Medical Acupuncture in Raynaud's Disease:Protocol Development for conducting Systematic Review and Meta-analysis

Running title: Protocol Development

Abstract

Background: Idiopathic Raynaud's disease is twice common in women than their counterparts, and secondary Raynaud's disease co-occurs with a variety of medicosurgical conditions. Both diseases are managed by several medications which are invariably associated with various adverse effects. **Objective:** This study aimed to describe several standardized SPIRIT and PRISMA steps and items that help in the development of research protocol directed towards systematic review and meta-analysis conduction concerning Raynaud's phenomenon managed by clinical acupuncture.**Results:** Statements, guidelines, list of items and processes related to SPIRIT and PRISMA and their extensions and updated versions are ideal methodological tools in framing Raynaud's disease and acupuncture research protocols for scientifically conducting not only randomized controlled trials but also systematic review and meta-analysis. By extension, these methodological tools could also be applied to develop research protocols for other diseases and nontraditional treatment interventions with some modifications. **Discussion:** In line with Traditional Chinese Medicine, the pattern of Raynaud's disease and pros and cons of medical acupuncture should make an important component of discussion, besides the details of included randomized clinical interventions insystematic review and meta-analysis, which arebut not limited to treatment effects, their strengths and limitations, quality, heterogeneity, and endpoints. **Conclusion:** The development of research protocol for conducting systematic review and meta-analysis is an art and while framing the draft researchers must take into account various SPIRIT and PRISMA statements and

guidelines and their latest versions applicable to various diseases including Raynaud's phenomenon managed by traditional and modern medications across the world.

Keywords; Raynaud's diseases, medical acupuncture, SPIRIT-statement, PRISMA-statement, systematic review, protocol development

1. INTRODUCTION

Primary Raynaud's disease (PRD) an idiopathic disorder with no underlying pathologies is precipitated mostly by cold and emotional upset. PRD is characterized by intermittent reversible vasospastic episodes of precapillary arterioles and arteriovenous anastomoses of the distal digits and toes, rarely nose, ears and penis [1,2,3].PRD is characterized by symmetrical paresthesia and pain in both extremities, severe distress and loss of hand functions with reduced quality of life attributed to temporary tissue and sensory nerve ischemia [1,2,3].Vasospastic attacks lead to ischemic blanching (whitening) of all fingers, followed by cyanosis due to desaturation of residual blood (blue) and finally reperfusion hyperemia (red) [1-6]. The trio of white, blue and red color is termed as tricolor phenomenon of Raynaud's disease. In between the vasospastic attacks, the digital perfusion is apparently normal. PRD is typically seen in adult woman of age 30 or below and affects females twice compared to their counterparts. The prevalence of PRD is up to 5% in general population which varies geographically due to cold weather variations around the world [5]. The diagnostic criteria for PRD include typical symmetrical reversible symptoms of digital vasospasm, absence of peripheral vascular obstructive disease and tissue necrosis or digital ulceration or gangrene, normal nail fold capillaries, and a negative antinuclear antibody test and normal sedimentation rate. PRD is a diagnosis of exclusion and reversible condition. A comprehensive clinical workup, physical systemic examination, diagnostic criteria, laboratory tests and computerized tomography and magnetic resonance imaging tend to rule out most systemic, genetic, autoimmune and mixed or deep connective tissue conditions underlying secondary Raynaud's disease[1-8].

Conversely, secondary Raynaud's disease (SRD) is caused primarily by several underlying diseases which are but not limited to systemic sclerosis or scleroderma, systemic lupus erythematosus, rheumatoid arthritis, hypothyroidism, hematologic conditions, and several medications such as anticancer drugs [1,7].Both PRD and SRD are referred to as Raynaud's phenomenon[7].Raynaud's disease constitutes an important component of the CREST syndrome associated with scleroderma.SRD occurs after the age of 30, and co-occurs with multiple systemic diseases and manifests additional diagnostic criteria which are asymmetrical, severe pain, specific autoantibodies, increased erythrocyte sedimentation rate (ESR), rheumatoid arthritis factor (RAF), anti-nuclear factor (ANF), C-reactive Protein (CRP), extractable nuclear antibody to detect the causative disorders and ulcerations on distal digits and toes due to ischemia. Furthermore, microvascular disease of nail capillaries in SRD leads to severe psychophysical disability and amputation [1,6,9]. However, both PRD and SRD are associated with poor quality of life and overwhelming psychological suffering including anxiety and depression. Raynaud's phenomenon share some clinico-diagnostic features; however, the prevalence of SRP is much higher (up 90%) among patients with comorbid conditions[1,6-10].

Concerning treatment, Raynaud's episodes are managed by life style changes such as avoiding cold exposure and smoking cessation, exercise and conserving heat loss, and managing stress effectively, complementary and alternative medicine such as acupuncture, electroacupuncture and Chinese Herbal Medicines, modern medications such as calcium channel blockers, vasodilators such as local nitroglycerin, losartan, sildenafil citrate,fluoxetine, and prostacyclin analogues,sympathectomy and Botox injectionand integrated approaches with variable outcomes, low to moderate efficacy[1-13] and poor adherence remains a global problem. A review of relevant literature on Raynaud's phenomenon found scanty systematic reviews, meta-analysis and randomized and non-randomized clinical trials [3], though acupuncture is reported to treat diverse medical and surgical conditions[14], especially non-Raynaud's conditions. Overall, Raynaud's phenomenon needs further clinical as well as interventional research globally.

1.2 Raynaud's Disease and Traditional Chinese Medicine

It is customary to describe brief snapshots of disease pattern and intervention in accordance to Chinese concepts when developing protocol for systematic reviews and meta-analysis. Medical acupuncture is an ancient Traditional Chinese Medicine (TCM) now increasingly used in a variety of diseases including Raynaud's phenomenon and postpartum depression with pain in the western world[15], and both disorders preferentially affect woman population. Medical acupuncture is linked with inconsistent effectiveness in pain disorders attributed to different study designs and methodologies, and requires further researches.

