Efficacy And Safety of Jian-Pi Huo-Xue Granule For Non-Alcoholic Fatty Liver Disease: Study Protocol For a Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background:

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease with a prevalence of 25% worldwide, but there is a lack of consensus treatment drugs. Previous studies have shown that Jian-Pi Huo-Xue granule (JPHX) can reduce hepatic steatosis by ultrasound image, but lacks quantitative observation of liver fat content. This study aims to improve the efficacy and safety evaluation of JPHX for NAFLD using magnetic resonance imaging-proton density fat fraction (MRI-PDFF) as the primary outcome.

Methods: This is a randomized, double-blind, placebo-controlled clinical trial. This trial will enroll 84 participants with NAFLD, which will be randomized into JPHX or placebo granule groups in equal proportions, and receive JPHX or placebo granules treatment for 24 weeks. A follow-up will be performed 12 weeks after intervention. The primary outcome is the change of MRI-PDFF from baseline to week 24. Secondary outcomes are the body weight, body mass index (BMI), waist circumference, waist-to-hip ratio (WHR), serum hepatic function, serum lipids, blood glucose-related indicators, life quality measuring health surveys, and Traditional Chinese Medicine (TCM) Syndrome Scale. Outcomes will be monitored at baseline, 12 and 24 weeks after enrolment. Adverse events that occurred in this trial will be managed and recorded in time.

Discussion: We design a clinical trial for NAFLD management with JPHX, a TCM formula. The results of this trial will present the efficacy and safety of JPHX, and provide clinical evidence for the treatment of NAFLD.

Trial registration: Chinese Clinical Trial Registry, ID: ChiCTR2100046132. Registered on May 4, 2021.

Introduction

Background

Non-alcoholic fatty liver disease (NAFLD) is the main clinical manifestation of diffuse hepatic bullous steatosis. Except for alcohol and other liver damage factors, NAFLD can be divided into simple fatty liver disease, non-alcoholic steatohepatitis (NASH)(1), non-alcoholic fatty hepatic fibrosis, and liver cirrhosis according to the degree of intrahepatic steatosis, inflammation, and fibrosis(2).

NAFLD has become the most common chronic liver disorder worldwide. The prevalence of NAFLD is increasing year by year, ranging from 6.3–45% in general adults, of which 10–30% are NASH(3). 25% of the global population is projected to have NAFLD(4), and the incidence of NASH is estimated to increase by up to 56% in 2030(5). According to the epidemiological survey in China, the prevalence of NAFLD in adults diagnosed by abdominal ultrasound has increased from 15% to more than 31% in 10 years. NAFLD has become the main reason for the increase of ALT and GGT(6, 7). NAFLD patients have occult

onset and chronic progression of liver disorders that are usually associated with metabolic syndrome including obesity, abnormal lipid metabolism, hypertension diabetes, and insulin resistance(8–10). NAFLD is one of the factors for the increasing incidence of liver cirrhosis(11) and hepatocellular carcinoma (12, 13).

The western medicine treatment of NAFLD mainly includes lipid-lowering drugs, glucagon-like peptide (GLP-1) and dipeptide acylase 4 (DPP4) inhibitors, intestinal microecological therapy, apoptosis signal-regulated kinase 1 (ASK1)(14), silymarin, Farnesoid X receptor (FXR) agonist, and surgical treatment(15). However, there is a lack of consensus on the treatment of NAFLD, and there may be some errors and biases in the research methods and results.

Jian-Pi Huo-Xue Granule (JPHX), composed of 8 herbs, is a TCM experience prescription for alcoholic liver disease (ALD) and NAFLD in clinical. Both ALD and NAFLD are accompanied by the disruption of gut barrier integrity and homeostasis, which leads to intestinal leakage and liver damage(16–18). The previous *in vivo* experiments(19) showed that JPHX can correct the injury of microvilli on the surface of intestinal mucosal epithelial cells and restore the disorder of intestinal microbiota induced by the Lieber-DeCarli liquid diet(20), reduce the leakage of intestinal endotoxin (21), ameliorate alcoholic liver injury(22), liver steatosis(23) and inflammation in the ALD model rat. Similarly, the effect in repairing intestinal barrier integrity also indicates a potential therapeutic effect of JPHX on NAFLD.

