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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 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 randomised 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 1–3 treatment cycles. They will be randomised into a 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 V.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

⇒ The overall and individual therapeutic effects will be estimated synchronously by hierarchical Bayesian analysis.
⇒ Sample size is calculated according to a simulation-based two-step method.
⇒ Blinding of patients is infeasible because waiting list is used as a control.
⇒ The study period may last more than 1 year because patients are recruited from only a hospital.

## INTRODUCTION

Low back pain (LBP) is a frequently seen health issue globally.[1] The age-standardised global prevalence of LBP reaches up to 7.50%.[2] Most of the 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 labelled 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$1516.67 in KwaZulu-Natal, South Africa.[7] The average cost of care per presentation for older adults with non-specific LBP was $A5844 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, such as 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 not been 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.

Randomised 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 individualised clinical decision should be made with caution based on the evidence from RCTs.[28 29] N-of-1 trial is a randomised cross-over self-controlled trial conducted in one patient,[30] and its results can be directly used to make individualised 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 have been 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.

## METHODS AND ANALYSIS

### 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. First, patients will be assessed for eligibility and participate in a Baduanjin exercise training. Then, eligible participants will receive 1–3 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 1-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 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 1 October 2023 to 31 December 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 WHO Trial Registration Data Set, registration date and protocol version are available at https://www.chictr.org.cn/showprojEN.html?proj=172369.