Traditional Chinese Medicine conceptualizes RP to stagnationof qi energy and blood in the meridian channels attributed to severe cold along with dampness. In another way, balanceof Yin (Cold) and Yang (Hot)must be sustainedthroughout the body, and any disturbance in this equilibrium tends to cause pathology in the body.The pathologic flow of Cold (Kidney Yin) into the hands and feet is due to a deficiency of Kidney Yang (Hot), which can triggeran afflux (*Jue*) of Kidney Yin (Cold) to the organs or extremities.Kidney Yang and Yin should strike a balance between Hot and Cold for reestablishing internal homeostasis. Further details concerning how to treat RP by medical acupuncture and Moxibustion and Chinese herbs are available here, and one of the coauthors of this paper has contributed to the Clinical Pearls[16].Additional contributory factors are alcohol and tobacco use that tend to produce internal fire exacerbating the stagnation.

Acupuncture points are located at meridians and needles are accurately inserted there. Although there are large numbers of acupuncture points used in RP, commonly recommended are LI 11 and ST36 (Homeostatic points) and LU 9 (Grand Point) for impacting blood vessels. For the upper extremities, HT 3, TB 5, PC 6, C-6 to T-3 (Jiaji points) and the Baxie Extra Points are used whereas for the lower extremities, GB 34, SP 9, GB 39, ST 32,SP 6, and LI to LI II (Jiaji Points) and the Bafeng extra points are commonly recommended. Using the Yin Linking Vessel which is extra meridian tend to boosts the effects of the medical acupuncture bypromoting the circulation of qi and blood in the meridian channels.This step is completed by using PC 6 right and SP 4 left, in that order inwomen, and in men the sides are reversed and KI 9 bilaterally, where thechannel enters the surface. Acupuncture treatment is given

dailycomprising a course of 16 to 20 sessions followed by monthly treatments formaintenance for months and even years. Furthermore, auricular points used are the Sympathetic AutonomicPoint, Endocrine Point, Adrenal Gland C, Adrenal Gland E,Heart C1, Heart C2, Heart E, Heat Point, Lesser OccipitalNerve, Liver, Spleen C, Shenmen, Thalamus Point, Occiput,and Sympathetic Chain. Those points are selected according to tenderness on palpation.Chinese herbal formulas used in RP are: Si Ni Tang, if theperson has features of Cold syndrome characterized by a slow pulse, apale tongue, and a desire for hot drinks; and Si Ni San, if theperson has signs of stagnation such as irritability, muscle tension, and alternating calmness and agitation.Currently, we have described comprehensively RP, mechanisms of actions and effects of medical acupuncture, acupoints and specifics of acupuncture needles [17].Overall medical acupuncture with inconsistent number of courses/sessions is reported having moderate effectiveness in Raynaud's phenomenon using a variable number of acupoints unilaterally/bilaterally and needles with specific lengths and diameter worldwide.

1.3 Aim

This study aimed to develop systematic review protocol with concise description of its several steps with a special focus on Raynaud's disease and its management by medical acupuncture. The underlying principles of this protocol development will also apply to other medicosurgical conditions with pain managed by drug interventions other than medical acupuncture including anesthetic analgesia with some modifications.The secondary objective includes identification of what authors can learnfrom the studies reviewed concerningintegrated or alternative interventions for PRD and SRD and other medical conditions with prime pain symptom.

The significance of tailoring this protocol lies in the fact that it will enhance the knowledge of researchers who will conduct systematic reviews on Raynaud's disease and other medical conditions primarily with pain across the world as there is scanty published literature on Raynaud's disease and other painful conditions managed by alternative and integrative interventions, especially in the Eastern world. Research professionals will also benefit from this protocol in tailoring similar systematic review proposals with or without different intervention for submitting to sponsor or funding

or non-funding research organizations for ethical approval and, thereafter, conducting systematic review and meta-analysis. The greater relevance of this research is that this protocol development steps would be of tremendous help to young researchers, who might contribute to further advance research concerning women's common health condition associated with pain, and managed by complementary and integrated interventions.

2. METHODS

2.1 Main Sources for Protocol Development

This protocol draft follows PRIMSA-P guidelines[18]forwriting and appraising systematic review and meta-analysis. The synopsis and protocol for systematic review needs to be registered in the InternationalProspective Register of Systematic Reviews [3,10].Reference was also made to the most comprehensive generic Cochrane protocol for pharmacological interventions for the treatment of RP [19]. The document related to PRISMA-P 2015 statement was also considered in developing this protocol for RP and acupuncture intervention [20]. Of note, researchers use SPIRIT statement for developing protocols for reviewing and conducting randomized clinical trials (RCTs)[21,22].Authors will also take into account the SPIRIT-13 TCM extension, PRISMA-P 15 and its latest extensions for the development of this protocol [23]. Notably, the results of RCTs, observational studies, and NRCTs make the food for systematic reviews and meta-analyses and, therefore, the items considered for conducting systematic review and meta-analysis overlap with RCT items. Overall, a detailed knowledge in SPIRIT items and PRISMA-P helps researchers in developing protocols for RCTs, systematic reviews and meta-analysis.

2.2 Search strategy

Researchers should conduct e-searches (-2019) using medical search engines; Ovid, EMBASE, CINAHL, Cochrane Library and Databases of Systematic reviews, PubMed, Google Scholar, MEDLINE, MedlinePlus, PsychINFO, Web of Science, ScienceDirect, SpringerLink, Scopus and Trip Database. Keywords to MESH (Medical Subject Headings) and Boolean operators help in locating and retrieving specific articles. ThenRCTs and observational studies meeting exclusion and

inclusion criteria need to be retained for screening and eligibility purposes. Additional searches of the reference lists of all primary studies and reviewed articles should also be conducted manually in order to identify and increase the number of RCTs concerning Raynaud's phenomenon or any disease comorbid with RP and acupuncture intervention alone or combined with other interventions. Important detailsof search process and strategy are described in Tables1, 2 a&b.

