Study on efficacy and safety of Tong-luo Qu-yu plaster treatment for knee osteoarthritis: study protocol for a randomised, double-blind, parallel positive control, multi-center clinical trial

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SUBJECT AREAS
  Internal Medicine Specialties

KEYWORDS
  Clinical trials, Knee osteoarthritis, Tong-luo Qu-yu plaster, Randomized, Protocol
Abstract

**Background:** Knee osteoarthritis (KOA) is a common chronic musculoskeletal disorder that seriously affect quality of life. Patients with KOA frequently develop one or more of the typically following symptoms: joint pain, stiffness, joint friction noise, impaired functionality. Traditional Chinese medicines (TCM) have showed a superior effect and peculiar advantage on the treatment of KOA, among TCMs, the Tong-luo Qu-yu plaster is the convenient and most commonly used method in China to improve symptoms including pain, stiffness and limited mobility in patients with KOA, as it causes few adverse effects. But there is a lack of high quality of clinical evidences to support the therapeutic effect that Chinese adhesive plaster can relieve pain and stiffness. The purpose of this study will be to evaluate the efficacy and safety of Tong-luo Qu-yu plaster in patients with KOA.

**Methods:** This study will be a randomised, double-blind, parallel positive control, multi-center clinical trial. A total of 2000 participants older than 40 years with KOA, will be randomly allocated into a experimental group (n=1500) and a control group (n=500). All participants will receive a conventional conservative treatment lasted for 14 days as two courses, daily 1 time. Tong-luo Qu-yu plaster will be administered externally to participants in the experimental group, while the control group will receive a Qi-zheng Xiao-tong plaster. The outcome of the total Western Ontario and McMaster Universities Arthritis Index scores, TCM syndrome quantitative score, visual analog scale scores will be measured during the assessment visits (baseline and 1-, 2-week follow-up). In addition, adverse events concerning clinical symptoms and signs as well as laboratory tests will be documented during clinical trials.

**Discussion:** This study will be a randomized, double-blind, parallel positive control trial to further evaluate the effectiveness and safety of Tong-luo Qu-yu plaster for patients with KOA in nine medical centers compared with control group, it is expected that the patients with KOA will benefit from this study.

**Trial Registration:** ClinicalTrials.gov, NCT03309501. Registered on 08 November 2017.

**Keywords:** Clinical trials, Knee osteoarthritis, Tong-luo Qu-yu plaster, Randomized, Protocol
Knee osteoarthritis (KOA), also known as degenerative arthritis, is a kind of chronic joint disease characterized by the progressive degeneration and breakdown of the articular cartilage and bone hyperplasia [1]. Patients with severe osteoarthritis frequently develop one or more of the typically following symptoms: joint pain, stiffness, stairs joint friction noise when activity occurs, impaired functionality, such as difficulty walking and climbing [2, 3]. It has been estimated that prevalence of osteoarthritis is more than 10% in old people above 60 years old reported symptomatic osteoarthritis worldwide, an epidemiological survey found that the overall prevalence of OA was about 16% in a rural Chinese adult population [4]. KOA affects over 70 millions people in Europe and the direct medical costs exceed 2 billion euros, which represented a social, economic burden and was the 11th leading cause of disability according to World Health Organization (WHO) global burden of disease study 2010 [1, 5]. Surgical treatment and conservative management are often used for patients with KOA [6], surgical treatment including total knee replacement (TKA), arthroscopic surgery and so on for KOA is well-known to substantially improve KOA related pain and function [7, 8]. However, part of TKA candidates are not actually willing to undergo the surgery, due in large part to lack of confidence in beneficial surgery outcomes and postoperative complications such as chronic pain after TKA which can affect all dimensions of health related quality of life [9, 10]. Additionally, each of these surgical options permanently modifies the knee joint via an invasive, irreversible surgical procedure, which may also negatively impact patient willingness to undergo these procedures and limits clinical utility. Therefore, conservative treatment such as nonsteroidal anti-inflammatory drugs (NSAIDs), paregoric, cartilage protective agents and so on play an important role in the treatment of KOA. However, the application of NSAIDs is reported to lead to some incidences of adverse effects, including gastrointestinal tract impairment and the possible promotion of articular deterioration [6, 11]. Because of lack of effectiveness, the of recommendation against chondroprotective agents such as glucosamine and chondroitin have existed in recent decades [12]. In a randomized controlled double-blind placebo study, efficacy of glucosamine has been questioned, there was no significant clinical benefit compared to the placebo group [13]. Traditional Chinese medicine (TCM) have showed a better effect and unique advantage on the treatment of KOA, of which the herbal plaster is a
common approach and a convenient choice for many patients with KOA [14]. Our earlier studies also proved the safety of Tong-luo Qu-yu plaster, which can help significantly reduce pain and improve function with better clinical curative effect and no serious adverse reactions in people with KOA [15, 16]. But the lack of large sample randomised, double-blind, controlled clinical trial, the clinical evidence of Tong-luo Qu-yu plaster for KOA need to be further completed. Therefore, the purpose of this study was assess the effectiveness and safety of Tong-luo Qu-yu plaster on patients with KOA in randomised, double-blind, parallel positive controlled, multicenter clinical trial.