For the researches of JPHX for NAFLD, JPHX significantly improved the liver function of the diet-induced NAFLD model, reduced hepatic steatosis and blood lipids, and normalized the NAFLD activity score (24, 25). JPHX also has satisfactory clinical efficacy for NAFLD patients. He et al(26) used JPHX to treat patients with NAFLD and found that compared with the control group, JPHX significantly improved the assessment of fatty liver degree by ultrasound image, restored liver function, and reduced serum triglyceride (TG)(27) and total cholesterol (14) levels(26). However, this study lacks quantitative observation of liver fat content. Therefore, this study will use MRI-PDFF as the primary outcome to investigate the clinical evidence of efficacy and safety of JPHX as a treatment of NAFLD.

Methods/design

This randomized, double-blind, placebo-controlled superiority trial will investigate the efficacy and safety of JPHX granule as a treatment for NAFLD. A flow diagram of this trial is shown in Figure. 1. This study will be conducted in Shuguang Hospital Affiliated with Shanghai University of Traditional Chinese Medicine.

Five visits including one follow-up were designed in this trial: week 6, 12, 18, 24 after enrolment and week 36 for follow-up. Each time point has five-day time flexibility. The study schedule is shown in Figure.2.

Sample size

According to the results of a previous clinical trial in Shuguang hospital, after treated with JPHX, there were 26 patients (65%) whose abdominal ultrasonography diagnostic scores had at least 3 indicators each decreased by 1 point or more than before treatment(28). It is expected that the percentage of liver fat in MRI-PDFF after treatment with JPHX decreased by at least 1-level (an absolute decrease of 4.8% or a relative decrease of 26% in MRI-PDFF from baseline) in 60% cases and 30% in the placebo control group. Assuming a = 0.05, β = 0.2, π_T = 0.6, π_C = 0.3, δ = 0.01, n_T: n_C = 1:1. According to the optimal sample size calculation formula, 33 samples in each group will be obtained. Considering the leakage rate of 20%, at least 42 samples will be obtained from each group.

$$n_T = n_C = \frac{(z_{1-\alpha} + z_{1-\beta})^2[\pi_T(1-\pi_T) + \pi_C(1-\pi_C)]}{[(\pi_T - \pi_C) - \delta]^2}$$

Diagnostic criteria

The diagnosis of NAFLD according to the “Guidelines of prevention and treatment for nonalcoholic fatty liver disease” updated in 2018 by the National Workshop on Fatty Liver and Alcoholic Liver Disease CSoH, Chinese Medical Association, Fatty Liver Expert Committee CMDA.(29). The diagnosis of TCM syndromes is based on the ‘Diagnostics of Traditional Chinese Medicine’(30) and the ‘Consensus opinion on diagnosis and treatment of nonalcoholic fatty liver disease with integrated traditional Chinese and Western Medicine’(31).

Inclusion criteria

(1) Met the diagnostic criteria of NAFLD or NASH with spleen deficiency and blood stasis syndrome;

(2) Aged 18 to 65 years;
(3) MRI-PDFF fat fraction ≥ 5% ;

(4) BMI < 35 kg/m^2;

(5) Willing and able to follow the scheduled visit plan, diet and exercise guidance, laboratory tests, and other research procedures;

(6) Serum alanine aminotransferase (ALT) < 5 times the upper normal limit;

(7) Signed informed consent of participants.

