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STUDY PROTOCOL

Efficacy and Safety of the Bushen Quhan Zhiwang Decoction to Achieve Clinical Deep Remission in Rheumatoid Arthritis: Protocol for a Double-Blind, Randomized, Placebo-Controlled Trial

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Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by significant disability, with effective management of disease activity and pain constituting critical clinical objectives. The herbal formulation Bushen Quhan Zhiwang Decoction (BQZD) has demonstrated potential efficacy in symptom alleviation, suggesting a promising role in achieving sustained clinical remission in RA. The present study aims to systematically evaluate the efficacy and safety profile of BQZD for managing RA disease activity and pain relief.

Patients and Methods: This randomized, double-blind, placebo-controlled, single-center clinical trial will enroll a total of 72 RA patients, randomly assigning them into either the intervention group (n=36) receiving BQZD or the placebo control group (n=36). Participants will consume either BQZD or placebo (100 mL, twice daily) over a 12-week intervention period. Clinical assessments are scheduled at enrollment and subsequently at 4-week intervals, continuing through the 16-week mark post-intervention initiation. The primary outcome measure is the Disease Activity Score for 28 joints (DAS28). Secondary outcome variables include visual analogue scale (VAS) pain scores, mechanical pain threshold (MPT), central sensitization inventory (CSI), patient-reported outcomes (PROs), Traditional Chinese medicine (TCM) symptom scores, and biomarkers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Safety endpoints will encompass monitoring of hematological parameters, urinalysis results, and adverse events.

Discussion: This study seeks to generate robust clinical evidence verifying the therapeutic efficacy and safety of BQZD for alleviating pain and achieving deep remission in RA patients. These findings are anticipated to facilitate broader integration of traditional herbal medicine within clinical practice. Additionally, this research endeavors to provide clinically relevant insights into precision treatments for RA by integrating traditional Chinese medicine and Western medical approaches, and aims to lay foundational evidence for future investigations into underlying regulatory mechanisms and potential therapeutic targets of TCM.

Keywords: rheumatoid arthritis, Bushen Quhan Zhiwang Decoction, clinical deep remission, pain, randomized controlled trial

Introduction

Rheumatoid arthritis (RA) is a prevalent autoimmune disease characterized by chronic joint inflammation and is a leading cause of disability, affecting approximately 0.5–1.0% of the global population.[1,2] The hallmark features of RA include synovial inflammation, immune cell infiltration, and elevated levels of inflammatory mediators, which collectively result in joint swelling and pain. If left unchecked, these processes can lead to structural joint damage,

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restricted mobility, and even permanent disability.[3] Beyond the physical consequences, RA significantly diminishes patients' quality of life and imposes a substantial economic burden on both families and society.[4,5] Pain management remains a major clinical concern, and the American College of Rheumatology Pain Management Task Force has identified pain as arguably the most critical and persistent complaint among individuals with rheumatic diseases.[6]

The introduction of biological disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) has markedly improved RA treatment outcomes and long-term prognosis, contributing to higher remission rates. However, limitations in cost-effectiveness and narrow therapeutic indications have led to suboptimal patient adherence and low drug retention rates. As a result, conventional synthetic DMARDs (csDMARDs) remain the cornerstone of RA therapy for the majority of patients.[7] International guidelines advocate for early initiation of csDMARDs following diagnosis, citing benefits such as symptom relief, delayed radiographic progression, and improved clinical outcomes.[8] Nevertheless, even with appropriate csDMARD therapy, a considerable proportion of patients do not achieve adequate disease control and continue to experience pain that interferes with daily functioning.[9,10] Clinical trials have demonstrated that only 30–50% of patients with active RA attain remission after six months of combination DMARD therapy.[11–13] Pain is often perceived by RA patients as the most immediate and debilitating symptom, with up to 90.4% seeking medical care primarily for pain-related issues.[14] Notably, some patients experience persistent pain despite effective suppression of inflammation,[15,16] suggesting the involvement of non-inflammatory mechanisms such as pain sensitization.[17,18] In these cases, intensifying anti-inflammatory treatment may prove ineffective and may increase the risk of adverse effects.[19] Therefore, the development of new therapeutic strategies capable of achieving deep remission and relieving chronic, diffuse, and intractable pain represents an urgent clinical need.

