SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Acupuncture as prophylaxis for chronic migraine: a protocol for a single-blinded, double-dummy, randomised controlled trial	1
Trial registration	2a	Trial registration number: ISRCTN13563102	2
	2b		
Protocol version	3	2018-03-07 Version 1.0	
Funding	4	Beijing Municipal Science & Technology Commission (grant number Z171100001017033), China National Natural Science Foundation (grant number 81603683), and National Basic Research Program of China (grant number 2014CB543203)	18

Roles and responsibilities	5a	Contributors BL, X-HJ, LL and L-PZ conducted the study. LL and L-PZ drafted the protocol. C-SZ, K-LW and J-XZ participated in the design of the study and contributed to the revising the protocol manuscript. LZ was responsible for the statistical design of the study. L-PW provided clinical advice and made critical revisions. BL is a principal investigator of the study and is responsible for making final decisions on the trial design and manuscript preparation. All authors approved the final manuscript.	18
	5b	Beijing Municipal Science & Technology Commission (Telephone number: 0086 010 66153395)	
	5c	Beijing Municipal Science & Technology Commission is the sponsor and will not affect the result of this trial.	
	5d	This trial will be monitored by the scientific research department of Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University.	

Introduction

Background and rationale	6a	Approximately 1.4% to 2.2% of the global population suffers from chronic migraine. Acupuncture may serve as an alternative management for chronic migraine, where pharmacological prophylaxis is not suitable. However, the effects of acupuncture as migraine prophylaxis have not been confirmed. This study is designed as a single-blinded, double-dummy, randomised controlled trial to evaluate the efficacy and safety of acupuncture compared to topiramate in chronic migraine patients.	2

	6b	In the control group, participants will be treated with medicine (topiramate) and sham acupuncture. Topiramate, as an anti-epileptic medication (AED), is Food and Drug Administration (FDA)-approved and widely accepted as a treatment for chronic migraine prevention. Several placebo-controlled randomised clinical trials have shown that topiramate significantly reduced the number of migraine headache days in patients with chronic migraine. Topiramate is considered safe, effective and generally well-tolerated for the prophylactic treatment of chronic migraine. Therefore, we will compare the efficacy of acupuncture with topiramate, which was chosen as the standard drug therapy. It is a reasonable control intervention that meets ethical standards.	14-15
Objectives	7	This study is designed as a single-blinded, double-dummy, randomised controlled trial to evaluate the efficacy and safety of acupuncture compared to topiramate in chronic migraine patients.	2
Trial design	8	A single-blinded, double-dummy, randomised controlled trial	

Methods: Participants, interventions, and outcomes

Study setting	9	A single centre in Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University	

Eligibility criteria	10	Inclusion criteria: (1) diagnosed as having chronic migraine according to the diagnostic criteria specified by the International Classification of Headache Disorders (International Classification of Headache Disorders-Third edition (beta version) [ICHD-Ⅲβ]), (2) aged between 18 and 65 years old, (3) received no prophylactic treatments using acupuncture or pharmacological medicine in the past three months, and (4) provided written informed consent. Exclusion criteria: (1) tension-type headache, cluster headache, or other primary headaches, (2) relatively severe systemic diseases (cardiovascular disease, acute infectious disease, hematopathy, endocrinopathy, allergy, or methysis), (3) headache caused by otorhinolaryngology diseases or intracranial pathological changes, (4) secondary headache or other neurological diseases, or (5) pregnancy, lactation, or insufficient contraception.	6

Interventions	11a	All participants will receive treatment for 12 weeks. In the treatment group, participants will receive three acupuncture sessions each week, together with placebo medication. In the control group, participants will be given medicine (topiramate) and three sessions of sham acupuncture each week. Each acupuncture session (both verum and sham acupuncture) will last for 30 min. Sterilised, single-use needles (Hwato Needles, made in Suzhou, China) will be used for acupuncture in this trial. The number of needles will be no more than 10 in each session for both groups. Thirty-gauge (0.3 mm in diameter) needles with 40 mm in length will be used for limb points and 32-gauge (0.25 mm in diameter) needles with 25 mm in length will be used for head points. All needles will be inserted 10 to 15 mm in depth and manually manipulated with rotation methods to produce a characteristic sensation known as De Qi (feeling of needle sensation that refers to the tenseness around the needle felt by the practitioner and numbness, distension, soreness, and heaviness around the point felt by the participant). The placebo medication will be made by Xi'an Janssen Pharmaceutical LTD and will have the exact same appearance as the real medicine (topiramate). During the titration period, participants will receive topiramate 25 mg/day at bedtime for one week, followed by a weekly increase of 25 mg up to either 100 mg/day of topiramate or to the maximal tolerated dose. Starting in Week 2, topiramate will be given daily in equally divided twice daily doses. During the maintenance period, a stable topiramate dose of at least 50 mg/ day will be required.	7-8