Exclusion criteria

(1) Participants who regularly used other hepatoprotective drugs in the past 1 month before screening;

(2) History of taking drugs that may affect lipid metabolism in 3 months before screening, such as tamoxifen, amiodarone, sodium valproate, methotrexate, and glucocorticoid;

(3) The patients combined with special conditions that may lead to fatty liver, such as total parenteral nutrition, inflammatory bowel disease, celiac disease, hypothyroidism, Cushing's syndrome, β-lipoprotein deficiency, lipoatrophic diabetes, and Mauriac syndrome;
(4) Patients with alcoholic fatty liver disease (male alcohol intake > 30g/d, female alcohol intake > 20g/d), liver cirrhosis, liver decompensation, and other chronic liver diseases, such as hepatitis B, hepatitis C, autoimmune liver diseases;
(5) Type 2 diabetes patients with unstable control (HbA1c ≥ 9.5% before enrolment);
(6) Patients with high risk or extremely high risk of arteriosclerotic cardiovascular disease (ASCVD);
(7) Those who have had bariatric surgery in the past year or who have taken weight-loss drugs in the past three months have lost more than 10% of their weight;
(8) Participants with a history of drug or narcotic abuse;
(9) Pregnant women, lactating women, and participants with major primary diseases or malignant tumors.

Randomization and concealment

Allocation

A researcher in an independent data center will conduct the design of the randomization sequence with SPSS Ver 24.0 software. Enrolled participants will be randomly assigned to the JPHX group or the placebo-controlled group in a 1:1 ratio. The sequence will be sealed as confidential documents in opaque envelopes and kept independently.

Blinding

All patients and researchers will be blinded to the treatment assignments until the study is completed. Personnel unrelated to this clinical trial will complete the preparation of drug blinding and emergency letters. Duplicate blinding is adopted in this study. All the data will enter into the database in double copies, and the final statistical plan is confirmed by question answering, verification, and blind review, the database will be locked. After that, the first unblinding will be carried out and the results of the undefined group information corresponding to random numbers for necessary statistical analysis can be obtained. After the analysis, the main researcher will perform the second unblinding with the identification of two groups. All the unblinding processes will be recorded. In case of emergency, the reason, time, and place of blindness breaking will be recorded, and the cases are treated as missing cases.

Recruitment

The potential participants will get the basic information of this trial from outpatient physicians or through the advertisements located in the hospital, and communicated with the researchers through the contact information. Trained researchers will conduct the investigation. Participants will be informed of the detailed process of this trial, collection of laboratory and imaging evaluation, storage of biological specimens, and be shown the informed consent form with an oral explanation of the probable benefits and potential risks to assure that participation is entirely voluntary. Participants will be offered a choice to

proceed after they have signed the informed consent form. During the enrolment, the biological and imaging examinations will be conducted, and the results with other needed information of participants will be confidentially recorded in the case report form (CRF).

Withdrawal, dropout, and discontinuation

Participants are free to withdraw at any time and will be investigated the reason for withdrawal. The reason and its connection with this trial will be recorded after investigation. If severe adverse events occur, or participants do not meet the requirements of this trial, such as gestation or take forbidden drugs concomitantly, participants will be advised to discontinue the participation. If moderate or severe adverse reactions judged to be related to the clinical trial occur in more than 25% of the total participants, or if the required number of participants has not been fully enrolled within the schedule, this clinical trial may be terminated early.

Interventions

Participants in the JPHX group will receive JPHX granule, while JPHX simulated granule as placebo will be applied in the control group. Both groups of participants will receive regular health education, including diet control, exercise, and behavior modification. diet adjustment: low sugar, low fat, and high vitamin diet are recommended. The fat content is less than 30%, protein content accounts for 15%-18%, and carbohydrate accounts for 52%-55% of the daily total energy; Strengthen physical exercise: exercise for more than 30 minutes each time, 4 times a week; Adjust emotion and keep a good mood; During the experimental period, other traditional Chinese medicine and Western medicine with lipid-lowering or fatty liver treatment as the main treatment are prohibited.

The JPHX granule is compounded of 8 Chinese herbs, whose ingredients are equivalent to Atractylodes Macrocephala Koidz. (Bai Zhu), Radix Salviae. (Dan Shen), Aurantii Fructus. (Zhi Ke), Paeoniae Radix Alba. (Bai Shao), Radix Puerariae. (Ge Gen), Alisma Orientale. (Sam.) Juz. (Ze Xie), Schisandrae Chinensis Fructus. (Wu Wei Zi), Curcumaelongae Rhizoma (Jiang Huang, and packaged at a unit of 6.39 g. The placebo will have a similar appearance, weight, and taste compared to the JPHX. Both JPHX and placebos will be produced by Jiangyin Tianjiang Pharm Co. Ltd, Jiangsu, China, and will be packaged follow the randomization sequence. Granules will be instructed to take 2 packs two times per day for 24 weeks. Participants will receive the drug for 6 weeks at each visit and give back the drugs left over from the previous visit. Other medications and their doses during this period will also be recorded in CRF. Any questions raised by participants will be answered to facilitate completion. Participants will be advised to get more medical advice in the clinic after the trial. The detailed study schedule is shown in Figure. 2.

