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Efficacy of electro-acupuncture and manual acupuncture versus sham acupuncture for knee osteoarthritis: statistical analysis plan for a randomized controlled trial

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Update

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Abstract

Background: Acupuncture therapies are widely used for knee osteoarthritis (KOA), despite contradictory evidences. Current study is designed to determine the efficacy of electro-acupuncture and manual acupuncture versus sham acupuncture for KOA. Methods/design: Current study is a multi-center, three-arm, randomized controlled trial which will enroll 480 participants with KOA in China. Participants will be randomly assigned (1:1:1) to receive 24 sessions of electro-acupuncture, manual acupuncture, or sham acupuncture over 8 weeks. The primary outcome is the response rate - the proportion of patients who simultaneously achieve minimal clinically important improvement in pain and function domains at 8 weeks. The primary outcome will be analyzed using Z-test with intention-to-treat set. Secondary outcomes contain pain, function, global patient assessment and quality of life. Full details of the statistical analysis plan for the primary and secondary outcomes will be described in this article. The statistical analysis plan was written and submitted without knowledge of the study data. Discussion: The data will be analyzed according to this pre-specified statistical analysis plan to avoid data-driven analysis and enhance the transparency of current trial. The trial will provide high-quality evidence on the efficacy of acupuncture for KOA.

Background

Knee osteoarthritis (KOA) is one of the leading causes of chronic pain and disability in older adults [1], with symptomatic knee osteoarthritis affecting 8.1% of Chinese [2] and 1.6% - 14.9% of European according to age class [3]. The socioeconomic burden of KOA is large, costing between 1·0% and 2·5% of gross domestic product in developed countries [4].

Since there is no disease-modifying treatment available, current KOA managements are symptomatic [5]. Non-steroid anti-inflammatory drugs are commonly used to treat this disorder. However, limited effect sizes for non-steroid anti-inflammatory drugs of KOA have been shown [6, 7]. Although total knee replacement is an effective treatment for symptomatic end-stage disease, approximately 15% of patients have continuing pain and mobility problems after surgery and the lifespan of prostheses is limited [8].

Acupuncture is increasingly used in clinical practice [9], although evidence of its efficacy is contradictory [10, 11]. Acupuncture has a dose-effect relationship [12]. However the dose of acupuncture in several previous trials is far from adequate [13]. Frequency of acupuncture is one of key factors of dose [14]. A review suggested that the frequency of acupuncture is usually 3-5 sessions per week in China, whereas the frequency is mostly one session per week in Europe and America [15]. Based on previous pilot trial [16], high-dose acupuncture (24 sessions in 8 weeks) may be an effective option for knee osteoarthritis. Electro-acupuncture (EA) combines manual acupuncture (MA) with electric stimulus [17]. Both EA and MA are frequently used in clinical practice. Therefore, current trial is designed to evaluate the effect of EA and MA, compared with sham acupuncture (SA), in patients with knee osteoarthritis.

The protocol of the trial has been published previously [18] and provides more detail on the trial rationale, eligibility criteria, and interventions. This article aims to report in detail the statistical analysis plan (SAP) to

reduce the risks of reporting bias and enhance the transparency of the trial. The SAP was approved on 30 October 2017 (Version 1.0) and drafted without knowledge of any of the results.

Methods/design

Study Design

This three-arm, randomized, sham-controlled trial has been approved by ethics committees at all 9 hospitals. Eligible KOA participants diagnosed according to the American College of Rheumatology criteria [19] are randomly assigned (1:1:1) to receive 24 sessions of electro-acupuncture, manual acupuncture, or sham acupuncture over 8 weeks. Block randomization with random block size of 6 and 9, is stratified by study centre, and is performed via a web-based randomization system. Superficial insertion at non-acupoints with no electric current will be used in sham acupuncture group, which is one of the most commonly used approaches for administering sham treatments in acupuncture trials. The nature of acupuncture means that acupuncturists are not blinded to treatment allocation; however, patients, outcome assessors and statisticians remain masked where possible. Informed consent is obtained from each participant before randomization. The trial has been registered with ClinicalTrials.gov (NCT03366363).

Objectives

The objective of current study is to determine if EA and MA improve the outcome at 8 weeks in patients with knee osteoarthritis. The following two null hypotheses are tested: there is no difference in patients' response rate between EA group and SA group; there is no difference in patients' response rate between MA group and SA group.

