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Baduanjin exercise for chronic non-specific low back pain: protocol for a series of N-of-1 trials

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Abstract:

Introduction Chronic non-specific low back pain (CNLBP) is one of the most common health problems worldwide. Exercise has been recommended for treating chronic low back pain according to a clinical guideline from the American College of Physicians. Traditional Chinese medicine (TCM) has become increasingly popular for the management of chronic low back pain in recent years. Baduanjin exercise is one of exercise therapies in TCM. N-of-1 trial is a randomized cross-over self-controlled trial and is suitable for patients with the chronic disease. A series of similar N-of-1 trials can be combined to estimate overall and individual treatment effects synchronously by hierarchical Bayesian analysis. A review showed that N-of-1 trial could be considered as a good tool to evaluate the efficacy of TCM. This study will conduct a series of N-of-1 trials with hierarchical Bayesian analysis to assess the

efficacy and safety of Baduanjin exercise for CNLBP.

Methods and analysis This study is a series of N-of-1 trials on Baduanjin exercise for treating CNLBP. Fifty participants will experience one to three treatment cycles. They will be randomly assigned into the Baduanjin exercise or waiting list group for a week during two periods of each treatment cycle. The primary outcome is a 10-point Visual Analog Scale. The secondary outcomes include the Oswestry Dability Index, Japanese Orthopaedic Association Back Pain Evaluation Questionnaire, and Short Form Health Survey 12. The statistical analysis will be conducted by WinBUGS 1.4.3 software. Overall and individual treatment effects will be estimated synchronously by hierarchical Bayesian analysis.

Ethics and dissemination This study was approved by the medical ethics committee of Tianjin University of Traditional Chinese Medicine with the reference number TJUTCM-EC20220005. The results will be published in a peer-reviewed journal or international conferences.

Trial registration number ChiCTR2200063307.

Strengths and limitations of this study

1. This study is a series of N-of-1 trials on Baduanjin exercise for the management of chronic non-specific low back pain.

2. Overall and individual treatment effects will be estimated synchronously by hierarchical Bayesian analysis.

3. Sample size is calculated based on a simulation-based two-step method.

4. Patients will be recruited from the department of orthopedics in a teaching hospital.

1. Introduction

Low back pain (LBP) is one of the most common health problems worldwide[1]. The global prevalence of LBP reached up to 11.9% according to a systematic review[2]. Most of patients with LBP have no specific pathological changes associated with LBP and are classified as non-specific LBP patients[3]. When non-specific LBP lasts more than 12 weeks, it progresses to a chronic stage and is labeled as chronic non-specific low back pain (CNLBP)[4]. LBP may increase physician visits and years lived with disability, and contribute to absence from work and growing financial burden[1,5,6]. Therefore, a call for action on the management of LBP was proposed[7].

There are many pharmaceutical and non-pharmaceutical therapies for LBP[4]. Some studies showed the insufficient evidence on the efficacy of long-term opioids for chronic pain relief and function improvement[8,9]. A systematic review found more adverse effects after non-steroid anti-inflammatory drugs and opioids treatments compared with placebo in patients with CNLBP[10]. Some systematic reviews reported that exercise and physical activity were beneficial for the recovery of CNLBP[11,12]. Exercise has been recommended for chronic LBP according to a clinical guideline from the American College of Physicians[4]. However, no optimal exercises have been recommended for CNLBP at present[11].

Traditional Chinese medicine (TCM) has become increasingly popular for the management of chronic LBP in recent years[13]. Baduanjin exercise is one of exercise therapies in TCM, and consists of eight simple and separate core movements[14,15]. Each movement is learned easily and completed slowly to keep patients breathing

smoothly and rhythmically[16]. A review reported that Baduanjin exercise might relieve the pain by promoting the balance between sympathetic and parasympathetic activities, and stimulating the brain regions associated with emotion and stress[17]. A systematic review showed that Baduanjin exercise could relieve the musculoskeletal pain in patients with chronic diseases[18]. A review found that LBP was one of the most extensively investigated diseases in clinical studies on Baduanjin exercise[16]. A recent systematic review reported that Baduanjin exercise might be effective for the pain relief and function improvement in patients with low back pain[19]. Nonetheless, the efficacy on Baduanjin exercise for CNLBP has been not confirmed due to the lack of high-quality clinical trials on this topic.

Randomized control trials (RCTs) are known as the gold standard of therapeutic evaluation[20]. However, the average effects estimated from RCTs may represent a mixture of different therapeutic effects in individual patients[21]. The individualized clinical decision should be made cautiously based on the evidence from RCTs in view of the gap between clinical trials and clinical practice[22,23]. N-of-1 trial is a randomized cross-over self-controlled trial conducted in a patient[24]. The result of N-of-1 trial can be directly used to make individualized clinical decision[24]. It is useful to fill the gap between clinical trials and clinical practice[25]. A series of similar N-of-1 trials can be combined to estimate overall and individual treatment effects synchronously by hierarchical Bayesian analysis[26,27]. A review showed that Bayesian analysis was used in 23% of N-of-1 trials with the pooled analysis[28]. Bayesian analysis is also recommended for combining N-of-1 trials according to the Agency for

Healthcare Research and Quality[29]. N-of-1 trials are suitable for patients with chronic disease[29]. Many N-of-1 trials on chronic pain have been published in recent years[30]. A review showed that N-of-1 trial could be considered as a good tool to evaluate the efficacy of TCM[31]. Therefore, this study will conduct a series of N-of-1 trials with hierarchical Bayesian analysis to assess the efficacy and safety of Baduanjin exercise for CNLBP.

2. Methods and analysis

2.1 Study design

This study is a series of N-of-1 trials on Baduanjin exercise for the management of chronic non-specific low back pain. The flow diagram is showed in figure 1. Firstly, patients will be assessed for eligibility and participate in a Baduanjin exercise training. Then, eligible participants will experience one to three treatment cycles. Each cycle will include a period of Baduanjin exercise and a period of waiting list. A washout period will be set between the above-mentioned two periods. It is developed following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[32]. Outpatients or inpatients will be recruited from the department of orthopedics in the first teaching hospital of Tianjin University of traditional Chinese medicine after January 1, 2023. To bring potentially eligible patients' attention, recruitment advertisements will be posted at the entrance of outpatient and inpatient department.

2.2 Patients

2.2.1 Inclusion criteria

Patients will be considered for inclusion when they meet all of items in the following inclusion criteria:

(1) Suffering from the pain and discomfort in the low back and/or lumbosacral region for more than 12 weeks;

(2) Score of 10-point Visual Analog Scale (VAS) is at least 3 point;

(3) Adults aged 18 to 75 years;

(4) Gender is unrestricted;

(5) The informed consent form is signed.

2.2.2 Exclusion criteria

Patients will be excluded if they meet at least one of the following exclusion criteria:

(1) Suffering from serious spinal diseases, such as spinal fracture, spine malformation, and spinal degenerative change;

(2) History of spinal surgery;

(3) Low back pain caused by soft tissue injuries or infectious diseases;

(4) Low back pain caused by visceral diseases, such as kidney stone, and hysteritis;

(5) History of serious cardiovascular and cerebrovascular diseases, diabetes, mental diseases, and cancer;

(6) Pregnant or lactating women.

2.2.3 Withdraw or termination criteria

Patients can withdraw from N-of-1 trials voluntarily at any time for any reason or are discontinued from N-of-1 trials passively due to poor compliance, rapid

progression of disease, or serious adverse events.

2.3 Random assignment and allocation concealment

The eligible patients will be randomly assigned into the Baduanjin exercise group or waiting list group during two periods of each treatment cycle. For example, a patient will take Baduanjin exercise during the first period and do not receive Baduanjin exercise during the second period in a treatment cycle. The random sequence may be different across the treatment cycles. For example, a patient may take Baduanjin exercise during the first period of the first treatment cycle and do not receive Baduanjin exercise during the first period of the second treatment cycle. Before these N-of-1 trials are conducted, the random sequence will be generated with SAS 9.1 software by a statistician who is not directly involved in these N-of-1 trials. A doctor will acquire each patient's random sequence by contacting the above-mentioned statistician to manage the assignment of interventions. It means that random allocation will be concealed to the doctors and patients before each treatment cycle begins.

2.4 Interventions

Patients in the Baduanjin exercise group will receive the standard Baduanjin exercise recommended by the General Administration of Sport of China[33,34]. It consists of a beginning posture, eight separate movements, and a ending posture represented graphically by some studies[33,34].

Before starting the first cycle, eligible participants will complete a training session to master the technical essentials of Baduanjin exercise guided by a

professional being engaged in the Baduanjin training. During each period of Baduanjin exercise, patients will perform a half-hour Baduanjin exercise once a day for a week. Nonstandard movements will be corrected by the professional via video conversation with patients if necessary. Any other treatment for alleviating chronic non-specific low back pain will be inhibited in all of treatment periods.

In the waiting list group, patients will not receive Baduanjin exercise and any other treatment for relieving chronic non-specific low back pain. Generally, therapies for relieving pain will be also not allowed during the wash-out periods. However, routine drugs for pain relief recommended by clinical guidelines may be used according to the doctor's advice if low back pain is intolerable. The use of painkillers will be recorded in detail.

2.5 Outcomes

The primary outcome is the pain intensity measured by a 10-point VAS. A higher VAS score indicates a more severe pain. The secondary outcomes include the physical functioning measured by the Oswestry Dability Index (ODI) and Japanese Orthopaedic Association Back Pain Evaluation Questionnaire (JOABPEQ), and the health-related quality of life measured by Short Form Health Survey 12 (SF-12). ODI is a patient-reported outcome tool with ten items, and ranges from 0% to 100%[35]. A higher ODI score indicates a worse physical functioning. JOABPEQ is self-administered questionnaire, and consists of 25 items in 5 domains: LBP, lumbar function, walking ability, social life function, and mental health[36]. The score ranges from 0 to 100, and higher scores indicate better condition for each domain of

JOABPEQ. SF-12 is a 12-item questionnaire to measure the physical and mental health[37]. VAS, ODI, and SF-12 are recommended as the core outcome measure instruments for clinical trials on the non-specific low back pain according to a consensus[38]. Safety outcomes include respiratory rate, heart rate, pulse, systolic blood pressure, diastolic blood pressure, adverse reactions, and so on.

2.6 Time schedule

Time schedule of participant enrolment, interventions, assessments and visits is presented in table 1. During the screening period, patients will be assessed for eligibility according to inclusion and exclusion criteria. Eligible patients will be asked to sign the informed consent, and take a Baduanjin training course. Then, patients will experience three treatment cycles one by one. During the first washout period of the first cycle, general characteristics such as age, gender, history of diseases will be collected by a trained researcher. Then, patients will be assigned to the Baduanjin exercise or waiting list group randomly at the beginning of each treatment period. VAS, ODI, JOABPEQ, and SF-12 belong to patient-reported outcomes. Patients will be asked to answer the questions in these four scales at the beginning and the end of each treatment period. Any used drug or adverse event will be recorded in detail.

Table 1. Time schedule of participant enrolment, interventions, assessments and visits

Items	Screening	Cycle 1				Cycle 2				Cycle 3			
		Washout period 1	Treatment period 1	Washout period 2	Treatment period 2	Washout period 1	Treatment period 1	Washout period 2	Treatment period 2	Washout period 1	Treatment period 1	Washout period 2	Treatment period 2
	Day -3 to -1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Eligibility criteria	X												
Informed consent	X												
Baduanjin training	X												
Demographic characteristic		X											
Randomization			X		X		X		X		X		X
VAS			X		X		X		X		X		X
ODI			X		X		X		X		X		X
JOABPEQ			X		X		X		X		X		X
SF-12			X		X		X		X		X		X
Drug combination		X	X	X	X	X	X	X	X	X	X	X	X
Safety		X	X	X	X	X	X	X	X	X	X	X	X

VAS, Visual Analog Scale; ODI, Oswestry Dability Index; JOABPEQ, Japanese Orthopaedic Association Back Pain Evaluation Questionnaire; SF-12, Short Form Health Survey 12

2.7 Data management

An electronic case report form (eCRF) based on WeChat social platform will be designed to collect patients' data. WeChat is one of the most widely used social networking platforms in China, and has been used as the data management platform in some clinical trials[39.40]. During the screening period, each patient's WeChat account will be collected. At the beginning and the end of each treatment or washout period, data managers will provide an unfilled eCRF to patients via WeChat platform. Patients will fill in the eCRF based on their own conditions. Data managers are blinded to each patient's random allocation. However, they can check the completed eCRF online in real time, and contact the patients to verify and modify the questionable data if necessary. When a treatment cycle is completed, the individual data will be exported in time for the statistical analysis. The individual information, such as the patient's name and mobile phone number, will be hidden to protect the patient's privacy.

2.8 Sample size

The estimation of sample size depends on the primary outcome, statistical analysis method, etc. In this study, VAS as the primary outcome will be analyzed using Bayesian hierarchical models. However, no convenient software packages are accessible for estimating sample size of N-of-1 trials with Bayesian hierarchical models. So, sample size is calculated based on a simulation-based two-step method described by Stunnenberg et al[41]. Firstly, the simulated data of N-of-1 trials with three cycles is generated based on the following parameters. A small effect on pain

relief is defined as a 10-point VAS score reduction of 0.5 to 1.0 point according to a clinical practice guideline from the American College of Physicians[4]. Therefore, the minimum clinically significant difference is set to 0.5. It means that a clinically significant difference is reached when mean difference of VAS score between two groups is more than 0.5. The standard deviation is set to 1.0 according to our previous study[19]. The autocorrelation coefficient between two groups is set to 0.5[42]. The proportion of random missing values is set to 20%. Secondly, Bayesian hierarchical model is built based on the above-mentioned simulated data by WinBUGS 1.4.3 software. The process is repeated for 50000 times with a burn-in of 5000 times using Markov Chain Monte Carlo methods[43]. When the simulated data from 50 N-of-1 trials is used to build Bayesian hierarchical models, the posterior probability of posterior mean difference > 0.5 is 82.7%, which exceeds a pre-defined threshold of 80%. Therefore, 50 patients will be recruited.

2.9 Statistical analysis

The mean with the standard deviation will be calculated for the quantitative data. The frequency and the percentage will be calculated for the qualitative data. The mean difference of VAS, JOABPEQ, ODI, and SF-12 score between two groups will be compared using Bayesian hierarchical models by WinBUGS 1.4.3 software. Non-informative prior distribution will be used because of the lack of prior information. The number of iterations will be set to 50000 with a burn-in of 5000 times[43]. Overall and individual posterior mean difference with 95% credibility intervals between two groups will be estimated synchronously. Overall and individual

posterior probability of posterior mean difference > 0.5 mentioned in sample size section will be computed. The posterior probabilities of 80% and 20% will be considered as the cut-off values to stop a N-of-1 trial[41]. When a treatment cycle is completed and individual posterior probability is more than 80%, this patient will not participate in the next treatment cycle because of the sufficient benefit, and is advised to perform Baduanjin exercise to improve CNLBP. If individual posterior probability falls in between 20% and 80%, this patient will participate in the next treatment cycle because of the uncertain benefit. If individual posterior probability is less than 20%, this patient will not participate in the next treatment cycle because of the insufficient benefit, and is advised to seek for alternative treatments.