Methods

Trial design

This will be a randomised, double-blind, parallel positive controlled, multicenter clinical trial, each participant will sign a informed consent form (ICF) before the research was performed. A total of eleven medical institutions are involved in the study, subjects will be enrolled at eleven hospitals, including Longhua Hospital Affiliated to Shanghai University of TCM, The first Affiliated hospital of Guangzhou University of TCM, Zhengzhou Central Hospital, Suzhou Hospital of TCM, Luoyang Orthopaedics-Traumatological Hospital, Xiangyang First People’s Hospital, Liaoning Hospital of TCM, The Second Hospital of Nanjing Medical University, The Fourth Central Hospital of Tianjing, Changchun University of TCM, Shandong University of TCM. Longhua Hospital Affiliated to Shanghai University of TCM take charge of the total clinical scheme design. The study protocol has been approved by the ethics committee Shanghai University of TCM on the use of human subjects for research (approval number: 2016LCSY097), each participating center has conducted ethical filing and agreed with the ethical approval of the main centre hospital.

The study phases are shown in Fig. 1. A total of 2000 patients with KOA will be recruited and randomly allocated into experimental group (n=1500) or control group (n=500), each patient will undergo a 2-week treatment with herbal patches for one session per day, a flow chart of trial participation is provided in Fig. 2. Efficacy and safety data will be collected throughout the whole study.

Inclusion criteria
The following inclusion criteria should be met:

1) Participants who have symptomatic KOA, diagnosis of KOA was based on criteria developed by the American College of Rheumatology (ACR) in 1986 [17];
2) Standard of TCM disease and syndrome diagnosis[18, 19];
3) Symptomatic KOA with a pain of at least 30 mm on a 100-mm visual analog scale (VAS);
4) The patient who were 20 years of age;
5) All the patients signed the ICF before study begins.

Moreover, if the patient has osteoarthritis in both knees, we chose the more severe side of the knee-joint. If the pain scores of two knees are the same, the researchers chose one side of the knee-joint for intervention according to the research demands.

**Exclusion criteria**

1) There is a history of trauma or surgery in the knee joint in the last six months before the trial began;
2) Arthroscopy and intra-articular injection was performed in the last three months before the trial began or hormone therapy was used in the first month of screening or participants who have underwent knee arthroplasty;
3) Subjects are undergoing or have participated in other clinical trials in the last three months;
4) Participants with other knee joint diseases such as chondromalacia patellae, rheumatic arthritis or rheumatoid factor positive (RF>40) will be excluded from the trial;
5) Patients has mental disorder or severe diseases and complications such as severe diabetes, serious liver and kidney disease, malignant tumors, infectious diseases or complications affect the joints;
6) Plaster allergy and pregnant and lactating women were not considered for this study.