Table 1 Search process documentation, adapted from references

Data source	Documentation
Electronic database	Name of database; Search strategy for each database; Date of search; and Years covered by search
Journal hand searches	Name of journal; Years searched; Any issues not searched
Conference proceedings	Title of proceedings; Name of conference (if different); Title translation (if necessary); Journal name (if published as part of a journal)
Efforts to identify unpublished studies	Research groups and researchers contacted (Names and contact details); Research web sites searched (Date and URL)
Other sources	Date searched/contacted; URL; Any specific conditions pertaining to the search

Table 2 a: Search Strategy

Search engines used: Medline (PubMed), PsychINFO, Cochrane Search terms

Number	Strategy
1.	"Raynaud's disease" OR Raynaud* OR "Raynaud's phenomenon"
2.	Acupuncture* OR Manual acupuncture* OR electroacupuncture OR laser acupuncture* OR Medical Acupuncture OR Acupuncture AND Other interventions*
3.	1 AND 2

Note. Searching for above terms within 'title and article' and only clinical trials; * = truncation to find plurals, alternative spellings and related concepts.

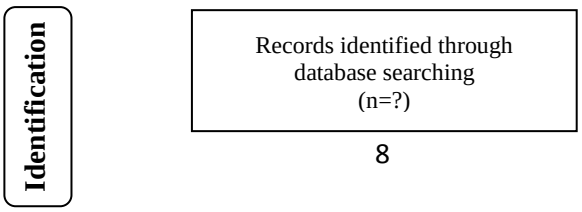
Table 2b: Embase Search strategy and search terms

Number	Strategy
1	'Raynaud phenomenon'
2.	'Acupuncture* OR Medical acupuncture* OR electroacupuncture OR laser Acupuncture* OR other interventions'
3.	1 AND 2

Note. Searching for above terms within 'title and article' and only clinical trials; * = truncation to find plurals, alternative spellings and related concepts.

2.3Selection and Types of Studies

First the titles and then the abstracts of potentially relevant articles were read independently by two authors. Articles need to be rejected only if both authors determined from the title or abstract that the article was not a randomized clinical trial (RCT) or relevant observational study or other studies. All papers that are considered of relevance will be obtained and read independently by two authors.Thereafter, reviewing the full articles, the studies that are not relevant to the systematic review and meta-analysis should also be excluded. Remaining retrieved records will be independently screened by the same review authors for retaining all published accessible RCTs concerning all types of medical acupuncture intervention used in primary and secondary Raynaud's disease, and compared with other interventions. The identified RCTs and observational studies needto be reviewedby tworeview authors for eligibility. Then full texts will be retrievedfor those studies which meet eligibility criteria. The retained articles should be ratedindependently by two review authors using a prespecifieddata extraction form (Tables3 and 4).RCTs with more than one active treatment intervention with a comparator arm should be included. Both individual and clusterrandomization RCTs should be included provided cluster sitesmeet other inclusion criteria. When there is paucity of RCTs in RD (or other pain conditions), non-randomized clinical trials (NRCTs) and observational studies that addressed the use of acupuncture in RD phenomenon will be included in conducting systematic review and meta-analysis. Evidently, blinding innon-drug interventions is not always possible and, therefore, non-blinded studies using medical acupuncture approaches should be included. Finally bibliographies of included studies will also besearched for inclusion of relevant studies, which will thenbe subjected to independent review of eligibility, as all studies reviewed for eligibility. Identified discrepancies should be reviewed and resolved through discussion with a third author reviewer. Level of agreement between three reviewers will be calculated.We will record the selection process in detail through a PRISMA flow diagram (Figure 1).