3. Patient and public involvement

Patients/the public were not involved in the design, the recruitment to and conduct of the study.

4. Ethics and dissemination

This study was approved by the medical ethics committee of Tianjin University of Traditional Chinese Medicine with the reference number TJUTCM-EC20220005. The results will be published in a peer-reviewed journal or international conferences.

Authors' contributions

JZ conceived the study. AL and WY designed the inclusion and exclusion criteria. TG designed the time schedule. JZ drafted the manuscript. AL, WY and TG reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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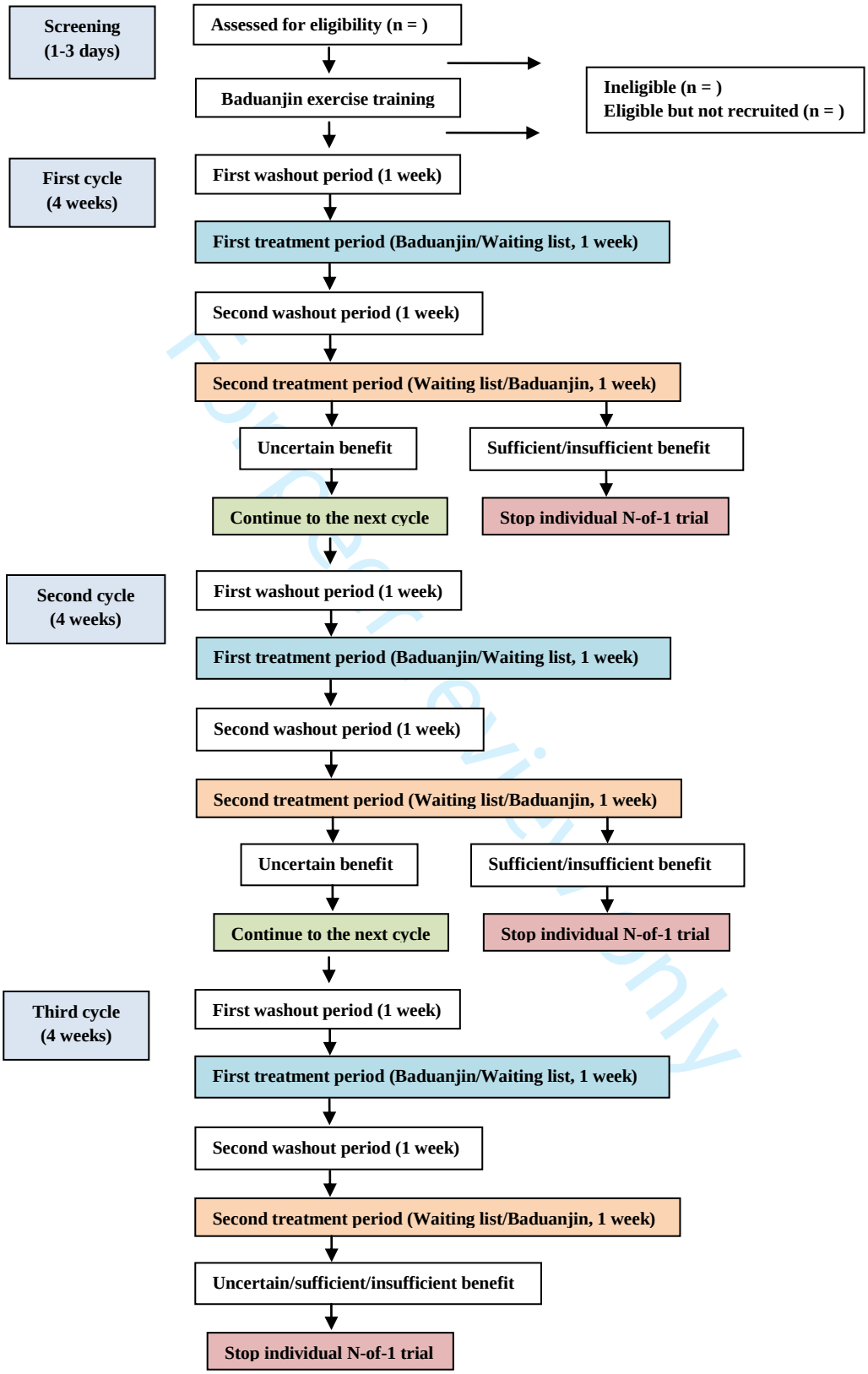
Figure Legends:

Figure 1. Flow diagram of a series of N-of-1 trials



SPIRIT checklist

Section/Item	Item Number	Description	Reported on page #
Administrative information			
Title	**1**	**Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym**	**1**
Trial registration	**2a**	**Trial identifier and registry name. If not yet registered, name of intended registry**	**2**
	2b	**All items from the World Health Organization Trial Registration Data Set**	**2**
Protocol version	**3**	**Date and version identifier**	**2**
Funding	**4**	**Sources and types of financial, material, and other support**	**14**
Roles and responsibilities	**5a**	**Names, affiliations, and roles of protocol contributors**	**1,13**
	5b	**Name and contact information for the trial sponsor**	**1,13**
	5c	**Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities**	**13**
	5d	**Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable**	**13**
Introduction			
Background and rationale	**6a**	**Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention**	**3-5**
	6b	**Explanation for choice of comparators**	**3-5**
Objectives	**7**	**Specific objectives or hypotheses**	**5**
Trial design	**8**	**Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority,**	**5**

		exploratory)	
Methods Participants, interventions, and outcomes			
Study setting	**9**	**Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained**	**5**
Eligibility criteria	**10**	**Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)**	**6,7**
Interventions	**11a**	**Interventions for each group with sufficient detail to allow replication, including how and when they will be administered**	**7,8**
	11b	**Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)**	**7,8**
	11c	**Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)**	**7,8**
	11d	**Relevant concomitant care and interventions that are permitted or prohibited during the trial**	**7,8**
Outcomes	**12**	**Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended**	**8,9**
Participant timeline	**13**	**Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended**	**9,10**
Sample size	**14**	**Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations**	**11,12**

Recruitment	**15**	**Strategies for achieving adequate participant enrollment to reach target sample size**	**5**
Assignment of interventions (for controlled trials)			
Allocation			
Sequence generation	**16a**	**Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions**	**7**
Allocation concealment mechanism	**16b**	**Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned**	**7**
Implementation	**16c**	**Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions**	**7**
Blinding (masking)	**17a**	**Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how**	**11**
	17b	**If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial**	**7,8**
Data collection, management, and analysis			
Data collection methods	**18a**	**Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol**	**11**
	18b	**Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention**	**11**

		protocols	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12,13
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	12,13
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	12,13
Monitoring			
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12,13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking REC/IRB approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators)	2
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized	9,10

		surrogates, and how (see item 32)	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the tri	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogate	9,10
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

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Baduanjin exercise for chronic non-specific low back pain: protocol for a series of N-of-1 trials

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Baduanjin exercise for chronic non-specific low back pain: protocol for a series of N-of-1 trials

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Abstract:

Introduction Chronic non-specific low back pain (CNLBP) is one of the most common health problems worldwide. Exercise has been recommended for treating chronic low back pain according to a clinical guideline from the American College of Physicians. Traditional Chinese medicine (TCM) has become increasingly popular for the management of chronic low back pain in recent years. Baduanjin exercise is one of exercise therapies in TCM. N-of-1 trial is a randomized cross-over self-controlled trial and is suitable for patients with the chronic disease. A series of similar N-of-1 trials can be combined to estimate overall and individual treatment effects synchronously by hierarchical Bayesian analysis. A review showed that N-of-1 trial could be considered as a good tool to evaluate the efficacy of TCM. This study will conduct a series of N-of-1 trials with hierarchical Bayesian analysis to assess the efficacy and safety of Baduanjin exercise for CNLBP.

Methods and analysis This study is a series of N-of-1 trials on Baduanjin exercise for treating CNLBP. Fifty participants will experience one to three treatment cycles. They will be randomly assigned into the Baduanjin exercise or waiting list group for a week during two periods of each treatment cycle. The primary outcome is a 10-point Visual Analog Scale. The secondary outcomes include the Oswestry Disability Index, Japanese Orthopaedic Association Back Pain Evaluation Questionnaire, and Short Form Health Survey 12. The statistical analysis will be conducted by WinBUGS 1.4.3 software. Overall and individual treatment effects will be estimated synchronously by hierarchical Bayesian analysis.

Ethics and dissemination This study was approved by the medical ethics committee of Tianjin University of Traditional Chinese Medicine with the reference number TJUTCM-EC20220005. The results will be published in a peer-reviewed journal or international conferences.

Trial registration number ChiCTR2200063307.

Strengths and limitations of this study

1. This study is a series of N-of-1 trials on Baduanjin exercise for the management of chronic non-specific low back pain.

2. Overall and individual treatment effects will be estimated synchronously by hierarchical Bayesian analysis.

3. Sample size is calculated based on a simulation-based two-step method.

4. Patients will be recruited from the department of orthopedics in a teaching hospital.

1. Introduction

Low back pain (LBP) is one of the most common health problems worldwide[1]. The age-standardized global prevalence of LBP reaches up to 7.50%[2]. Most of patients with LBP have no specific pathological changes associated with LBP and are classified as non-specific LBP patients[3]. When non-specific LBP lasts more than 12 weeks, it progresses to a chronic stage and is labeled as chronic non-specific low back pain (CNLBP)[4]. LBP may increase physician visits and years lived with disability, and contribute to absence from work and growing financial burden[1,5,6]. The average direct medical cost per patient with chronic LBP is US$1,516.67 per year in KwaZulu-Natal, South Africa[7]. The mean cost of care per presentation for older adults with non-specific LBP was A$5,844 in the 2019/2020 financial year in Australia[8]. Therefore, a call for action on the management of LBP is proposed[9].

There are many pharmaceutical and non-pharmaceutical therapies for LBP[4]. Some studies showed the insufficient evidence on the efficacy of long-term opioids for chronic pain relief and function improvement[10,11]. A systematic review found more adverse events (such as headache and nausea) after non-steroid anti-inflammatory drugs and opioids compared with placebo in patients with CNLBP[12]. Some systematic reviews reported that exercise and physical activity were beneficial for the recovery of CNLBP[13-15]. Exercise has been recommended for chronic LBP according to a clinical guideline from the American College of Physicians[4]. However, no optimal exercises have been recommended for CNLBP at present[13].

Traditional Chinese medicine (TCM) has become increasingly popular for the

management of chronic LBP in recent years[16]. Baduanjin exercise is one of exercise therapies in TCM, and consists of eight simple and separate core movements[17,18]. Each movement is learned easily and completed slowly to keep patients breathing smoothly and rhythmically[19]. It has no specific requirements for users. It might relieve the pain by promoting the balance between sympathetic and parasympathetic activities, and stimulating the brain regions associated with emotion and stress[20]. A systematic review showed that Baduanjin exercise could relieve the musculoskeletal pain in patients with chronic diseases[21]. LBP was one of the most extensively investigated diseases in clinical studies on Baduanjin exercise[19]. It might be effective for the pain relief and function improvement in patients with low back pain[22]. Nonetheless, the efficacy on Baduanjin exercise for CNLBP has been not confirmed due to the lack of high-quality clinical trials on this topic.

Randomized control trials (RCTs) are known as the gold standard of therapeutic evaluation[23]. However, the average effects estimated from RCTs may represent a mixture of different therapeutic effects in individual patients[24]. The individualized clinical decision should be made cautiously based on the evidence from RCTs in view of the gap between clinical trials and clinical practice[25,26]. N-of-1 trial is a randomized cross-over self-controlled trial conducted in a patient[27]. The result of N-of-1 trial can be directly used to make individualized clinical decision[27]. It is useful to fill the gap between clinical trials and clinical practice[28]. A series of similar N-of-1 trials can be combined to estimate overall and individual treatment effects synchronously by hierarchical Bayesian analysis[29,30]. A review showed that Bayesian

analysis was used in 23% of N-of-1 trials with the pooled analysis[31]. Bayesian analysis is also recommended for combining N-of-1 trials according to the Agency for Healthcare Research and Quality[32]. N-of-1 trials are suitable for patients with chronic disease[32]. Many N-of-1 trials on chronic pain have been published in recent years[33]. A review showed that N-of-1 trial could be considered as a good tool to evaluate the efficacy of TCM[34]. Therefore, this study will conduct a series of N-of-1 trials with hierarchical Bayesian analysis to assess the efficacy and safety of Baduanjin exercise for CNLBP.

2. Methods and analysis

2.1 Study design

This study is a series of N-of-1 trials on Baduanjin exercise for the management of chronic non-specific low back pain. The flow diagram is showed in figure 1. Firstly, patients will be assessed for eligibility and participate in a Baduanjin exercise training. Then, eligible participants will experience one to three treatment cycles. Each cycle will include a period of Baduanjin exercise and a period of waiting list. A one-week washout period will be set between the above-mentioned two periods. It is developed following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[35]. Outpatients or inpatients will be recruited from the department of orthopedics in the first teaching hospital of Tianjin University of traditional Chinese medicine. This study will be conducted from May 1, 2023 to December 31, 2025. To bring potentially eligible patients' attention, recruitment advertisements will be posted at the entrance of outpatient and inpatient department.

2.2 Patients

2.2.1 Inclusion criteria

Patients will be considered for inclusion when they meet all of items in the following inclusion criteria:

(1) Suffering from the pain and discomfort in the low back and/or lumbosacral region for more than 12 weeks[4];

(2) Score of 10-point Visual Analog Scale (VAS) is at least 3 point[36,37];

(3) Adults aged 18 to 75 years;

(4) Gender is unrestricted;

(5) The informed consent form is signed.

2.2.2 Exclusion criteria

Patients will be excluded if they meet at least one of the following exclusion criteria:

(1) Suffering from serious spinal diseases, such as spinal fracture, spine malformation, and spinal degenerative change;

(2) History of spinal surgery;

(3) Low back pain caused by soft tissue injuries or infectious diseases;

(4) Low back pain caused by visceral diseases, such as kidney stone, and hysteritis;

(5) History of serious cardiovascular and cerebrovascular diseases, diabetes, mental diseases, and cancer;

(6) Pregnant or lactating women.

2.2.3 Withdraw or termination criteria

Patients can withdraw from N-of-1 trials voluntarily at any time for any reason or are discontinued from N-of-1 trials passively due to serious deviation from the protocol, poor compliance, rapid progression of disease, or serious adverse events.

