

Efficacy of acupuncture in improving the symptoms and the quality of life of patients with moderate or severe acne vulgaris: a protocol for a randomized controlled trial

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Study protocol

Keywords: acupuncture, acne vulgaris, quality of life, randomized-controlled trial, protocol.

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Abstract

Background : Acne vulgaris (AV) is a common chronic dermatologic disease that tends to impair the appearance and the quality of life (QoL) of patients. Although several trials have indicated the effectiveness of acupuncture for treatment of patients with AV, the results of these trials have been contested owing to potential bias in their design. Thus, there is a lack of robust data to evaluate the efficacy of acupuncture in patients with AV. In addition, none of the previous clinical trials of acupuncture therapy for AV used QoL as a primary outcome or employed a sham acupuncture control arm. The aim of the study is to evaluate the effect of acupuncture on the symptoms and the QoL of patients with moderate or severe AV. **Methods/design:** One hundred eligible participants with AV will be randomly assigned to acupuncture or sham acupuncture groups (1:1 allocation). All participants will receive 4-week treatment comprising of a total of 12 sessions (3 sessions per week). The primary outcome will be change from baseline in the Skindex-16 scale total score at treatment completion. The secondary outcomes will be: Skindex-16 subscale score; the Dermatology Life Quality Index scale total score; the total lesion count and inflammatory lesion count; visual analogue scale scores for assessment of itch and pain; patient expectations of acupuncture; and the blinding of the effect of sham acupuncture. Follow-up evaluation will be performed at weeks 16 and 28. All outcome analyses will be performed in the intention-to-treat population. **Discussion:** We expect to evaluate the effectiveness of acupuncture in ameliorating the symptoms and improving the QoL of patients with moderate or severe AV compared with sham acupuncture with more robust evidence. The limitations of the trial design are its single center scope, relatively small sample size, and lack of blinding of the acupuncturists. **Trial Registration:** Chinese Clinical Trial Registry, ChiCTR-1900023649 (Date of registration: Jan 2, 2019). **Keywords:** acupuncture, acne vulgaris, quality of life, randomized-controlled trial, protocol.

Background

Acne vulgaris (AV) is a common chronic dermatologic disease involving pilosebaceous units^[1,2]. Skin lesions are the main symptoms of AV, which typically appear over the face, chest, and back^[1,3]. An estimated 79–95% of adolescent population is affected by AV^[4]. The skin lesions include comedones, erythematous papules, pustules, nodules, deep pustules, and scarring. The occurrence of AV lesions on face may induce anxiety and lower the self-esteem^[5,6], thus leading to a decline in the quality of life (QoL)^[5-8].

The American Society of Dermatology recommends benzoyl peroxide, topical retinoids, or systemic antibiotic therapy as the first-line treatment for mild to severe AV^[1-3]. However, these pharmaceutical therapies may cause side effects of drying, peeling, erythema, skin irritation; in addition, prolonged treatment may result in drug resistance and the associated recurrence rate is relatively high^[9]. Therefore, there is an increasing interest in exploring natural and safer therapies for AV^[9,10]. These natural and safer treatment options include complementary and alternative treatment remedies, such as herbal medicine and acupuncture^[9,10].

Several trials have indicated that acupuncture may alleviate the skin lesions and improve the QoL of patients with AV [11-15]. However, these trials were affected by potential bias due to the small sample sizes, non-placebo/sham/waiting list control, or use of self-defined outcome measures; thus, these trials did not provide robust evidence of the efficacy of acupuncture in AV patients. Therefore, we conducted a pilot trial (unpublished) from April 2017 to March 2018 in which 42 patients with moderate or severe AV were randomly allocated to acupuncture group (n=21) or sham acupuncture (n=21) group. After 4-week treatment, the reduction in the number of skin lesions in the acupuncture and sham acupuncture groups was -6.62 ± 15.42 and -15.10 ± 20.13 , respectively, with no significant between-group difference ($P=0.137$). These findings contradict the results of previous trials [11-14]. On the contrary, after 4-week treatment, the reduction in the Skindex-16 scale total score in the acupuncture and sham acupuncture groups was -12.50 ± 19.09 (32.39 ± 21.36 at baseline and 19.89 ± 15.40 after treatment) and 0.40 ± 21.12 (30.03 ± 20.78 at baseline and 30.43 ± 19.39 after treatment); there was a significant between-group difference in this respect ($P=0.044$). The Skindex-16 scale is a sensitive and specific tool for assessing the symptoms and the QoL of patients with AV; it includes 7 questions related to the symptoms (itch or pain) and characteristics (lesions) of AV [16, 17]. The results of our pilot study indicated that acupuncture may help relieve the symptoms and improve the QoL of patients with moderate or severe AV. Several recent randomized controlled trials have used the Skindex-16 scale score as an outcome measure to evaluate the effect of drugs (such as isotretinoin and/or antibiotics) in relieving symptoms and improving the QoL of patients with AV [18, 19]. Therefore, we intend to use the Skindex-16 scale score as a primary outcome measure in our planned study to evaluate the effect of acupuncture on the symptoms and the QoL of patients with moderate or severe AV, compared with sham acupuncture.