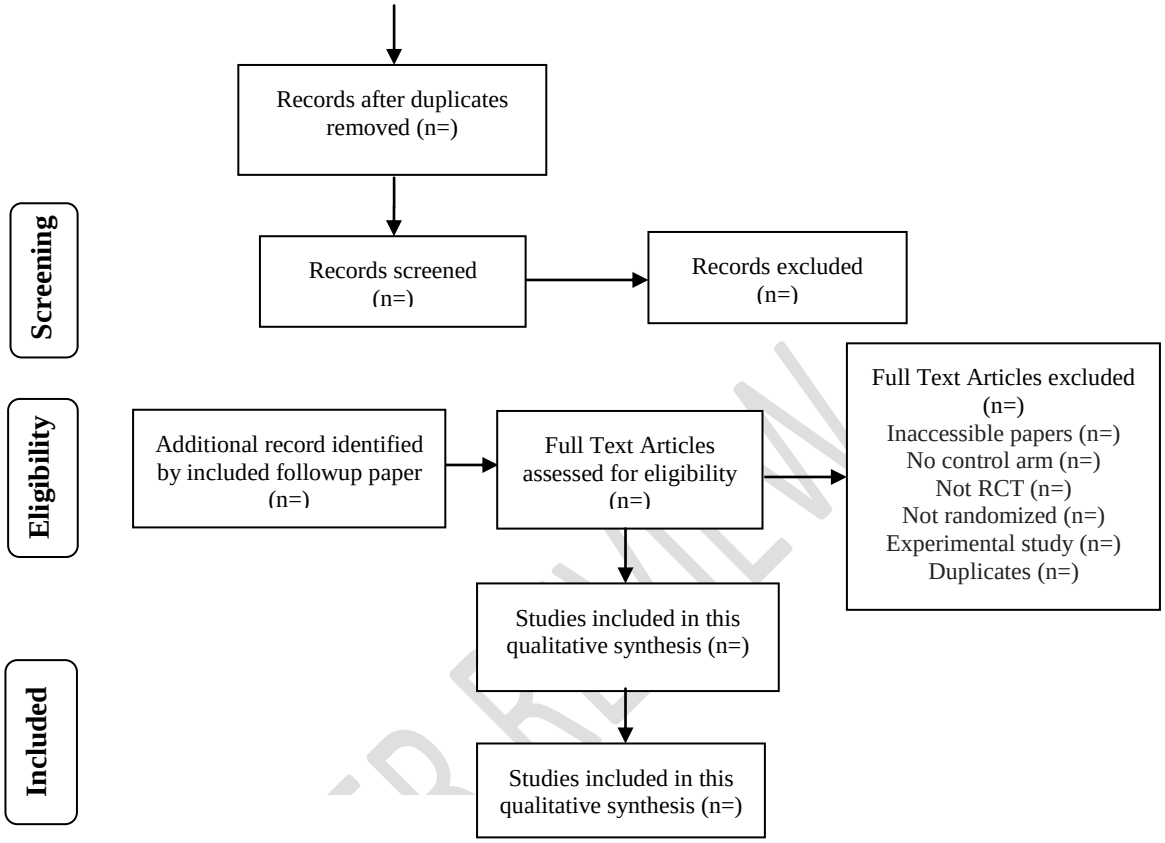


Figure 1 PRISMA diagram summarizing the flow of search results

2.4 Additional Criteria

Studies published in languages other than English, duplicate publications and studies without full texts and abstracts will be excluded. However, researchers well versed with their native language may not follow the criterion of including only English literature and hybrid language model works best in such circumstances. Articles with abstracts but not full articles should be included. Studies must be fully publishedat the time of search; early view online publications will beincluded.Some researchers include conference proceedings and presentations published in abstract booklet should also be part of systematic review and meta-analyses. Furthermore, researchers having access to unpublished research data or negative results also included in systematic reviews and meta-analysis. The search will be limited only to studies with human subjects.

Table 3: Data extraction items adapted from PRISMA-P Checklist and other adapted references

Section and topic	Checklist item
Administrative Information	
Title: Identification Update	Identify the report as a protocol of a systematic review If the protocol is for an update of a previous systematic review, identify as such
Registration	If registered, provide the name of the registry and registration number
Authors: Contact Contributions	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Describe contributions of protocol authors and identify the guarantor of the review
Amendments	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support: Sources Sponsor Role of sponsor or funder	Indicate sources of financial or other support for the review Provide name for the review funder and/or sponsor Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
Introduction	
Rationale Objectives	Describe the rationale for the review in the context of what is already known Provide an explicit statement of the question (s) the review will address concerning participants, interventions, comparators, and outcomes (PICO)
Methods	
Eligibility criteria	Specify the study characteristics-PICO, study design, setting, time frame,) in addition to years considered, language, and publication status- to be used as criteria for eligibility for the review
Information sources	Describe all intended information sources-electronic databases, contact with study authors, trial registers or other grey literature links-with planned dates of coverage
Search strategy	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:Data management Selection process Data collection process Data items	Describe the mechanisms that will be used to manage records and data throughout the review State the process that will be used for selecting studies-two independent reviewers-through each phase of the review including screening, eligibility and inclusion in meta-analysis Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	Describe anticipated methods for assessing risk of bias of individual studies-whether this will be done at the outcome or study level, or both and state how this information will be used in data synthesis
Data synthesis	Describe criteria under which study data will be quantitatively synthesized If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency-I^2, Kendall's τ Describe any proposed additional analyses-sensitivity or subgroup analyses, or meta-regression If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	Specify any planned assessment of meta-bias(es)-publication bias across studies, selective reporting within studies
Confidence in cumulative evidence	Describe how the strength of the body of evidence will be assessed by GRADE

Table 4: Data extraction form for Medical Acupuncture Intervention in Raynaud's phenomenon,adapted from references

Citation including live link	NAQ
Retrieval information including date/location	

Eligibility Criteria		
Adults with Raynaud's (primary or secondary) Randomized controlled trials At least one active intervention (Acupuncture) and control(active or placebo)		
Study Details		
Patient population	**Primary Raynaud's Dis (n)**	**Sec Raynaud's Dis (n)***
Diagnostic criteria used		
Year of publication		
Study design		
Format of Intervention		
Study setting / country		
Sample characteristics(Size and sub-grouping)		
Gender		
Age		
Ethnicity		
Active treatment Interventions		
Pre-defined change model/theory	Yes / No	Please state:
Control intervention		
Duration of study		
Primary end-points		
Secondary end-points		
No. treatment sessions		
Level of therapist training		
Integrity of the intervention checked?		
Primary and secondary Outcomes		
Primary Outcomes: Frequency of attacks, duration of attacks, severity of attacks,pain, patient assessment of disability,adverse eventsand withdrawal		
Secondary Outcomes: Physician global assessment of severity**,** Patient global assessment of disability, change in digital ulceration, treatment preference, general improvement, anxiety and depression**.**		
Comments:		

2.5 Participants

The participants in included RCTs should meet the inclusion criteria which are; primary and secondary Raynaud's disease; age range between ≥18 and ≤60 years; both males and females; and exclusion criteria are; disabling conditions with cognitive dysfunctions, and infectious diseases. Mixed samples with PRD and SRD studies will be included.

2.6 Interventions

Medical acupuncture (Electrostimulation, or laser, or manual or its other types) alone and or integrated with other treatment interventions for the improvement of RD phenomenon (both PRD and SRD). The authors will also be interested in interventional studies consistent with NationalInstitute for Health and Care Excellence (NICE) guidelines directed for RP [24]; however, authors will include all

interventions combined with medical acupuncture which are designed to reasonably improvesymptoms of Raynaud's phenomenon.

2.7 Outcome measures

2.7.1 Primary Outcome

1. Pain intensity; usually assessed by10-point Visual Analogue Scale [VAS], Numerical Rating Scale, and McGill Pain Score.
2. Functional status; usually measured by Roland-Morris questionnaire and Oswestry Disability Index.
3. Global improvement assessment; usually assessed by the proportion of patients recovered.

Notably, RCTs usually use aforesaid scales in measuring pain, disability and global improvement but all RCTs may not use all above scales and, accordingly, data tabulation should address only those scales used in several selected RCTs, observational researches and other relevant selected studies.The primary outcome measures used in systematic reviews include mainly the Raynaud'sCondition Score (RCS) diary, Visual Analogue Scales, Likert Scales and the Scleroderma Health Assessment Questionnaire (HAQ) RP VAS, which assess RP severity, daily or weekly frequency of RP attacks with their duration over 1–2 weeks, and pain intensity and disability. The admission to hospital or death and withdrawal from study should be included as part of primary outcomes.