	11b	Reasons for discontinuation of treatment may include, but are not limited to, the following: (1) participant's decision to discontinue treatment at any time for any reason, (2) investigator's determination to discontinue treatment for the patient's safety and best interests at any time, (3) inability to tolerate the treatment stimulation at any time during the course of the study, (4) occurrence of serious side effects during the treatment course, (5) exacerbation of the disease making it difficult for the participant to continue treatment, (6) inability of the participant to cooperate during assessment for any reason, and (7) concomitant therapy during the trial that may affect the study results.	
	11c	All participants will receive free treatment.	
	11d	All participants will be permitted to treat acute headaches as required; Ibuprofen will be recommended to all participants as their first choice for acute medication. The name and dosage of these medications will be recorded in the headache diaries.	8
Outcomes	12	The primary outcome measure will be the reduction of monthly headache days, which will be calculated using the data collected from the second to the fourth headache diaries (treatment phase) compared to the first diary (collected in the screening period, four weeks before the beginning of the trial). Headache diaries are designed to record the details of migraine attacks, including duration, frequency, location, intensity, presence of aura, causality of the headache and concomitant symptoms in each migraine attack. The participants will also document the number of days with acute headache medication intake (including name, dosage, time of taking medicine, time of pain relief and side effects of analgesic drugs) for each migraine attack and study medication received in the headache diaries.	9
Participant timeline	13	Table 1	26-27

Sample size	14	In a previous study, the reduced number of chronic migraine days after treatment was 10.5 ± 2.8 days in the acupuncture group and 7.8 ± 3.6 days in the control group. PASS 11 software (NCSS, Kaysville, Utah, USA) was used to calculated that, based on 80% power to detect a significant difference ($\alpha = 0.05$, two-sided), 26 participants will be required for each group. Allowing for a 10% withdrawal rate, we plan to include a total of 60 participants with 30 participants in each group.	11
Recruitment	15	Trial participants with chronic migraine are being recruited by clinicians from outpatient clinics at the Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University. Meanwhile, information flyers introducing the details of the trial are being posted at the outpatient clinics for greater exposure.	5

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	The randomisation will be performed by the Research Centre of Clinical Epidemiology, Peking University Third Hospital. A block randomisation method (with a block size of four) will be used to generate the random allocation sequence; predetermined computer-generalised randomisation opaque sealed envelopes will be used to ensure the allocation concealment.	6
Allocation concealment mechanism	16b	The opaque sealed envelopes, with the participant's screening order printed outside and randomly assigned group printed inside, will be numbered consecutively and connected into a strain.	6
Implementation	16c	Researchers will enrol the eligible participants after screening, then separate and open each envelope from the strain in the sequence corresponding to the participant's screening order, and assign the eligible participant into either the treatment group or control group.	6

Blinding (masking)	17a	In this study, the participants will be informed that they will have a 50% chance of being allocated to receive either of the two treatments: verum acupuncture plus placebo medication in the treatment group, or sham acupuncture plus real medication (topiramate) in the control group. The placebo medication will be identical to the real medication (topiramate) and sham acupuncture will produce the same stimulation as the verum acupuncture. Hence participants will be blinded to their group allocation. The credibility of blinding will be tested at the beginning and end of the treatment phase (Week 1 and Week 12). Furthermore, outcome assessors and personnel involved in data collection and data analysis will be blinded to participants' group allocation throughout the entire trial. The acupuncturist cannot be blinded due to the nature of the intervention, but they will be trained not to communicate with participants or outcome assessors regarding treatment procedures and responses.	7
	17b		

Methods: Data collection, management, and analysis

Data collection methods	18a	All researchers including the acupuncturists, outcome assessors, data collector, data manager, data entry personnel, and statistician will receive special training regarding the standard procedure and data management. During the recruitment period, our data collector will record the baseline characteristics of participants in CRFs, and all data will be checked by the data manager.	10
	18b	Dropouts and withdrawals from the study will be recorded in detail.	