Traditional Chinese medicine (TCM), with its long-standing history and unique theoretical system, offers a diverse array of therapeutic options for rheumatologic conditions.[20] Its efficacy in managing RA has been increasingly recognized, with fewer side effects compared to conventional therapies, making it suitable for long-term use.[21] Bushen Quhan Zhiwang Decoction (BQZD) is a compound herbal formula composed of 18 herbs, derived from two classical prescriptions—Guizhi Shaoyao Zhimu Decoction from Synopsis of Golden Chamber (Jingui Yaolue) and Hugu San from Taiping Huimin Heji Ju Fang. Clinically, BQZD is widely utilized in the treatment of musculoskeletal disorders such as RA[22,23] and knee osteoarthritis,[24,25] particularly in individuals sensitive to cold or whose symptoms worsen in low temperatures. Experimental studies have shown that BQZD reduces bone erosion and exhibits anti-inflammatory properties,[26] potentially via modulation of the Wnt/β-catenin signaling and TRAF6/P38/JNK MAPK pathway.[27,28] It also downregulates TNF-α and MMP13 expression and significantly decreases serum levels of IL-1 and IL-2 in collagen-induced arthritis (CIA) rat models, thereby reducing joint swelling.[29,30] Clinical research has indicated that combining BQZD with methotrexate significantly improves outcomes—such as morning stiffness, joint tenderness, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF)—compared to methotrexate alone.[23,31] Moreover, a recent meta-analysis highlighted BQZD's superiority in reducing the incidence of treatment-related adverse events.[32] However, more robust evidence is needed to confirm its efficacy in RA patients who fail to achieve deep remission with csDMARDs alone. Evaluating mechanical pain threshold (MPT) and central sensitization inventory (CSI) scores will provide further insight into the potential of BQZD to alleviate pain sensitization, offering a basis for exploring its underlying mechanisms. This could ultimately support a more precise and integrative approach to RA treatment, combining TCM and Western medicine.

Accordingly, we are conducting a randomized controlled trial to rigorously evaluate the efficacy and safety of BQZD in relieving pain and achieving deep remission in RA patients.

Trial Design and Methods

Study Design and Setting

A single-center, randomized, double-blind, placebo-controlled superiority trial has been meticulously designed to assess the efficacy and safety of BQZD among RA patients who have not achieved clinical deep remission despite ongoing treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and who remain in a state of low disease activity. Efficacy will be determined by comparing the benefits of BQZD against placebo, specifically evaluating its effectiveness in reducing disease activity and alleviating pain. The study protocol adheres rigorously to the guidelines outlined in the CONSORT

and SPIRIT Statement.[33,34] The detailed flowchart of the study procedures is illustrated in Figure 1. Stringent inclusion criteria, rigorous randomization, comprehensive blinding methods, and appropriate statistical techniques will be employed to minimize biases. Ethical approval for this trial has been obtained from the Clinical Research Ethics Committee of the China-Japan Friendship Hospital (Approval No. 2024-KY-058-2), and the study is registered on ClinicalTrials.gov (NCT06309030).