Outcomes

The primary outcome is the percentage change of liver fat content tested by MRI-PDFF, MRI-PDFF correlates with histology-determined steatosis grade in adults with NAFLD and is more accurate than conventional dual-phase imaging in classifying steatosis grade in patients with NAFLD(32, 33). The

secondary outcomes are body weight, body mass index (BMI), waist circumference, waist-to-hip ratio (WHR), serum liver function including ALT, aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IDBIL), alkaline phosphatase (34), albumin (35), pre-albumin (Pre-ALB), and total bile acid (TBA); fasting serum TC, TG, HDL-C, LDL-C; fasting plasma glucose (FPG), fasting insulin (FINS), Homeostasis model assessment - insulin resistance (HOMA-IR). All mentioned serum biochemical which will be measured at baseline, 12 and 24 weeks after randomization. The life quality will be measured by Medical Outcomes Study item short-form health survey (SF-36), the changes in the syndromes of Traditional Chinese Medicine (TCM) for participants will be measured using four TCM diagnostic methods and the Scores of TCM Syndrome Scale. The blood and urine routine examination, blood urea nitrogen, creatinine, and uric acid will be examined as safety outcomes in this trial.

Ethical consideration

The clinical trial protocol was jointly agreed upon by the main researcher and the sponsor and was approved by the Ethics Committee before implementation. If the protocol is revised in the process of this trial, it needs reapproval from the ethics committee before implementation. The process of this trial will be monitored by the IRB of Shuguang Hospital affiliated with Shanghai University of TCM and the Science and Technology Commission of Shanghai Municipality.

Data management

All collected data will be managed with an electronic data capture system program compiled by the statistical department in Shuguang hospital. The data will be input and proofread independently by two data administrators. For the questions that occurred in the proofread, the data administrator will generate a concentrator data ready queue (DRQ) and send questions to the researchers through the clinical supervisor. The researchers should deal with it and return it as a final version in time. The data administrator will confirm and input the final version according to the researchers, and issue DRQ again if necessary. The data will be locked by the principal investigator after double-checked. The locked data file will not be changed. The problems found after data locking will be corrected in the statistical analysis status after confirmation. All data collected will be kept confidential in this trial.

Statistical analysis

Statistical analysis will be performed by an independent researcher using SAS 9.1 statistical analysis software. The efficacy evaluation will be conducted in the full analysis set(36) according to the intention-to-treatment Principle. Cases that meet the trial protocol, have good compliance (80%-120%), did not take banned drugs during the trial, and completed the contents of the CRF regulations will be defined as the Per-Protocol Set.

For continuous data, the measurement of each visit between groups will be analyzed using the independent t-test or Wilcoxon rank-sum test according to the distribution of the data. Paired t-test or

Wilcoxon signed-rank test will be applied to compare the changes before and after treatment. The categorical data of each visit in different will be described by frequency and constituent ratio. Chi-square test / Fisher exact probability method will be adopted for comparison. All statistical analysis will be conducted by bilateral test, and the P-value less than or equal to 0.05 will be considered to be statistically significant. Subgroup analyses will be conducted with a list of variables based on information collected to explore the source of potential high heterogeneity.

Discussion

According to previous studies, JPHX has a liver protective effect on NAFLD patients, and no obvious adverse reactions were found(34). The research of Feng et al(25) showed that compared with NAFLD model mice, the serum ALT, AST, TC, and TG levels of mice in the JPHX group were significantly reduced, and the NAFLD activity score(24) was significantly lower. JPHX reduced tumor necrosis factor-α (TNF-α) (37), collagen, and matrix metalloproteinase, thus improving liver injury(25). In addition, JPHX can also prevent the apoptosis induced by methionine choline deficiency (MCD) and inhibit the activation of caspase 3 and 7 proteins(25). Therefore, We initiate this randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of JPHX in the treatment of NAFLD after 24 weeks to provide effective clinical evidence for the administration of NAFLD.