Outcomes

Primary outcome

The primary outcome is the response rate [20] - the proportion of patients who simultaneously achieve minimal clinically important improvement (MCII) in pain and function domains at 8 weeks post-randomization. The average pain over the previous week is assessed using an 11-point Numerical Rating Scale (NRS) [21] with scores ranging from 0 to 10. The MCII in pain domain is defined as 2 points in NRS [11, 22]. The average function over the previous week is measured using Western Ontario and McMaster Universities osteoarthritis index (WOMAC) function subscale [23] with scores ranging from 0 to 68. The MCII in function domain is defined as 6 points in WOMAC function subscale [11, 22]. The criteria of responder are presented in Fig 1. The response rate is also measured at weeks 4, 16, and 26 after randomization.

Secondary outcomes

Numerical Rating Scale [21]: an 11-point patient reported outcome measure (PROM) with scores ranging from 0 (no pain) to 10 (worst pain).

WOMAC [23] pain subscale: a 5-item PROM with total scores ranging from 0 to 20. Higher scores indicate worse pain.

WOMAC [23] function subscale: a 17-item PROM with total scores ranging from 0 to 68. Lower scores indicate better physical function.

WOMAC [23] stiffness subscale: a 2-item PROM with total scores ranging from 0 to 8. Higher scores indicate more stiffness.

Patient global assessment [24]: a 5-point Likert scale. Participants are asked how their knee symptoms were during the past week. The answers include ‘extremely improved’, ‘slightly improved’, ‘not changed’, ‘slightly aggravated’, and ‘extremely aggravated’.

12-item Short Form Health Survey (SF-12) [25] physical dimension: total score range from 0 to 100. Lower scores indicate a worse quality of life.

SF-12 [25] mental dimension: total score range from 0 to 100. Higher scores indicate a better quality of life.

NRS, WOMAC, Patient global assessment and SF-12 is measured at 4, 8, 16, and 26 weeks after randomization. Blinding assessment is measured at 4 and 8 weeks after randomization. Credibility and expectancy of participants are measured 5 minutes after the first acupuncture [26]. The use of rescue medicine is also counted throughout the trial.

Safety outcome

Adverse events are recorded throughout the trial. Based on the potential relationship between acupuncture and adverse events, adverse events are categorized as treatment-related or not.

Sample size

Based on the results of a previous trial [16], the response rates of EA, MA and SA group are assumed to be 70%, 60% and 40%, respectively. With a 2-sided significance level of 2.5% and power of 80%, 128 participants in each group will be required to detect a difference as small as 20% between each acupuncture group and control group. The 2-sided significance level of 2.5% is a Bonferroni-adjusted alpha level as per the two predefined primary comparisons: EA vs. SA and MA vs. SA. With an estimated loss-to-follow-up rate of 20%, 480 participants in the three groups will be recruited.

Statistical analysis

Statistical analysis population

Full analysis set (FAS) Modified full analysis set (mFAS), per-protocol set (PPS), and safety set (SS) will be used in current trial.

Modified full analysis set FAS will consist of all randomized participants who have at least one post-baseline measurement according to modified intention-to-treat principle. Logistic regression will be used to exam whether the data are missing at random or not [27]. If data is missing at random, multiple imputation method will be used [28]. FAS Modified full analysis set will be the primary analysis set, and all analyses will be conducted for this population if not otherwise stated. Analyses on mFAS will provide an estimate of the effect of electro-acupuncture and manual acupuncture.

PPS will include those who complete the treatment and follow-up timely according to protocol without major violations. Major violations of protocol will be judged during the blinded audit of data, including but not limited to: not meeting the inclusion criteria / meeting the exclusion criteria, receiving other treatments which might affect symptoms of KOA during the trial, completing ⩾ 20 sessions of acupuncture. PPS will be the secondary analysis set and be used for sensitivity analyses.

Those who receive randomization and at least one session of acupuncture will be defined as SS, which is used for safety analyses.