Methods/design

Study design

The proposed study is a prospective, randomized, sham acupuncture controlled trial with two parallel arms using a 1:1 allocation ratio. The trial will be conducted at the Guang'anmen Hospital, China Academy of Chinese Medical Sciences. The study protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [20] and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [21].

Study recruitment

Participants will be recruited between August 2019 and August 2020 at the Guang'anmen Hospital via advertisements on posters, Wechat, and hospital websites. A dermatologist will be responsible for the screening which will include diagnosis of the type of acne of patients and a series of physical examinations (discrimination between inflammatory and non-inflammatory lesions of AV by the face pictures obtained using a digital camera) according to the diagnostic criteria for AV [22, 23] and the classification of lesions of AV [24], respectively.

All participants will be asked to read the informed consent form that describes the trial, randomization process for treatments, and the potential benefits and risks of this trial by a research assistant. Participants will be informed that both acupuncture and sham acupuncture may be effective for AV and they will be randomly assigned to the acupuncture group or sham acupuncture group. Participants will be allowed to withdraw from the trial at any time. Written informed consent will be obtained from all subjects prior to their enrolment.

The demographic and clinical characteristics of the participants at baseline will be recorded by a research assistant: age; gender; race; BMI (kg/m²); marital status; educational level (primary education or below, secondary education, and tertiary education); working duration (<8 hours, 8–12 hours, and >12 hours); duration of sports activities (<7 hours; 7–9 hours; and >9 hours); sleep duration (0-3 times/ month, 1-2 times/week, 3-4 times/week, and ≥ 5 times/week); smoking history; history of alcohol intake; AV duration in months; severity of AV as assessed by global acne grading system (GAGS) score [none (0 score), mild (1-18 score), moderate (19-30 score), severe (31-38 score), and markedly severe (> 39 score)] [25].

Randomization and allocation concealment

The randomization scheme has been prepared by the National Clinical Drug Testing Institute of the Guang'anmen Hospital. Participants will be randomly assigned to receive acupuncture or sham acupuncture treatment in a 1:1 ratio with the fixed block of four. Sealed opaque envelope will be used to ensure randomization concealment. The number of randomization sequence and information of group allocation will be sealed in ordered envelopes. With the inclusion of patients, those envelopes will be opened one by one in sequence. The envelopes will be kept by a researcher assistant who is not involved in the treatment or assessment. Additionally, assistant researchers will perform a baseline assessment of all participants (-1 week to 0 week) prior to randomization.

Blinding

The participants, outcome assessors, and statisticians will be blinded to the group allocation. However, because of the characteristics of acupuncture, acupuncturists will not be blinded in this trial. To assess the blinding effect of sham acupuncture, participants will be asked to answer the following questions within 5 minutes after any treatment in week 4: "Do you think you have received traditional acupuncture?" The response options will be "Yes," "No," or "Unclear.". The study protocol is illustrated in Figure 1.

Ethical approval

This clinical trial will adhere to the principles of the Declaration of Helsinki and has been approved by the Ethics Committee of the Guang'anmen Hospital (2018-137-KY-01) (See Additional file 1).

Participants

One hundred eligible participants with AV will be recruited in the trial.

Inclusion criteria

1. Individuals aged between 18 and 48 years who qualify the diagnostic criteria for AV [22, 23];
2. GAGS score between 19 and 38 [25].