In addition to liver biopsy, imaging examination is still the main diagnosis of NAFLD. Abdominal ultrasound is commonly used in clinical practice to detect fatty liver, but the sensitivity will be significantly reduced when the fat content is less than 30%. Computed tomography(38) can reflect the fatty infiltration in the liver more directly. Controlled attenuation parameter (CAP) is a new technology for quantitative diagnosis of the fatty liver based on ultrasound transient elastography (TE) platform. CAP can detect hepatic steatosis over 5% and accurately distinguish mild hepatic steatosis from moderate to severe hepatic steatosis. However, when BMI > 30 kg/m^2, the distance between skin and liver capsule > 25 mm and the interquartile range (IQR) > = 40 dB/m, the accuracy of the cap in the diagnosis of fatty liver decreased(38–41).

Considering that it is difficult to carry out liver biopsies in the clinical treatment of fatty liver, this study takes the percentage change of MRI-PDFF before and after treatment as the primary outcome. MRI-PDFF is a new MR technique, which correlates with histology-determined steatosis grade in adults with NAFLD(42). MRI-PDFF has more accurate performance in the noninvasive diagnosis of liver steatosis and fibrosis in NAFLD patients than TE and CAP methods(42). It can also detect changes in fat content in the early phase of NASH(32). There was a significant correlation between the MRI-PDFF and the steatosis grade determined by invasive histologic examination in NAFLD patients(43). There are currently unclear criteria for MRI-PDFF use in NAFLD grading. Loomba's study included MRI-PDFF > = 5% (44) or liver biopsy > = 5% as diagnostic criteria for fatty liver disease and found that an absolute decrease of 4.8% in MRI-PDFF from baseline (p-value < 0.001) or a relative decrease of 26% (p-value < 0.001) were associated with a 1-point improvement in the level of steatosis (36) corresponding to the histological scoring system for NAFLD(34). Based on this, we set the fat fraction (FF) < 5% at the 24th week after enrolment as the

recovery criterion, absolute decrease of 4.8% or a relative decrease of 26% of FF from baseline as 1-level improvement in MRI-PDFF, no improvement in MRI-PDFF as invalid by curative effect. The liver function, blood lipid level, waist-hip circumference, and SF-36 score will also be observed as the effects of JPHX on NAFLD patients. The safety of JPHX in the treatment of NAFLD was observed by setting up safety biochemical indicators and adverse event records.

In conclusion, this is a randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of JPHX for NAFLD patients. The findings of this trial may provide an evidence base for a rigorous, large-scale, confirmatory RCT to confirm the efficacy and safety of JPHX for the administration of patients with NAFLD.

Trial Status

The final protocol version is 1.0 and is dated December 31, 2020. This trial has currently recruited the first participant on 20 June 2021.

Abbreviations

ALD, alcoholic liver disease; ALP, alkaline phosphatase; ALT, aspartate aminotransferase; AST, gamma-glutamyl transpeptidase; BMI, Body mass index; CRF, case report form; DRQ, concentrator data ready queue; FINS, fasting insulin; FINS, fasting insulin; FPG, fasting plasma glucose; GGT, total bilirubin; HDL-C, High density liptein cholesterol; HOMA-IR, Homeostasis model assessment - insulin resistance; IDBIL, indirect bilirubin; JPHX, Jian-Pi Huo-Xue granule; LDL-C, Low-density lipoprotein cholesterol; MRI-PDFF, Magnetic Resonance Imaging - proton density fat fraction; NAFLD, Non-alcoholic Fatty Liver Disease; NASH, non-alcoholic steatohepatitis; SF-36, Medical Outcomes Study item short-form health survey; TBA, total bile acid; TBIL, direct bilirubinDBIL; TC, total cholesterol; TCM, Traditional Chinese Medicine, alanine aminotransferase; TG, triglyceride; WHR, Waist-to-hip ratio

Declarations

Acknowledgments

Not applicable.