2.3 Random assignment and allocation concealment

The eligible patients will be randomly assigned into the Baduanjin exercise group or waiting list group during two periods of each treatment cycle. For example, a patient will take Baduanjin exercise during the first period and do not receive Baduanjin exercise during the second period in a treatment cycle. The random sequence may be different across the treatment cycles. For example, a patient may take Baduanjin exercise during the first period of the first treatment cycle and do not receive Baduanjin exercise during the first period of the second treatment cycle. Before these N-of-1 trials are conducted, the random sequence will be generated with SAS 9.1 software by a statistician who is not directly involved in these N-of-1 trials. A doctor will acquire each patient's random sequence by contacting the above-mentioned statistician to manage the assignment of interventions. It means that random allocation will be concealed to the doctors and patients before each treatment cycle begins.

2.4 Interventions

Patients in the Baduanjin exercise group will receive the standard Baduanjin exercise recommended by the General Administration of Sport of China[38,39]. It consists of a preparation posture, eight separate movements and a ending posture presented graphically by previous studies[38,39].

Before starting the first cycle, eligible participants will complete a training session to master the technical essentials of Baduanjin exercise guided by a professional who is engaged in the Baduanjin training. During each period of Baduanjin exercise, patients will perform a half-hour Baduanjin exercise once a day for a week. Nonstandard movements will be corrected by the professional via video conversation with patients if necessary. Any other treatment for alleviating chronic non-specific low back pain will be inhibited in all of treatment periods.

In the waiting list group, in order to assess the actual efficacy of Baduanjin exercise, patients will not receive Baduanjin exercise and any other treatment for relieving chronic non-specific low back pain. Generally, therapies for relieving pain will be also not allowed during the wash-out periods. However, routine drugs for pain relief recommended by clinical guidelines may be used according to the doctor's advice if low back pain is intolerable. The use of painkillers will be recorded in detail.

2.5 Outcomes

The primary outcome is the pain intensity measured by a 10-point VAS. A higher VAS score indicates a more severe pain. It has a good reliability (r=0.96) and validity (r=0.97)[40]. The secondary outcomes include the physical functioning measured by the Oswestry Disability Index (ODI) and Japanese Orthopaedic Association Back Pain Evaluation Questionnaire (JOABPEQ), and the health-related quality of life measured by Short Form Health Survey 12 (SF-12). ODI is a patient-reported outcome tool with a high reliability (r=0.89) and good validity (r=0.76)[41]. ODI ranges from 0% to 100%[42]. A higher ODI indicates a worse physical functioning. JOABPEQ is a self-administered questionnaire with a high reliability (r=0.977) and good validity (r=0.726)[43]. It consists of 25 items in 5 domains: LBP, lumbar function, walking ability, social life function, and mental health[44]. The score ranges from 0 to

100, and higher scores indicate better condition for each domain of JOABPEQ. SF-12 is a 12-item questionnaire to measure the physical and mental health[45]. The Cronbach alpha coefficients for two subscales of SF-12 are 0.77 and 0.80, respectively[46]. VAS, ODI, and SF-12 are recommended as the core outcome measure instruments for clinical trials on the non-specific low back pain according to a consensus[47]. Safety outcomes include respiratory rate, heart rate, pulse, systolic blood pressure, diastolic blood pressure, adverse reactions (such as elevation of blood pressure, increased pain), and so on.

2.6 Time schedule

Time schedule of participant enrolment, interventions, assessments and visits is presented in Supplementary Table 1. During the screening period, patients will be assessed for eligibility according to the inclusion and exclusion criteria. Eligible patients will be asked to sign the informed consent, and take a Baduanjin training course. Then, patients will experience three treatment cycles one by one. During the first washout period of the first cycle, general characteristics such as age, gender, history of diseases will be collected by a trained researcher. Then, patients will be assigned to the Baduanjin exercise or waiting list group randomly at the beginning of each treatment period. VAS, ODI, JOABPEQ, and SF-12 belong to patient-reported outcomes. Patients will be asked to answer the questions in the four scales at the beginning and the end of each treatment period. Any used drug or adverse event will be recorded in detail. Patients who suffer from adverse reactions will be properly treated.

2.7 Data management

An electronic case report form (eCRF) based on WeChat social platform will be

designed to collect patients' data. WeChat is one of the most widely used social networking platforms in China, and has been used as the data management platform in some clinical trials[48.49]. During the screening period, each patient's WeChat account will be collected. At the beginning and the end of each treatment or washout period, data managers will provide an unfilled eCRF to patients via WeChat platform. Patients will fill in the eCRF based on their own conditions. Data managers are blinded to each patient's random allocation. However, they can check the completed eCRF online in real time, and contact the patients to verify and modify the questionable data if necessary. When a treatment cycle is completed, the individual data will be exported in time for the statistical analysis. The individual information, such as the patient's name and mobile phone number, will be hidden to protect the patient's privacy.

A Data and Safety Monitoring Committee (DSMC) independent from the sponsor will be set up to assess the severity of the deviation from the protocol, poor compliance and serious adverse events. If necessary, patients will be discontinued from N-of-1 trials due to above-mentioned events.

2.8 Sample size

The estimation of sample size depends on the primary outcome, statistical analysis method, etc. In this study, VAS as the primary outcome will be analyzed using Bayesian hierarchical models. However, no convenient software packages are accessible for estimating sample size of N-of-1 trials with Bayesian hierarchical models. So, sample size is calculated based on a simulation-based two-step method

described by Stunnenberg et al[50]. Firstly, the simulated data of N-of-1 trials with three cycles is generated based on the following parameters. A small effect on pain relief is defined as a 10-point VAS score reduction of 0.5 to 1.0 point according to a clinical practice guideline from the American College of Physicians[4]. Therefore, the minimum clinically significant difference is set to 0.5. It means that a clinically significant difference is reached when mean difference of VAS score between two groups is more than 0.5. The standard deviation is set to 1.0 according to our previous study[22]. The autocorrelation coefficient between two groups is set to 0.5[51]. The proportion of random missing values is set to 20%. Secondly, Bayesian hierarchical model is built based on the above-mentioned simulated data by WinBUGS 1.4.3 software. The process is repeated for 50000 times with a burn-in of 5000 times using Markov Chain Monte Carlo methods[52]. When the simulated data from 50 N-of-1 trials is used to build Bayesian hierarchical models, the posterior probability of posterior mean difference > 0.5 is 82.7%, which exceeds a pre-defined threshold of 80%. Therefore, 50 patients will be recruited.

2.9 Statistical analysis

The mean with the standard deviation will be calculated for the quantitative data. The frequency and the percentage will be calculated for the qualitative data. The data will be analyzed based on intention-to-treat principle. The mean difference of VAS, JOABPEQ, ODI, and SF-12 score between two groups will be compared using Bayesian hierarchical models by WinBUGS 1.4.3 software. Non-informative prior distribution will be used because of the lack of prior information. The number of

iterations will be set to 50000 with a burn-in of 5000 times[52]. Overall and individual posterior mean difference with 95% credibility intervals between two groups will be estimated synchronously. Overall and individual posterior probability of posterior mean difference > 0.5 mentioned in sample size section will be computed. The posterior probabilities of 80% and 20% will be considered as the cut-off values to stop a N-of-1 trial[50]. When a treatment cycle is completed and individual posterior probability is more than 80%, this patient will not participate in the next treatment cycle because of the sufficient benefit, and is advised to perform Baduanjin exercise to improve CNLBP. If individual posterior probability falls in between 20% and 80%, this patient will participate in the next treatment cycle because of the uncertain benefit. If individual posterior probability is less than 20%, this patient will not participate in the next treatment cycle because of the insufficient benefit, and is advised to seek for alternative treatments.

3. Patient and public involvement

Patients/the public were not involved in the design, the recruitment to and conduct of the study.

4. Ethics and dissemination

This study was approved by the medical ethics committee of Tianjin University of Traditional Chinese Medicine with the reference number TJUTCM-EC20220005. Any protocol modification will be recorded by this medical ethics committee. The results will be published in a peer-reviewed journal or international conferences.

5. Discussion

Exercise is recommended for the treatment of chronic LBP according to the latest clinical guideline[4]. Baduanjin exercise is widely used for the management of the pain. In this study, we will conduct a series of N-of-1 trials to assess the efficacy and safety of Baduanjin exercise for CNLBP in the department of orthopedics in a teaching hospital. Overall and individual treatment effects will be estimated synchronously by hierarchical Bayesian analysis. The findings from this study will provide the high-quality evidence for the clinical decision-making in patients with CNLBP.

Authors' contributions

JZ conceived the study. AL and WY designed the inclusion and exclusion criteria. TG designed the time schedule. JZ drafted the manuscript. AL, WY and TG reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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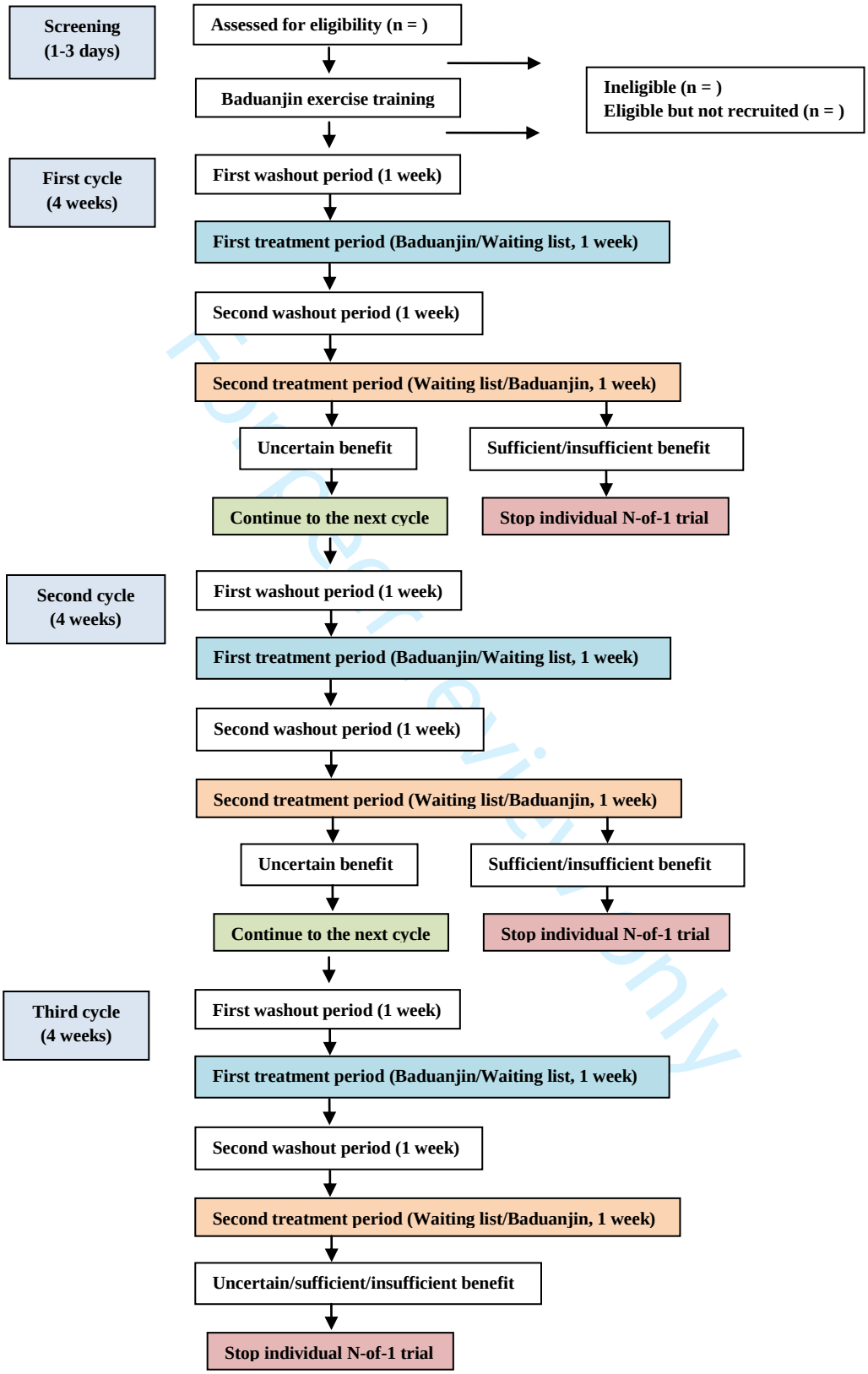
Figure Legends:

Figure 1. Flow diagram of a series of N-of-1 trials



Supplementary Table 1. Time schedule of participant enrolment, interventions, assessments and visits

Items	Screening	Cycle 1				Cycle 2				Cycle 3			
		Washout period 1	Treatment period 1	Washout period 2	Treatment period 2	Washout period 1	Treatment period 1	Washout period 2	Treatment period 2	Washout period 1	Treatment period 1	Washout period 2	Treatment period 2
	Day -3 to -1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Eligibility criteria	X												
Informed consent	X												
Baduanjin training	X												
Demographic characteristic		X											
Randomization			X		X		X		X		X		X
VAS			X		X		X		X		X		X
ODI			X		X		X		X		X		X
JOABPEQ			X		X		X		X		X		X
SF-12			X		X		X		X		X		X
Drug combination		X	X	X	X	X	X	X	X	X	X	X	X
Safety		X	X	X	X	X	X	X	X	X	X	X	X

VAS, Visual Analog Scale; ODI, Oswestry Disability Index; JOABPEQ, Japanese Orthopaedic Association Back Pain Evaluation Questionnaire; SF-12, Short Form Health Survey 12

SPIRIT checklist

Section/Item	Item Number	Description	Reported on page #
Administrative information			
Title	**1**	**Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym**	**1**
Trial registration	**2a**	**Trial identifier and registry name. If not yet registered, name of intended registry**	**2**
	2b	**All items from the World Health Organization Trial Registration Data Set**	**2**
Protocol version	**3**	**Date and version identifier**	**2**
Funding	**4**	**Sources and types of financial, material, and other support**	**13**
Roles and responsibilities	**5a**	**Names, affiliations, and roles of protocol contributors**	**1,13**
	5b	**Name and contact information for the trial sponsor**	**1,13**
	5c	**Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities**	**13**
	5d	**Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable**	**10**
Introduction			
Background and rationale	**6a**	**Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention**	**3-5**
	6b	**Explanation for choice of comparators**	**3-5**
Objectives	**7**	**Specific objectives or hypotheses**	**5**
Trial design	**8**	**Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority,**	**5**

		exploratory)	
Methods Participants, interventions, and outcomes			
Study setting	**9**	**Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained**	**5**
Eligibility criteria	**10**	**Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)**	**6**
Interventions	**11a**	**Interventions for each group with sufficient detail to allow replication, including how and when they will be administered**	**7,8**
	11b	**Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)**	**7**
	11c	**Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)**	**8**
	11d	**Relevant concomitant care and interventions that are permitted or prohibited during the trial**	**8**
Outcomes	**12**	**Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended**	**8,9**
Participant timeline	**13**	**Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended**	**9**
Sample size	**14**	**Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations**	**10,11**

Recruitment	**15**	**Strategies for achieving adequate participant enrollment to reach target sample size**	**5,6**
Assignment of interventions (for controlled trials)			
Allocation			
Sequence generation	**16a**	**Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions**	**7**
Allocation concealment mechanism	**16b**	**Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned**	**7**
Implementation	**16c**	**Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions**	**7**
Blinding (masking)	**17a**	**Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how**	**10**
	17b	**If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial**	**10**
Data collection, management, and analysis			
Data collection methods	**18a**	**Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol**	**10**
	18b	**Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention**	**10**

		protocols	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11,12
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	11,12
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	11,12
Monitoring			
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9,10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking REC/IRB approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized	9

		surrogates, and how (see item 32)	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigator for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions	12,13
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	12,13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogate	Not applicable
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

BMJ Open

Baduanjin exercise for chronic non-specific low back pain: protocol for a series of N-of-1 trials

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Baduanjin exercise for chronic non-specific low back pain: protocol for a series of N-of-1 trials

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Abstract:

Introduction Chronic non-specific low back pain (CNLBP) is one of the most common health problems worldwide. Exercise is recommended for the treatment of chronic low back pain (LBP) according to the clinical guideline released by the American College of Physicians. Traditional Chinese medicine (TCM) is becoming increasingly popular for the management of chronic LBP in recent years. Baduanjin exercise is one of the exercise therapies in TCM. N-of-1 trial is a randomized cross-over self-controlled trial that is suitable for patients with the chronic disease. A series of similar N-of-1 trials can be combined to estimate overall and individual therapeutic effects synchronously by hierarchical Bayesian analysis. N-of-1 trial can be considered as a good tool for evaluating the therapeutic effect of TCM. Therefore, this study aims to conduct a series of N-of-1 trials with hierarchical Bayesian analysis for the sake of assessing whether Baduanjin exercise is effective and safe for CNLBP.