Exclusion criteria

Participants with any of the following conditions will be excluded:

1. Individuals with polymerization acne, explosive acne, drug acne, premenstrual acne, cosmetic acne, occupational acne, or any other subtypes of acne;
2. Individuals with other severe diseases that may affect the acne, such as polycystic ovary syndrome, thyroid disease, or atypical congenital adrenal hyperplasia;
3. Individuals with other skin diseases that may influence the assessment of AV, such as rosacea, folliculitis, or other skin diseases;
4. Individuals who have received antibiotics, retinoic acid, steroids, or anti-inflammatory drugs in the preceding one month;
5. Individuals with severe heart, liver, kidney, hematopoietic system or autoimmune disorders, or severe systemic malnutrition;
6. Pregnant and lactating women or those planning to conceive within 12 months;
7. Individuals who have received acupuncture treatment in the past 3 months.

Intervention

All participants will receive treatment for 4 weeks with 3 sessions per week (ideally every other day), for a total of 12 sessions. Acupuncturists with undergraduate degree or above and clinical experience of over 1 year at the Guang'anmen Hospital will be responsible for treatment. Participants will be treated separately to avoid communication during the trial period. We will discourage all included participants to receive any other treatment for AV during the study period. If participants received any other treatment for AV, they will also be included in this study and all details of the other treatment for AV will be recorded in the case report form. We will compare the proportion of participants using other treatments between the two groups.

Acupuncture group

The locations of acupoints is described as per 'the Nomenclature and Location of Acupuncture Points (National Standard of People's Republic of China, 2006 [GB/T 12346-2006])' [26]. The selections of acupoints will be decided with reference to the 'Guidelines for AV treatment in China' (revised version 2014) [27]. Participants in the acupuncture group will receive stimulation at Dazhui (CV14), bilateral Quchi (LI11), bilateral Hegu (LI4), bilateral Zusanli (ST36), and bilateral Neiting (ST44) with disposable acupuncture needles (0.30×40 mm, Huatuo Brand, Suzhou Medical Appliance, China). After routine

disinfection, acupuncture needles will be inserted obliquely into CV14 to a depth of 30–40 mm at an angle of 15°–30°; acupuncture needles will be vertically inserted into bilateral LI11, bilateral LI4, bilateral ST36, and bilateral ST44 to a depth of 25–30 mm for 3 times (once every 10 minutes) with slight lifting, thrusting, and twisting manipulations to produce a sensation of de-qi. Each session of acupuncture will last for 30 minutes.

Sham acupuncture group

Participants in sham acupuncture group will receive sham acupuncture at sham CV14 (10 mm to CV14), LI11 (10 mm to LI11), LI4 (10 mm to LI4), ST36 (25 mm to ST36) and ST44 (10 mm to ST44) with disposable acupuncture needles (0.30×25 mm, Huatuo Brand, Suzhou Medical Appliance, China). Sham CV14, LI11, LI4, ST36, ST44 will be vertically inserted to a depth of 1–2 mm without any manipulation and de-qi. The treatment sessions will last for 30 minutes.

Participants will not be allowed use of other treatments for AV throughout the trial. Detailed information pertaining to use of other treatments will be recorded in the case report form.

Rescue medication

Participants will not be encouraged to receive any other treatment or medication during the study period to prevent any influence on the results. However, in case of deterioration of the condition of AV during the 4-week treatment period and the 24-week follow-up, oral minocycline hydrochloride capsules will be prescribed to the patients (100 mg per day for 7 days) to relieve the symptoms of pain or itching. Details of the medication used will be recorded in the case report form. The proportion of participants using rescue drugs in the groups will be compared.

Outcome measures

The primary outcome will be the change in the total score of Skindex-16 scale from baseline at the end of 4-week treatment. The Skindex-16 scale is a brief, skin-related, quality-of-life scale with satisfactory reliability and validity. It is used to evaluate the efficacy of acupuncture in improving the QoL of patients with AV [24, 25]. The scale includes a total of 16 items which are categorized into three domains: the symptoms of participants with AV, the emotions of participants with AV, and function of participants with AV [16, 17]. The Skindex-16 scale score ranges from 0 (best) to 100 (worst) with the minimal clinically important difference (MCID) as 10 [16, 17].