General analysis principles

All data will be summarized by treatment group. Numbers (percentages) will be used to describe categorical data. Either means (standard deviations) or medians (interquartile ranges) will be used for quantitative data depending on whether the variables are normally distributed or not. If not otherwise stated, the significance level will be set at 0.05. The Bonferroni method will be used to adjust the significance level for multiple comparisons for the primary outcome. The significance level will be adjusted for the multiple comparisons for the primary outcome. The conclusion will be based on the analysis of primary outcome, and all secondary outcomes will be analyzed to support the primary analysis. All analyses will be carried out using SAS 9.3 (Cary, NC).

Descriptive analyses

The number of participants screened, excluded, randomly assigned to each group, interviewed at each follow up, and analyzed will be summarized using a flow diagram recommended by CONSORT [27 29] (Fig. 2). Reasons for the losses to follow-up and withdrawals will also be listed by treatment arm.

Demographic characteristics and clinical outcomes at baseline will be presented in Table 1. When testing differences among the three groups, either one-way analysis of variance (ANOVA) or Krusal-Wallis one-way ANOVA (if normality is violated) will be used for continuous variables. Chi-square test or Fisher exact text will be used for categorical variables. Missing data of baseline characteristics will not be imputed. Differences among the treatment groups at baseline will not be statistically tested.

Analysis of primary outcome

For the analysis of primary outcome, the response rates of the three groups at 8 weeks will be calculated and the Z-test for comparisons of proportions will be used with FAS. The missing data at 8 weeks will be imputed using the baseline value. There will be two comparisons. The first comparison is the one between electro-acupuncture group and sham acupuncture group. The second comparison is the one between manual acupuncture group and sham acupuncture group. The significance level will be adjusted at 0.025 for the multiple comparisons using Bonferroni method.

Analysis of secondary outcomes

For NRS score, comparisons among three groups will be assessed by mixed-effect model with repeated measurement (MMRM) analysis using NRS scores at all follow up time points as dependent variable, treatment as main factor, baseline value as a covariate. We set the model as $y_{ij} = \alpha + u_i + \beta_1 + \beta_2 + \varepsilon_{ij} = \alpha + u_i + \beta_1 \bullet time_{ij} + \beta_2 \bullet treat_i + \varepsilon_{ij} = \alpha + u_i + \beta_1 \bullet time_{ij} + \beta_2 \bullet treat_i + \varepsilon_{ij}$, where α is total average, u_i is unknown random effect represented subject-specified effect, β_1 and β_2 are unknown fixed effect represented time and treatment effect, respectively. Set the covariance matrix G is unstructured, and $u_i \sim N(0, G)$. The random error $\varepsilon_{ij} \sim N(0, R_i)$. The MMRM for secondary outcome will be handled by PROC MIXED (SAS). The estimators of unknown parameters will be calculated by expectation maximalization algorithm. We expect that the expectation maximalization algorithm will converge with the 480 sample sizes in three groups and a single random intercept. Meanwhile, if non-convergence does happen, we will consider strategies such as correcting initial value, changing random effect, or using other analysis method like generalized estimating equations. Also, we will test the estimators or models based on likelihood test, Bayesian information criterion methods. The modified MMRM added the center effect and time*treatment effect will be presented in Sensitivity analysis. The modified MMRM as follows: $y_{ij} = \alpha + u_i + \beta_1 + \beta_2 + \beta_3 * treat_i + \beta_4 + \varepsilon_{ij} = \alpha + u_i + \beta_1 + \beta_2 + \beta_3 * treat_i + \beta_4 + \varepsilon_{ij}$. Where α, u_i, β_1, β_2, ε_{ij} defined as above, β_3, β_4 are unknown fixed effect. The same approach will be used to analyze WOMAC pain subscale, function subscale, and stiffness subscale, and SF-12. If there is a normality violation in the continuous variables, a transformation will be performed before the comparison. Chi-square test will be used for patient global assessment. These outcomes will be shown in Table 2.

Safety analyses

Based on the potential relationship between acupuncture and adverse events, adverse events are categorized as treatment-related or not. Acupuncture-related adverse events will be summarized by group and compared using Chi-square test (or Fisher exact test).

Blinding analyses

Kappa analysis will be used to determine whether participants correctly guessed their group assignment at a higher rate than would be expected by chance.