**Intervention**

All patients will be randomly divided into Tong-luo Qu-yu plaster group (experimental group) and Qi-zheng Xiao-tong plaster (control group), The experimental group and the control group received Tong-luo Qu-yu plaster and Qi-zheng Xiao-tong plaster respectively. Tong-luo Qu-yu plaster is a tape-type patch, which is made by Henan Lingrui Pharmaceutical Ltd, the validity period of Tong-luo Qu-yu
plaster is 24 months. Qi-zheng Xiao-tong plaster is a medicated plaster made by Tibet Qizheng Tibetan Medicine Ltd, it is valid for 36 months, Two kinds of plasters are identical to the tested formulation in terms of texture, size, color, and odor. Both groups use the plaster according to the instructions given by nurses, all participants will receive a conventional conservative treatment lasted for 14 days as two courses, daily 1 time. Patients will have three follow-up visits, the clinicians, subjects, investigators and assessors are masked to treatment allocation. In the process of trial, patients are not allowed to use other TCMs. The subjects were in severe pain with VAS scores above 80 mm, the researchers can be allowed to give celebrex for relieving pain within two daily dose, if patients have other accompanying disease that have to take the medicine for treatment, the principle is to not affect the evaluation of the trial drugs.

**Safety assessment**

Adverse events (AEs) concerning clinical symptoms and signs as well as laboratory tests will be documented during clinical trials. Skin irritation will be recorded by Berger Bowman scoring system [20], subjective symptoms including itching, pain, burning sensation and the skin lesions manifested as erythema, papules, edema, blisters, erosions, skin ulcer, and so on will be recorded after 1 and 2 weeks of the treatment. The drug safety monitoring is conducted by blood routine examination (BRE), urine routine test (URT), liver function tests (LFTs) including serum glutamic oxaloacetic transaminase (AST), serum glutamic pyruvic transaminase (ALT), serum total protein (TP), serum alkaline phosphatase (ALP), serum total bilirubin (TBIL), kidney function tests (KFT) including blood urea nitrogen (BUN) and serum creatinine between the start and end of the trial. erythrocyte sedimentation rate (ESR), antistreptococcus hemolysin (ASO), rheumatoid factor (RF), electrocardiogram (ECG) and X-ray examination is also detected. Serious adverse events (SAE) will be reported to the local drug administration authorities in 24 hours.

**Outcome assessment**

Assessment standards is based on the Chinese traditional medicine new drug clinical research guiding principle and standards for diagnosis and curative effect of Chinese medical symptom [18, 19].

*Primary Outcome*
The Western Ontario and McMaster universities osteoarthritis index (WOMAC) as objective indicators of efficacy is the primary efficacy endpoint of the study, which is a widely used, proprietary set of standardized questionnaires used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints [21]. The WOMAC measures 5 items for pain (score range 0–20), 2 for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68) to assess the severity of the arthritis and its therapeutic effect according to the symptom and sign of the patients. It can fully reflect the basic situation of osteoarthritis [22]. The primary outcome is the improvement of the total WOMAC scores, which will be measured during the assessment visits (baseline and 1-, 2-week follow-up).

**Secondary outcome assessment**

The secondary outcome is the changes in TCM syndrome quantitative score [19], visual analog scale (VAS) scores [23], onset time of drug for pain relief between baseline and the end of treatment. The VAS scores range from 0 mm to 100 mm, which is widely used for the clinical evaluation on the degree of pain. Onset time of drug for pain relief is determined by the time that was taken in the VAS scores fell at least 10 mm at the first time.

**Sample size estimation**

Our study was designed as a non-inferiority trial, sample size calculations are based on the primary outcome measurement. First, minimal clinically important differences for WOMAC scales in KOA are estimated as 15.50 points from previous studies [24]. Second, we assume that square deviation of WOMAC score is 318.88 based on previous literature [25]. Considering a power of 80 %, and a alpha value of 2.5 % (two-tailed), the sample size will be calculated using the following formula:

\[ n = \frac{4}{3} \left( u_{\alpha} (1 + u_{\beta}) \sigma^2 \right) / (\Delta - \delta)^2 \]

\[ (u_{\alpha} = 1.6449, \ u_{\beta} = 1.2816) \]

Thus we obtained the sample size of 1600 patients for this trial, allowing for a conservative 20% dropout rate, the total sample size was set to be 2000 patients (1500 in Tong-luo Qu-yu plaster group).