Secondary outcomes include:

1. The change from baseline in the Skindex-16 scale total score at weeks 16 and 28;
2. The change from baseline in the Skindex-16 subscale (the symptoms of participants with AV, the emotions of participants with AV, and functioning of participants with AV) scores at weeks 4, 16, and 28;

3. The change from baseline in the Dermatology Life Quality Index (DLQI) ^[28] scale total score at weeks 16 and 28. DLQI scale is a tool to assess the health-related QoL of patients with skin diseases. It has a total of 10 items. The total score of DLQI ranges from 0 (best) to 100 (worst) with 10 as the MCID ^[29].
4. The change from baseline in the total lesion (inflammatory and non-inflammatory lesions) counts (TLC) ^[30,31] at weeks 4, 16 and 28;
5. The change from baseline in the inflammatory lesions counts (ILC) ^[32] at weeks 4, 16 and 28. The inflammatory lesions include the inflammatory papules, pustules, and cysts. The non-inflammatory lesions include the black and white head comedones. The lesions are assessed on the forehead, cheeks, nose, and chin. The inflammatory and non-inflammatory lesions are counted from the face pictures obtained using a digital camera by a dermatologist.
6. The change from baseline in the degree of itch assessed by visual analogue scale (IVAS) ^[31] at weeks 4, 16 and 28;
7. The change from baseline in the severity of pain assessed by visual analogue scale (PVAS) ^[33] at weeks 4, 16 and 28;
8. The participants' expectations of acupuncture will be assessed at baseline using the following 2 questions: "Do you think acupuncture will be effective for treating the illness?" and "Do you think acupuncture will be effective for relieving the related symptoms of AV?" The response options will be "Yes," "No," or "Unclear."

The details of the evaluation of outcomes are shown in Table 1.

Safety evaluation

Adverse events (AE) including AEs related to acupuncture (broken needle, local hematoma, infection, abscess, and others), AEs related to post-acupuncture (nausea, vomiting, palpitations, dizziness, headache, insomnia, or any other symptoms after acupuncture treatment), and AEs unrelated to treatment. For safety assessment, details of all AEs will be recorded in the case report form by a research assistant. Any serious adverse events (SAEs) will be reported to the Ethics Approval Committee of the Guang'anmen Hospital of China Academy of Chinese Medical Sciences within 24 hours. The department of Acupuncture of the Guang'anmen Hospital of China will provide insurance coverage to compensate for any injuries related to the interventions during this study.

Sample size and statistical analysis

The sample size of this trial was calculated based on the primary outcome, which is the change from baseline in the Skindex-16 scale score at the end of week 4. In our unpublished pilot trial, the mean (\pm standard deviation) reduction in the Skindex-16 scale score after 4-week treatment in the acupuncture and sham acupuncture groups was -12.50 ± 19.09 and 0.40 ± 21.12 , respectively. Assuming an alpha risk

of 5% and a beta risk of 20%, a sample size of 100 (50 participants in each group) was calculated considering a 20% dropout rate.

The data will be analyzed using SPSS software V.20.0 (IBM SPSS Statistics; IBM Corp, Somers, NY) according to intention-to-treat principle. Normally distributed continuous variables will be reported as mean± standard deviation and 95% confidence intervals; non-normally distributed continuous variables will be reported as median (interquartile range). Categorical variables will be presented as frequency (%). For data pertaining to drop-outs, the actual observational value of the last observation will be used for statistical analysis. Between-group differences with respect to normally distributed continuous variables will be assessed using analysis of variance (ANOVA) and those with respect to non-normally distributed continuous variables will be assessed using the nonparametric tests for the primary outcome and the secondary outcomes. Data pertaining to the participants' expectations of acupuncture and the safety evaluation will be analyzed using the Chi-squared test or the Fisher exact test. For the blinding assessment, the percentage of participants choosing traditional acupuncture will be assessed using the Chi-squared test. All P values will be two-tailed; $P \leq 0.05$ will be considered indicative of statistical significance.

Quality control

All researchers will receive a training course before the beginning of this trial. Due measures will be implemented to ensure the traceability and confidentiality of the case report form, informed consent form, and other original data. Double input method will be used for data entry. AEs will be recorded in detail, properly handled, and tracked. All trial-related procedures and data management will be supervised. The Data Monitoring Committee of the Guang'anmen Hospital will regularly monitor the recruitment and screening of participants, data collection, monitoring and verification of AEs to ensure that the study is conducted in accordance with the approved protocol.

Discussion

AV is a common chronic inflammatory dermatologic disease. It may affect the physical and mental health of patients, and adversely affect their QoL [34]. According to an epidemiological study, approximately 20% of young people are affected by moderate-to-severe AV [35]. Several studies have demonstrated a correlation between the QoL and the severity of dermatologic disease [36, 37]. For this reason, this study will only include participants with moderate or severe AV.