Additional analyses

Another three schemes to deal with missing data for primary outcome will be carried out to examine the robustness of conclusion. First, the missing data at 8 weeks will be imputed using the last observation carried forward approach; second, remove the missing data directly; third, the missing data at 8 weeks will be imputed using multiple imputation [28]. Assume missing at random, the missing data will be imputed using the Monte Carlo Markov Chain method for multiple imputation with Proc MI (SAS). Set the initial seed is 1000 and impute five datasets. The missing data for primary outcome will be imputed by the observation value of age, gender, BMI, KL grade, and duration of disease. Sensitivity analysis of primary outcome and secondary outcomes will be carried out with PPS to examine the robustness of conclusion. Several researches have shown that the center stratified randomization lead to the correlation among treatment groups. Therefore, we will discuss the generalized linear mixed-effect model for primary outcome to analyze the group effect, in which centre effects is included. Subgroup analysis based on Kellgren - Lawrence grade will be performed.

Discussion And Trial Status

The trial will provide high-quality evidence on the efficacy of electro-acupuncture and manual acupuncture for KOA. This paper provides details of the planned statistical analyses for current trial and will help reduce the risks of outcome reporting bias and data-driven results [29 30]. This paper has been prepared in accordance with the published guidelines for the content of statistical analysis plans [30 31]. As of October 2018, 480 patients from 9 centers were randomized. Follow-up is currently ongoing and expected to finish on 10 April 2019. The final analysis will be conducted thereafter.

Abbreviations

ANOVA: One-way analysis of variance; EA: electro-acupuncture; mFAS: modified Full analysis set; KOA: knee osteoarthritis; MA: manual acupuncture; MCII: minimal clinically important improvement; MMRM: mixed-effect model with repeated measurement; NRS: Numerical Rating Scale; PPS: per-protocol set; PROM: patient reported outcome measure; SA: sham acupuncture; SAP: statistical analysis plan; SF-12: 12-item Short Form Health Survey; SS: safety set; WOMAC: Western Ontario and McMaster Universities osteoarthritis index.

Declarations

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Availability of data and materials

Of the current detailed statistical analysis plan no original data are available. The datasets used during the current study will be available from the corresponding author on reasonable request.

Contributors

JF Tu, JW Yang, ZS Yu and CZ Liu proposed the statistical analysis plan. JF Tu and Y Wang drafted the manuscript. CZ Liu led the trial concept and assembled the study group. All authors revised and approved the final manuscript.

Ethical Approval and Consent

Ethics approval was granted at the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (2017BL-077-01) and at each participating site. Written informed consent will be obtained from each participant prior to enrolment in the study.

Competing interests

None declared.

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Tables

Table 1 Baseline characteristics

Baseline characteristic	Type	Levels or scale
Gender	Categorical	Male; Female
Age	Continuous	Years
Nationality	Categorical	Han, Others
Duration of disease	Continuous	Years
Kellgren - Lawrence grade	Categorical	Grade ; Grade
Body mass index	Continuous	kg/m^2
Years of education	Categorical	9; 9-12; 12
Affected knee	Categorical	Unilateral; Bilateral
Past treatment	Categorical	Injections; Medication; Physical therapy; Acupuncture; Exercise, etc.
Concomitant diseases	Categorical	Hypertension; Coronary heart disease; Diabetes mellitus; Hyperlipidemia, etc.
Numerical Rating Scale	Continuous	point
WOMAC pain subscale	Continuous	point
WOMAC function subscale	Continuous	point
WOMAC stiffness subscale	Continuous	point
Physical health, SF-12	Continuous	point
Mental health, SF-12	Continuous	point

WOMAC: Western Ontario and McMaster Universities osteoarthritis index; SF-12: 12-item Short Form Health Survey

