both control and interventional arms after the course of acupuncture (6- week), and at 12-week, 24-week and 52-week intervals. 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).

Process Measurement

Adherence to treatment defined as the number of acupuncture sessions attended by the patients in the intervention will be assessed. We will also record the number of acupuncture and rheumatology consultations, length of session of each acupuncture session, number of needles of each acupuncture session and the drugs prescribed by rheumatologists. This is to ensure treatment fidelity and to ascertain the true effect of the intervention proposed.

2.3 Potential Risks and Benefits:

2.3.1 Potential Risks

Potential adverse effects of acupuncture include fainting, bent or broken needle, local pain, and slight bleeding. 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 and require review by the Data Safety Monitoring Board (DSMB).

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 acupuncture in the management of AxSpA.

3 STUDY POPULATION

3.1 List The Number and Nature of Subjects to be Enrolled.

A total of 160 patients with 80 patients per arm will be recruited from Singapore General Hospital. There is no subject restriction based on race of the subject.

3.2 Criteria for Recruitment and Recruitment Process

As patients with Spondyloarthritis are referred to a dedicated clinic in SGH Department of Rheumatology and Immunology, the attending rheumatologist will assess suitability for entry into this trial. In the case

whereby the PI is also the attending physician, he will directly make first contact and ask for informed consent. If not, 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 all patients with AxSpA that 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) and spinal pain score ≥4 on a 11-point NRS; has failed 2 sequential NSAIDs (including COX-2 inhibitor) at maximal tolerated doses for ≥ 4 weeks in total; and no biologic therapy (i.e tumour necrosis factor blocker or anti-interleukin 17) within the past three months. Patient who is on current treatment with concomitant methotrexate (MTX) or sulfasalazine (SSZ) at study entry must be on the drug for ⩾12 weeks and at stable dose for ⩾4 weeks prior to randomisation. Patients who are on non-biologic disease-modifying antirheumatic drugs (DMARDs) other than methotrexate or sulfasalazine must discontinue the DMARD 4 weeks prior to randomisation, except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed. Patients taking systemic corticosteroids have to be on stable dose of ⩽ 10mg/day prednisolone or equivalent for at least two weeks before randomisation. Patients with a BASDAI 50% response to NSAIDs were recruited in one block, whilst patients who did not have BASDAI 50% response to NSAIDs were recruited in another block.

3.4 Exclusion Criteria

We exclude patients who are pregnant or breastfeeding women; on anti-platelet agents (i.e. aspirin, clopidogrel, dipyridamole, etc) and anti-coagulants (i.e. warfarin, enoxaparin, rivaroxaban, dabigatran, etc); have bleeding disorders; or have blood-borne communicable diseases (e.g. hepatitis B, hepatitis C, human immunodeficiency virus, etc).

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 the usual care or the intervention on a 1:1 basis via random permuted block randomization. Randomization list will be provided by biostatistician in the study team.

4.2 Study Visits and Procedures

Control

The usual rheumatological care comprises 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 6-weekly to 6-monthly intervals depending on the patients' condition from the start of randomization till trial termination at 52 weeks. The attending rheumatologist will prescribe a variety of treatment inclusive of medications such as non-steroidal anti-inflammatory drugs and physiotherapy. At each session, the attending rheumatologist will conduct a thorough physical examination and 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 after 6 weeks. Escalation of

therapy to biologics requires persistently active disease for at least 12 weeks, and the primary outcome measurement lies within this period (at 6 weeks), hence patients will not be denied escalation of therapy if needed in this pragmatic trial.

Intervention

The intervention arm will involve the TCM physician in the management of patients with AxSpA in addition to the usual rheumatological care. The only difference the patients in the interventional arm will experience is the intervention given by the TCM physicians. The clinical interventions carried out by the TCM physicians include but is not limited to counseling of patients regarding their illness from the TCM perspective, diagnosing based on TCM clinical syndromes and prescribing acupuncture treatment accordingly. Assessing of disease activity (which includes pain) will be conducted after the acupuncture sessions and the TCM physician will refer the patient to the attending rheumatologist in the event of any adverse reactions. The TCM physician will be able to communicate freely with the attending physician to understand the patient better and to refer and schedule extra appointment with either the TCM physician or the attending rheumatologist as deemed appropriate. The TCM physician will schedule consultations as needed to achieve the holistic care intended. As the acupuncture sessions will be held over a short duration of 5 weeks, there will be no case coordination meeting.