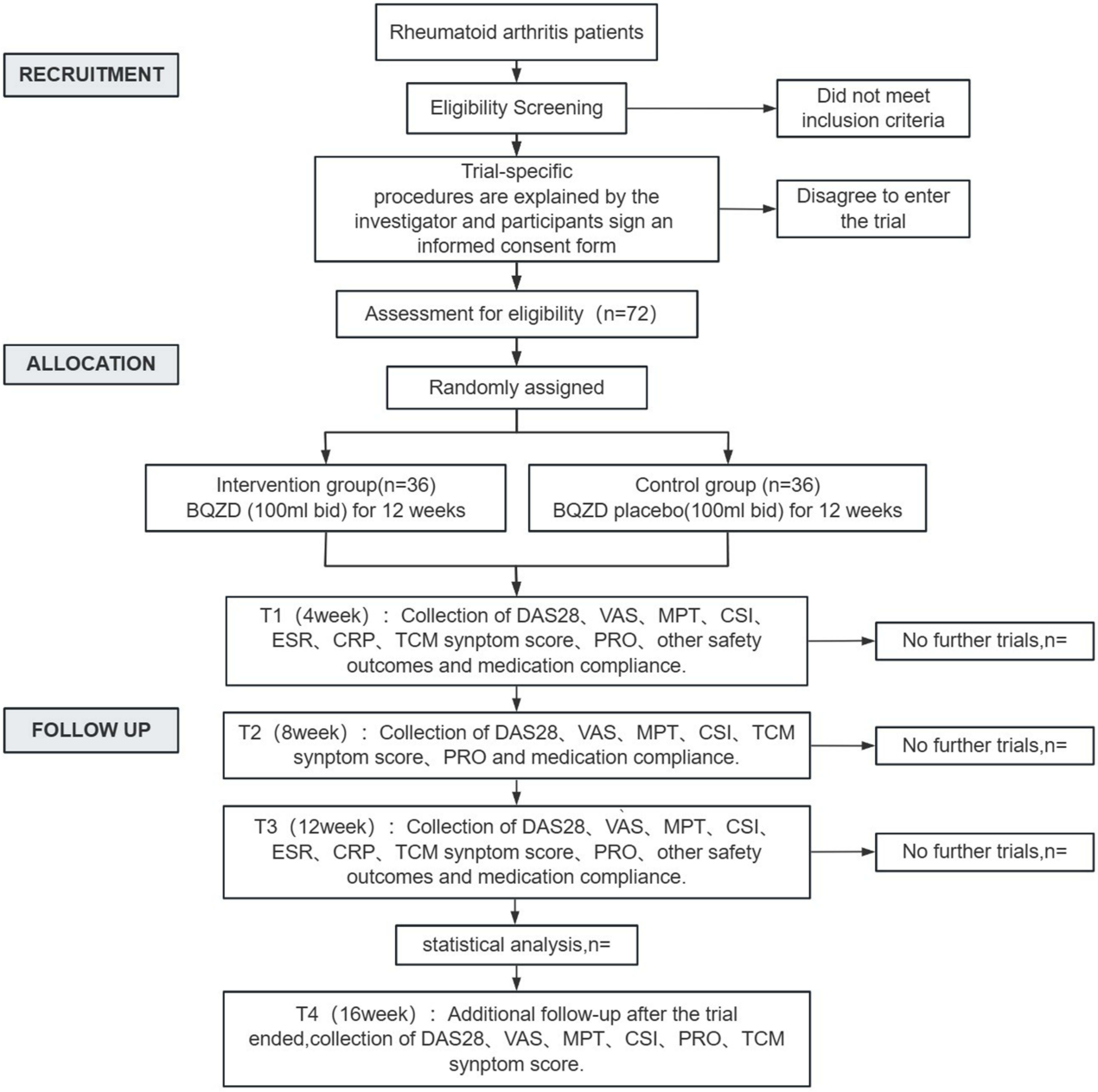

Figure 1 Flow diagram of the trial design.

Abbreviations: DAS28, disease activity score derivative for 28 joints; MPT, mechanical pain threshold; VAS, visual analog scale for pain; CSI, central sensitization inventory; TCM, traditional Chinese medicine; PRO, patient-reported outcomes; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; BQZD, Bushen Quhan Zhiwang Decoction.

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Participants

Inclusion Criteria

Patients eligible for inclusion must meet the following criteria: (1) aged between 18 and 75 years, no gender restrictions;[35] (2) confirmed RA diagnosis per the ACR/EULAR 2010 classification criteria;[36] (3) a Disease Activity Score for 28 joints (DAS28)[37] between 2.6 and 3.2; (4) consistent use of a single type of csDMARD at a stable dosage for at least 4 weeks prior to enrollment, which must remain unchanged during the study; and (5) voluntary agreement to participate, evidenced by providing written informed consent.

Exclusion Criteria

Patients will be excluded based on the following conditions: (1) usage of glucocorticoids or immunosuppressants (excluding csDMARDs) within 4 weeks preceding recruitment; (2) concurrent diagnosis of other definitive autoimmune diseases or severe multi-system illnesses; (3) presence of cognitive impairment (such as Alzheimer's disease, vascular cognitive impairment, etc), central nervous system disorders, psychosomatic disorders, or peripheral neurological disorders; (4) current pregnancy, breastfeeding, or planned pregnancy during the trial period; (5) known allergies to any study medications; and (6) other factors deemed unsuitable by the research investigators.

Recruitment

A total of 72 RA patients meeting the inclusion criteria will be recruited from outpatient and inpatient departments of the China-Japan Friendship Hospital via poster advertisements and online platforms. Prospective participants will receive comprehensive information regarding the trial, including its objectives, eligibility criteria, randomized interventions, follow-up schedule, and potential benefits and risks. Following voluntary agreement and signed informed consent, participants will undergo screening. Those eligible will be randomly allocated to either the intervention or control group. Participants retain the right to withdraw at any stage for any reason. All withdrawals post-enrollment will be documented accordingly.

Intervention

Participants meeting eligibility criteria will be randomized to either the intervention or control groups in a 1:1 ratio. Participants in the intervention group, continuing their baseline csDMARD regimen unchanged, will receive BQZD (100 mL twice daily) for 12 weeks. In parallel, control group participants will receive an identical placebo formulation and dosage.