2.7.2 Secondary Outcomes

1. Health related quality of life usually assessed using SF-36 and EuroQol.
2. Return to work by means of number of days to return to work or proportion of patients at work.
3. Physician global assessment of severity or impact of RP that would reflect patient global assessment.

Data tabulation and graphs will take into consideration only data from scales used in several selected RCTs and other included studies.

Accurate measurement of outcomes of any intervention in a particular disease is highly desirable mission. According to Gladue and colleagues, no consensus exists

regarding the domains of measurement or measurement tools [25]. However, assessment of RP is largely contingent on patient-reported outcomes, typically captured using instruments that monitor RP symptoms over 1–2 weeks [26].

Secondary outcomes will include physician global assessment of severity or impact of RP; patient global assessment of function or disability secondary to RP, the HAQ Score; change in digital ulceration (positive/negative); treatment preference and general improvement (self-reportedoverall improvement). Outcome data on anxietyand depression will also be collected where available. Sensitivity analyses shall be undertaken if the analysesinclude trials with marked differences in duration of treatment or assessment [3,10]. Researchers should also describe the assessor qualification, relevant assessment experience, and years in clinicalpractice, and identified methods used to enhance the quality of assessment reflecting multiple repeated observations, and training of assessors including concerning reference management. Of note, RCT outcomes reflect most importantly the efficacy and safety of the interventions. Concerning TCM, theoutcome variables can be categorized into Western Medicine-specific and TCM-specific [27], the former is measured by objective biomedical markers or standard subjective measures, while the latter is frequently evaluated by observed changes in the degree and nature of a disease pattern.The outcome of pattern trials should be fully described including the evaluation methods and rationale.

We will now describe briefly the common tools used in pain conditions including RP concerning RCTs, which certainly layout concrete informative foundation for systematic reviews and meta-analysis. Research wisdom suggests that investigators just cite source of measurement tools without their succinct description, and therefore, a shortaccount will enhance the knowledge of prospective researchers interested in using these tools in RCTs, systematic reviews and meta-analysis. Overall, a great knowledge of these measurement tools that not only assess the pain but also severity, frequency, disability, and quality in various diseases with pain is highly relevant.

2.8 Brief Description of Measurement Tools

2.8.1 Visual Analogue Scale

Visual analogue scale (s) is a unidimensional psychometric validated measurement tool. VAS documents the characteristics of severity of symptoms in individual patients with a specific disease such as Raynaud's phenomenon. VAS helps in rapid categorization of symptom severity and disease control and improvement, which is statistically measurable and reproducible. Other uses of VAS are reported in taking routine patient history, monitoring ofchronic disease course and assessingintervention effectiveness in chronic intermittent diseases such as RP in real life and real time through smartphones App. A detailed description including historical development, progress and advantages and disadvantages of several visual analogue scales is available here [28,29].

2.8.2 Numerical Rating Scale

The Numeric Rating Scale (NRS-11) a subjective validated scale is used in children (≥6-≥8 years), adolescents and adults to assess acute and chronic pain intensity and improvement in any disease with pain and disabilty [29-31]. NRS has 0 on the left extreme end and 10 on the right extreme end and each point on the scale represents 10 (11point scale; 0 to 100 score). Of note, 0 represents no pain and 10x10 (100) represents 'worst pain imaginable'. A score of 15 (1.5 x 10) indicates the minimal clinical improvement difference for NRS score regarding Raynaud's diseaseor any other condition with pain.Notably, the 0 to 10 NRS-11 is among the most commonly used measurement tool in five acute conditions mainly surgery, broken bones, dental work, burns or cuts and labor and child birth and more than 130 chronic pain disorders listed by American Chronic Pain Association [32].

2.8.3McGill Pain Questionnaire (MPQ)

MPQ is a multidimensional pain questionnaire designed to measure the sensory, affective and evaluative aspects of pain and pain intensity in adults with chronic pain. The scale contains 4 subscales evaluating the sensory, affective and evaluative, and miscellaneous aspects of pain, responses to which comprise the Pain Rating Index (PRI), and a 5-point pain intensity scale (Present Pain Intensity, PPI). Besides evaluation of the efficacy and effectiveness of pain interventions herein medical acupuncture concerning various nocioceptive, inflammatory and neuropathic pain

disorders, PPI is used to assess overall magnitude of pain intensity as each question has six answer choices from 0 to 5. These 0 to 6 levels of pain correspond tono pain (0), mild pain (1), discomforting (2), distressing (3), horrible (4), and excruciating (5). Of note, 30% improvement is considered the minimally clinically important differences (MCIDs) for PPI score [28,29]. A shorter version of the MPQ, the SF-MPQ, is also a multidimensional measure of perceived pain in adultswith chronic painapplied to many medical conditions. It is comprised of 15 words;11sensory and 4 affective from the original MPQ. The PRI is comprised of2 subscales: 1) sensory subscale with 11 words or itemsand 2) affective subscale with 4 words or items, which arerated on an intensity scale as 0=none, 1=mild, 2=moderate or 3-severe. The SF-MPQ also includes 1 itemeach for present pain intensity (PPI) and a 10-cm visualanalog scale (VAS) for average pain. Recall time for items is present time. SF-MPQ tends to discriminate among different pain syndromes and evaluate the responsiveness ofdifferent symptoms to treatment interventions [28,29].

2.8.4 The Roland-Morris Questionnaire (RMQ)

The RMQ is a self-administered disability measurement tool that indicates greater levels of disability by higher numbers on a 24-point scale. The RMQ has been shown to yield reliable measurements, which are valid for inferring the level of disability, and to be sensitive to change over time for groups of patients with low back pain and also other pain conditions including RD.The patient is instructed to put a mark next to each appropriate statement. Researcher need to add up the total number of marked statements to get a patient's score. One problem is that RMQ did not provide descriptions of the varying degrees of disability, such as 40%-60% informs severe disability. Clinical improvement over time can be graded based on the analysis of serial questionnaire scores. If, for example, at the beginning of treatment, a patient's score was 12 and, at the conclusion of intervention, the score was 2 so 10 points of improvement means 83% (10/12 x 100) improvement [33].