The TCM modality for treatment used here will be acupuncture, which is specially implemented by our experienced collaborators at Thong Chai Medical Institution. The recommended acupuncture treatment will consist of a total of 10 sessions (or 2 courses) in total. Each course of treatment will consist of 5 acupuncture sessions held over 2 weeks of 30 minutes each. The patient will take a break of 1 week in between each course of acupuncture. 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.

The acupoints are as follow:

Main acupoints: *Jiaji* (EXB2 华佗夹脊穴), *Shenshu* (BL23 肾俞穴), *Yaoyangguan* (DU3 腰阳关穴), *Mingmen* (DU4 命门穴), *Huantiao* (GB30 环跳穴), *Ashixue* (阿是穴)

Secondary acupoints:
Blockage due to dampness and heat: Main points plus *Yinlingquan* (SP9 阴陵泉), *Quchi* (LI11 曲池), *Hegu* (LI4 合谷), *Waiguan* (SJ5 外关)
Blockage due to dampness and coldness: Main points plus *Yinlingquan* (SP9 阴陵泉), *Zusanli* (ST36 足三里)
Blockage due to stagnated blood: Main points plus *Geshu* (BL17 膈俞), *Xuehai* (SP10 血海), *Neiguan* (PC6 内关)
"Yang" deficiency in kidneys: Main points plus *Taixi* (KI3 太溪), *Fuliu* (KI7 复溜), *Weizhong* (BL40 委中)
Deficiency in the liver and kidneys: Main points plus *Ganshu* (BL18 肝俞), *Sanyinjiao* (SP6 三阴交), *Yanglingquan* (GB34 阳陵泉)

Acupoints for symptoms:
Neck pain: Main points plus secondary points plus *Tianzhu* (BL10 天柱), *Dazhui* (DU14 大椎)
Thoracic pain: Main points plus secondary points plus *Dazhu* (BL11 大杼), *Shenzhu* (DU12 身柱),

Zhiyang (DU9 至阳)
Lumbar pain: Main points plus secondary points plus *Ciliao* (BL32 次髎), *Zhibian* (BL54 秩边)

After sanitization of the patient's skin, sterile disposable needles of (0.25mm diameter, 25mm length), (0.25mm diameter, 40mm length), or (0.30mm diameter, 50mm length) will be used for the all acupoints except *Huantiao* as per each patient's clinical needs. Sterile disposable needles of 0.30mm diameter, 75mm length will be used at *Huantiao*. In addition to the main acupuncture points specific for the treatment of AxSpA, the TCM physicians will be allowed to make adjustments to the acupuncture points in view of the differing constitution of the patients as per the holistic treatment philosophy of TCM. The patient will be lying prone during the acupuncture treatment. After eliciting the deqi sensation, the needles will be left in place for 30 minutes. The acupuncture treatment will be done 2-3 times a week, with 5 sessions constituting a treatment course. There will be a break of 1 week in between each acupuncture course. Patients in the intervention arm will undergo 2 treatment courses (or 10 sessions) in total.

4.2.1 Screening Visits and Procedures

As Bath AS Disease Activity Index (BASDAI) and spinal pain score are routinely performed 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

Recruitment and Randomization: Questionnaire and routine rheumatology consultation

Visit 1, 2, 3 and 4 (week 6, week 12, week 24 and week 52): Questionnaire and routine rheumatology consultation

If subject is randomised to the interventional arm, he/she will be required to undergo 10 sessions of acupuncture in total in addition to the above visits.

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 due to DSMB review.

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

5.1 Trial Intervention

The TCM modality for treatment used here will be acupuncture, which is specially implemented by our experienced collaborators at Thong Chai Medical Institution. The recommended acupuncture treatment will consist of a total of 10 sessions (or 2 courses) in total. Each course of treatment will consist of 5 acupuncture sessions held over 2 weeks of 30 minutes each. The patient will take a break of 1 week in between each course of acupuncture. 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 each visit and 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. From a pragmatic trial standpoint, this reflects real world condition, hence, 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 6-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) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

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

7.2 Collecting, Recording and Reporting of Adverse Events and Serious Adverse Events to CIRB

Reporting of adverse events involves the Principal Investigator submitting the SAE Reporting Form to CIRB within the stipulated timeframe. The Principal Investigator is responsible for informing the institution representative, the chairman medical board (when required by the institution for local SAE resulting in death), sponsor or regulatory bodies as required and appropriate.

