Traditional Chinese Patent Medicine Qi Zhi Jiang Tang Capsule Treatment For Non-Proliferative Diabetic Retinopathy: Study Protocol For A Randomized Controlled Trial

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Research Article

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Abstract

Background: Diabetic retinopathy is the most frequently occurring complication of diabetes mellitus and remains a leading cause of vision loss globally. Conventional treatments are focused on advanced stage of disease, targeting the early and potentially reversible retinal injury is a promising strategy for delaying non-proliferative diabetic retinopathy (NPDR). Here, we investigated the efficacy and safety of Qizhi Jiangtang capsule (QZJC), a kind of traditional Chinese patent medicine, for patients with NPDR.

Methods: This study is a randomized, single-blind, placebo-controlled, multi-center clinical trial. A total of 200 participants will be randomly assigned in a 1:1:1:1 ratio to QZJC plus calcium dobesilate (CaD) group, QZJC placebo plus CaD group, QZJC group or QZJC placebo group. The treatment duration lasts 24 weeks. The primary outcome is the changes in grading of retinal microvascular injury before and after treatment. The secondary outcome will be changes in the vision, glycolipid, blood pressure, urinary albumin excretion rate and improvement of traditional Chinese medicine symptoms. All statistics will be two-sided tests, $P < 0.05$ is considered statistically significant.

Discussion: We postulate that NPDR patients will benefit from QZJC. If successful, this work will provide preliminary evidence that QZJC could delay the progress of DR.

Trial registration: Chinese Clinical Trial Registry no. ChiCTR1900023506. Registered 31 May 2019. The Version identifier is 2018121702.

Introduction

Background and rationale

Diabetic retinopathy (DR) is the most frequently occurring complication of diabetes mellitus (DM) [1].The prevalence of DR increases steeply with the duration of diabetes mellitus (DM), the quantity of people suffered with DR has been estimated to increase from 463 million in 2019 to 700 million by 2045[2]. Epidemiological data from China suggested that the prevalence is 18.45% for any retinopathy, 15.06% for non-proliferative diabetic retinopathy (NPDR) and 0.99% for proliferative diabetic retinopathy (PDR) among diabetic patients [3]. It has been reported that DR is a primary reason of preventable blindness in labor age population globally. There is a 27% increase of DR-induced blindness and a 64% increase in visual impairment caused by DR in the past 10 years [4]. During the stage of PDR, the patients may experience severe vision impairment, which is irreversible and dramatically affects the life quality of diabetic patients [5-6]. Non-proliferative diabetic retinopathy represents the early stage of DR, which involves retinal pathologies including microaneurysms, hemorrhages, changes in vascular caliber and capillary nonperfusion can be detected by fundus photography but the patients are typically asymptomatic [7].The conventional accepted treatment of preventing DR include regulating hyperglycemia and dyslipidemia, lowering hypertension and quitting smoking. Current therapies for DR mainly aimed at PDR or diabetic macular edema, drugs intervention for early stage are still limited [8].

Traditional Chinese herbal medicine may provide an effectively alternative therapy for preventing or delaying the progression of DR [9-12]. In China, traditional Chinese herbal medicine is widely used in clinical practice. Qizhi Jiangtang capsule (QZJC), a kind of traditional Chinese patent medicine, which has been approved in China and in one batch number, is manufactured by Jilin YiZheng Pharmaceutical Co. (Jilin, China). QZJC consists of Astragalus mongholicus Bunge, Rehmannia glutinosa (Gaertn.) DC., Polygonatum cyrtonema Huaand, and Terminalia chebula Retz [13]. The main therapeutic principle includes fortifying qi and nourishing yin, activating blood and dissolve stasis. QZJC has been proven to regulate glucolipid metabolism, improve the insulin resistance, inhibit the glomerulosclerosis and renal interstitial fibrosis, protect retinal vascular endothelial cells, inhibit retinal neovascularization formation, and alleviate the pathological damage of renal and retinal tissue *et al* [14-16]. Previous clinical trials demonstrated that QZJC was mainly used for treating diabetic kidney disease, DM with coronary heart disease, diabetic lower limbs arteriosclerosis obliterans, diabetic peripheral neuropathy [14, 17-19]. However, its effect on DR is still unclear.