The BQZD formulation comprises 18 herbal constituents: Rehmanniae Radix Praeparata (12 g), Dipsaci Radix (20 g), Epimedii Folium (10 g), Drynariae Rhizoma (15 g), Psoraleae Fructus (10 g), Cinnamomi Ramulus (10 g), Paeoniae Radix Alba (10 g), Paeoniae Radix Rubra (10 g), Anemarrhenae Rhizoma (15 g), Atractylodis Rhizoma (10 g), Saposhnikoviae Radix (10 g), Ephedrae Herba (6 g), Clematidis Radix et Rhizoma (15 g), Lycopodii Herba (30 g), Eupolyphaga Steleophaga (9 g), Achyranthis Bidentatae Radix (10 g), Angelicae Pubescentis Radix (10 g), and Aconiti Lateralis Radix Praeparata (9 g). Detailed descriptions of each botanical and zoological ingredient are presented in Table 1.

The Chinese herbal medicines utilized in the trial will be supplied by Beijing He Yan Ling Pharmaceutical Development Co., Ltd. (Beijing, China) and rigorously monitored and evaluated by the company's quality control department, adhering strictly to the standards outlined in the Pharmacopoeia of China (2020 edition). According to standardized protocols, decoction will occur within the specialized decoction facility at the China-Japan Friendship Hospital. Initially, herbs will be immersed in distilled water at a 1:10 ratio (herbs to water) for one hour, followed by a one-hour decoction. Subsequently, an additional decoction step will incorporate distilled water at an 8-fold ratio, with decoction continuing for another hour. Finally, 200 mL of BQZD filtrate will be produced through combined vacuum concentration processes, portioned into individual 100 mL containers. The placebo, containing 10% of the active BQZD preparation, caramel coloring, and a bittering agent, will be simultaneously decocted in the same cooking vessel to ensure identical appearance and comparable aroma. Post-coding and documentation, both BQZD and placebo solutions will be stored consistently at 2–8°C in the pharmacy department of the China-Japan Friendship Hospital.

Table 1 Components of BQZD (Intervention Drug)

Chinese Pinyin	Scientific Name	Family	Part Used	Dosage (g)
Shu Di Huang	*Rehmannia glutinosa* (Gaertn.) DC.	Orobanchaceae	Steamed root	12
Xu Duan	*Dipsacus asper* Wall. ex DC.	Caprifoliaceae	Dried root	20
Yin Yanghuo	*Epimedium sagittatum* (Siebold & Zucc.) Maxim.	Berberidaceae	Dried aerial parts	10
Gu Suibu	*Drynaria roosii* Nakaike	Polypodiaceae	Dried rhizome	15
Bu Guzhi	*Cullen corylifolium* (L.) Medik	Fabaceae	Dry ripe fruit	10
Gui Zhi	*Cinnamomum cassia* Presl.	Lauraceae	Dried twigs	10
Bai Shao	*Paeonia lactiflora* Pall.	Ranunculaceae	Dried root	10
Chi Shao	*Paeonia ladiflora* Pall.	Ranunculaceae	Dried root	10
Zhi Mu	*Anemarrhena asphodeloides* Bge.	Asparagaceae	Dried root	15
Cang Zhu	*Atractylodes lancea* (Thunb.) DC	Asteraceae	Dried root	10
Fang Feng	*Saposhnikovia divaricata* (Turcz.) Schischk.	Apiaceae	Dried root	10
Ma Huang	*Ephedra sinica* Stapf.	Ephedraceae	Dried herbaceous stem	6
Wei Lingxian	*Clematis chinensis* Osbeck	Ranunculaceae	Dried root and rhizome	15
Shen Jincao	*Lycopodium japonicum* Thunb.	Lycopodiaceae	Dried herb	30
Tu Biechong	*Eupolyphaga sinensis* Walker	Eupolyphaga	Dried worms	9
Niu Xi	*Achyranthes bidentata* Blume	Amaranthaceae	Dried root	10
Du Huo	*Angelica biserrata (R.H. Shan & C.Q. Yuan) C.Q. Yuan & R.H. Shan*	Apiaceae	Dried root	10
Hei Shun pian	*Aconitum carmichaelii* Debx.	Ranunculaceae	Daughter root	9

Throughout the trial, participants must maintain daily medication record cards to track adherence and symptom evolution. Participants are instructed to return any unused medications for proper disposal at each follow-up visit. Researchers will meticulously record the quantities dispensed and returned on each participant's case report form. Participants must refrain from taking any additional botanical, animal-based, or Western medicines with immunosuppressive or immunomodulatory properties, excluding the trial's investigational medications. In cases of intolerable pain, low-dose NSAIDs may be administered under investigator oversight; any deviations or dosage modifications must be explicitly documented.