Table 2 Primary and Secondary Outcomes

Outcomes	EA (n=)	MA (n=)	SA (n=)	*P* value	Pairwise comparison					
					EA vs SA		MA vs SA		EA vs MA	
					Difference (95% CI)	*P* value	Difference (95% CI)	*P* value	Difference (95% CI)	*P* value
Success rate, No. (%)										
4 weeks	x (xx.x)	x (xx.x)	x (xx.x)	-	xx.x (xx.x-xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x	-	-
8 weeks	x (xx.x)	x (xx.x)	x (xx.x)	-	xx.x (xx.x-xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x	-	-
16 weeks	x (xx.x)	x (xx.x)	x (xx.x)	-	xx.x (xx.x-xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x	-	-
26 weeks	x (xx.x)	x (xx.x)	x (xx.x)	-	xx.x (xx.x-xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x	-	-
Numerical Rating Scale, mean (SD)										
Baseline	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x
4 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
8 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
16 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
26 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
WOMAC pain subscale, mean (SD)										
Baseline	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x
4 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
8 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
16 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
26 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
WOMAC function subscale, mean (SD)										
Baseline	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x	xx.x (xx.x-xx.x)	xx.x
4 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
8 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
16 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
26 weeks	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	

Figures

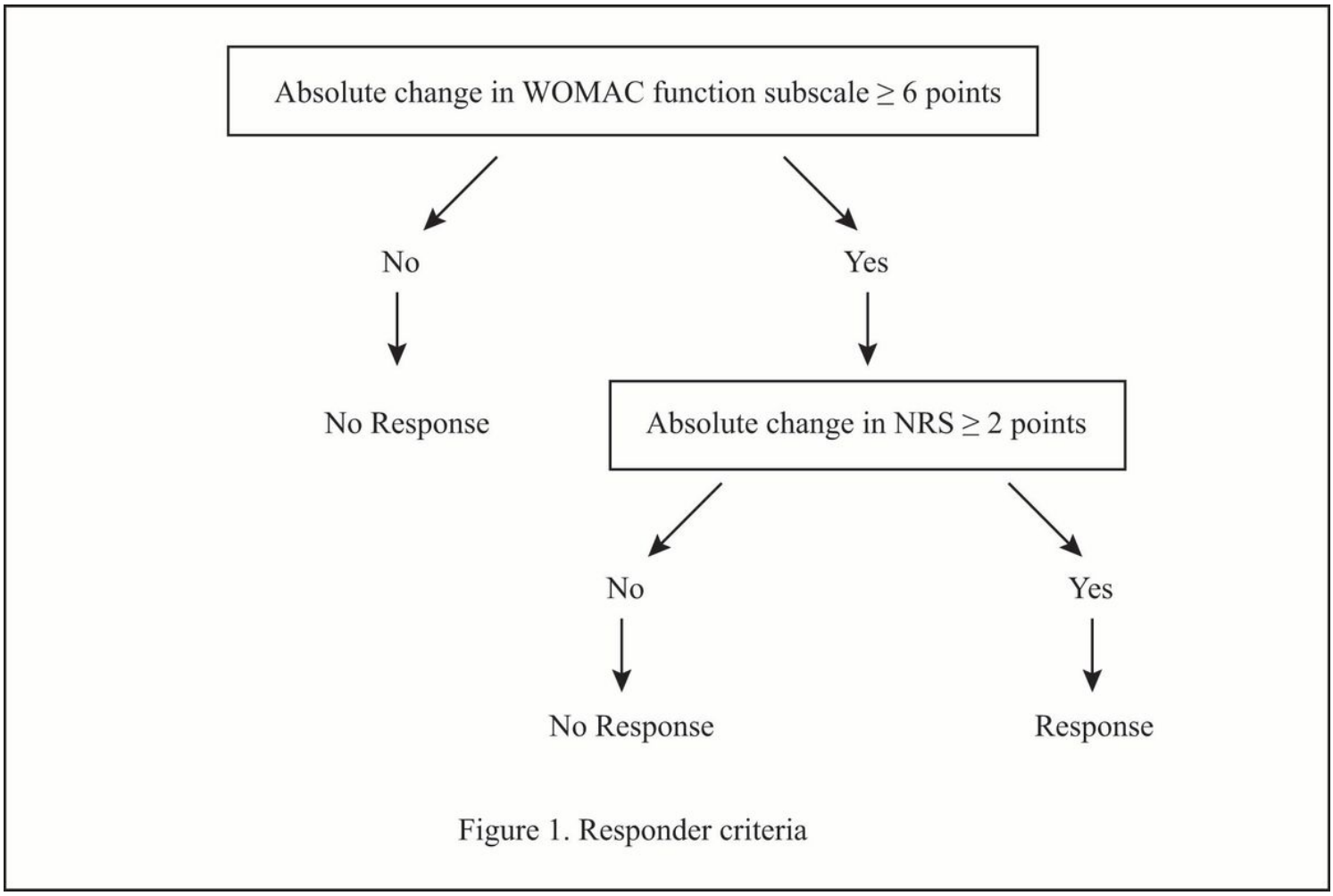

Figure 1

Responder criteria

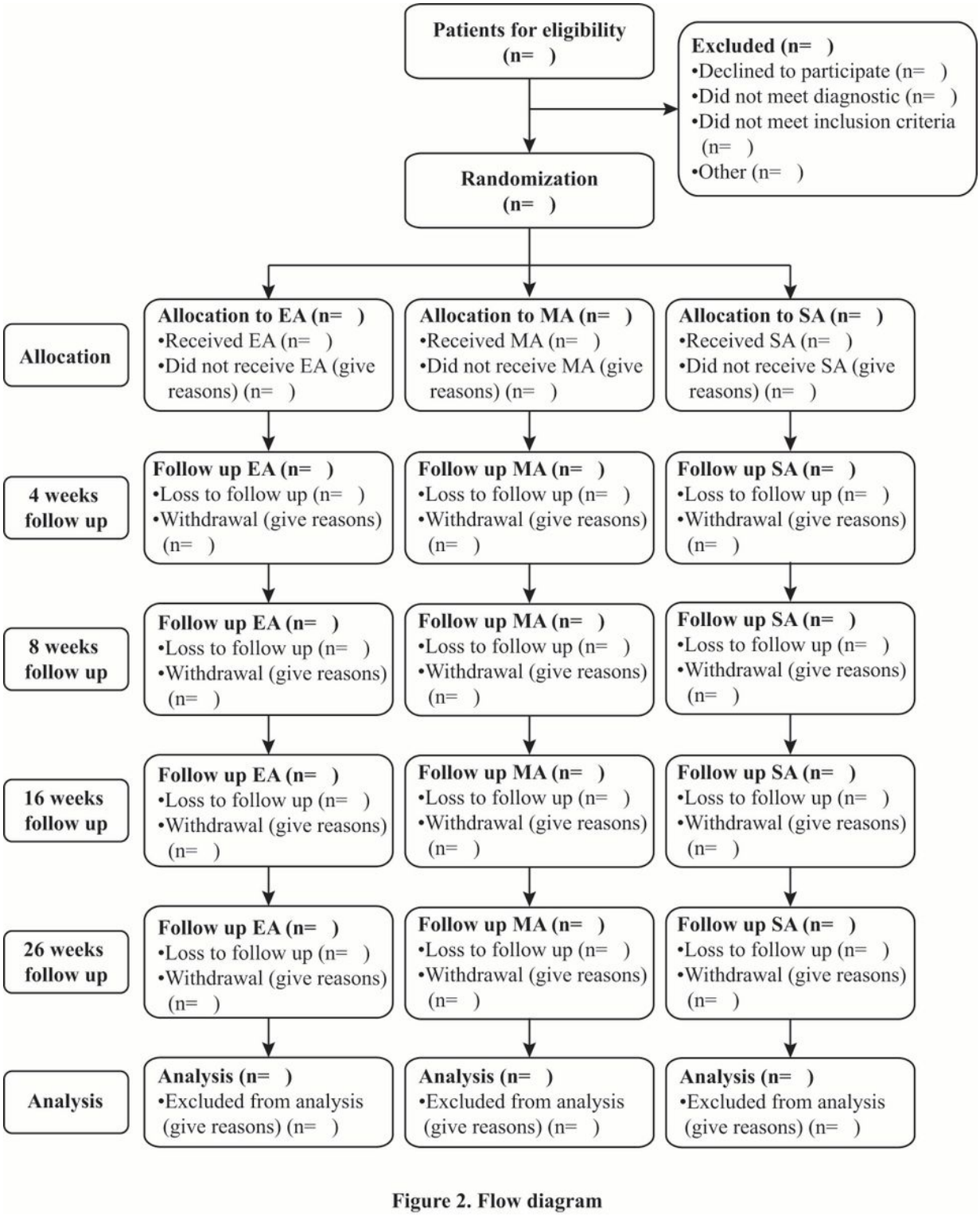

Figure 2. Flow diagram

Figure 2

Flow diagram