### Patients

#### 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.

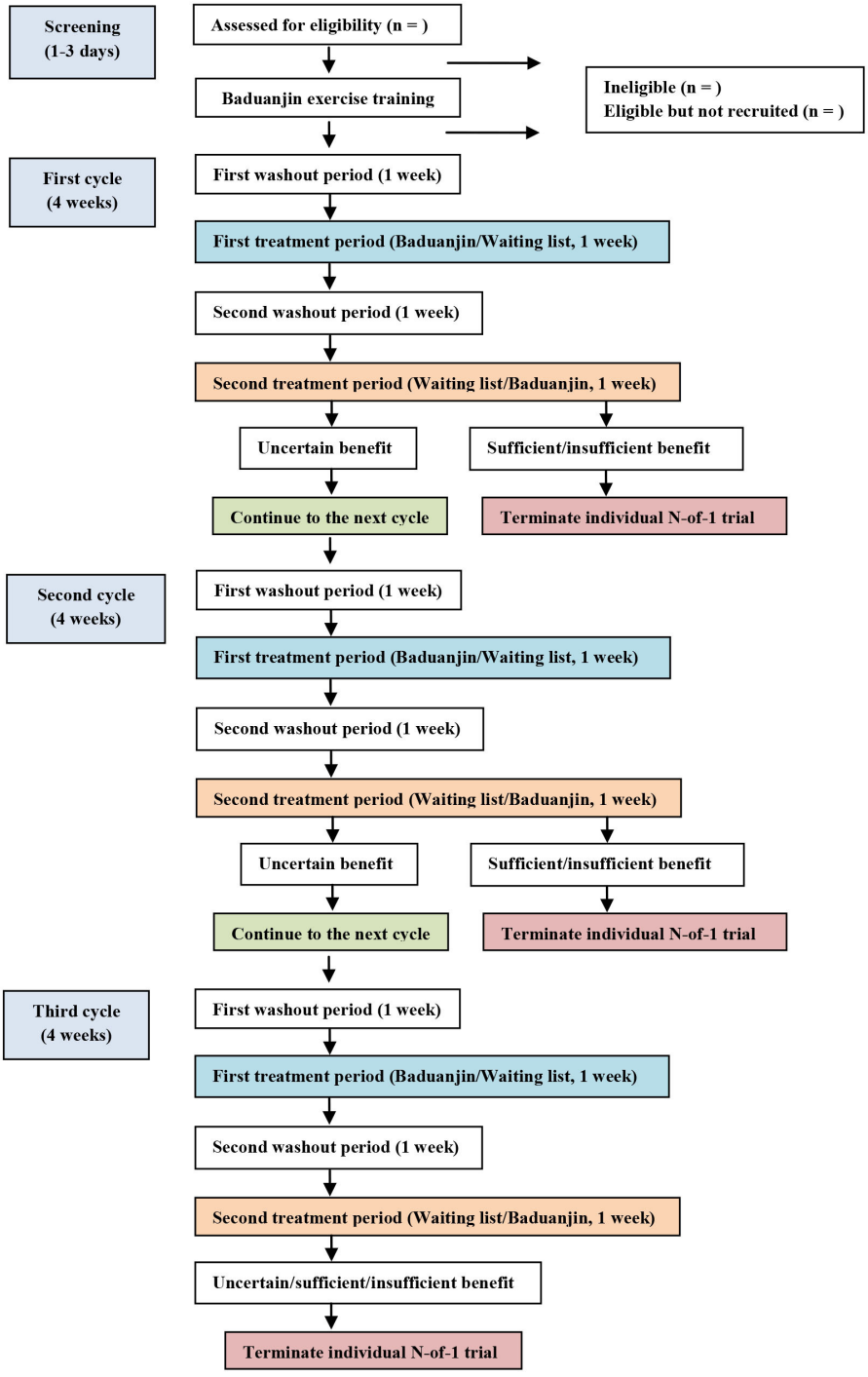


**Figure 1** Flow diagram of a series of N-of-1 trials.

5. Patients signed the informed consent form.

### 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 Examina-

tion (MMSE). Patients with MMSE<27 are diagnosed with cognitive impairment[41] and will be excluded from this study.
6. Pregnant or lactating women.

### 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.

## Random assignment and allocation concealment

The eligible patients will be randomised 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 V.9.1 software by a statistician who is not directly involved in these N-of-1 trials. The doctor (WY) 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 WY and each patient before the initiation of each treatment cycle.

## Interventions

### 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 (AFL) 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 5 min, and then perform the Baduanjin exercise. It will take the patient about 3 min 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 2 min and then repeat the above-mentioned process (including the completion of a Baduanjin exercise session and resting for 2 min) 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 AFL after daily exercise to monitor the adherence. Non-standard movements will be corrected by AFL via video conversation with patients to improve patient adherence if necessary.

### 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 washout 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.

## 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's 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.

### Time schedule

Online supplemental table 1 presents the time schedule of participant enrolment, interventions, assessments and visits. The researcher (JZ) will recruit the participants from the Department of Orthopedics in the First Teaching Hospital of Tianjin University of TCM. During the patient screening period, JZ 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 JZ. 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 AFL. 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 JZ. 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 WY. 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 TG. 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.

### 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 (JZ). 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 (TG) 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. TG 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, TG will contact the sponsor (JZ) and the doctor (WY) 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 TG 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 TG. 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 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.

### Auditing

A researcher who is employed in Tianjin University of TCM will audit the core trial processes and documents related to participant enrolment, 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.

### 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 analysed 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] First, 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 0–100 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 the Baduanjin exercise group and the 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 0.5–1.0 on a VAS of 0–10 according to the American College of Physicians guideline.[4] Therefore, the MCID on a VAS of 0–10 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 SD 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%. Second, the Bayesian hierarchical model is built based on the above-mentioned simulated data by WinBUGS V.1.4.3 software. The process is repeated for 50 000 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 predefined threshold of 80%. Therefore, 50 patients will be recruited.

### Statistical analysis

Quantitative data will be expressed as mean with SD, 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 the last observation carried forward. The mean differences in VAS, JOABPEQ, ODI and SF-12 score between two groups will be compared using the Bayesian hierarchical models with WinBUGS V.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. In addition, the number of iterations will be set to 50 000 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 alternative treatments. The sponsor (JZ) will have access to these interim results and make the final decision to terminate the trial.

### Patient and public involvement

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

## 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 (JZ) 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.

## 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 cannot gain benefits from Baduanjin exercise will be advised to seek for alternative treatments. It is helpful to make an individualised 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 summarising 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.

**Contributors** JZ was the trial sponsor and funder, and conceived the study. AFL and WY designed the inclusion and exclusion criteria. TG designed the time schedule. JZ drafted the manuscript. AFL, WY and TG reviewed and revised the manuscript. All authors read and approved the final manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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