Methods and analysis This study is a series of N-of-1 trials on Baduanjin exercise for the management of CNLBP. Fifty participants will experience one to three treatment cycles. They will be randomized into Baduanjin exercise or waiting list group for a week during the two periods of each treatment cycle. The primary outcome is the 10-point Visual Analogue Scale. The secondary outcomes include the Oswestry Disability Index, the Japanese Orthopaedic Association Back Pain Evaluation Questionnaire, and the Short Form Health Survey 12. The statistical analysis will be conducted with WinBUGS 1.4.3 software. Overall and individual therapeutic effects will be estimated synchronously by hierarchical Bayesian analysis.

Ethics and dissemination This study is approved by the Medical Ethics Committee of Tianjin University of TCM (reference number TJUTCM-EC20220005). Our findings will be published in a peer-reviewed journal or international conferences.

Trial registration number ChiCTR2200063307.

Strengths and limitations of this study

1. This study is a series of N-of-1 trials on Baduanjin exercise for the management of CNLBP.

2. Overall and individual therapeutic effects will be estimated synchronously by hierarchical Bayesian analysis.

3. Sample size is calculated according to a simulation-based two-step method.

4. Patients will be recruited from the Department of Orthopedics in a teaching hospital.

1. Introduction

Low back pain (LBP) represents a frequently seen health issue globally [1]. The age-standardized global prevalence of LBP reaches up to 7.50% [2]. Most of patients with LBP do not exhibit any specific pathological changes associated with LBP and are classified as non-specific LBP patients [3]. Non-specific LBP lasting over 12 weeks will progress to a chronic stage, which is labeled as chronic non-specific LBP (CNLBP) [4]. LBP may increase physician visits and years lived with disability, and contribute to absence from work and growing financial burden [1,5,6]. The annual average direct medical cost per patient with chronic LBP is US$1,516.67 in KwaZulu-Natal, South Africa [7]. The average cost of care per presentation for older adults with non-specific LBP was A$5,844 in the 2019/2020 financial year in Australia [8]. Therefore, it is urgently needed to manage LBP [9].

There are many pharmaceutical and non-pharmaceutical therapies for LBP [4]. Of them, opioid analgesics are the common prescribed medications for pain management. However, for patients with chronic pain, repeated administration may cause opioid-induced tolerance and hyperalgesia [10]. Subsequently, the patients may need a higher dose of opioids to maintain the initial level of analgesia, which increases the risk of overdose. In the case of opioid dependence, abrupt discontinuation of opioids can lead to withdrawal symptoms, such as insomnia, nausea and vomiting [11]. There is insufficient evidence regarding the long-term opioid application in relieving chronic pain and improving function [12]. Moreover, the long-term opioid therapy can increase the risk of harms, like opioid abuse and myocardial infarction [12].

Non-steroid anti-inflammatory drugs (NSAIDs) have been frequently used for acute LBP, which can achieve mild to moderate effects on chronic LBP [13]. As shown in a network meta-analysis, multiple drugs can significantly relieve chronic LBP [14]. In particular, cyclo-oxygenase 2-selective NSAIDs are effective on both pain relief and functional improvement. However, NSAIDs may be associated with more adverse events than placebo for chronic LBP [15]. At present, drug recommendations for chronic LBP are heterogeneous among different countries [16]. For example, the use of opioids is inconclusive in the Canada clinical guideline, but it is recommended in the USA clinical guideline. Non-pharmacological therapies should be considered as the first-line therapies for CNLBP [16]. It is reported in some systematic reviews that exercise and physical activity are beneficial for the recovery of CNLBP [17-19]. According to the American College of Physicians guideline, exercise is recommended for chronic LBP [4]. However, the optimal exercises for CNLBP have not been reached yet [17].

Traditional Chinese medicine (TCM) is becoming increasingly popular for the management of chronic LBP in recent years [20]. Baduanjin exercise is one of the exercise therapies in TCM, which consists of eight simple and separate core movements [21,22]. Each movement can be learned easily and completed slowly so that the patients can breathe smoothly and rhythmically [23]. In general, it has no specific requirements for users. In a systematic review, Baduanjin exercise is demonstrated to relieve the musculoskeletal pain in chronic disease patients [24]. LBP is one of the most extensively investigated diseases in clinical studies on Baduanjin

exercise [23]. Baduanjin exercise may be effective on the pain relief and functional improvement in patients with LBP [25]. Nonetheless, the efficacy of Baduanjin exercise in CNLBP has been not confirmed since relevant high-quality clinical trials are lacking.

Randomized control trials (RCTs) have been identified as the gold standard of therapeutic evaluation [26]. However, the average effects estimated from RCTs may represent a mixture of different therapeutic effects in individual patients [27]. In view of the gap between clinical trials and clinical practice, the individualized clinical decision should be made with caution based on the evidence from RCTs [28,29]. N-of-1 trial is a randomized cross-over self-controlled trial conducted in one patient [30], and its result can be directly used to make individualized clinical decision [30]. In this regard, it is useful to fill the gap between clinical trials and clinical practice [31]. Moreover, it is feasible to combine a series of similar N-of-1 trials for estimating the overall and individual therapeutic effects synchronously by hierarchical Bayesian analysis [32,33]. A review shows that Bayesian analysis is used in 23% of N-of-1 trials with the pooled analysis [34]. In addition, Bayesian analysis can be recommended for the combination of N-of-1 trials according to the Agency for Healthcare Research and Quality [35]. N-of-1 trials are suitable for chronic disease patients [35]. Many N-of-1 trials on chronic pain are published recently [36]. As reported in a review, N-of-1 trial can be considered as a good tool for evaluating the therapeutic effect of TCM [37]. Therefore, this study aims to conduct N-of-1 trials with hierarchical Bayesian analysis for the sake of assessing whether Baduanjin

exercise is effective and safe for CNLBP.

2. Methods and analysis

2.1 Study design

The present study will conduct a series of N-of-1 superiority trials on Baduanjin exercise for the management of CNLBP. The flow diagram is shown in Figure 1. Firstly, patients will be assessed for eligibility and participate in a Baduanjin exercise training. Then, eligible participants will experience one to three treatment cycles. The number of experienced treatment cycles in each patient depends on the results of statistical analysis at the end of each cycle. Each cycle includes a period of Baduanjin exercise and a period of waiting list. Typically, a one-week washout period, during which therapies for relieving CNLBP are not allowed to eliminate the efficacy of previously received interventions, will be set between the above-mentioned two periods in view of the feasibility of N-of-1 trials. It is set in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [38]. Outpatients or inpatients will be recruited from the Department of Orthopedics in the First Teaching Hospital of Tianjin University of TCM. This study will be conducted from October 1, 2023 to December 31, 2025. To catch the attention of potentially eligible patients and obtain sufficient participant recruitment to reach the target sample size, recruitment advertisements will be posted at the entrance of outpatient and inpatient departments. Items of the World Health Organization Trial Registration Data Set, registration date and protocol version are available at https://www.chictr.org.cn/showprojEN.html?proj=172369.

2.2 Patients

2.2.1 Inclusion criteria

Patients conforming to the criteria below will be included:

(1) Patients suffering from chronic LBP that is defined as the pain and discomfort in the low back and/or lumbosacral region for more than 12 weeks according to the clinical practice guideline released by the American College of Physicians [4].

(2) Patients having at least 3 points on the Visual Analogue Scale (VAS) (range, 0-10). Pain of at least 3 points is considered as a perceptible persistent pain. This standard has also been used in some previous studies on this topic [39,40].

(3) The age of patients ranging from 18 to 75 years.

(4) Gender is unrestricted.

(5) Patients signing the informed consent form in supplementary file.

2.2.2 Exclusion criteria

Patients conforming to the criteria below will be eliminated:

(1) Patients suffering from severe spinal diseases, such as spinal fracture, spine malformation, and spinal degenerative change.

(2) Patients with a history of spinal surgery.

(3) Patients with LBP caused by soft tissue injuries or infectious diseases.

(4) Patients with LBP caused by visceral diseases, such as kidney stone, and hysteritis.

(5) Patients having a history of severe cardiovascular and cerebrovascular diseases, diabetes, mental diseases, cognitive impairment, and cancer. Patients with cognitive

impairment may be unable to complete the N-of-1 trials, such as mastering the technical essentials of Baduanjin exercise, and completing the measurement of patient-reported outcomes. Cognitive impairment can be often determined using the mini-mental state examination (MMSE). Patients with MMSE < 27 are diagnosed with cognitive impairment [41] and will be excluded from this study.

(6) Pregnant or lactating women.

2.2.3 Withdrawal or termination criteria

Patients can withdraw from N-of-1 trials voluntarily at any time for any reason including participant request and rapid progression of disease. On the other hand, patients can be discontinued from N-of-1 trials passively due to serious deviation from the protocol, poor compliance, rapid progression of disease, or serious adverse events. N-of-1 trials will be terminated when patients meet the termination criteria based on the interim analysis or complete three treatment cycles.

2.3 Random assignment and allocation concealment

The eligible patients will be randomized into Baduanjin exercise or waiting list group during the two periods of each treatment cycle. For example, a patient may take Baduanjin exercise during the first period but not take during the second period in a treatment cycle. The random sequence may be different across the treatment cycles. For instance, a patient may take Baduanjin exercise during the first period of the first treatment cycle but not take during the first period of the second treatment cycle. Before these N-of-1 trials are conducted, the random allocation sequence will be generated with SAS 9.1 software by a statistician who is not directly involved in these

N-of-1 trials. The doctor (WJ Yu) will acquire the random sequence of each patient by contacting the above-mentioned statistician to manage the assignment of interventions, and inform the patients to perform the Baduanjin exercise. It means that random allocation will be concealed to WJ Yu and each patient before the initiation of each treatment cycle.

2.4 Interventions

Patients in the Baduanjin exercise group will receive the standard Baduanjin exercise recommended by the General Administration of Sport of China [42,43]. It consists of a preparation posture, eight separate movements and an ending posture. These postures and movements are presented graphically in previous studies [42,43]. Before the first cycle, eligible participants will complete a training session in the Department of Orthopedics guided by a doctor (AF Liu) who is engaged in the Baduanjin training to master the technical essentials of Baduanjin exercise. In each period of Baduanjin exercise, patients will do Baduanjin exercise for half an hour once a day for a week. Specifically, when a patient is free at a certain time of the day like in the morning or evening, he/she should seek a quiet room at home or somewhere else, rest in a quiet state for about five minutes, and then perform the Baduanjin exercise. It will take the patient about three minutes to complete a Baduanjin exercise session, since each movement is performed twice and slowly to avoid additional damage such as muscle strain. Thereafter, the patient will rest for about two minutes. Next, the patient will repeat the above-mentioned process (including the completion of a Baduanjin exercise session and resting for 2 minutes)

five times. The whole process will take half an hour. Importantly, the patient is asked to record the entire exercise process with his/her mobile phone and send it to AF Liu after daily exercise for the sake of monitoring adherence. Nonstandard movements will be corrected by AF Liu via video conversation with patients to improve patient adherence if necessary.

Many physical exercises have been applied in the treatment of CNLBP. Some studies have compared the benefits of these exercises in treating LBP [17-19], however, there are no optimal physical exercises for the management of CNLBP [17]. Therefore, it is difficult to select the most appropriate physical exercise as a control for Baduanjin exercise. In this study, we expect to evaluate the actual effect of Baduanjin exercise on CNLBP. If the other physical exercise is used in the control group, only the relative efficacy of Baduanjin exercise compared with the other exercise can be estimated. In addition, it is hard to select a placebo as a control for Baduanjin exercise. We have reviewed some published clinical trials on physical exercise for CNLBP, consulted with clinical and methodological experts, and finally set the control group as waiting list group. Patients in the control group will not receive Baduanjin exercise or other physical exercises for relieving CNLBP. Other non-pharmaceutical therapies for alleviating CNLBP will be prohibited during the treatment periods and wash-out periods. Not all patients will receive pain medications as part of the interventions. Routine painkillers recommended by clinical guidelines may be used according to the doctor's advice if CNLBP is intolerable. The use of painkillers will be recorded in detail.

2.5 Outcomes

In this study, the pain intensity determined using the 10-point VAS will be our primary outcome, with a higher VAS score indicating the more severe pain, which displays good reliability (r=0.96) and validity (r=0.97) [44]. The secondary outcomes include the Oswestry Disability Index (ODI), the Japanese Orthopaedic Association Back Pain Evaluation Questionnaire (JOABPEQ), and the Short Form Health Survey 12 (SF-12). ODI is a patient-reported outcome tool, which is highly reliable (r=0.89) and valid (r=0.76) [45], with the value ranging from 0% to 100% [46]. A higher ODI indicates the worse physical functioning. JOABPEQ, the self-administered questionnaire, shows high reliability (r=0.977) and good validity (r=0.726) [47]. It consists of 25 items in 5 domains, namely, LBP, lumbar function, walking ability, social life function, and mental health [48], with the score of 0-100, and a higher score indicates the superior condition for each domain of JOABPEQ. SF-12 is a 12-item questionnaire developed to measure the physical and mental health [49]. The Cronbach alpha coefficients for the two subscales of SF-12 are 0.77 and 0.80, respectively [50]. Notably, a consensus has been reached to apply VAS, ODI, and SF-12 as the core outcome measure for clinical trials on non-specific LBP [51]. The starting value, final value and change from baseline of these outcomes will be determined in each period of a cycle, and adverse reactions such as elevation of blood pressure and increased pain will be recorded as well.