Data management	19	Upon the completion of the treatment and follow-up phases, all participants' data will be completed and recorded on the original CRFs and then entered into Excel spreadsheets by two data-entry personnel independently, following which the data manager will cross-check two datasets to ensure accuracy. If any inconsistencies are noted, corrections will be made according to, and marked on, the original CRFs. All data will be managed in accordance with the Data Protection Act of 1998.40 All hard copy documents related to the research will be saved in a locked filing cabinet, while electronic documents will be stored in a special computer that will remain password-protected and accessible only to the principal investigators. All research documents, including both the hard copy documents and electronic files, will be saved for at least five years after publication. If readers have any questions regarding our published data, they will be permitted to contact our first author or corresponding author to obtain the original data.	_____10_____

Statistical methods	20a	Data analysis will be performed by statisticians who are blinded to the entire allocation and intervention process. The statisticians are affiliated with the Research Centre of Clinical Epidemiology, Peking University Third Hospital, which is one of the most authoritative statistics centres in the country. All data in this trial will be assessed using the SPSS statistical software package (V.22.0) (International Business Machines Corporation). Two-tailed analyses will be conducted, with the level of statistical significance defined as $P < 0.05$. Demographic characteristics and baseline measurements of the variables of each group will be summarised. Continuous variables will be shown as the means ± standard deviations (SDs) with a 95% CI. Independent two-sample t-tests or the Mann-Whitney U-test will be performed to compare the continuous data from each group. For dichotomous or categorical data, frequency and percentage will be presented, and the difference between groups will be compared using the chi-square test or the Fisher's exact test.The mean change of the monthly headache days is the primary outcome measure of this study. One sample of the Kolmogorov-Smirnov test will be used to test the normal distribution of continuous variables. Continuous variables will be shown as the means ±SDs if they are normally distributed or as medians with IQRs if they are not normally distributed. If the measurement data are normally distributed, independent two-sample t-tests will be used for comparisons among the groups, while paired t-tests will be used for within-group comparisons. If the measurement data have a non-normal distribution, the Mann-Whitney U-test will be used for comparisons among the groups, while Wilcoxon signed-ranks test will be used for within-group comparisons.The secondary outcome measures include the mean change of days with acute headache medications, and the changes of MIDAS, MSQ, HIT-6, STAI-T, and BDI-II scores from baseline to endpoints in the study. The secondary outcome measures will be analysed following the same methods used for the primary outcome measure analysis. AEs will be analysed in the safety set, which consists of all participants who received at least one treatment in this trial. AEs will be pooled for each organ system class and preferred term, and then the percentage of patients with AEs and percentage of patients with laboratory AEs will be summarised with descriptive statistics.	11-12

	20b		
	20c	The intention-to-treat population will be the main set used for all efficacy analyses. The per-protocol set will be utilised for the sensitivity and consistency analysis to compare the results from the intention-to-treat set. The per-protocol set will consist of the participants who have completed the trial without major protocol violations and will finally provide all outcome measures. The last observation carried forward method will be used to process the missing data for the primary outcome.	11

Methods: Monitoring

Data monitoring	21a	This trial will be monitored by the scientific research department of Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University.	
	21b		

Harms	22	Safety assessments will include the incidence of adverse events (AEs), clinical laboratory tests (including urine pregnancy test), vital sign measurements, and physical examination findings. The clinical laboratory tests will include hematology, chemistry and urinalysis tests. Vital sign measurements will include sitting blood pressure, heart and respiration rate, and body temperature. AEs are defined as negative or unintended clinical manifestations following the treatment. Our investigators will collect information regarding AEs throughout the treatment and follow-up phases. Participants will be instructed to report any abnormal reactions or uncomfortable feelings experienced to any researcher. All unexpected AEs will be recorded with details in the Case Report Forms (CRFs), including time of occurrence, degree of AE, and possible causes. Participants with mild and moderate AEs will be treated for their symptoms and closely monitored as necessary by the researcher. Severe AEs will be reported to the Research Ethics Committee, which will provide medical advice to the research team within 48 hours, and the Research Ethics Committee will determine whether a termination of the trial is required.	9-10
Auditing	23	The study will be audited by Beijing Municipal Science & Technology Commission every year.	

Ethics and dissemination

Research ethics approval	24	Ethical approval was granted on 21 July 2017, by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (Ethics Reference Number: 2017BL-045-01).	18
Protocol amendments	25	If it is necessary to modify the protocol, we should submit applications to Beijing Municipal Science & Technology Commission.	
Consent or assent	26a	Researchers will obtain informed consent or assent from potential trial participants. Participants will write informed consent.	

	26b		
Confidentiality	27	Research data will be gathered and saved. Paper files will be kept in a locked filing cabinet. Electronic documents will be stored in a password protected computer, with access restricted to the principal investigator. All research documents will be preserved for at least 5 years after publication.	
Declaration of interests	28	The authors declare that they have no competing interests.	18
Access to data	29	Dataset will be stored in a computer which will be password protected, with access restricted to the principal investigator	
Ancillary and post-trial care	30		
Dissemination policy	31a	The results will be published after the study.	
	31b	Researchers in this trial will have authorship eligibility.	
	31c	The results will be published.	
Appendices			
Informed consent materials	32	Written informed consent will be obtained from all participants.	
Biological specimens	33		

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.