2.8.5 The Oswestry Disability Questionnaire (ODQ)

The ODQ, an extremely important tool that researchers and disability evaluators use to measure a patient's permanent functional disability [34], is considered the 'gold

standard' tool for measuring low back pain but could be used in secondary RD associated with physical disability. The ODQconsists of 10 questions that target common daily activities. Each question needs to be answered by one of the six given choices, i.e., 0 to 5 whereas 0 means ''no restriction in daily activities,'' and 5 informs ''the most restrictions indaily activities or bed-bound''. The maximum possible score is 50 and 0% to 20% is considered minimal disability while 81% to 100% indicates patient being bed-bound or psychologically exaggerating the symptoms. Ten percent improvement is considered as the MCIDs concerning Oswestry Disability Questionnaire [34].

2.8.6 Short Form-36 (SF-36)

The short form 36 questionnaire developed by RAND as part of Medical Outcome Study consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower score reflects more disability. Conversely, the higher score indicates less disability. For example, a score of zero reflects maximum disability whereas a score of 100 means no disability. The eight sections concern vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Another version of SF-36 is SF-12. Software programs are available to calculate the final score [35].

2.8.7 EuroQol- 5 Dimension

The EuroQol-5 Dimension (EQ-5D) is useful for those researchers working in Complementary and Alternative Medicine (CAM), rehabilitation and physiotherapy and pain centers. EQ-5D, a measurement tool developed in Europe, evaluates the generic quality of life and widely used across the world. The EQ-5D measures preference-based health related quality life (HRQL) with one question for each of the five dimensions including mobility, self-care, usual activities, pain-discomfort, and anxiety-depression. The answers given to EQ-5D permit to find 243 unique health states or can be converted into EQ-5D index, which is an utility scores anchored at 0 for death and 1 for perfect health. The EQ-5D questionnaire also includes a Visual

Analog Scale (VAS), by which respondents can report their perceived health status with a grade ranging from 0 means the worst health status to 100 means the best health status [36].All the details of historical development, interpretations, explanations and scoring system of all the above assessment toolsand others concerning adult pain are available here [28,29]. In sum, these pain measurement scales are specifically used in RCTs for the assessment of pain in various medical conditions including RD phenomenon across the world, and RCTs are the most relevant source of information for conducting quantitative systematic reviews and meta-analysis.

2.9 Data Extraction and Management

A data collection form designed after reviewing pertinent literature especially aforesaid main sources of information [6,18,20,21,37-39] will be used for study characteristics, patient population and outcome information. The data extraction form will feature a brief eligibility check box with core inclusion criteria: adults with RP; intervention by acupuncture with at least one or more comparator or integrated intervention; RCT; Raynaud's Condition Score or equivalent or VAS. All criteria need to be present in order to demonstrate eligibility. Two authors will extract study characteristics from all the included full RCTs and other important researches in the following ways:

2.9.1Methods: study design, total duration of study, study setting/country,study language, date of the study publication with all authors'names and references, retrieval informationincluding date and name of database (s).

2.9.2 Participants: sample size and description, mean age, gender, diagnosis of PRD and SRD, other co-morbid diseases, diagnostic criteria used for RP, and inclusion and exclusion criteria.

2.9.3 Interventions: Types and format of interventions - acupuncture and other treatments including general treatments and rescue intervention meeting the ethical requirementsand number of courses with sessions, and comparators including active and placebocontrols [3,10](Box 1& 2). In a systematic review, Chen et al (2016) reported that the type of control is likely to affect the conclusion in

acupuncture analgesic trials, and, therefore, appropriate control should be chosen that meets the aims of studies [40]. Furthermore, design of acupuncture RCT impact the outcome when sham acupuncture with classical or modern needles is used [41]. Of course, all these technicalities affect the treatment effects generated by systematic review and meta-analysis concerning acupuncture in RP.

Box 1. Description of items for Acupuncture as active intervention, adapted from references

Acupuncture
1. Treatment environment and participant posture.
2. Number of needle insertions per subject per session- mean and range if possible.
3. Names and location of acupoints- unilateral or bilateral. Name ofall the acupoints should be presented in Chinese (Pinyin) andinternational code.
4. Angle and depth of insertion, which should be presented in a specified unit of measurement or on a particular tissue level.
5. Response sought- de qi or muscle twitch response.
6. Needle stimulation- manual or electrical (ectroacupuncture apparatus) will be utilized; the brand,manufacturer and frequency should be indicated.
7. Needle retention time.
8. Needle type, including diameter, length, manufacturer, and material.
9. Number of treatment sessions.
10. Frequency and duration of treatment sessions

Box 2. Descriptive items for control(inactive) intervention of Acupuncture, adapted from references

Acupuncture (Active) VS. Blank/ Waitlist Control
Describe any special arrangements in pre-treatment, treatment and post-treatment periods corresponding to the experimental intervention: 1.Examinations in pre-treatment period, 2.Unaltered lifestyle and medication in treatment period, and 3. Compensatory interventions in post-treatment period
Acupuncture (Active) VS. Sham Acupuncture or Acupuncture-Like Control
Describe the comparability of the sham acupuncture or acupuncture-like control and comprehensively provide details as for the recommendations of acupuncture Intervention

2.9.4 Outcomes: primary and secondary endpoints including frequency, duration, pain and severity of RP attacks, outcome/results, comments, and adverse events including hospitalization, ulceration, disability and amputation.Authors will attemptto retrieve missing outcome measurement data with study authors.

2.9.5Notes: Sources of funding or sponsorship for RCTs and declaration of conflicts of interest of all authors on each included RCT will be recorded in the protocol. This is necessary because funded agencies and sponsor have many times hidden agendas which bias the results of RCTs, weaker positive results undershadow negative results.