Reporting timeline to CIRB:

- Local unexpected SAE resulting in death that are related events should be reported immediately - within 24 hours of the Principal Investigator becoming aware of the event. This should be followed by a full report within 7 calendar days.
- Local unexpected, life-threatening SAE that are related events should be reported as soon as possible but no later than 7 calendar days after the Principal Investigator is aware of the event. This should be followed by a full report within 8 additional calendar days.
- Local unexpected, not life-threatening SAE that are related events should be reported no later than 15 calendar days after the Principal Investigator is aware of the event.
- An increase in the rate of occurrence of Local expected SAE that are related events, which is judged to be clinically important, should be reported within 15 calendar days after the Principal Investigator is aware of the event.
- Local unexpected AE that are related events should be reported at least annually (together with Study Status Report for annual review).
- Non-local unexpected SAE that are fatal or life threatening and related should be reported not later than 30 calendar days after the Principal Investigator is aware of the event.

7.3 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Science Authority (HSA)

All SAEs that are unexpected and related to the study drug will be reported to HSA. Please refer to the HSA website for more information on Safety Reporting Requirements for Clinical Trials.

The investigator is responsible for informing HSA no later than 15 calendar days after first knowledge that the case qualifies for expedited reporting. Follow-up information will be actively sought and submitted as it becomes available. For fatal or life-threatening cases, HSA will be notified as soon as possible but no later than 7 calendar days after first knowledge that a case qualifies, followed by a complete report within 8 additional calendar days.

7.4 Safety Monitoring Plan

The data and safety monitoring committee will consist of 3 external members. The review will be conducted every twelve months. All adverse events such as skin injuries and infections will be monitored for safety.

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

1. The severity grade (mild, moderate, severe)
2. Its relationship to the study intervention
3. Its duration (start and end dates or if continuing at final examination)
4. Whether it constitutes a SAE
5. Outcome

The DSMB will review all expedited adverse event reports in its convened meetings. The annual summary of all adverse events and any audit reports will be reviewed annually by the DSMB. The study will be stopped if a serious adverse event occurs. The IRB and DSMB will be consulted, and if it is determined that the serious adverse event was not study intervention related, 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 study drug will be elucidated, and the DSMB and IRB 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 data and safety monitoring committee 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

As this is the first study to explore a collaborative model between TCM physician and rheumatologists in the field of AxSpA, we based our sample size calculation from a study by Meng et al.19 With a conservative estimate of 0.6 point difference on a 10-point scale in pain score between the two arms, and assuming a standard deviation of 1.2 for both arms, approximately 64 patients are needed for each arm to obtain a statistical power of 80% (two sided Type I error rate of 0.05) based on a 1:1 treatment allocation. After taking into account a dropout rate of approximately 20%, a total of 160 patients with 80 patients per arm will be needed for this trial. This number is feasible to recruit on the ground because our centre manages about 600 AxSpA patients a year.

9.2 Statistical and Analytical Plans

All patients will be analyzed using intention-to-treat approach. The primary outcome of interest is the difference in pain score at 6 weeks between the interventional and control arms. Patient's characteristics will be summarized using mean and standard deviation (or median and interquartile range where adequate) for continuous variables, and count and percentage for categorical variables. Primary outcome of pain score at 6 weeks will be analyzed using Student's t-test to obtain the crude estimate of difference and its associated 95% confidence interval, between the intervention and control. Further adjustment will be made with baseline pain score using ANCOVA. For secondary outcomes with repeated measurements, we will use the linear mixed model to account for within-individual correlation among measurements and the sandwich estimator to obtain robust standard error estimates. The intervention indicator and time factor will be included into the linear predictors adjusting for baseline covariates.

All evaluations will be made assuming a two-sided type I error rate set at 0.05.
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.