Authors' contributions

YS, YH, and YZ were involved in the study concept and design. YS, GC, SC, and YW participated in the generation of the study protocol. YS drafted the manuscript. All authors reviewed and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study has been approved by the ethics committee in Shuguang Hospital (Ethics approval number: 2021-934-09-01). Patients are included after giving written informed consent.

Consent for publication

We will give informed consent for the publication of the dataset from patients at the point of recruitment to the Trials. All the patient details will be strictly confidential. Any information that is published will not reveal the identity of the participants.

Competing interests

The authors declare that they have no conflict of interests.

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Figures

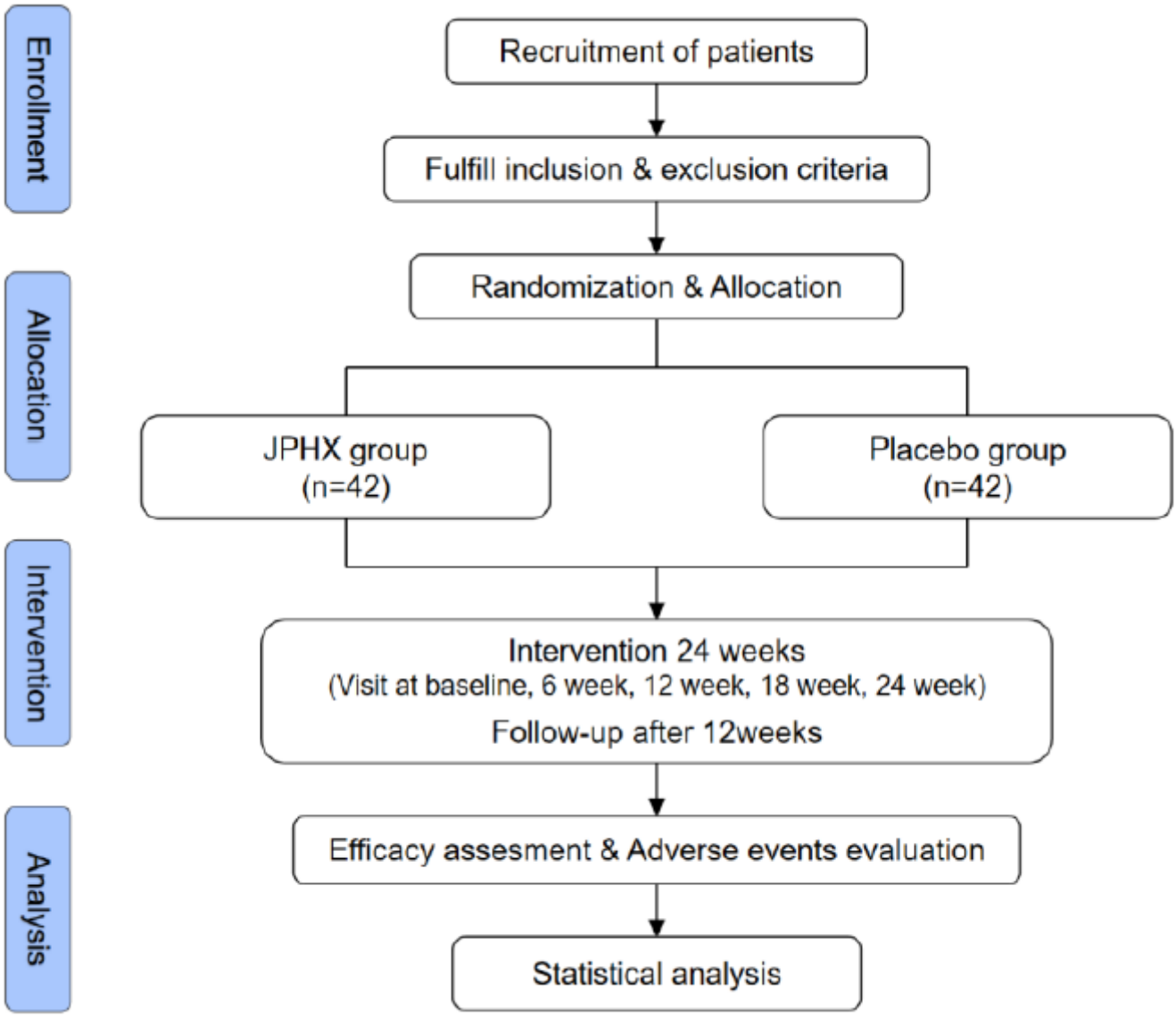
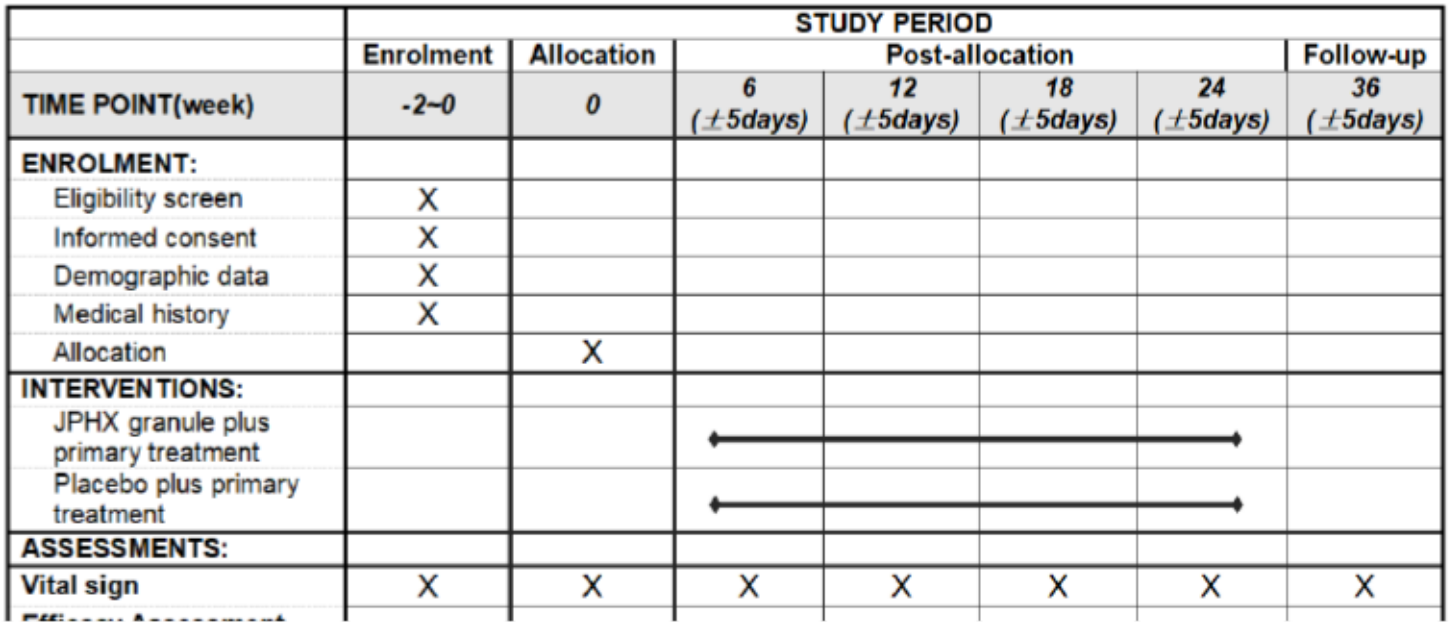


Figure 1

Flow diagram of this study



	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Follow-up
TIME POINT(week)	-2~0	0	6 (±5days)	12 (±5days)	18 (±5days)	24 (±5days)	36 (±5days)
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Demographic data	X						
Medical history	X						
Allocation		X					
INTERVENTIONS:							
JPHX granule plus primary treatment			←	—	—	→	
Placebo plus primary treatment			←	—	—	→	
ASSESSMENTS:							
Vital sign	X	X	X	X	X	X	X

Figure 2

Study schedule of enrolment, interventions, and assessments.

Supplementary Files

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