Objective

We will carry out a clinical trial to investigate the efficacy and safety of QZJC on non-proliferative diabetic retinopathy. This study describes the methodology details underlying the study.

Trial design

The trial is a randomized, multi-center, single-blinded, controlled clinical trial. A total of 200 participants will be recruited. The participants will be randomly divided into four groups, the group 1 will be received the intervention with oral Qizhi jiangtang capsule plus calcium dobesilate (CaD) capsules, the group 2 will be received oral Qizhi jiangtang capsule placebo plus calcium dobesilate capsules, the group 3 will be received Qizhi jiangtang capsule alone, and the group 4 will be received Qizhi jiangtang capsule placebo alone. Furthermore, diabetes education, diet and exercise, as well as rational control of blood glucose, blood lipids, and blood pressure will be accompanied in four groups. The treatment duration is set for 24 weeks. The trial flow diagram is illustrated in **Fig. 1**.

Methods: Participants, Interventions And Outcomes

Study setting

Six hospitals in mainland China participate in this study, listed as follows: Guang’ anmen Hospital of China Academy of Chinese Medical Sciences, Beijing Shijitan Hospital, Capital Medical University, Beijing Changping District Hospital of Chinese Medicine, Beijing Shunyi District Hospital of Chinese Medicine, Beijing Miyun District Hospital of Chinese Medicine, and Beijing Pinggu District Hospital of Chinese Medicine.

Eligibility Criteria

Diagnostic criteria

Diagnostic criteria for type 2 diabetes (T2DM) are based on the guideline for the prevention and control of T2DM in China (2017 Edition) [20], which is defined as: (1) In patients with classic symptoms of hyperglycemia, a random plasma glucose ≥ 11.1 mmol/L; or (2) Fasting plasma glucose ≥ 7.0 mmol/L; or (3) Two-hour plasma glucose ≥ 11.1 mmol/L after an oral glucose tolerance test.

Diagnostic criteria for DR are based on Proposed International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales by American Academy of Ophthalmology.Diagnosis and classification of type 2 diabetic retinopathy is defined as: (1) Mild NPDR: microaneurysm only; (2)Moderate NPDR: More than just microaneurysms but less than severe NPDR; (3)Severe NPDR: Any of the following: more than 20 intraretinal hemorrhages in each of 4 quadrants; definite venous beading in 2+ quadrants; Prominent intraretinal microvascular abnormalities in 1+ quadrant; And no signs of proliferative retinopathy; (4) Proliferative DR: One or more of the following: neovascularization, vitreous/preretinal hemorrhage [21-23].

TCM syndrome pattern differentiation

Traditional Chinese medicine syndrome pattern differentiation type indicating deficiency of dual qi and yin combined with blood stasis are based on Traditional Chinese medicine Clinical Pathway of *Xiaoke* disease and Traditional Chinese medicine Diagnosis and Treatment Scheme of *Xiaoke* disease [24]. The diagnostic criteria are listed:

1.Primary symptoms and signs include lack of strength, dry throat and mouth, shortness of breath, reddish yellow urine, heat in the palms and soles; and numbness or pain in the limbs.

2. Secondary symptoms and signs include palpitations, vexation, lumbago, chest pain, hypochondriac pain, back pain, insomnia, forgetfulness, encrusted skin, or wind-stroke hemiplegia, or blurred vision, facial ecchymosis, thin white fur, or dark tongue, purple mouth and tongue or purpura, the sublingual vein is purple and tortuous, string-like and fine pulse.

If participants have two terms of primary symptoms or signs, two terms of the secondary symptoms or signs, they will be diagnosed with this syndrome. A symptom scores survey will be conducted.