Outcomes

Participants will attend four scheduled follow-up assessments: at enrollment, and subsequently at 4, 8, and 12 weeks post-intervention. Each in-person hospital assessment will last at least 20 minutes, with an additional follow-up visit conducted one month after trial completion. The trial timeline is detailed in Table 2.

Primary Outcome

The primary outcome measure is the Disease Activity Score 28 (DAS28),[37] a validated instrument frequently employed for assessing rheumatoid arthritis (RA) activity. Expert rheumatologists will perform evaluations at baseline and at the 12-week mark to assess intervention efficacy. Participants achieving a DAS28 score below 2.6 will be classified as having reached deep clinical remission.[12]

Table 2 Schedule of the Study Procedure

	Study Period						
	Enrolment	**Allocation**	**Post-Allocation**				**Follow-up**
Timepoint	**$-T_1$**	**0***	**T_0***	**T_1***	**T_2***	**T_3***	**T_4***
Enrolment:							
Eligibility screen	X						
Informed consent	X						
Demographic information	X						
Allocation		X					
Interventions:							
BQZD			◆———	———	———	———◆	
Placebo			◆———	———	———	———◆	
Assessments:							
DAS28			X	X	X	X	X
MPT/CSI			X	X	X	X	X
VAS pain scores			X	X	X	X	X
TCM symptom scores			X	X	X	X	X
PRO			X	X	X	X	X
RF/ACPA			X			X	
ESR/CRP			X	X		X	
Blood/urine routine			X	X		X	
ALT/AST/Scr/ECG			X	X		X	
Adverse event record				X	X	X	X

Note: *Allows (±7 days) on specified days.

Abbreviations: BQZD, Bushen Quhan Zhiwang Decoction; DAS28, disease activity score derivative for 28 joints; MPT, mechanical pain threshold; CSI, central sensitization inventory; VAS, visual analog scale for pain; TCM, traditional Chinese medicine; PRO, patient-reported outcomes; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; ECG, electrocardiograph.

Secondary outcomes

(1) Visual Analogue Scale (VAS)[38] for Pain: This validated tool quantifies pain intensity on a scale ranging from 0 (no pain) to 10 (extreme pain).

(2) Mechanical Pain Threshold (MPT): This measure employs a Von Frey tactile measurement kit in a controlled environment. The Von Frey filament is placed perpendicular to the participant's skin surface, applying sufficient pressure to bend the filament for 2 seconds, starting at a baseline of 60 g. Pressure is incrementally increased until the participant indicates a transition from tactile sensation to sharp pain, at which point the pressure is recorded as the MPT.

(3) Central Sensitization Inventory (CSI):[39] Central sensitization is evaluated using the CSI scale, comprising two sections. Section A encompasses 25 symptoms characteristic of central sensitization syndrome (CSS), rated from 0 (never) to 4 (always), yielding a maximum potential score of 100. Higher scores indicate more severe symptoms. Section B queries previous diagnoses, specifically three CSS-associated disorders (depression, anxiety,

neck injury) and seven central nervous system sensitivity syndromes (tension headaches/migraines, fibromyalgia, irritable bowel syndrome, restless legs syndrome, temporomandibular joint disorder, and multiple chemical sensitivity). The Chinese adaptation of the CSI has demonstrated high reliability within the Chinese population.[40]

(4) Traditional Chinese Medicine (TCM) Symptom Scores: Symptoms are assessed using scales outlined in the Guidelines for Clinical Research of Chinese Medicine (New Drug).[41] The assessment covers 15 clinical manifestations including joint pain, joint swelling, fatigue, and poor appetite, graded according to severity across four levels.

(5) Patient-Reported Outcomes (PRO): This instrument evaluates patient-perceived health status, quality of life, functional capabilities, symptoms, and sensations, offering distinct advantages over traditional clinician-based outcome metrics in RA management, medication efficacy assessments, and chronic disease monitoring.[42,43]

(6) Laboratory Assessments (CRP and ESR): Blood and other required biological samples are collected from fasting participants early in the morning by the Laboratory Medicine Department at China-Japan Friendship Hospital. Samples are subsequently frozen and securely stored at the hospital's Clinical Research Institute.

Safety Outcomes

Safety outcomes include the monitoring of adverse events, electrocardiograms (ECGs), and laboratory evaluations such as complete blood counts, urinalysis, and liver and renal function tests. BQZD, a well-established decoction compound widely utilized in China for RA and other rheumatic autoimmune conditions, is generally considered safe. However, patients may occasionally experience drug-related adverse reactions, including allergic reactions and diarrhea. To mitigate and manage adverse events effectively, rigorous standards for adverse event assessment will be implemented, and continuous improvements in safety endpoint evaluations will be pursued by supervising authorities.