The primary outcome of the study will be the Skindex-16 scale score. It is a validated and sensitive scale to measure the QoL of patients with dermatologic diseases [16, 17]. As lesions of AV mainly occur on the area of face and are accompanied by other symptoms of itch and pain [31, 33], patients tend to present with psychosocial symptoms and impaired QoL. The Skindex-16 scale consist of 16 questions in the symptoms, emotion, and function domains; responses to each question is scored on a seven-point Likert scale [17]. This scale includes 7 questions related to the symptoms (itch or pain) and characteristics

(lesions) of AV. It is a sensitive and specific tool to assess the symptoms and the QoL of patients with moderate or severe AV. Moreover, we also used the DLQI scale to evaluate the QoL. It is a brief, skin-related, quality-of-life scale with satisfactory reliability and validity; this was used to further evaluate the effectiveness of acupuncture in improving the QoL of patients with AV [28]. In addition, TLC, ITC, IVAS, and PVAS will also be used as secondary outcomes to assess the lesion counts and main symptoms (itch or pain) related to AV. These would provide a comprehensive evaluation of the overall effectiveness of acupuncture.

In this trial, we aim to evaluate the therapeutic effect of acupuncture on the symptoms and QoL of patients with moderate or severe AV. The possible placebo effects of acupuncture may be attributable to the participants' expectations of acupuncture, the degree of trust between the acupuncturist and the participant, and any difference in the type, frequency, or course of the intervention of acupuncture [38, 39]. To partially exclude the placebo effects and demonstrate the real effect of acupuncture, we plan to use sham acupuncture as comparator. Non-insertion-type needle on non-acupoints was shown to be an optimal method to reduce the possible biological effects [38, 39]. However, the non-insertion-type needle leaves no marks or wounds on the skin. In this condition, the lack of any needle marks may compromise the blinding of participants. Therefore, we will opt for non-acupoints and minimal acupuncture without any manipulation as the sham acupuncture in this trial. Non-acupoints are in the proximity of the classical acupoints, which will increase the feasibility of blinding.

However, some limitations of our study should be acknowledged. First, the single center scope of the study and the relatively small sample size may lead to overestimation of the effects of acupuncture. Second, because of the characteristics of acupuncture, the acupuncturist will not be blinded in our trial, which may cause potential bias. Lastly, the use of non-acupoints and minimal acupuncture without any manipulation may cause some biological effect leading to false-negative results [38].

Trial Status

No recruitment at the present.

Abbreviations

AV = Acne vulgaris; QoL = quality of life; SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials; STRICTA = Standards for Reporting Interventions in Clinical Trials of Acupuncture; GAGS = global acne grading system; MCID = minimal clinically important difference; DLQI = Dermatology Life Quality Index; TLC = total lesion counts; ITC = inflammatory lesion counts; IVAS = Itch Assessment with Visual Analogue Scale; PVAS = Pain Assessment with Visual Analogue Scale; AE = Adverse events; SAE = Serious adverse event.

Declarations

Ethics approval and consent to participate: The study protocol has been approved by the Institutional Review Board of the Guang'anmen Hospital in China (approval no. 2018-137-KY-01; TEL +86-10-88001552) (See Additional file 1). All investigators will comply with the Declaration of Helsinki. All study participants will be voluntarily enrolled after screening and written informed consent will be obtained prior to enrolment. All study participants will have a discussion with the researchers about the procedure, treatment, and possible risks and benefits of the trial. Moreover, all participants will have the right to opt out of the study at any time after enrolment.

Consent for publication: Not applicable.

Availability of data and material: All relevant data will be shared for a period beginning 3 months after publication and ending 5 years after publication.

Competing interests: The authors declare that they have no competing interests.

Author contributions: Zhishun Liu and Ruimin Jiao conceived the idea of this trial and the design this study. Man Huang and Weina Zhang are responsible for statistical analysis. Ruimin Jiao, Weina Zhang, and Man Huang are responsible for the recruitment and treatment of participants. This manuscript was drafted by Ruimin Jiao and revised by Zhishun Liu. All authors have read and approved the final manuscript.