Inclusion criteria

1. Participants should be between 30 and 70 years old;

2. Participants should meet the diagnostic criteria for T2DM.

3. Participants should meet the diagnostic criteria for diabetic retinopathy and the stage of NPDR.

4. Participants should meet the diagnostic criteria of deficiency of dual qi and yin combined with blood stasis syndrome.

5. Participants should sign informed consent forms.

Exclusion criteria

1. Participants suffer with the stage of PDR, type 1 diabetic retinopathy, other ocular complications, such as glaucoma, severe cataracts, poor vision, retinal detachment, ophthalmic nerve disease, uveitis and retinopathy not related to DM.

2. Participants with severe cardiovascular and respiratory disease, or severe complications of liver, kidney, brain or other primary diseases.

3. Participants that serum transaminase level is two times higher than the upper limit of normal value; serum creatinine is two times higher than the upper limit of normal value.

4. Participants with recurrent hypoglycemia, diabetic ketoacidosis and severe infection within one month.

5. Participants with systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg.

6. Pregnant, pregnant or lactating women, or have a history of drug allergy.

7. Participants with psychiatric conditions.

Drop-out criteria

1. Participants who experience some complications or physiological changes, which are not suitable for further study.

2. Participants whose fundus lesions progress to the PDR stage or received laser photocoagulation, participants should be withdrawn from the study, and the effect will be judged as invalid, which is a complete case.

3. Participants whose vision decrease by 3 lines or more, participants should be withdrawn from the study, and the effect was judged as invalid.

4. Participants with poor drug compliance.

5. Participants who break blinding or emergency unsealing of his/her information.

Interventions

Drug Treatment

Participants will be randomly assigned to receive any of the following four options: group 1: QZJC (2.5g three times per day) plus CaD(0.5g three times per day); group 2: QZJC placebo (2.5g three times per day) plus CaD (0.5g three times per day); group 3: QZJC (2.5g three times per day); group 4: QZJC placebo (2.5g three times per day). QZJC and QZJC placebo will be provided by Jilin Yi Zheng Pharmaceutical Co., Ltd. (Jinlin, China). The drugs are recommended to be taken after meals with boiled warm water. If

the patient shows an intolerable adverse reaction related to the drug, the patient should discontinue the drugs. During the study, other drugs that could treat DR will be prohibited. These include TCMs that aim to fortifying qi and nourishing yin, activating blood and dissolve stasis, or drugs such as anti-VEGF therapy, fenofibrate, etc.

Concomitant treatment

Based on the guidelines for the prevention and control of type 2 diabetes in China (2017 Edition)[20], all participants will receive the standard intervention of blood glucose: fasting blood glucose (FBG) will be controlled to < 7.0 mmol/L and two hour plasma glucose (2h PG) will be controlled to < 10.0 mmol/L, and glycosylated hemoglobin (HbA1c) will be controlled to < 7%. The standard intervention will include achieving a blood pressure control target of < 130/80 mmHg, and paying close attention to other cardiovascular risk factors and giving appropriate intervention measures. Moreover, the participants will not change the drugs used to treat chronic diseases. The researchers will guide the participant to have a healthy lifestyle and keep detailed records in the CRFs, in order to maintain two groups in general balance.

Outcomes

Primary outcome

The primary outcome is the changes in grading of retinal microvascular injury before and after treatment. The stage is divided into the condition of exacerbated, stable, and improved. The exacerbated state is defined that the severity of retinal microaneurysm injury exacerbated > 1 grade after treatment. The stable state is defined that the severity of retinal microaneurysm injury is unchanged before and after treatment, while the improved state is defined that the severity of retinal microaneurysm injury is reduced by >1 grade after treatment. The grade is defined as the stage of DR that the same as the diagnostic criteria.

Secondary outcomes

Secondary outcomes are listed as the changes of vision, FBG and 2h PG, HbA1c, blood lipids [total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)], urinary albumin excretion rate (UAER) and improvement in TCM symptoms (evaluated by TCM symptom score scale) from baseline to 24 week.