To ensure maximal protection of participant rights and welfare, stringent control over patient inclusion and exclusion criteria will be enforced. Researchers will undergo comprehensive training and authorization prior to the initiation of the study to promptly recognize and address adverse reactions. Should adverse events—including serious adverse events—occur, comprehensive documentation detailing the onset time, clinical manifestations, treatment administered, duration, outcomes, and causal relationship to investigational drugs will be meticulously recorded in the case report form. Patients with abnormal laboratory findings will undergo close monitoring until values normalize, return to baseline, or until causality with the investigational drug is excluded. Serious adverse events must be reported to the study sponsor and ethics committee within 24 hours. The trial will be considered for termination if participants require additional immunosuppressive treatments, alternative medications, surgery, or other substantial interventions, categorizing these instances as withdrawals. Relationships between adverse events, the interventions implemented, and severity will be comprehensively analyzed.

Allocation and Blinding

Participants will be randomly allocated to either the intervention or control group using stratified block randomization to ensure balanced group sizes and comparability. A block size of four will generate six permutations: AABB, ABAB, ABBA, BAAB, BABA, and BBAA, where A denotes the treatment group and B denotes the control group. SPSS software will produce a randomized numerical sequence by selecting integers from 1 to 6, determining the final allocation order of the blocks. The randomization process, alongside medication distribution and collection, will be independently managed by a designated study administrator who remains blinded to the study's objectives.

Consistent with double-blind methodology, neither participants nor investigators will be aware of group assignments during the study. After enrollment completion, all clinical data will be systematically entered into a database, verified thoroughly for accuracy, and secured against further modifications. Initial unblinding will categorize participants into Groups A and B without revealing their treatment assignments. Upon finalizing the statistical analysis, a second unblinding will clearly designate the intervention and control groups.

We will use Bang's Blinding Index (BI) to quantify the effectiveness of the blinding method.[44] Based on the subjects' guesses regarding their own intervention measures, specifically whether they belong to the intervention group or the control group. The Bang BI calculation formula will be employed to analyze this data and obtain an index value that

reflects the success of the blinding method. Blinding is considered successful when the BI < 0.2. The closer the BI is to 0, the more effectively the blinding method has been implemented.[45]

In instances of serious or unexpected adverse events, premature unblinding will be conducted with the Principal Investigator's (PI) authorization. Detailed records of unblinding—including timing, rationale, and personnel involved—will be promptly documented and reported to the Clinical Research Ethics Committee of the China-Japan Friendship Hospital.

Sample Size

This study employs a superiority design, referencing previous research on combined BQZD and methotrexate treatment for RA.[31] The results indicated that after 12 weeks of treatment, the DAS28 for the methotrexate group was 3.37 ± 1.46, while the DAS28 for the methotrexate plus BQZD group was 2.96 ± 1.09. To ascertain the deep remission effects of BQZD, a clinically meaningful difference in DAS28 scores of at least 0.5 points between the intervention and control groups has been established ($\delta = -0.5$). Applying a unilateral calculation with $\alpha = 0.025$ and $\beta = 0.2$, and considering a 1:1 allocation ratio between groups, the calculated sample size requirement is 32 participants per group. Allowing for a dropout rate of 10%, 36 participants per group are required, totaling 72 participants.

Statistical Analysis

Database construction will utilize EpiData (Version 3.1), with subsequent statistical analyses and graphical representations performed using IBM SPSS (Version 26.0) and R software (Version 4.4.1). Baseline characteristics will be summarized through descriptive statistics; continuous variables will be reported as mean ± standard deviation or median with interquartile ranges after normality test, while categorical variables will be expressed in frequencies and percentages. Group comparisons for continuous data will involve independent *t*-tests or Mann–Whitney *U*-tests, whereas chi-square tests or Fisher's exact tests will assess categorical data differences.

Initial statistical analyses of the primary outcome will adhere to the intention-to-treat principle, comparing DAS28 score changes and deep remission rates between the BQZD and placebo groups. An analysis of covariance (ANCOVA) will evaluate outcome variables across both groups at four distinct time intervals. Employing repeated measures ANCOVA will facilitate the identification of inter-group differences at multiple time points, while also assessing interactions between group assignment and temporal factors. Additionally, adverse reaction rates will be compared using chi-square or Fisher's exact test. Sensitivity analyses will be conducted concurrently to strengthen the robustness and interpretability of the findings. Subgroup analyses, defined by concurrent pharmacological treatments and comorbid medical conditions, will replicate the primary analyses to validate the consistency of results. Missing data constituting 20% or less of total observations will be addressed via multiple imputation using the MICE package in R. Statistical significance will be established at $P < 0.05$.