2.9.6 Risk of Bias and Data Extraction

Two researchers need to extract independently outcome data from the included studies. Both authors should resolve any discrepancies with the help of a third reviewer. One expert experienced researcher should transfer data into the Review Manager 5.3 software (RevMan 2014) [37] for analysis purpose. One author will crosscheck study characteristics for accuracy against the randomized controlled trial report.

2.9.7 Assessment of Risk of Bias

Two coauthors will independently assess risk of bias for each included study using the criteria outlined in the Cochrane Hand Book for Systematic Reviews of Interventions [38].Third reviewer will be consulted for resolving any discrepancy. We will grade each potential source of bias as high, low or unclear, and will provide a quote from the study report together with a justification for our judgment in the "Risk of bias Table". We will assess the risk of bias according to the following domains.

2.9.7.1. Random sequence generation;adequate description and methodof participant allocation in accordance with standard randomization for preventing selection bias.

2.9.7.2 Allocation concealment; adequate concealment of group assignment to prevent selection bias.

2.9.7.3 Blinding of participants and personnel; blinding of participants and personnel reflecting adequacy of measures taken to prevent performance bias and the concealment of group assignment.

2.9.7.4 Blinding outcome assessors; adequacy of measures taken to prevent detection of bias and conceal group assignment to outcome assessors.

2.9.7.5 Incomplete outcome data; adequacy of the management of missing data and potential implications for attrition bias.

2.9.7.6 Selective outcome reporting (reporting bias); reporting bias relating to the consistency between prespecified and reported outcomes.

2.9.7.7 Other sources of bias; other concerns not covered but may lead to a risk of bias[10]. Finally, Funnel plot will be used to assess bias and will be stratified based on bias assessment, if considered useful and appropriate provided included studies are more than 10. Evidently, funnel plot is used to assess whether or not systematic review is likely to be vulnerable to publication bias. Funnel plot takes into account treatment effect which is the mean difference between intervention group and controlagainst the inverse of the variance (I variance) or the sample size. A systematic review that exhibits the Funnel shape (Figure 2) would be assumed not to be showing evidence of publication bias. It would be consistent with studies based on small samples showing more variability in outcome than studies based on large samples. However, the points (blobs) as filled in black dots were not present, the plot would be asymmetric and it would suggest the presence of publication bias and, hence, the results of the systematic review must be treated with caution [42].

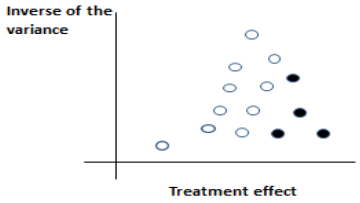


Figure 2: An example of funnel plot adapted from reference

2.9.8 Assessment of Quality of Evidence

The authors will assess the quality of evidence of the primary outcomes using Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [39,43]. Often the components of quality evidence assessed are as follows; (in) consistency of effect, imprecision, indirectness and publication bias [39]. If possible we will construct a Tableof findings based on GRADE specifically using the seven primary outcomes of RP. Where possible, we will express dichotomous

outcomes, e.g. no less than mild pain defined as <30 on a 100-point scale, [44] or 50% reduction in the number of episodes, or minimally clinically important differences (MCIDs) [45]. The results will be presented in a Table format summarizing findings of all included studies. Authors should also assess for quality of each intervention, and further compare theoretical and pragmatic interventions concerning Raynaud's phenomenon [10].

2.9.9 Measures of Treatment Effect

The measurement of intervention effect informs the efficacy of an active treatment compared to other active or passive controls. Currently, Review Manager 5 and Endnote and Covidence software are used to manage the data, references and conduct the data analyses [46,47]. Authors will report dichotomous outcomes as risk ratios (RRs) with 95% confidence interval (95% CI), pooling those data with identical outcomes and interventions. For continuous outcomes, researchers will calculate mean difference/differences in mean with 95% CI when the studies used the same scale for collecting continuous data. Standardized mean difference (SMD) and 95% CI will be used when discrepant scales were used in included studies. The Cochrane handbook needs to be used for translation of outcomes of scales [10].

2.9.10 Unit of Analysis Issue

Sometimes RCTs may have more than two intervention groups in multi-arm studies, and in that case authors will include only direct relevant arm (s).

2.9.11 Dealing with Missing Data

Researchers will need to contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where it is possible.

2.9.12Dealing with heterogeneity

In meta-analysis, investigators will use the I^2 statistic to measure heterogeneity in included RCTs. The I^2 statistic describes the percentage of variation across RCTs attributed to heterogeneity rather than chance [10]. However, this statistics could be biased in small meta-analysis with fewer studies, less than 7 RCTs [48]. However, inclusion of confidence intervals supplements or replaces the biased point estimate I^2.

Notably, heterogeneity is assessed on the basis of design of the study, number of participants, interventions and outcomes, using forest plot choosing 10% level. Higgins I^2 statistic, X^2 and visual inspection of forest plot will be used to assess homogeneity with thresholds of 50%-75% for moderate heterogeneity and 75% for significant heterogeneity. We anticipate the use of random-effects meta-analysis in case of heterogeneity related to participant and the outcome data; however fixed models will be used where appropriate as suggested by Daniel and associates [10].

The most common method for presenting quantitative results is a forest plot (Figure 3). A forest plot presents the means and variance for the difference for each study. The line represents the standard error of the difference, the box represents the mean difference and its size is proportional to the number of subjects in the study. A forest plot may also be interpreted with the numerical information concerning the number of subjects in each group, the mean difference and the confidence interval on the mean. If a formal meta-analysis is undertaken, the bottom entry in a forest plot will be the summary estimate of the treatment difference and confidence interval for the summary difference. Figure 3 represents the ideal result of a quantitative summary, the results of the studies basically agree. There is clearly a genuine treatment effect and a single overall summary statistics would be a good estimate of that effect. If effects were very different from study to study, our results would suggest heterogeneity. A single overall summary statistics would probably be of little value. The systematic review should continue with an investigation of the reasons for heterogeneity. To avoid the problems of post-hoc analysis, researchers should identify possible sources of heterogeneity when they construct the review protocol.