**Randomization assignment**

This study is designed as a randomized, double-blind, parallel positive drug control, multi-center
clinical trial. A total of 2000 eligible participants will be randomized (3:1) using a stratified-block randomized method based on the disease and the center, select the appropriate length to one of the two treatment groups: experimental group (Tong-luo Qu-yu group) and control group (Qi-zheng Xiao-tong group). SAS statistical software 9.2 (SAS Institute, Cary, NC, USA) will be used to generate a randomization scheme based on the PROC PLAN function, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient.

**Drug management**

During the study, one experimental drug administrator was set up to be responsible for drug save, delivery, recording and recycle. The whole process of drug coding is written by a blind coder and forge a document. The drug boxes and emergency envelope contains the corresponding drug number are randomly divided into each center according to the central number of random stratification. Emergency unblinding can only happen when there was a serious adverse event in the study, the subject will exit the trial and the investigator should record detailed reason for withdrawing from the trial in the case report form.

**Statistical analysis**

The statisticians are responsible for the statistical analysis plan with the main researchers, SAS 9.2 statistical software was adopted for all statistical analyses. Data sets including full analysis set (FAS), per-protocol set (PPS), safety set (SS) are analyzed, actual subjects, shedding cases, excluding cases, demographic and characteristics of cases, efficacy and safety analyses will be conducted according to the intention-to-treat (ITT) principle.

Categorical data including frequency tables or percentages and continuous variable data including presented as mean±standard deviation, median, superior and inferior quartiles, minimum value, maximum value will be used to describe characteristics of patients in both groups. Primary outcome will be compared between both groups, categorical data will be conducted by performing a chi-squared test or Fisher's exact test, continuous data fitted normal distribution is performed by t tests or the variance test method. If the data doesn't satisfy the normal distribution or homogeneity of
variance, it will be analysed using a Wilcoxon rank sum test or Wilcoxon symbols test to compare the
two treatment arms. A two-sided $P$ value of $\leq 0.05$ or $\leq 0.01$ is considered to be statistically
significant.

Discussion

KOA is a common degenerative disease, particularly in older adults. In the last 20 years, there was a
increase about 26 % in the burden of KOA as measured by years lived with disability per 100,000
persons [26]. Tong-luo Qu-yu plaster, also known as external medication is a conventional method of
treating chronic musculoskeletal diseases in TCM, the treatment is convenient and inexpensive [15,
16]. But there is a lack of high quality of clinical evidences to support the therapeutic effect that
Chinese adhesive plaster can relieve pain and stiffness. Well-designed randomized controlled trials
are needed to examine the efficacy of TCM treatments for KOA, the objective of this clinical trial is to
evaluate the efficacy and safety of Tong-luo Qu-yu plaster in patients with KOA. The study is guided
by practice-based scientific evidence for the use of Tong-luo Qu-yu plaster for this condition. Upon
completion of data collection, it is expected that the patients with KOA will benefit from this study,
the data will be published after the study is completed.

The study is designed in accordance with Standard Protocol Items: Recommendations for
Interventional Trials (SPIRIT) guidelines. The SPIRIT checklist is given in Additional file 1.

Abbreviations

KOA: Knee osteoarthritis; WHO: World Health Organization; TCM: Traditional Chinese medicine;
WOMAC: Western Ontario and McMaster Universities Arthritis Index scores; VAS: Visual analog scale;
NSAIDs: Nonsteroidal anti-inflammatory drugs; AE: Adverse event; SAE: Serious adverse event; ACR:
American college of rheumatology; LFTs: Liver function tests; BRE: Blood routine examination; URT:
Urine routine test; RF: Rheumatoid factor; AST: Transaminase; ALT: Serum glutamic pyruvic
transaminase; TP: Serum total protein; ALP: Serum alkaline phosphatase; TBIL: Serum total bilirubin;
KFT: Kidney function tests; BUN: Blood urea nitrogen; ESR: Erythrocyte sedimentation rate; ASO:
Antistreptococcus hemolysin; ECG: Electrocardiography; FAS: Full analysis set; ITT: Intention-to-treat;
PPS: Per protocol set; SS: safety set; ICF: Informed consent form; SPIRIT: Standard Protocol Items:
Recommendations for Interventional Trials.