2.6 Time schedule

Supplementary Table 1 presents the time schedule of participant enrollment,

interventions, assessments and visits. The researcher (JB Zhai) will recruit the participants from the Department of Orthopedics in the First Teaching Hospital of Tianjin University of TCM. During the patient screening period, JB Zhai will inform patients interested in the trial of more details of this trial. Patients who are willing to take part in this trial should sign the informed consent form, and will be assessed for eligibility in line with relevant eligibility criteria by JB Zhai. No additional consent form will be signed because there will be no ancillary studies that involve the extraction and use of participant data and biological specimens for purposes that are separate from the main trial. Eligible patients will take a Baduanjin training course in the Department of Orthopedics guided by AF Liu. Patients who take Baduanjin exercise before participating in the N-of-1 trials will be not excluded in the screening stage. Afterwards, patients will experience three treatment cycles one by one. During the first washout period of the first cycle, general characteristics such as age, gender, and history of diseases will be collected by JB Zhai. Additionally, the efficacy of previously received interventions will be eliminated if the patients receive interventions for CNLBP before participating in N-of-1 trials. Then, patients will be classified into Baduanjin exercise or waiting list group randomly at the beginning of each treatment period by WJ Yu. VAS, ODI, JOABPEQ, and SF-12 belong to the patient-reported outcomes. Patients will be asked to answer the questions in the four scales at the beginning and end of every treatment period by TC Guo. There are no plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies.

Any used drugs or adverse events will be recorded in detail. Patients who suffer from adverse reactions will be properly treated.

2.7 Data management

WeChat, one of the most widely used social networking platforms in China, has been used as the data management platform in some clinical trials [52.53]. An electronic case report form (eCRF) based on WeChat will be designed to collect patient data, which can be available by contacting the sponsor (JB Zhai). It is conducive to improving patient adherence and promoting data quality. During the screening period, the WeChat account of each patient will be collected. At the beginning and end of every treatment or washout period, a trained and qualified data manager (TC Guo) will provide an unfilled eCRF to each patient via the WeChat platform. Patients are asked to fill in the eCRF based on their own conditions. If possible, participants discontinuing or deviating from intervention protocols will be asked to fill in all electronic forms. TC Guo is blinded to the random allocation of each patient. However, he can check the completed eCRF online in a real time manner, and contact the patients to verify and modify the questionable data if necessary. If an emergency such as adverse reaction arises and is needed to reveal the assigned intervention of a participant, TC Guo will contact with the sponsor (JB Zhai) and the doctor (WJ Yu) to obtain the allocated intervention. When a treatment cycle is completed, individual data will be exported in time for statistical analysis. The following measures will be adopted for the sake of protecting confidentiality of potential and enrolled participants before, during, and after the trial. The identification

information of a participant will be replaced with an irrelevant sequence of characters. All digital files will be encrypted by TC Guo who has access to the final trial dataset. The data used in quality control, auditing, and statistical analysis will be available by filing an application with TC Guo. The individual information, such as the name and mobile phone number of the patients, will be hidden during statistical analysis. Furthermore, a Data and Safety Monitoring Committee (DSMC) independent from the sponsor will be set up to assess the severity of the deviation from the protocol, poor compliance and severe adverse events. If necessary, patients will be discontinued from N-of-1 trials due to the above-mentioned events.

2.8 Auditing

A researcher who is employed in Tianjin University of TCM will audit the core trial processes and documents related to participant enrollment, eligibility, random allocation, patient adherence, as well as policies to protect participants by visiting the Department of Orthopedics in the First Teaching Hospital of Tianjin University of TCM, and check the data quality by browsing eCRF. The process will be performed once every month independently from the sponsor and investigators. The detected problems and suggestions will be delivered to the sponsor and investigators in writing.

2.9 Sample size

The estimation of sample size depends on multiple factors such as primary outcome and statistical analysis method. In this study, VAS, the primary outcome, will be analyzed using the Bayesian hierarchical models. However, no convenient

software packages are accessible for estimating the sample size of N-of-1 trials using the Bayesian hierarchical models. Therefore, we determine the sample size according to a simulation-based two-step method described by Stunnenberg et al [54]. Firstly, the simulated data of N-of-1 trials with three cycles is generated based on the following parameters. The minimal clinically important change (MCIC) refers to the smallest change of health status that leads to the clinically significant benefit in patients, such as the smallest change of VAS before and after treatment that brings about the clinically significant benefit in a particular population. Ostelo et al. reported that the MCIC for chronic LBP on a VAS of 0 to 100 mm should be at least 20 mm [55]. The minimum clinically important difference (MCID) indicates the smallest difference in health status with clinical significance between patients, like the smallest difference in VAS after treatment that is clinically significant between two groups. The present study aims to assess the difference in VAS after treatment between Baduanjin exercise group and waiting list group. Therefore, MCID instead of MCIC is used to estimate the sample size. A small effect on pain relief is defined as a reduction of 0.5 to 1.0 on a VAS of 0 to 10 according to the American College of Physicians guideline [4]. Therefore, the MCID on a VAS of 0 to 10 is set to 0.5 in our study. It means that a clinically important difference is reached when the mean difference in VAS score between the two groups is more than 0.5. The standard deviation is set to 1.0 according to our previous study [25]. At the same time, the autocorrelation coefficient between two groups is set to 0.5 [56], while the proportion of random missing values is set to 20%. Secondly, the Bayesian hierarchical model is

built based on the above-mentioned simulated data by WinBUGS 1.4.3 software. The process is repeated for 50000 times with a burn-in of 5000 times by the Markov Chain Monte Carlo methods [57]. When the simulated data from 50 N-of-1 trials are applied in building the Bayesian hierarchical models, the posterior probability of posterior mean difference > 0.5 is 82.7%, which exceeds the pre-defined threshold of 80%. Therefore, 50 patients will be recruited.

2.10 Statistical analysis

Quantitative data will be expressed as mean with the standard deviation, while qualitative data as frequency and the percentage. Data analysis will be conducted in line with the intention-to-treat principle. The missing data will be handled through last observation carried forward (LOCF). The mean differences in VAS, JOABPEQ, ODI, and SF-12 score between two groups will be compared using the Bayesian hierarchical models with WinBUGS 1.4.3 software. Additionally, the use of painkillers as a covariate will be included in the Bayesian hierarchical models to eliminate the impact of pain medications on the efficacy. Non-informative prior distribution will be used because of the lack of prior information. Besides, the number of iterations will be set to 50000 with a burn-in of 5000 times [57]. The overall and individual posterior mean differences with 95% credibility intervals between two groups will be estimated synchronously. It remains unclear whether the difference in pain relief between two groups is of clinical significance. In the sample size section, MCID is set to 0.5. Therefore, the overall and individual posterior probabilities of posterior mean difference > 0.5 will be calculated. In this case, posterior probability

gives a possibility that a patient achieves a clinically significant benefit. Posterior probabilities of 80% and 20% will be considered as the cut-off values to terminate the N-of-1 trial [54]. When a treatment cycle is completed and individual posterior probability is more than 80%, this patient will not participate in the next treatment cycle due to the sufficient benefit, instead, he/she will be advised to perform Baduanjin exercise to improve CNLBP. If the individual posterior probability falls in between 20% and 80%, this patient will participate in the next treatment cycle because of the uncertain benefit. If the individual posterior probability is less than 20%, this patient will not participate in the next treatment cycle because of insufficient benefit, and will be advised to seek for alternative treatments. The sponsor (JB Zhai) will have access to these interim results and make the final decision to terminate the trial.

3. Patient and public involvement

Patients/the public were not involved in the design, the recruitment and conduct of the study.

4. Ethics and dissemination

Our study protocol has gained approval from the Medical Ethics Committee of Tianjin University of TCM (reference number TJUTCM-EC20220005). Any amendments to the protocol will be reviewed and approved again by the above-mentioned medical ethics committee. Individuals who contribute substantively to protocol development and drafting are listed as authors. No professional writers are employed. The sponsor (JB Zhai) will communicate the trial results to participants via

WeChat. Our findings will be published in a peer-reviewed journal or international conferences. The complete trial protocol and report, anonymised participant level dataset, and statistical code for result generation will be available by contacting the corresponding author after the trial is completed.

5. Discussion

Exercise is recommended for the treatment of chronic LBP according to the latest clinical guideline [4]. Baduanjin exercise has been widely used for pain management. In this study, we will conduct a series of N-of-1 trials for assessing whether Baduanjin exercise is effective and safe for CNLBP in the Department of Orthopedics in a teaching hospital. Patients with CNLBP may show pronounced inter-individual heterogeneity in terms of pain intensity and response to Baduanjin exercise. In this study, participants who can gain benefits from Baduanjin exercise will be identified by hierarchical Bayesian analysis. Participants who can't gain benefits from Baduanjin exercise will be advised to seek for alternative treatments. It is helpful to make an individualized clinical decision for each participant and bridge the gap between clinical research and practice. Meanwhile, the mean treatment effect and posterior probability of a clinically significant difference in VAS at the group level will be estimated synchronously through summarizing the N-of-1 trials. We have searched PubMed, Embase, Web of Science, China National Knowledge Infrastructure, Wanfang Digital Periodicals, and Chinese Science and Technology Periodicals database, and no mechanism research on Baduanjin exercise for the management of CNLBP is identified. Therefore, the mechanisms of Baduanjin

exercise in CNLBP remain to be fully elucidated. However, Bayesian N-of-1 trials can provide rich information. We believe that the results can assist doctors in the optimal clinical decision-making.

Authors' contributions

JB Zhai was the trial sponsor and funder, and conceived the study. AF Liu and WJ Yu designed the inclusion and exclusion criteria. TC Guo designed the time schedule. JB Zhai drafted the manuscript. AF Liu, WJ Yu and TC Guo reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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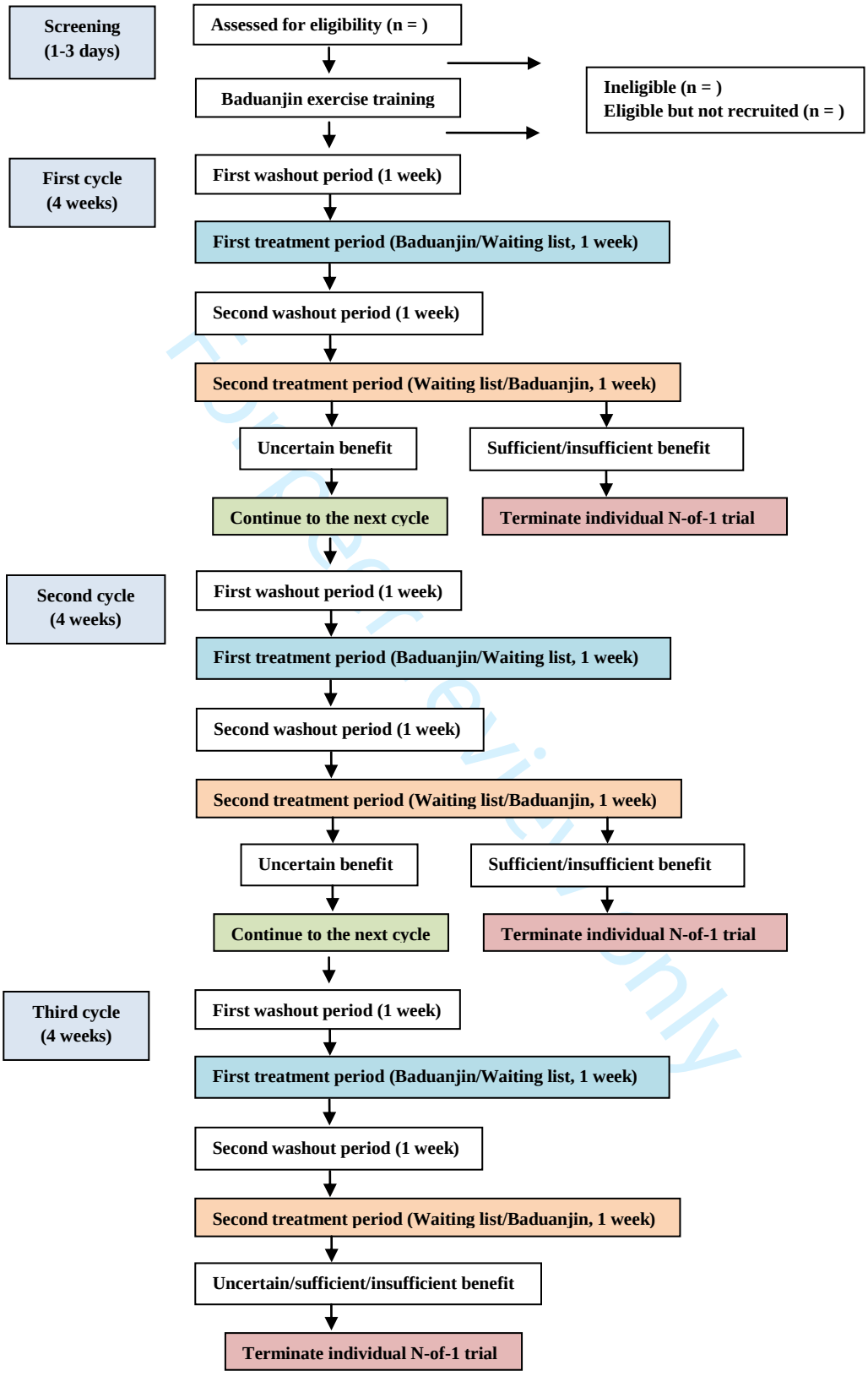
Figure Legends:

Figure 1. Flow diagram of a series of N-of-1 trials



Supplementary Table 1. Time schedule of participant enrollment, interventions, assessments and visits

Items	Screening	Cycle 1				Cycle 2				Cycle 3			
		Washout period 1	Treatment period 1	Washout period 2	Treatment period 2	Washout period 1	Treatment period 1	Washout period 2	Treatment period 2	Washout period 1	Treatment period 1	Washout period 2	Treatment period 2
	Day -3 to -1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Eligibility criteria	X												
Informed consent	X												
Baduanjin training	X												
Demographic characteristic		X											
Randomization			X		X		X		X		X		X
VAS			X		X		X		X		X		X
ODI			X		X		X		X		X		X
JOABPEQ			X		X		X		X		X		X
SF-12			X		X		X		X		X		X
Drug combination		X	X	X	X	X	X	X	X	X	X	X	X
Safety		X	X	X	X	X	X	X	X	X	X	X	X

VAS, Visual Analogue Scale; ODI, Oswestry Disability Index; JOABPEQ, Japanese Orthopaedic Association Back Pain Evaluation Questionnaire; SF-12, Short Form Health Survey 12

Informed Consent Form

Dear Sir or Madam,

You have been diagnosed with chronic non-specific low back pain (CNLBP). We invite you to participate in a series of N-of-1 trials to assess the efficacy and safety of Baduanjin exercise for CNLBP. This study has been approved by the Medical Ethics Committee of Tianjin University of Traditional Chinese Medicine (TCM) (reference number TJUTCM-EC20220005).