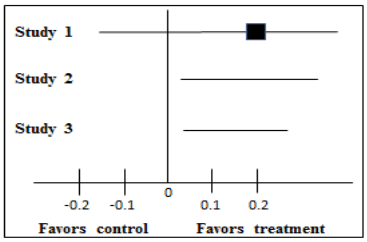


Figure 3: An example of forest plot adapted from reference

In the absence of a meta-analysis, a narrative (descriptive) analysis of primary and secondary outcomes willbe provided that will include: aggregated data onmean daily frequency, severity, and duration of episodes, patient global assessment of disability and changes in RCS; analysis of reported design or intervention flaws in acupuncture change interventions; and analysis of study reported outcomes and/or limitations. This is for the purpose of informing future researchers to overcome identified caveats concerning acupuncture intervention for Raynaud's phenomenon. Due to a lack of consensus over reliable measurement endpoints in RP treatment trials, we will specify MCIDs measures to allow clinically meaningful interpretation of change on standardized measures, more specifically a 15-point difference on RCS, 20% difference on VAS and Likert Scales based upon previous estimates in RP and Reliable Change Index for other standardized measures [25,49].

2.9.13 Subgroup Analysis

Two subgroup analyses are planned based on specific clinical hypotheses. First, we will analyse outcomes by diagnosis; studies will be divided into primary and secondary RP. Studies which combine both primary and secondary RP will only separate into two subgroups ifdata are available to do so. Evidence suggests that primary and secondary RP may have different underlying pathogeneses, with studies reporting clear differences in onset, course and prognosis between the groups [50]. Second, we will analyse outcomes based on the presence or absence of identified psychological model of behavior change, and comparing theoretically informed interventions with pragmatic interventions [10]. Interventions that are empirically supported and evidence-based are more likely to be efficacious than their counterparts, therefore subdivision will allow us to identify whether there is a discrepancy or a more meaningful interpretation of findings. Analysis of subgroups will include the aforementioned test of homogeneity to assess potential group effects

and findings will be interpreted accordingly and further analysis will be performed where appropriate.

For meta-analysis purpose, authors will summarize and analyze all eligible studies in Review Manager 5 [37]. We will use same methods of data extraction, data entry, crosscheck all entries and discrepancies will be resolved by two authors with the help of third reviewer. We will undertake meta-analyses only where this is meaningful and RCTs or other studies including observational are more than 7 in a systematic review. Unlike fixed effects model meta-analysis, authors will combine the data using a random-effects model which allows for differences in the treatment effect from study to study in order to give only the average effect across all studies as also mentioned up [51].

4. RESULTS

The collected data from various RCTs and other studies such as observational will be analyzed using various statistical tests and software programs such as review manager. The results will be described concisely in the text complemented by Tables and figures of forest and funnel plot.

5. DISCUSSION

We will focus on and provide the detailed interpretation of results extracted from selected RCTs and will compare with previous systematic reviews published on Raynaud's disease across the world. We will primarily restrict our discussion to randomized controlled trials only but studies of potential interest will be included for the interpretations of results. Furthermore, we will discuss efficacy of high quality interventions such as RCTs using medical acupuncture and utilize the primary and secondary outcomes of this systematic review and meta-analysis to inform researchers to conduct further high-quality interventions for Raynaud’s phenomenon, a under researched condition among women. However, we also intend to discuss noteworthy findings of non-randomized intervention trials or observational studies or non-systematic reviews, as these studies will complement discussion concerning RCTs.

Another reason is that RCTs related to medical acupuncture in RP are very limited and of poor quality.

With special reference to the SPIRIT 2013 Statement, which was developed based on evidence from systematic reviews, international guidelines, and a Delphi consensus process serves as an important tool for investigators in developing high-quality protocols for interventional clinical trials. The unique characteristics of TCM, both in diagnosis according to pattern and treatment using medical acupuncture (and moxibustion and TCM herbs), however, call for special consideration in terms of the SPIRIT-TCM Extension items' utility in TCM RCT protocol development. This initiative with a precise checklist with comparative interpretation involving SPIRIT 13 statement and its latest versions [52,53] would guide TCM researchers in designing sophisticated RCTs protocols linked with CAM interventions for ensuring high quality results in RP or other diseases with pain. Notably, consistency between RCT protocol and final reporting is one of the concerns about the quality of clinical studies. In conclusion, the SPIRIT-TCM Extension 2018 was developed through a rigorous systematic process. Its items encompass 3 major interventions: Chinese Herbal Medicine formulae, acupuncture and moxibustion in diverse diseases. This comprehensive SPIRIT-Extension is expected not only to help investigators develop high quality RCT trial protocols in general, but will also specifically improve the quality of clinical trials of TCM, and by extension the results of systematic reviews and meta-analysis. As a consequence, efficacy of medical acupuncture in RP would be well defined and systematic reviews and meta-analysis will produce better treatment effects in Raynaud’s phenomenon.

Conclusion

The systematic review and meta-analysis protocol development directed towards CAM therapies in RP or other painful conditions using several guidelines, checklists, interpretations and advantages and disadvantages related to SPIRIT Statements, and PRISMA and their versions and extensions is a wise step to produce evidence-based results that will be derived from RCTs developed and conductedutilizing aforesaid advanced guidelines.

Ethics Consideration

This protocol complies with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines including TCM SPIRIT statement and their extension. This protocol will be submitted in a peer-reviewed journal for publication and reported according to PRISMA. The synopsis and protocol for the proposed systematic review and meta-analysis will be registered with the International Prospective Register of Systematic Reviews and registration number will be recorded herewith. If this protocol is submitted for research funding or supported by a sponsor, it will require ethical approval from the ethical committee of the research setting.

Publication

This protocol for systematic review and meta-analysis concerning Raynaud's phenomenon manage by medical acupuncture will be submitted to a decided journal by team members**.**

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