Safety assessment

Safety assessment outcomes are listed as vital signs (body temperature, blood pressure, respiration, heart rate), routine blood test, routine urine test and routine stool test, electrocardiogram, liver function [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], renal function [serum creatinine (SCr) and blood urea nitrogen (BUN)] will be performed at every 12 weeks from baseline.

Adverse events (AEs) will be documented at every visit, including the occurrence time, severity, duration, solution and transfer. Every AE will be classified as a mild, moderate, or severe AE, and its correlation with the intervention drugs will be evaluated. Severe AEs will be reported to the principal investigator and the Ethics Committee within 24 hours, and fill out the “Severe Adverse Event (SAE)” form. All the adverse events will be correctly recorded in the CRF, and treated until resolved.

Participant timeline

The study duration will last for 26 weeks, including a 2-week run-in period, the treatment will last for 24 weeks. After treatment begin, visits will conduct every 4 weeks. All data will be documented on the CRFs. Schedule of enrollment, allocation, visits, and assessments is listed in **Table 1**.

Table 1 Schedule of enrollment, allocation, visits, and assessments

	Enrolment	Allocation	Post-allocation					
Time of visits (weeks)	**-2-0w**		4w	8w	**12w**	16w	20w	**24w**
Collect basic medical history								
Sign informed consent form	√							
Determine inclusion and exclusion criteria	√	√						
Determine withdrawal criteria	√	√	√	√	√	√	√	√
Fill in general information	√	√						
History of diabetes and treatment	√							
Comorbidity and symptom	√							
Physical examination and consultation	√	√	√	√	√	√	√	√
Concomitant medication	√	√	√	√	√	√	√	√
Efficacy assessment								
Fundus photography		√						√
Fluorescence fundus angiography		√						√
Routine ophthalmic examination, fundus		√			√			√
Vision		√			√			√
Fasting blood glucose		√	√	√	√	√	√	√
Two-hour plasma glucose		√	√	√	√	√	√	√
Blood pressure		√	√	√	√	√	√	√
Glycosylated hemoglobin		√			√			√
Blood lipids		√			√			√
Urinary albumin excretion rate		√			√			√
TCM symptoms		√			√			√
Safety assessment								
Vital signs		√	√	√	√	√	√	√
Routine blood, urine and stool examination		√			√			√

Liver function	√			√			√
Renal function	√			√			√
Electrocardiogram	√			√			√
Adverse events		√	√	√	√	√	√
Other work							
Randomization	√						
Drug distribution and patient journal cards	√	√	√	√	√	√	√
Recovery drugs, quantity statistics		√	√	√	√	√	√
Recycle patient's diary card		√	√	√	√	√	√
Research summary				√			√

Note: The follow-up time was within 3 days of the day appointed.

Sample size

The sample size of clinical study will be estimated based on previously published studies [25]. The results showed that the rate of retinal microvascular disease decreased by 3.6% in the placebo group, and we deduce that QZJC could decrease the rate of retinal microvascular disease by 6.5%. The following sample size formula is used for calculation.

$$n = \frac{u\alpha\sqrt{2p(1-p)} + u\beta\sqrt{p1(1-p1)+p2(1-p2)}^{2}}{(p1-p2)^{2}}$$

In this formula, assuming that α = 0.05 and β = 0.20 according to the one-sided test to obtain the tabular value, uα = 1.64485 and uβ = 0.84162; Take each value into the formula and get n = 42. Therefore, each group needs 42 participants. Considering that the drop-out rate is no more than 15%, finally 50 participants are needed in each group and a total of 200 participants is set as the sample size.