Before you decide whether to participate in this study, please read the following content carefully. It can help you understand the study and why it is being conducted, the procedure and duration of the study, the benefits, risks and discomfort that may arise from participating in the study. If you wish, you can also discuss it with your relatives and friends, or ask your doctor for an explanation to help you make a decision.

Name of Project: Baduanjin exercise for CNLBP: a series of N-of-1 trials

Name of Organization: Tianjin University of TCM

Name of Sponsor: Jingbo Zhai

This informed consent form has two parts:

- Information Sheet (to share information about the study with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full informed consent form.

Part I: Information Sheet

1. Introduction

CNLBP is one of the most common health problems worldwide. Exercise is recommended for the treatment of chronic low back pain (LBP) according to the clinical guideline released by the American College of Physicians. TCM is becoming increasingly popular for the management of chronic LBP in recent years. Baduanjin exercise is one of the exercise therapies in TCM. N-of-1 trial is a randomized

cross-over self-controlled trial that is suitable for patients with the chronic disease.

2. Purpose

This study will conduct a series of N-of-1 trials to assess the efficacy and safety of Baduanjin exercise for CNLBP.

3. Setting and sample size

Fifty patients will be recruited from the Department of Orthopedics in the First Teaching Hospital of Tianjin University of TCM.

4. Participant selection

4.1 Inclusion criteria

Patients conforming to the criteria below will be included:

(1) Patients suffering from chronic LBP that is defined as the pain and discomfort in the low back and/or lumbosacral region for more than 12 weeks according to the clinical practice guideline released by the American College of Physicians.

(2) Patients having at least 3 points on the Visual Analogue Scale (VAS) (range, 0-10). Pain of at least 3 points is considered as a perceptible persistent pain.

(3) The age of patients ranging from 18 to 75 years.

(4) Gender is unrestricted.

(5) Patients signing the informed consent form.

4.2 Exclusion criteria

Patients conforming to the criteria below will be eliminated:

(1) Patients suffering from severe spinal diseases, such as spinal fracture, spine malformation, and spinal degenerative change.

(2) Patients with a history of spinal surgery.

(3) Patients with LBP caused by soft tissue injuries or infectious diseases.

(4) Patients with LBP caused by visceral diseases, such as kidney stone, and hysteritis.

(5) Patients having a history of severe cardiovascular and cerebrovascular diseases, diabetes, mental diseases, cognitive impairment, and cancer.

(6) Pregnant or lactating women.

5. What will you need to do if you participate in the study?

If you'd like to participate in the study, you will be asked to sign the informed consent form, and be assessed for eligibility according to the inclusion and exclusion criteria. If you are eligible, you will take a Baduanjin training course in the Department of Orthopedics. Then, you will experience three treatment cycles one by one. During the first washout period of the first cycle, general characteristics such as age, gender, history of diseases will be collected. Then, you will be assigned to the Baduanjin exercise or waiting list group randomly at the beginning of each treatment period. During each period of Baduanjin exercise, you will perform a half-hour Baduanjin exercise once a day for a week. You will be asked to answer the questions about VAS, ODI, JOABPEQ, and SF-12 at the beginning and the end of each treatment period.

6. Benefits

Low back pain may be reduced and functional status may be improved after Baduanjin exercise.

7. Risks

If you become unwell during the study period, or if your condition changes in a new way, or if anything unexpected occurs, whether or not it is related to the study, you should inform your doctor in time and he/she will make a judgment and give appropriate medical treatment.

8. Cost

This study will provide a free training for Baduanjin exercise. During the study period, doctors will do their best to prevent and treat any injuries that may result from this study. The sponsor will provide appropriate treatment costs and financial compensation for research-related damages in accordance with relevant regulations.

9. Confidentiality

Any information and data obtained about you personally during the study will be kept strictly confidential.

10. Sharing of the results

The results will be published in a peer-reviewed journal or international conferences.

11. Right to refuse or withdraw

You can voluntarily choose to participate in the research and withdraw from the research. Whether to participate in the study is entirely up to you. You may decline to participate in the study, or withdraw from the study at any time during the study, without affecting your relationship with your doctor or the loss of your medical or other benefits. In your best interest, your doctor or investigator may suspend your participation in the study at any time during the study.

12. How to get more information?

You can ask any questions about this study at any time and get answers accordingly. Your doctor will notify you if there is any important new information during the study that may affect your willingness to continue participating in the study.

13. What should you do now?

It is up to you (and your family) to decide whether to participate in the study. Before you make a decision to participate in this study, ask your doctor as many questions as possible.

Thank you for reading the above material. If you decide to participate in this study, please tell your doctor and he/she will arrange everything for you. Please keep this information.

Part II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this study.

Print Name of Participant_____

Signature of Participant_____

Date_____

If illiterate

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print Name of witness_____ AND Thumb print of participant

Signature of witness_____

Date_____

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant. I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher/person taking the consent_____

Date_____

SPIRIT checklist

Section/Item	Item Number	Description	Reported on page #
Administrative information			
Title	**1**	**Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym**	**1**
Trial registration	**2a**	**Trial identifier and registry name. If not yet registered, name of intended registry**	**2**
	2b	**All items from the World Health Organization Trial Registration Data Set**	**6,7**
Protocol version	**3**	**Date and version identifier**	**6,7**
Funding	**4**	**Sources and types of financial, material, and other support**	**19**
Roles and responsibilities	**5a**	**Names, affiliations, and roles of protocol contributors**	**1,19**
	5b	**Name and contact information for the trial sponsor**	**1,19**
	5c	**Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities**	**19**
	5d	**Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable**	**14**
Introduction			
Background and rationale	**6a**	**Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention**	**3-5**
	6b	**Explanation for choice of comparators**	**3-5**
Objectives	**7**	**Specific objectives or hypotheses**	**6**
Trial design	**8**	**Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority,**	**6**

		exploratory)	
Methods Participants, interventions, and outcomes			
Study setting	**9**	**Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained**	**6**
Eligibility criteria	**10**	**Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)**	**7,8**
Interventions	**11a**	**Interventions for each group with sufficient detail to allow replication, including how and when they will be administered**	**9-11**
	11b	**Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)**	**8**
	11c	**Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)**	**10,13**
	11d	**Relevant concomitant care and interventions that are permitted or prohibited during the trial**	**10,11**
Outcomes	**12**	**Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended**	**11**
Participant timeline	**13**	**Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended**	**12-13**
Sample size	**14**	**Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations**	**15-16**

Recruitment	**15**	**Strategies for achieving adequate participant enrollment to reach target sample size**	**6**
Assignment of interventions (for controlled trials)			
Allocation			
Sequence generation	**16a**	**Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions**	**9**
Allocation concealment mechanism	**16b**	**Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned**	**9**
Implementation	**16c**	**Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions**	**9,12**
Blinding (masking)	**17a**	**Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how**	**13**
	17b	**If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial**	**13**
Data collection, management, and analysis			
Data collection methods	**18a**	**Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol**	**11-14**
	18b	**Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention**	**13**

		protocols	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13,14
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16,17
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	16
Monitoring			
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13,14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
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		surrogates, and how (see item 32)	
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Declaration of interests	28	Financial and other competing interests for principal investigator for the overall trial and each study site	19
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Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10,11,13
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Baduanjin exercise for chronic non-specific low back pain: protocol for a series of N-of-1 trials

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Baduanjin exercise for chronic non-specific low back pain: protocol for a series of N-of-1 trials

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Abstract:

Introduction Chronic non-specific low back pain (CNLBP) is one of the most common health problems worldwide. According to the clinical guideline released by the American College of Physicians, exercise has been recommended for the treatment of chronic low back pain (LBP). In recent years, traditional Chinese medicine (TCM) is becoming increasingly popular for the management of chronic LBP. Baduanjin exercise is one of the exercise therapies in TCM. N-of-1 trial is a randomized cross-over self-controlled trial suitable for patients with this chronic disease. A series of similar N-of-1 trials can be pooled to estimate the overall and individual therapeutic effects synchronously by hierarchical Bayesian analysis. And N-of-1 trials are considered as a good tool for evaluating the therapeutic effect of TCM. Therefore, this study aims to conduct a series of N-of-1 trials with hierarchical Bayesian analysis for assessing whether Baduanjin exercise is effective and safe for

CNLBP.

Methods and analysis This study conducts a series of N-of-1 trials on Baduanjin exercise for the management of CNLBP. Fifty participants will receive one to three treatment cycles. They will be randomized into Baduanjin exercise or waiting list group for a week during the two periods of each treatment cycle. The primary outcome is the 10-point Visual Analogue Scale. The secondary outcomes include the Oswestry Disability Index, the Japanese Orthopaedic Association Back Pain Evaluation Questionnaire, and the Short Form Health Survey 12. Statistical analysis will be conducted with WinBUGS 1.4.3 software. Overall and individual therapeutic effects will be estimated synchronously by hierarchical Bayesian analysis.

Ethics and dissemination This study is approved by the Medical Ethics Committee of Tianjin University of TCM (reference number TJUTCM-EC20220005). Our findings will be published in a peer-reviewed journal or international conference.

Trial registration number ChiCTR2200063307.

Strengths and limitations of this study

1. The overall and individual therapeutic effects will be estimated synchronously by hierarchical Bayesian analysis.

2. Sample size is calculated according to a simulation-based two-step method.

3. Blinding of patients is infeasible because waiting list is used as a control.

4. The study period may last more than one year because patients are recruited from only a hospital.

1. Introduction

Low back pain (LBP) is a frequently seen health issue globally [1]. The age-standardized global prevalence of LBP reaches up to 7.50% [2]. Most of patients with LBP do not exhibit any specific pathological changes associated with LBP and are thereby classified as non-specific LBP patients [3]. Non-specific LBP that lasts over 12 weeks will progress to a chronic stage, which is labeled as chronic non-specific LBP (CNLBP) [4]. LBP may increase the physician visits and years lived with disability, and contribute to absence from work and growing financial burden [1,5,6]. The annual average direct medical cost per patient with chronic LBP is US$1,516.67 in KwaZulu-Natal, South Africa [7]. The average cost of care per presentation for older adults with non-specific LBP was A$5,844 in the 2019-2020 financial year in Australia [8]. Therefore, it is urgently needed to manage LBP [9].

Currently, many pharmaceutical and non-pharmaceutical therapies are available for LBP [4]. Of them, opioid analgesics are the commonly prescribed medications for pain management. However, for patients with chronic pain, repeated administration may cause opioid-induced tolerance and hyperalgesia [10]. Subsequently, patients may need a higher dose of opioids to maintain the initial level of analgesia, which will increase the risk of overdose. When patients develop opioid dependence, abrupt discontinuation of opioids can lead to withdrawal symptoms, such as insomnia, nausea and vomiting [11]. There is insufficient evidence regarding the long-term opioid application in relieving chronic pain and improving function [12]. Moreover, the long-term opioid therapy can increase the risk of harms, like opioid abuse and

myocardial infarction [12]. Non-steroid anti-inflammatory drugs (NSAIDs) have been frequently used for acute LBP, which can achieve mild to moderate effects on chronic LBP [13]. As shown in a network meta-analysis, multiple drugs can significantly relieve chronic LBP [14]. In particular, cyclo-oxygenase 2-selective NSAIDs are effective on both pain relief and functional improvement. However, NSAIDs may be associated with more adverse events than placebo when used to treat chronic LBP [15]. At present, drug recommendations for chronic LBP are heterogeneous among different countries [16]. For example, the use of opioids is inconclusive in the Canada clinical guideline, but it is recommended in the USA clinical guideline. Non-pharmacological therapies should be considered as the first-line therapies for CNLBP [16]. It is reported in some systematic reviews that exercise and physical activity are beneficial for the recovery of CNLBP [17-19]. According to the American College of Physicians guideline, exercise is recommended for chronic LBP [4]. However, the optimal exercises for CNLBP have not been reached yet [17].

In recent years, traditional Chinese medicine (TCM) is becoming increasingly popular for the management of chronic LBP [20]. Baduanjin exercise is one of the exercise therapies in TCM, which consists of eight simple and separate core movements [21,22]. Each movement can be learned easily and completed slowly so that the patients can breathe smoothly and rhythmically [23]. In general, it has no specific requirements for users. In a systematic review, Baduanjin exercise is demonstrated to relieve the musculoskeletal pain in patients with chronic disease [24]. LBP is one of the most extensively investigated diseases in clinical studies on

Baduanjin exercise [23]. Baduanjin exercise may be effective on pain relief and functional improvement in patients with LBP [25]. Nonetheless, the efficacy of Baduanjin exercise in CNLBP has been not confirmed since relevant high-quality clinical trials are lacking. Electronic databases including PubMed, Embase, Web of Science, China National Knowledge Infrastructure, Wanfang Digital Periodicals, and Chinese Science and Technology Periodicals database have been searched, but no mechanism research on Baduanjin exercise for the management of CNLBP is identified. Therefore, the mechanisms of Baduanjin exercise in CNLBP remain to be fully elucidated.

Randomized controlled trials (RCTs) have been identified as the gold standard of therapeutic evaluation [26]. However, the average effects estimated from RCTs may represent a mixture of different therapeutic effects in individual patients [27]. In view of the gap between clinical trials and clinical practice, the individualized clinical decision should be made with caution based on the evidence from RCTs [28,29]. N-of-1 trial is a randomized cross-over self-controlled trial conducted in one patient [30], and its results can be directly used to make individualized clinical decision [30]. In this regard, N-of-1 trial is useful to fill the gap between clinical trials and clinical practice [31]. Moreover, it is feasible to combine a series of similar N-of-1 trials to estimate the overall and individual therapeutic effects synchronously by hierarchical Bayesian analysis [32,33]. As reported in a review, Bayesian analysis is used in 23% of N-of-1 trials with the pooled analysis [34]. In addition, Bayesian analysis is recommended by the Agency for Healthcare Research and Quality for the

combination of N-of-1 trials [35]. N-of-1 trials are suitable for patients with chronic disease [35]. Many N-of-1 trials on chronic pain are published recently [36]. As reported in a review, N-of-1 trial can be considered as a good tool for evaluating the therapeutic effect of TCM [37]. Therefore, this study aims to conduct a series of N-of-1 trials with hierarchical Bayesian analysis for assessing whether Baduanjin exercise is effective and safe for CNLBP.