The economic evaluation will be conducted from the health care system and societal perspectives. Both a cost-effectiveness analysis (i.e. cost of reduction in 1 pain score point) and a cost-utility analysis (cost of reduction in 1 quality-adjusted life year saved) will be performed. Effectiveness will be measured as the reduction in pain score at 6-week (primary outcome) and 24-week (main secondary outcome) for the cost-effectiveness analysis. For the cost-utility analysis, utility will be measured at all observed time points using the SF-6D scale which is a subsample of the SF-36 scale (secondary outcome). Effectiveness will be measured exclusively through improvements in quality of life. We will regress the effectiveness on follow-up time in order to assess the time profile of the effectiveness of the intervention. In case of residual effectiveness at 52-week, we will extrapolate using the estimated effectiveness profile in order to assess additional effectiveness arising beyond study completion. Utility weights from Singapore will be applied to determine the corresponding societal preferences. All AxSpA-related and non-AxSpA-related health care use (secondary economic outcomes) will be used for the health care system perspective. Costs associated with TCM physician intervention will be estimated based on the salary of the TCM physician involved. As our partner site is a free clinic, we will cost the intervention with the average costs by 3 other TCM providers to allow suitable calculations to be made. Non-health care financial consequences (secondary economic outcomes) will be added for the societal perspective. All costs will be adjusted to 2017 values using consumer price index health care component. The incremental cost effectiveness ratio will be calculated in which the difference in total costs between intervention arm and control arm is divided by the difference in the reduction of pain score between the two arms. 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 data and safety monitoring committee 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 Centralised Institutional Review Board (CIRB) and regulatory approval from Health Sciences Authority (HSA), prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB and HSA 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 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. The place where consent will be taken is suitable as it is a closed and private environment. Participants are informed that participation to the study is voluntary and they have the rights not to participate. The place where consent will be taken is suitable as it is a closed and private environment. 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, the designated coordinator and the 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

Funding will be through Ministry of Health Traditional Chinese Medicine Research Grant (Amount: $ 213,564.00). 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 blanket insurance for clinical trials (Ministry of Health Clinical Trial Insurance) conducted in SingHealth.

List of Attachments

Appendix 1 Study Schedule

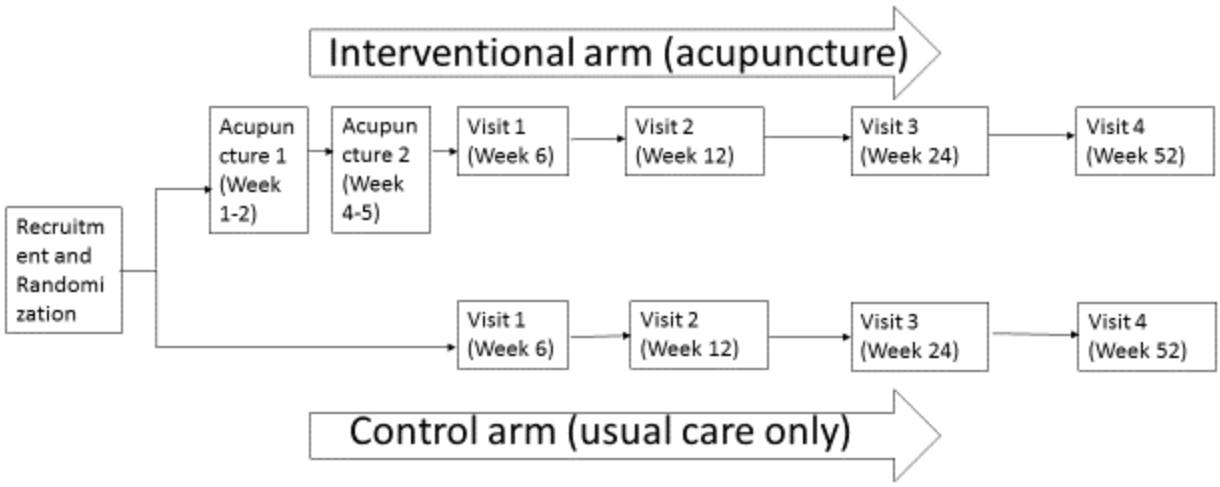

Figure 1: Study schedule of participants. In addition to the baseline visit where recruited participants will be randomized, participants will be scheduled for visit 1, 2, 3 and 4 (at week 6, week 12, week 24 and week 52).

If participants are randomised to the interventional arm, they will be required to undergo 10 sessions of acupuncture in total in addition to the above visit.