Assignment of interventions: Blinding and allocation

Participants will be randomly assigned to any of the four groups at an equal probability. The stratified block randomization will be adopted, a specific randomized sequence will be generated using SAS software. The clinical research coordinator enters participant information and will be acquired a random number. The allocation list file will not be available to any participant for the duration of the trial, and be uncovered after completion of the trial. If a medical emergency happens, the participant's random number and group allocation list can be exposed. Considering the safety of the trial, research assistants may be aware of random distribution. However, the data evaluators and the statisticians of research results will not be involved in distribution situation.

Data collection and management

The researchers should document the data into the case report form (CRF) timely, completely, correctly and clearly according to original data. The clinical supervisor will confirm that all the CRFs are filled correctly and completely, and consistence with the original data. The errors and omissions must correct them in time, the original records should be kept clear and visible when modifying, and the correction should be signed and dated by the researcher. After checked and signed by the supervisor, the CRFs will be sent to the trial data administrator. The data administrator will check the data again before data entry. If any problem is found, they will notify the supervisor, and asks the researcher to respond. The exchange between them should be kept in the form of query table. The data administrator also should understand the content and coding of each item before data entry. The data entry personnel should input the data twice. After data entry, the quality and l logicality will be checked. The documents will be requested to conserve by every unit after the study. Researchers should preserve the documents of clinical trial for five years.

Statistical methods

Data will be collected and analyzed using SAS 9.3 software. Three analysis sets, the intention-to-treat set (ITT), the per-protocol analysis set (PPS) and the safety analysis set (SAS), will be used for assessing the data. FAS and PPS will be used for assessing baseline characteristics and clinical efficacy, SAS will be used for assessing the safety. All statistics will be two-sided tests, $P < 0.05$ is considered statistically significant. Quantitative data will be expressed as the mean, median, standard deviation, minimum, and maximum, and analyzed using the t-test or Wilcoxon rank-sum test, whereas qualitative data will be analyzed using the chi-square test and Fisher's exact test. For the main outcome, the number of cases, mean, median, standard deviation, minimum, and maximum will be calculated, its changes relative to baseline after treatment will be compared within each group using a paired-samples t test or the Wilcoxon signed-rank test; changes relative to baseline after treatment will be compared between groups using an independent-samples t test or the Wilcoxon rank-sum test. For the secondary outcomes, the changes in vision, blood glucose, blood lipids, urinary albumin excretion rate, and TCM symptoms will be assessed, and their changes relative to baseline after treatment will be described, the number of cases, mean, median, standard deviation, maximum, and minimum will be calculated and compared within each group using a paired-samples t test or the Wilcoxon signed-rank test; changes relative to baseline after treatment will be compared between groups by an independent-samples t test or Wilcoxon rank-sum test. Statistical analysis will be completed by the third-party statisticians.

Oversight and monitoring

Quality control will run through the whole test process. Before the trial starts, the protocol will be sent to each center, and all research assistants will be trained according to a standardized operation practice (SOP). When the trial starts, the clinical research coordinator (CRC) will inspect and monitor the data collection process regularly, they will understand the progress of the trial, review the CRFs, confirm the informed consent form, inspect the selection of participants and the consistency of intervention drugs

and protocols, the consistency of index filling and original data, and record of adverse events, *etc*. Whether the intervention drugs will be stored to meet the requirements or not will also be checked, drugs distribution and recovery should be recorded. When the trial ends, the CRFs and data will be kept intact and filed in time. The third-party quality control will be implemented.

Dissemination plans

The results will be disseminated through peer-reviewed journal articles and presented abstracts and posters at scientific conferences in the field of diabetes and TCM, as well as the general public through internet and newspaper.

Discussion

Diabetic retinopathy is characterized by progressive microvascular injury, such as microaneurysms, oedema, haemorrhages, hard exudates and intraocular pathological neovascularisation. DR is the most common cause of preventable blindness in working-aged adults. Treatment strategies are mainly for advanced stages of the disease, including laser photocoagulation, intravitreal pharmacologic agents and vitrectomy. Intravitreal administration of anti-VEGF agents is currently the main therapies for each stage of DR. However, the majority of patients failed to achieve clinically-significant visual improvement [26]. Therefore, the development of drugs capable of preventing or treating the early stages of DR remains a priority.