2. Methods and analysis

2.1 Study design

The present study will conduct a series of N-of-1 superiority trials on Baduanjin exercise for the management of CNLBP. The flow diagram is shown in Figure 1. Firstly, patients will be assessed for eligibility and participate in a Baduanjin exercise training. Then, eligible participants will receive one to three treatment cycles. The number of experienced treatment cycles in each patient depends on the results of statistical analysis at the end of each cycle. Each cycle includes a period of Baduanjin exercise and a period of waiting list. Typically, a one-week washout period, during which therapies for relieving CNLBP are not allowed to eliminate the efficacy of previously received interventions, will be set between the above-mentioned two periods in view of the feasibility of N-of-1 trials. It follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [38]. Outpatients or inpatients will be recruited from the Department of Orthopedics in the First Teaching Hospital of Tianjin University of TCM. This study will be conducted from October 1, 2023 to December 31, 2025. To catch the attention of potentially

eligible patients and obtain sufficient participant recruitment to reach the target sample size, recruitment advertisements will be posted at the entrance of outpatient and inpatient departments. Items of the World Health Organization Trial Registration Data Set, registration date and protocol version are available at https://www.chictr.org.cn/showprojEN.html?proj=172369.

2.2 Patients

2.2.1 Inclusion criteria

Patients conforming to the criteria below will be included:

(1) Patients suffering from chronic LBP that is defined as pain and discomfort in the low back and/or lumbosacral region for more than 12 weeks according to the clinical practice guideline released by the American College of Physicians [4].

(2) Patients having at least 3 points on the Visual Analogue Scale (VAS) (range, 0-10). Pain of at least 3 points is considered as a perceptible persistent pain. This standard has also been used in some previous studies on this topic [39,40].

(3) The age of patients ranging from 18 to 75 years.

(4) Gender is unrestricted.

(5) Patients signing the informed consent form in supplementary file.

2.2.2 Exclusion criteria

Patients conforming to the criteria below will be eliminated:

(1) Patients suffering from severe spinal diseases, such as spinal fracture, spine malformation, and spinal degenerative change.

(2) Patients with a history of spinal surgery.

(3) Patients with LBP caused by soft tissue injuries or infectious diseases.

(4) Patients with LBP caused by visceral diseases, such as kidney stone, and hysteritis.

(5) Patients having a history of severe cardiovascular and cerebrovascular diseases, diabetes, mental diseases, cognitive impairment, and cancer. Patients with cognitive impairment may be unable to complete the N-of-1 trials, such as mastering the technical essentials of Baduanjin exercise, and completing the measurement of patient-reported outcomes. Cognitive impairment will be determined using the mini-mental state examination (MMSE). Patients with MMSE < 27 are diagnosed with cognitive impairment [41] and will be excluded from this study.

(6) Pregnant or lactating women.

2.2.3 Withdrawal or termination criteria

Patients can withdraw from N-of-1 trials voluntarily at any time for any reason including participant request and rapid progression of disease. On the other hand, patients can be discontinued from N-of-1 trials passively due to serious deviation from the protocol, poor compliance, rapid progression of disease, or serious adverse events. N-of-1 trials will be terminated when patients meet the termination criteria based on the interim analysis or complete three treatment cycles.

2.3 Random assignment and allocation concealment

The eligible patients will be randomized into Baduanjin exercise or waiting list group during the two periods of each treatment cycle. For example, a patient may take Baduanjin exercise during the first period but not take the exercise during the second

period in a treatment cycle. The random sequence may be different across the treatment cycles. For instance, a patient may take Baduanjin exercise during the first period of the first treatment cycle but not take it during the first period of the second treatment cycle. Before these N-of-1 trials are conducted, the random allocation sequence will be generated with SAS 9.1 software by a statistician who is not directly involved in these N-of-1 trials. The doctor (WJ Yu) will acquire the random sequence of each patient by contacting the above-mentioned statistician to manage the assignment of interventions, and inform the patients to perform the Baduanjin exercise. It means that random allocation will be concealed to WJ Yu and each patient before the initiation of each treatment cycle.

2.4 Interventions

2.4.1 Baduanjin exercise

Patients in the Baduanjin exercise group will receive the standard Baduanjin exercise recommended by the General Administration of Sport of China [42,43]. It consists of a preparation posture, eight separate movements and an ending posture. These postures and movements are presented graphically in previous studies [42,43]. Before the first cycle, eligible participants will complete a training session in the Department of Orthopedics guided by a doctor (AF Liu) who is engaged in the Baduanjin training to master the technical essentials of Baduanjin exercise. In each period of Baduanjin exercise, patients will do Baduanjin exercise for half an hour once a day for a week. Specifically, when a patient is free at a certain time of the day like in the morning or evening, he/she should seek a quiet room at home or

somewhere else, rest in a quiet state for about five minutes, and then perform the Baduanjin exercise. It will take the patient about three minutes to complete a Baduanjin exercise session, since each movement is performed twice and slowly to avoid additional damage like muscle strain. Thereafter, the patient will rest for about two minutes and then repeat the above-mentioned process (including the completion of a Baduanjin exercise session and resting for 2 minutes) five times. The whole process will take half an hour. Importantly, the patient is asked to record the entire exercise process with his/her mobile phone and send it to AF Liu after daily exercise to monitor the adherence. Nonstandard movements will be corrected by AF Liu via video conversation with patients to improve patient adherence if necessary.

2.4.2 Waiting list

Patients assigned to the waiting list group will not receive the Baduanjin exercise or other physical exercises for relieving CNLBP. The waiting list instead of physical exercise is used in the control group for the following reasons. Many physical exercises have been applied in the treatment of CNLBP. Some studies have compared the benefits of these exercises in treating LBP [17-19], however, there are no optimal physical exercises for the management of CNLBP [17]. Therefore, it is difficult to select the most appropriate physical exercise as a control for Baduanjin exercise. In this study, we expect to evaluate the actual effect of Baduanjin exercise on CNLBP. If the other physical exercise is used in the control group, only the relative efficacy of Baduanjin exercise compared with the other exercise can be estimated. In addition, it is hard to select a placebo as a control for Baduanjin exercise. We have reviewed

some published clinical trials on physical exercise for CNLBP, consulted with clinical and methodological experts, and finally set waiting list as the control group. Other non-pharmaceutical therapies for alleviating CNLBP will be prohibited during the treatment periods and wash-out periods. Not all patients will receive pain medications as part of the interventions. Routine painkillers recommended by clinical guidelines may be used according to the doctor's advice if CNLBP is intolerable. The use of painkillers will be recorded in detail.

2.5 Outcomes

In this study, the pain intensity determined using the 10-point VAS will be our primary outcome, with a higher VAS score indicating the more severe pain. The 10-point VAS displays good reliability (r=0.96) and validity (r=0.97) [44]. The secondary outcomes include the Oswestry Disability Index (ODI), the Japanese Orthopaedic Association Back Pain Evaluation Questionnaire (JOABPEQ), and the Short Form Health Survey 12 (SF-12). ODI is a patient-reported outcome tool, which is highly reliable (r=0.89) and valid (r=0.76) [45]. The value ranges from 0% to 100% [46], with the higher ODI indicating the worse physical functioning. JOABPEQ, the self-administered questionnaire, shows high reliability (r=0.977) and good validity (r=0.726) [47]. It consists of 25 items in 5 domains, namely, LBP, lumbar function, walking ability, social life function, and mental health [48], with the total score of 0-100, and a higher score indicates the superior condition for each domain of JOABPEQ. SF-12 is a 12-item questionnaire developed to measure the physical and mental health [49]. The Cronbach alpha coefficients for the two subscales of SF-12

are 0.77 and 0.80, respectively [50]. Notably, a consensus has been reached to apply VAS, ODI, and SF-12 as the core outcome measures for clinical trials on non-specific LBP [51]. The starting value, final value and change from baseline of these outcomes will be determined in each period of a cycle, and adverse reactions such as elevation of blood pressure and increased pain will be recorded as well.

2.6 Time schedule

Supplementary Table 1 presents the time schedule of participant enrollment, interventions, assessments and visits. The researcher (JB Zhai) will recruit the participants from the Department of Orthopedics in the First Teaching Hospital of Tianjin University of TCM. During the patient screening period, JB Zhai will inform patients interested in the trial of more details of this trial. Patients who are willing to take part in this trial should sign the informed consent form, and will be assessed for eligibility in line with relevant eligibility criteria by JB Zhai. No additional consent form will be signed because there will be no ancillary studies that involve the extraction and use of participant data and biological specimens for purposes that are separate from the main trial. Eligible patients will take a Baduanjin training course in the Department of Orthopedics guided by AF Liu. Patients who take Baduanjin exercise before participating in the N-of-1 trials will not be excluded in the screening stage. Afterwards, patients will undergo three treatment cycles one by one. During the first washout period of the first cycle, general characteristics such as age, gender, and history of diseases will be collected by JB Zhai. Additionally, the efficacy of previously received interventions will be eliminated if the patients receive

interventions for CNLBP before participating in N-of-1 trials. Then, patients will be classified into Baduanjin exercise or waiting list group randomly at the beginning of each treatment period by WJ Yu. VAS, ODI, JOABPEQ, and SF-12 are the patient-reported outcomes. Patients will be asked to answer the questions in the four scales at the beginning and end of every treatment period by TC Guo. There are no plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies. Any used drugs or adverse events will be recorded in detail. Patients who suffer from adverse reactions will be properly treated.

2.7 Data management

WeChat, one of the most widely used social networking platforms in China, has been used as the data management platform in some clinical trials [52.53]. An electronic case report form (eCRF) based on WeChat will be designed to collect patient data, which can be obtained by contacting the sponsor (JB Zhai). It is conducive to improving patient adherence and promoting data quality. During the screening period, the WeChat account of each patient will be collected. At the beginning and end of every treatment or washout period, a trained and qualified data manager (TC Guo) will provide an unfilled eCRF to each patient via the WeChat platform. Patients will be asked to fill in the eCRF based on their own conditions. If possible, participants discontinuing or deviating from intervention protocols will be asked to fill in all electronic forms. TC Guo is blinded to the random allocation of each patient. However, he can check the completed eCRF online in a real time manner,

and contact the patients to verify and modify the questionable data if necessary. If an emergency such as adverse reaction arises and is needed to reveal the assigned intervention of a participant, TC Guo will contact with the sponsor (JB Zhai) and the doctor (WJ Yu) to obtain the allocated intervention. When a treatment cycle is completed, individual data will be exported in time for statistical analysis. The following measures will be adopted for protecting confidentiality of potential and enrolled participants before, during, and after the trial. The identification information of a participant will be replaced with an irrelevant sequence of characters. All digital files will be encrypted by TC Guo who has access to the final trial dataset. The data used in quality control, auditing, and statistical analysis will be available by filing in an application form with TC Guo. The individual information, such as the name and mobile phone number of the patients, will be hidden during statistical analysis. Furthermore, a Data and Safety Monitoring Committee (DSMC) independent from the sponsor will be set up to assess the severity of the deviation from the protocol, poor compliance and severe adverse events. If necessary, patients will be discontinued from N-of-1 trials due to the above-mentioned events.

2.8 Auditing

A researcher who is employed in Tianjin University of TCM will audit the core trial processes and documents related to participant enrollment, eligibility, random allocation, patient adherence, as well as policies to protect participants by visiting the Department of Orthopedics in the First Teaching Hospital of Tianjin University of TCM, and check the data quality by browsing eCRF. The process will be performed

once every month independently from the sponsor and investigators. The detected problems and suggestions will be delivered to the sponsor and investigators in writing.

2.9 Sample size

The estimation of sample size depends on multiple factors such as primary outcome and statistical analysis method. In this study, VAS, the primary outcome, will be analyzed using the Bayesian hierarchical models. However, no convenient software packages are accessible for estimating the sample size of N-of-1 trials using the Bayesian hierarchical models. Therefore, we determine the sample size according to a simulation-based two-step method described by Stunnenberg *et al.* [54]. Firstly, the simulated data of N-of-1 trials with three cycles are generated based on the following parameters. The minimal clinically important change (MCIC) refers to the smallest change of health status that leads to the clinically significant benefit in patients, such as the smallest change of VAS before and after treatment that brings about the clinically significant benefit in a particular population. Ostelo *et al.* reported that the MCIC for chronic LBP on a VAS of 0 to 100 mm should be at least 20 mm [55]. The minimum clinically important difference (MCID) indicates the smallest difference in health status with clinical significance between patients, like the smallest difference in VAS after treatment that is clinically significant between two groups. The present study aims to assess the difference in VAS after treatment between Baduanjin exercise group and waiting list group. Therefore, MCID instead of MCIC is used to estimate the sample size. A small effect on pain relief is defined as a

reduction of 0.5 to 1.0 on a VAS of 0 to 10 according to the American College of Physicians guideline [4]. Therefore, the MCID on a VAS of 0 to 10 is set to 0.5 in our study. It means that a clinically important difference is reached when the mean difference in VAS score between the two groups is more than 0.5. The standard deviation is set to 1.0 according to our previous study [25]. At the same time, the autocorrelation coefficient between two groups is set to 0.5 [56], while the proportion of random missing values is set to 20%. Secondly, the Bayesian hierarchical model is built based on the above-mentioned simulated data by WinBUGS 1.4.3 software. The process is repeated for 50000 times with a burn-in of 5000 times by the Markov Chain Monte Carlo methods [57]. When the simulated data from 50 N-of-1 trials are applied in building the Bayesian hierarchical models, the posterior probability of posterior mean difference > 0.5 is 82.7%, which exceeds the pre-defined threshold of 80%. Therefore, 50 patients will be recruited.

2.10 Statistical analysis

Quantitative data will be expressed as mean with standard deviation, while qualitative data as frequency and percentage. Data analysis will be conducted in line with the intention-to-treat principle. The missing data will be handled through last observation carried forward (LOCF). The mean differences in VAS, JOABPEQ, ODI, and SF-12 score between two groups will be compared using the Bayesian hierarchical models with WinBUGS 1.4.3 software. Additionally, the use of painkillers as a covariate will be included in the Bayesian hierarchical models to eliminate the impact of pain medications on the efficacy. Non-informative prior

distribution will be used because of the lack of prior information. Besides, the number of iterations will be set to 50000 with a burn-in of 5000 times [57]. The overall and individual posterior mean differences with 95% credibility intervals between two groups will be estimated synchronously. It remains unclear whether the difference in pain relief between two groups is of clinical significance. In the sample size section, MCID is set to 0.5. Therefore, the overall and individual posterior probabilities of posterior mean difference > 0.5 will be calculated. In this case, posterior probability gives a possibility that a patient achieves a clinically significant benefit. Posterior probabilities of 80% and 20% will be considered as the cut-off values to terminate the N-of-1 trial [54]. When a treatment cycle is completed and individual posterior probability is more than 80%, this patient will not participate in the next treatment cycle due to the sufficient benefit, instead, he/she will be advised to perform Baduanjin exercise to improve CNLBP. If the individual posterior probability falls in between 20% and 80%, this patient will participate in the next treatment cycle because of the uncertain benefit. If the individual posterior probability is less than 20%, this patient will not participate in the next treatment cycle because of insufficient benefit, and will be advised to seek for alternative treatments. The sponsor (JB Zhai) will have access to these interim results and make the final decision to terminate the trial.