Declarations

**Trial status**

The trial was registered at ClinicalTrials.gov on 08 November, 2017, identifier NCT03309501, protocol version 2.1/20170923 is currently active. We started recruitment in September 2017 and will be completed in December 2020, the first patient was included at the Second Hospital of Nanjing Medical University.

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**Availability of data and materials**

The data for this study has not been collected in full and, therefore, is not yet available to the public. Trial information can be found at ClinicalTrials.gov, NCT0330950.

**Authors’ contributions**

BX, MY and XC designed the trial, XC is the principal investigator of this study. BX and MY drafted the manuscript, XC and YW revised the manuscript critically for important content. ZT, LZ, LY, ZL, SZ, XW,
JL participated in the coordination of the trial as well as in recruiting patients. All authors reviewed and approved the final manuscript.

Competing interests
The author(s) declare that they have no competing interests.

Consent for publication
Not applicable.

Ethical approval and informed consent
The ethics committee of the Shanghai University of TCM approved the study (approval number: 2016LCSY097). Each participating center has conducted ethical filing and agreed with the ethical approval of the main centre hospital. All volunteers signed the informed consent form before the trial.

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References
1. Cucchiarini M, de Girolamo L, Filardo G, Oliveira JM, Orth P, Pape D, et al. Basic science of osteoarthritis. J Exp Orthop. 2016; 3(1):22.

2. Herrero-Beaumont G, Roman-Blas JA, Bruyere O, Cooper C, Kanis J, Maggi S, et al. Clinical settings in knee osteoarthritis: Pathophysiology guides treatment. Maturitas. 2017; 96:54-7.

3. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. 2012; 64(6):1697-707.

4. Liu Y, Zhang H, Liang N, Fan W, Li J, Huang Z, et al. Prevalence and associated factors of knee osteoarthritis in a rural Chinese adult population: an epidemiological survey. BMC Public Health. 2016; 16:94.

5. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003; 81(9):646-56.

6. Taylor N. Nonsurgical Management of Osteoarthritis Knee Pain in the Older Adult: An Update. Rheum Dis Clin North Am. 2018; 44(3):513-24.

7. Farr II J, Miller LE, Block JE. Quality of life in patients with knee osteoarthritis: a commentary on nonsurgical and surgical treatments. Open Orthop J. 2013; 7:619-23.

8. Moseley JB, O’Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002; 347(2):81-8.

9. Passias PG, Bono OJ, Bono JV. Total Knee Arthroplasty in Patients of Advanced Age: A Look at Outcomes and Complications. J Knee Surg. 2018.[Epub ahead of print]

10. Wylde V, Beswick A, Bruce J, Blom A, Howells N, Gooberman-Hill R. Chronic pain after total knee arthroplasty. EFORT Open Rev. 2018; 3(8):461-70.

11. Doi T, Akai M, Fujino K, Hoshino Y, Iwaya T, Sunami Y. Effect of nonsteroidal anti-inflammatory drug plasters for knee osteoarthritis in Japanese: a randomized
12. Sawitzke AD, Shi H, Finco MF, Dunlop DD, Harris CL, Singer NG, et al. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. Ann Rheum Dis. 2010; 69(8):1459-64.

13. Hauk L. Treatment of knee osteoarthritis: a clinical practice guideline from the AAOS. Am Fam Physician. 2014; 89(11):918-20.

14. State Administration of TCM. Clinical Path of Traditional Chinese Medicine 22 Professional 95 Diseases. Beijing: China Traditional Chinese Medicine Press; 2011.