Traditional Chinese herbal medicine has a long history of treating diabetes and its complications around the world, it may provide an alternative therapy for preventing or delaying the progression of DR [27]. QZJC is composed of Astragalus mongholicus Bunge, Rehmannia glutinosa (Gaertn.) DC., Polygonatum cyrtonema Huaand, and Terminalia chebula Retz. In the UPLC-QE-Orbitrap-MS analysis, a total of 52 compounds were identified in QZJC capsules, the main compounds include Amino acids, phenylpropanoids, iridoid glycosides, coumarins and triterpenes and flavonoids [28]. Many of the compounds have been proved by modern pharmacological studies to have the effect of improving related symptoms of DM and its complications, reflecting the characteristics of synergistic action of multiple components in QZJC. In the previous pharmacological studies, Astragalus mongholicus Bunge ameliorated DR mainly by reducing retinal ganglion cell apoptosis, alleviating oxidative stress and inflammation, and inhibiting angiogenesis [29]. *Polygonatum sibiricum* polysaccharide has a protective effect on diabetic retinal injury with possible underlying mechanisms involved in lowering blood glucose, limiting pathological angiogenesis and inhibiting cellular apoptosis through downregulated signaling of Bax, EGF, p38, VEGF and TGF-β, and upregulation of Bcl-2 [30]. Terminalia chebula Retz exerts anti-inflammation effects by regulating PARs/p38/NF-κB pathway [31]. In the previous experiments, QZJC has been demonstrated that ameliorated retinal vascular permeability and inhibit retinal neovascularization via up-regulating prostacyclin2 (PGI2) and down-regulating VEGF and von willebrand factor (vWF); it also attenuates inflammation via promotion of nitric oxide (NO) and superoxide dismutase (SOD)

expression [32]. Currently, we therefore design a randomized and controlled multicenter clinical trial to assess the efficacy and safety of QZJC.

We hypothesize that QZJC could have a potential retinal protective effect on NPDR patients. If successful, the findings of this trial may provide an alternative treatment for NPDR patients. It may also provide scientific evidence for delaying the progress of DR. This trial also has some limitations. Firstly, as the test instruments of each research center are different, the error of test results is inevitable. Secondly, due to the setting of treatment schedule, this trial could not achieve strict double-blind, which may have an impact on the therapeutic effect.

Declarations

Trial status

Patient recruitment began in Feb 2019 and it will be completed in Dec 2019. At the time of manuscript submission, 200 patients had been recruited.

Acknowledgements

Not applicable.

Authors' contribution

PB drafted the trial protocol. NQ provided critical advice and comments on the protocol. GH, ZYY, HHJ, SY, CAM, LCQ, and ZWH referred and recruited the patients. All of the authors participated in the design and development of the trial protocol. All authors read and approved the final manuscript.

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Availability of data and material

Once the main findings of the project have been published, the trial steering committee will review all requests for data before access is granted. If appropriate, we will make the anonymized data and associated documentation available to users under a data-sharing agreement.

Ethics approval and consent to participate

The protocol has been approved by the Medical Ethics Committee of Guang’anmen Hospital of the China Academy of Chinese Medical Sciences (No.2019-008-KY). The trial registration number is as follows:

Chinese Clinical Trial Registry no. ChiCTR1900023506, and any important changes in the protocol will be reflected there. The study will implement in accordance with the items of the Declaration of Helsinki. The trial will perform based on the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines. All participants will provide voluntary written informed consent form (ICF) after a full discussion about the potential benefits and risks before the study, and ICFs will be signed by participants prior to entry into the trial.

Consent for publication

All authors gave consent for the publication of the manuscript.

Competing interests

The authors declare no conflict of interest.