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Table

Table 1. The time-points for assessment of outcomes

	Enrollment allocation	and Treatment				Follow-up	
Measure outcomes	Baseline	Week 1	Week 2	Week 3	Week 4	Week 16	Week 28
Skindex-16 total score	×				×	×	×
Skindex-16 subscales score	×				×	×	×
DLQI total score	×				×	×	×
TLC	×				×	×	×
ILC	×				×	×	×
IVAS score	×				×	×	×
PVAS score	×				×	×	×
Blinding assessment Expectation	×				×		
Safety assessment	×	×	×	×	×	×	×

DLQI, Dermatology Life Quality Index scale; TLC, total lesion count; ILC, inflammatory lesion count; IVAS, itch assessment with visual analogue scale; PVAS, pain assessment with visual analogue scale

Additional File Legend

Additional file 1. Ethics Approval of Acne vulgaris

Figures

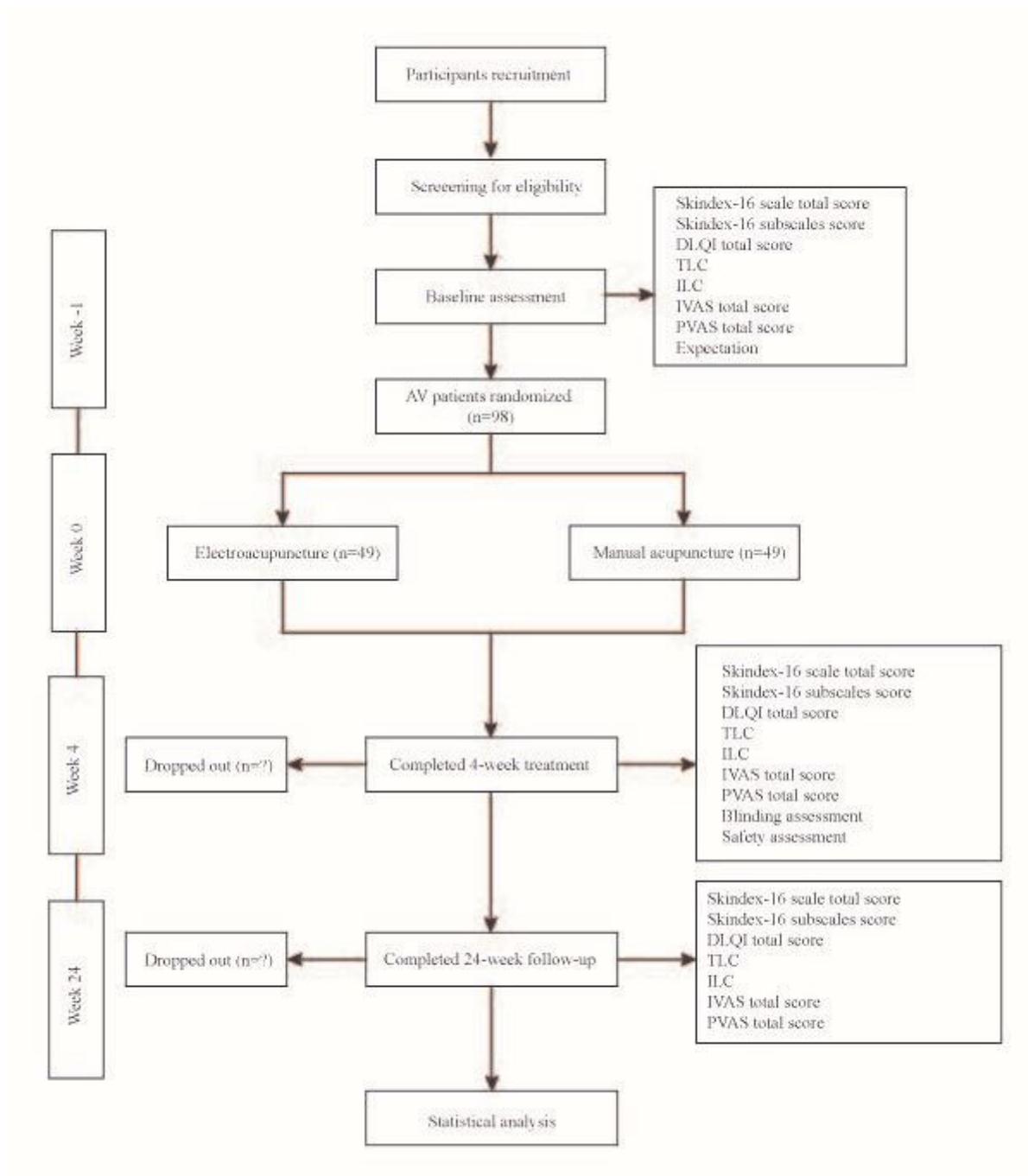


Figure 1

Trial flow diagram

Supplementary Files

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- [SPIRITchecklist.doc](#)