Appendix 2 Study Intervention

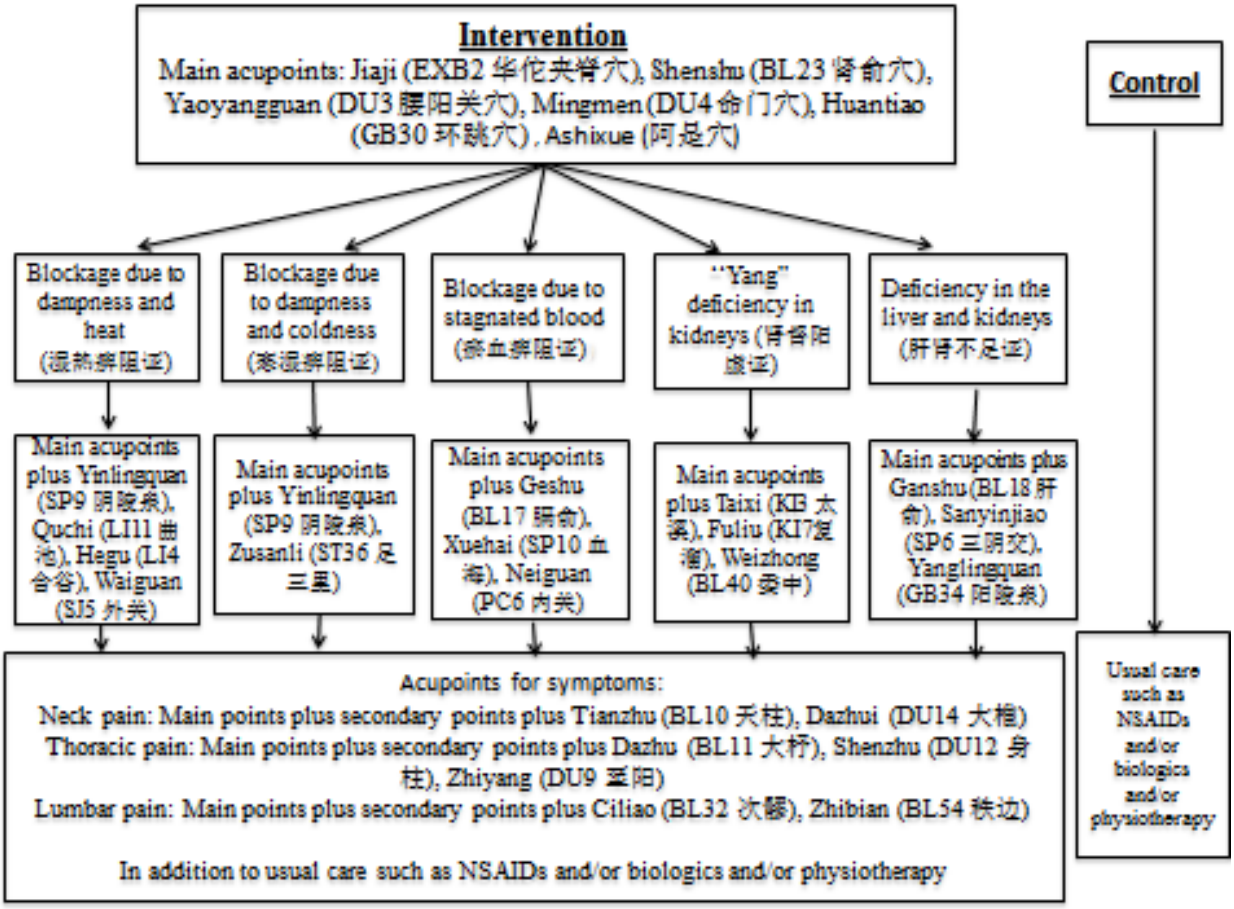

Figure 2: The acupuncture points employed in this study. The main acupoints are *Jiaji, Shenshu, Yaoyangguan, Mingmen, Huantiao, and Ashixue*. The intervention group would then be classified into one of the five syndromes based on their clinical presentation, and have secondary acupuncture points chosen based on their respective syndromes. There will also be additional acupuncture points for patients with neck pain, thoracic pain and/or lumbar pain. Patients in both intervention and control group will be given usual care consisting of as NSAIDs and/or biologics and/or physiotherapy as deemed necessary by the attending rheumatologists.