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Figures

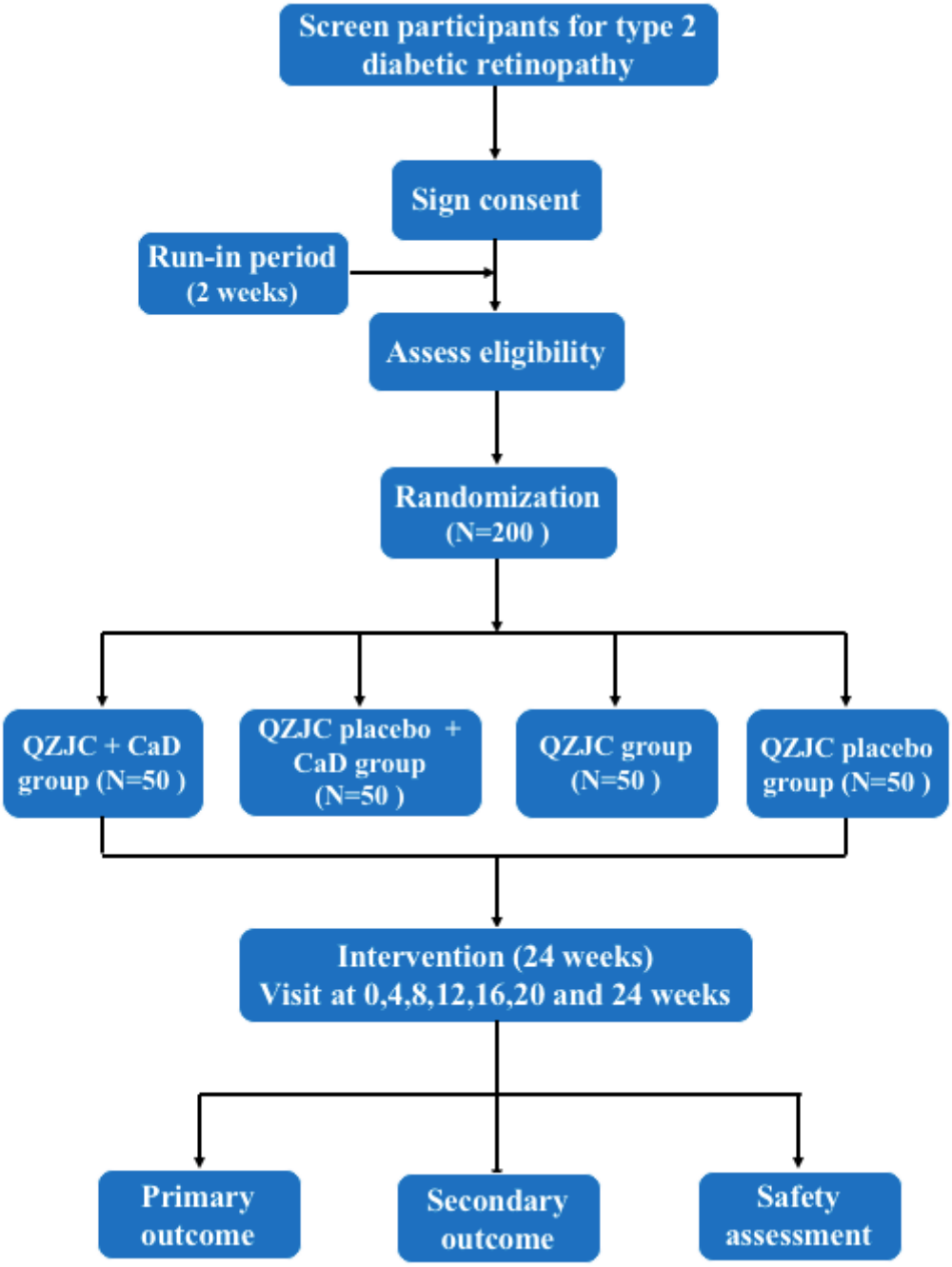

Figure 1

Flow diagram of enrollment, intervention and assessments

Supplementary Files

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