Practitioner Training and Quality Control

Given the inherently subjective nature of pain assessments and other patient-reported measures, including Traditional Chinese Medicine (TCM) symptom scores and visual analogue scale (VAS) scores, the lead researcher will deliver comprehensive protocol training to all involved researchers prior to study initiation. This will ensure consistent adherence to the established guidelines. To mitigate subjective evaluation bias, each follow-up assessment will be independently performed by two researchers, and the mean of their scores will serve as the final recorded value. In instances of substantial discrepancy, a third researcher will adjudicate. Additionally, prior to each assessment, participants will receive clear instructions to improve the accuracy of self-reported evaluations. Original paper-based reports and associated objective measures will be securely stored for subsequent verification.

The Clinical Research Ethics Committee of China-Japan Friendship Hospital will oversee the trial, ensuring protection of participant rights and interests, as well as accuracy and completeness of trial data.

Data Collection Methods and Management

All data obtained from follow-up evaluations will be accurately documented in dedicated case report forms. In the event of participant withdrawal prior to study completion, the latest available data will serve as the final record. Epidata software will be utilized to establish a specialized database, and data entry from paper records will be conducted by two data managers using the double-entry method for quality assurance and unified management.

Discussion

The pathogenesis of RA remains unclear. Currently, clinical objectives primarily include controlling disease progression, delaying bone destruction,[23] and preserving joint function. Prospects for complete recovery remain uncertain, highlighting an urgent need for more effective treatments. Pain, one of the most prevalent symptoms in RA patients, frequently constitutes their primary complaint.[16] Indeed, up to 70% of patients prioritize pain relief above other symptom improvements.[46] Traditionally, RA-related pain has been attributed predominantly to peripheral joint inflammation. While conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) are effective as first-line therapies, persistent pain in some patients, even after normalization of inflammatory markers,[47,48] suggests involvement of non-inflammatory pain mechanisms. In such cases, escalating anti-inflammatory medication alone may be ineffective and increase adverse event risks, complicating chronic pain management. Traditional herbal medicine offers a more accessible, safer, and cost-effective alternative. Traditional Chinese Medicine (TCM) has demonstrated substantial therapeutic potential in RA management through its characteristic multi-target mechanisms and holistic treatment paradigm.[49] Combining Western medicine and TCM may represent a promising strategy for achieving significant recovery in RA patients.[50]

Pharmacological action forms the foundation of effective drug treatment. Clarifying the pharmacological action is essential not only for elucidating the mechanisms behind clinical efficacy but also for advancing precision medicine in the future. Dipsaci Radix, Psoraleae Fructus, Rehmanniae Radix Praeparata, and Aconiti Lateralis Radix Praeparata are the core drugs in BQZD to jointly play the role of tonifying the kidney and strengthening the bone. Modern pharmacological research has demonstrated that extracts from Dipsaci Radix, particularly Akebia Saponin D, can protect cartilage by inhibiting the production of inflammatory factors, promoting cartilage repair, and preserving the extracellular matrix of cartilage cells.[51] Isopsoralen promotes the differentiation and proliferation of osteoblasts by upregulating osteogenic gene expression through the activation of the Notch signaling pathway.[52] Catalpol, an iridoid compound found in Rehmanniae Radix Praeparata, significantly inhibits osteoclast differentiation and regulates bone homeostasis by modulating gene expression. In addition, catalpol can enhance the expression of anti-inflammatory factors, thereby preventing the activation of inflammatory agents that impact the nervous system and alleviating osteoarthritis pain.[53] The alkaloids and flavonoids found in aconite exhibit pharmacological effects, including anti-inflammatory, antioxidant, and immune-regulating properties.[54] Total flavonoids, primarily naringin, found in Rhizoma Drynariae exhibit various pharmacological activities, including osteoblast induction, anti-osteoporosis effects, anti-inflammatory properties, and antioxidant activity.[55] Previous studies by our research group have identified the chemical constituents, absorption components, and metabolites of BQZD. A total of 182 compounds were identified in BQZD, comprising 40 flavonoids, 34 alkaloids, 23 phenylpropanoids, 18 saponins, 9 iridoids using ultra-performance liquid chromatography with Q-Ex active Orbitrap mass spectrometry combined with parallel reaction monitoring. Moreover, network pharmacology analysis and validation using the collagen-induced arthritis (CIA) rat model indicated that BQZD exhibits bone-protective effects through the TRAF6/p38/JNK MAPK pathway.[28]