3. Patient and public involvement

Patients/the public were not involved in the design, the recruitment and conduct of the study.

4. Ethics and dissemination

Our study protocol has gained approval from the Medical Ethics Committee of Tianjin University of TCM (reference number TJUTCM-EC20220005). Any amendments to the protocol will be reviewed and approved again by the above-mentioned medical ethics committee. Individuals who contribute substantively to protocol development and drafting are listed as authors. No professional writers are employed. The sponsor (JB Zhai) will communicate the trial results to participants via WeChat. Our findings will be published in a peer-reviewed journal or international conference. The complete trial protocol and report, anonymised participant level dataset, and statistical code for result generation will be available by contacting the corresponding author after the trial is completed.

5. Discussion

Exercise is recommended for the treatment of chronic LBP according to the latest clinical guideline [4]. Baduanjin exercise has been widely used for pain management. In this study, we will conduct a series of N-of-1 trials for assessing whether Baduanjin exercise is effective and safe for CNLBP in the Department of Orthopedics in a teaching hospital. Patients with CNLBP may show pronounced inter-individual heterogeneity in terms of pain intensity and response to Baduanjin exercise. In this study, participants who can gain benefits from Baduanjin exercise will be identified by hierarchical Bayesian analysis. While participants who can't gain benefits from Baduanjin exercise will be advised to seek for alternative treatments. It is helpful to make an individualized clinical decision for each participant and bridge the gap

between clinical research and practice. Meanwhile, the mean treatment effect and posterior probability of a clinically significant difference in VAS at the group level will be estimated synchronously through summarizing the N-of-1 trials. Bayesian N-of-1 trials can provide rich information. We believe that the results can assist doctors in the optimal clinical decision-making.

Authors' contributions

JB Zhai was the trial sponsor and funder, and conceived the study. AF Liu and WJ Yu designed the inclusion and exclusion criteria. TC Guo designed the time schedule. JB Zhai drafted the manuscript. AF Liu, WJ Yu and TC Guo reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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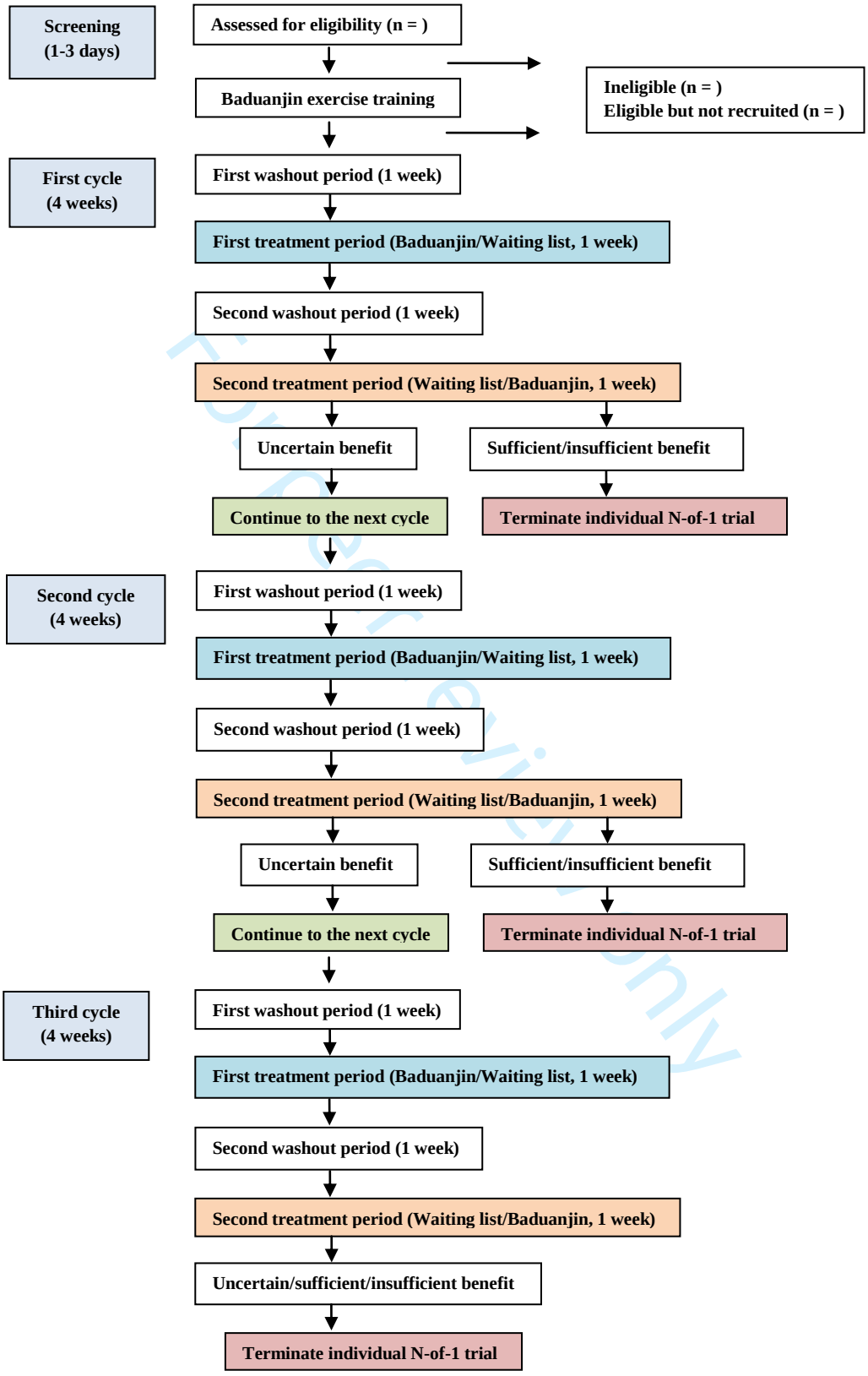
Figure Legends:

Figure 1. Flow diagram of a series of N-of-1 trials



Supplementary Table 1. Time schedule of participant enrollment, interventions, assessments and visits

Items	Screening	Cycle 1				Cycle 2				Cycle 3			
		Washout period 1	Treatment period 1	Washout period 2	Treatment period 2	Washout period 1	Treatment period 1	Washout period 2	Treatment period 2	Washout period 1	Treatment period 1	Washout period 2	Treatment period 2
	Day -3 to -1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Eligibility criteria	X												
Informed consent	X												
Baduanjin training	X												
Demographic characteristic		X											
Randomization			X		X		X		X		X		X
VAS			X		X		X		X		X		X
ODI			X		X		X		X		X		X
JOABPEQ			X		X		X		X		X		X
SF-12			X		X		X		X		X		X
Drug combination		X	X	X	X	X	X	X	X	X	X	X	X
Safety		X	X	X	X	X	X	X	X	X	X	X	X

VAS, Visual Analogue Scale; ODI, Oswestry Disability Index; JOABPEQ, Japanese Orthopaedic Association Back Pain Evaluation Questionnaire; SF-12, Short Form Health Survey 12

Informed Consent Form

Dear Sir or Madam,

You have been diagnosed with chronic non-specific low back pain (CNLBP). We invite you to participate in a series of N-of-1 trials to assess the efficacy and safety of Baduanjin exercise for CNLBP. This study has been approved by the Medical Ethics Committee of Tianjin University of Traditional Chinese Medicine (TCM) (reference number TJUTCM-EC20220005).

Before you decide whether to participate in this study, please read the following content carefully. It can help you understand the study and why it is being conducted, the procedure and duration of the study, the benefits, risks and discomfort that may arise from participating in the study. If you wish, you can also discuss it with your relatives and friends, or ask your doctor for an explanation to help you make a decision.

Name of Project: Baduanjin exercise for CNLBP: a series of N-of-1 trials

Name of Organization: Tianjin University of TCM

Name of Sponsor: Jingbo Zhai

This informed consent form has two parts:

- Information Sheet (to share information about the study with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full informed consent form.

Part I: Information Sheet

1. Introduction

CNLBP is one of the most common health problems worldwide. Exercise is recommended for the treatment of chronic low back pain (LBP) according to the clinical guideline released by the American College of Physicians. TCM is becoming increasingly popular for the management of chronic LBP in recent years. Baduanjin exercise is one of the exercise therapies in TCM. N-of-1 trial is a randomized

cross-over self-controlled trial that is suitable for patients with the chronic disease.

2. Purpose

This study will conduct a series of N-of-1 trials to assess the efficacy and safety of Baduanjin exercise for CNLBP.

3. Setting and sample size

Fifty patients will be recruited from the Department of Orthopedics in the First Teaching Hospital of Tianjin University of TCM.

4. Participant selection

4.1 Inclusion criteria

Patients conforming to the criteria below will be included:

(1) Patients suffering from chronic LBP that is defined as the pain and discomfort in the low back and/or lumbosacral region for more than 12 weeks according to the clinical practice guideline released by the American College of Physicians.

(2) Patients having at least 3 points on the Visual Analogue Scale (VAS) (range, 0-10). Pain of at least 3 points is considered as a perceptible persistent pain.

(3) The age of patients ranging from 18 to 75 years.

(4) Gender is unrestricted.

(5) Patients signing the informed consent form.

4.2 Exclusion criteria

Patients conforming to the criteria below will be eliminated:

(1) Patients suffering from severe spinal diseases, such as spinal fracture, spine malformation, and spinal degenerative change.

(2) Patients with a history of spinal surgery.

(3) Patients with LBP caused by soft tissue injuries or infectious diseases.

(4) Patients with LBP caused by visceral diseases, such as kidney stone, and hysteritis.

(5) Patients having a history of severe cardiovascular and cerebrovascular diseases, diabetes, mental diseases, cognitive impairment, and cancer.

(6) Pregnant or lactating women.

5. What will you need to do if you participate in the study?

If you'd like to participate in the study, you will be asked to sign the informed consent form, and be assessed for eligibility according to the inclusion and exclusion criteria. If you are eligible, you will take a Baduanjin training course in the Department of Orthopedics. Then, you will experience three treatment cycles one by one. During the first washout period of the first cycle, general characteristics such as age, gender, history of diseases will be collected. Then, you will be assigned to the Baduanjin exercise or waiting list group randomly at the beginning of each treatment period. During each period of Baduanjin exercise, you will perform a half-hour Baduanjin exercise once a day for a week. You will be asked to answer the questions about VAS, ODI, JOABPEQ, and SF-12 at the beginning and the end of each treatment period.

6. Benefits

Low back pain may be reduced and functional status may be improved after Baduanjin exercise.

7. Risks

If you become unwell during the study period, or if your condition changes in a new way, or if anything unexpected occurs, whether or not it is related to the study, you should inform your doctor in time and he/she will make a judgment and give appropriate medical treatment.

8. Cost

This study will provide a free training for Baduanjin exercise. During the study period, doctors will do their best to prevent and treat any injuries that may result from this study. The sponsor will provide appropriate treatment costs and financial compensation for research-related damages in accordance with relevant regulations.

9. Confidentiality

Any information and data obtained about you personally during the study will be kept strictly confidential.

10. Sharing of the results

The results will be published in a peer-reviewed journal or international conferences.

11. Right to refuse or withdraw

You can voluntarily choose to participate in the research and withdraw from the research. Whether to participate in the study is entirely up to you. You may decline to participate in the study, or withdraw from the study at any time during the study, without affecting your relationship with your doctor or the loss of your medical or other benefits. In your best interest, your doctor or investigator may suspend your participation in the study at any time during the study.

12. How to get more information?

You can ask any questions about this study at any time and get answers accordingly. Your doctor will notify you if there is any important new information during the study that may affect your willingness to continue participating in the study.

13. What should you do now?

It is up to you (and your family) to decide whether to participate in the study. Before you make a decision to participate in this study, ask your doctor as many questions as possible.

Thank you for reading the above material. If you decide to participate in this study, please tell your doctor and he/she will arrange everything for you. Please keep this information.

Part II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this study.

Print Name of Participant_____

Signature of Participant_____

Date_____

If illiterate

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print Name of witness_____ AND Thumb print of participant

Signature of witness_____

Date_____

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant. I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher/person taking the consent_____

Date_____

SPIRIT checklist

Section/Item	Item Number	Description	Reported on page #
Administrative information			
Title	**1**	**Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym**	**1**
Trial registration	**2a**	**Trial identifier and registry name. If not yet registered, name of intended registry**	**2**
	2b	**All items from the World Health Organization Trial Registration Data Set**	**7**
Protocol version	**3**	**Date and version identifier**	**7**
Funding	**4**	**Sources and types of financial, material, and other support**	**19**
Roles and responsibilities	**5a**	**Names, affiliations, and roles of protocol contributors**	**1,19**
	5b	**Name and contact information for the trial sponsor**	**1,19**
	5c	**Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities**	**19**
	5d	**Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable**	**14**
Introduction			
Background and rationale	**6a**	**Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention**	**3-5**
	6b	**Explanation for choice of comparators**	**3-5**
Objectives	**7**	**Specific objectives or hypotheses**	**6**
Trial design	**8**	**Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority,**	**6,7**

		exploratory)	
Methods Participants, interventions, and outcomes			
Study setting	**9**	**Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained**	**6**
Eligibility criteria	**10**	**Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)**	**7,8**
Interventions	**11a**	**Interventions for each group with sufficient detail to allow replication, including how and when they will be administered**	**9-11**
	11b	**Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)**	**8**
	11c	**Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)**	**10,13**
	11d	**Relevant concomitant care and interventions that are permitted or prohibited during the trial**	**10,11**
Outcomes	**12**	**Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended**	**11,12**
Participant timeline	**13**	**Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended**	**12-13**
Sample size	**14**	**Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations**	**15-16**

Recruitment	**15**	**Strategies for achieving adequate participant enrollment to reach target sample size**	**7**
Assignment of interventions (for controlled trials)			
Allocation			
Sequence generation	**16a**	**Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions**	**9**
Allocation concealment mechanism	**16b**	**Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned**	**9**
Implementation	**16c**	**Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions**	**9,12**
Blinding (masking)	**17a**	**Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how**	**14**
	17b	**If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial**	**14**
Data collection, management, and analysis			
Data collection methods	**18a**	**Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol**	**11-14**
	18b	**Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention**	**13,14**

		protocols	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13,14
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16,17
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	16,17
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	16,17
Monitoring			
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13,14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14,15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking REC/IRB approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized	12

		surrogates, and how (see item 32)	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigator for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10,11,13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogate	7,12
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13