15. Chen W, Zhang C. Knee osteoarthritis with rheumatic syndrome and stasis treated by Tongluo Qutong Plaster. Journal of Changchun University of Chinese Medicine. 2016.

16. Qin YM. To Explore the Curative Effect of Treating Knee Joint Osteoarthritis with Rheumatism and Blood Stasis Syndrome by Dredging Collaterals and Removing Pain Plaster. China & Foreign Medical Treatment. 2016; 19:169-70.

17. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis and rheumatism. 1986; 29(8):1039-49.

18. State Administration of TCM. Standards for diagnosis and curative effect of Chinese medical symptom. Nanjing: Nanjing University Publishing House; 1994.

19. Zhen XY. Guidelines for clinical research on Chinese new herbal medicines. Beijing: Medical Science and Technology Publishing House of China; 2002.

20. Bowman JP, Berger RS, Mills OH, Kligman AM, Stoudemayer T. The 21-day human cumulative irritation test can be reduced to 14 days without loss of sensitivity. J Cosmet Sci. 2003; 54(5):443-9.
21. Ackerman I. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Aust J Physiother. 2009; 55(3):213.

22. Gandek B. Measurement properties of the Western Ontario and McMaster Universities Osteoarthritis Index: a systematic review. Arthritis Care Res. 2015; 67(2):216-29.

23. Reips UD, Funke F. Interval-level measurement with visual analogue scales in Internet-based research: VAS Generator. Behav Res Methods. 2008; 40(3):699-704.

24. Hmamouchi I, Allali F, Tahir L, Khazzani H, Mansouri LE, Ali Ou Alla S, et al. Clinically important improvement in the WOMAC and predictor factors for response to non-specific non-steroidal anti-inflammatory drugs in osteoarthritic patients: a prospective study. BMC Res Notes. 2012; 5:58.

25. Wang X, Cao Y, Pang J, Du J, Guo C, Liu T, et al. Traditional chinese herbal patch for short-term management of knee osteoarthritis: a randomized, double-blind, placebo-controlled trial. Evid Based Complement Alternat Med. 2012; 2012(4):171706.

26. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England). 2012; 380(9859):2163-96.

Figures

| STUDY PROTOCOL |
|----------------|
|                |
| **Enrollment** | **Treatment** |
| Visit 1 (-7 to 0 day) | Visit 2 (7±1 day) | Visit 3 (14±2 day) |
| ENROLLMENT      |               |
| Eligibility and exclusion criteria | ✓ |               |
| Informed consent | ✓ |               |
| Random allocation | ✓ |               |
| Intervention                                      | Tong-luo Qu-yu group | Qi-zheng Xiao-tong group | Efficacy and safety assessment | WOMAC scores | TCM syndrome quantitative scores | VAS | Onset time |
|--------------------------------------------------|----------------------|--------------------------|-------------------------------|--------------|----------------------------------|-----|------------|
| Medical history                                  | √                    |                          |                               |              |                                  |     |            |
| Complications and medication                     | √                    |                          |                               |              |                                  |     |            |
| Physical examination                             | √                    |                          |                               |              |                                  |     |            |
| Vital signs                                      | √                    |                          |                               |              |                                  |     |            |
| Routine urine test                               | √                    |                          |                               |              |                                  |     |            |
| Blood routine examination                       | √                    |                          |                               |              |                                  |     |            |
| Liver function and renal function                | √                    |                          |                               |              |                                  |     |            |
| ESR, ASO, RF                                     | √                    |                          |                               |              |                                  |     |            |
| Electrocardiogram                                | √                    |                          |                               |              |                                  |     |            |
| Knee joint X-ray examination                     | √                    |                          |                               |              |                                  |     |            |

**INTERVENTIONS**

**OTHERS**

- Combination medication
- Drug distribution
- Drug recycling

Figure 1

SPIRIT Figure. Study phases schedule of the randomized controlled trial for patients.
Figure 2

Study flow diagram of trial participation.

Supplementary Files
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