This randomized controlled trial aims to investigate the efficacy of BQZD in achieving deep clinical remission in RA patients. Beyond evaluating the Disease Activity Score (DAS28), the study will assess the effectiveness of BQZD in alleviating pain sensitization by measuring mechanical pain threshold (MPT), a standard assessment of nociceptive sensitization reflecting the minimal mechanical stimulus eliciting pain response. Concurrently, the Central Sensitization Inventory (CSI), a simple and non-invasive tool, will be used to evaluate central sensitization, increasingly recognized as a significant contributor to chronic pain of RA.[17,18] Central sensitization involves heightened responsiveness of nociceptive neurons to both normal and subthreshold stimuli.[18] Emerging evidence indicates that herbal components,

including alkaloids from Sinomenii Caulis, Corydalis Rhizoma, and Chuanxiong Rhizoma, effectively mitigate central pain through multi-target mechanisms.[56] Aconite modulates gene expression in spinal cord and dorsal root ganglia, alleviating nociceptive hypersensitivity.[57] Preliminary studies by our research group demonstrated that BQZD effectively reduces cold-induced RA pain, potentially through modulation of the thermosensitive channel protein TRPA1, a critical mediator of pain sensitization. Oral administration of TRPA1 inhibitors reversed mechanical pain sensitization in spinal nerve ligation models,[58] while intrathecal administration attenuated sensitization in both spinal nerve ligation and rapid eye movement sleep deprivation model.[59] Besides clinical efficacy, this study explores the mechanism underlying central sensitization-associated RA pain at a metabolomic level through analyses of biological markers (eg, blood inflammatory factors), providing foundational insights into BQZD's potential effects on central sensitization and guiding future research into TCM's role in managing RA pain sensitization.

Differences in outcomes between groups will be analyzed, along with correlation assessments, to precisely determine BQZD's effectiveness in RA pain relief. This research aims to generate evidence-based medical insights that enhance clinical management strategies for RA pain.

This study, however, has several inherent limitations. Firstly, some scales, especially those assessing pain, rely heavily on subjective patient reports, introducing variability. Secondly, the placebos used include a standardized 10% dose of herbal extracts to closely mimic the odor and taste of active treatments,[60] although this raises debate regarding their potential pharmacological activity. Additionally, practical constraints preclude long-term follow-up in this study. As a single-center investigation, regional population characteristics may influence the findings. Thus, further validation through multicenter, large-sample randomized controlled trials remains essential.

Integrating TCM with modern medical treatments for RA can effectively leverage the synergistic potential of both methodologies. This combined approach is anticipated to substantially improve patients' quality of life and enhance the long-term sustainability of therapeutic outcomes.[21] The findings from this study are expected to yield robust, evidence-based insights into the efficacy of BQZD in achieving deep remission in RA, while establishing a foundation for future extensive investigations.

Finally, it is important to emphasize that this study protocol is solely a randomized controlled trial protocol. As a model of clinical trials, it does not actually investigate the effects of herbs on rheumatoid arthritis, and is not a completed study.

Trial Registration

ClinicalTrials.gov identifier (https://clinicaltrials.gov/ct2/show/NCT06309030): NCT06309030, registered on March 13, 2024.

Trial Status

This study is currently in the recruitment phase. We started recruitment in October 2024, and it was expected to be completed in December 2025.

Abbreviations

DAS28, disease activity score derivative for 28 joints; MPT, mechanical pain threshold; CSI, central sensitization inventory; VAS, visual analogue scale for pain; TCM, traditional Chinese medicine; PRO, patient-reported outcomes; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factors; ACPA, anti-citrullinated protein antibodies; BQZD, Bushen Quhan Zhiwang Decoction; ECG, electrocardiograph.

Data Sharing Statement

No datasets were generated or analyzed during the course of this study. All relevant data for this research will be obtained upon the completion of the study.

Ethics Approval and Consent to Participate

Ethics approval was obtained from the Clinical Research Ethics Committee of the China-Japan Friendship Hospital (NO. 2024-KY-058-2) on 14 May 2024. The study has been registered in the Clinical Trials Registry (NCT06309030) on 13 March 2024. All participants will sign a written informed consent prior to inclusion. The study will follow the Declaration of Helsinki, participants can make the decision to withdraw from the trial at any time, and all data that may reveal personal privacy will be hidden.

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We appreciate the efforts and cooperation of all research staff and patients involving this study. The findings will be disseminated in peer-reviewed publications.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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