

Efficacy and Safety of Polysaccharide Iron Complex Capsules in Hemodialysis Patients: Study Protocol for a Randomized, Open-Label, Positive Control, Multicenter Trial (IHOPE)

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Research Article

Keywords: End-stage renal disease, Renal anemia, Oral iron, Multi-center, Efficacy and safety

Posted Date: June 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-585563/v1>

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Abstract

Background: Anemia is one of the main complications of chronic kidney disease especially end-stage renal disease, which includes treatment with erythropoiesis-stimulating agents and ferralia, including intravenous and oral iron. However, intravenous iron may pose limitations, such as potential and lethal infusion reactions. Oral iron is mainly composed of divalent iron, which can excessively stimulate the gastrointestinal tract. Iron polysaccharide complex capsules (PIC) is a novel oral iron trivalent supplement with higher iron content and lower gastrointestinal irritation. However, since high-quality evidence-based medicinal support is lacking, it is necessary to conduct clinical studies to further evaluate the effectiveness and safety of oral PIC in chronic kidney disease patients.

Methods: This randomized controlled trial uses an open-label, parallel group design, where the efficacy and safety of maintenance hemodialysis (MHD) patients is evaluated. The experimental group is assigned a conventional drug treatment and PIC and the control group is assigned a conventional drug treatment and sucrose iron injection. The primary endpoint is transferrin saturation (TSAT). Secondary endpoints include hemoglobin (Hb) concentration, hematocrit (Hct), hypersensitive C-reactive protein (HsCRP), pharmacoeconomic evaluation, quality of life, etc. The treatment will last for 24 weeks with follow-up visit at baseline (within 7 days prior to initial treatment) and weeks 4, 8, 12, 16, 20, and 24 after initial treatment. Leading unit of this clinical research is Renji Hospital, School of Medicine, Shanghai Jiao Tong University; 8 well-known hemodialysis centers in Mainland China are included in this study with 186 patients selected through competitive enrollment.

Discussion: It is expected that it will provide strong evidence to reveal the clinical efficacy and safety of oral iron in the treatment of chronic renal anemia in MHD patients through this clinical trial.

Trial registration: This study has been registered with the Chinese Clinical Trial Registry (<http://www.chictr.org.cn/index.aspx>) on March 23rd, 2020. Trial registration number is ChiCTR2000031166.

Background

Kidney disease is a serious threat to the health of people globally. According to the latest epidemiological data published in *The Lancet* in 2019, the prevalence of chronic kidney disease (CKD) among Chinese adults is 10.8%^[1]. Anemia is one of the major complications in patients with chronic kidney disease, especially those undergoing renal dialysis. The incidence of anemia was 51.5% in 2,420 patients with CKD as seen in results from a Chinese cross-sectional epidemiological study, published in 2016^[2]. The study showed a high rate of iron deficiency anemia in Chinese patients with CKD, and the degree of iron deficiency was relatively serious^[2]. According to a survey conducted for CKD, the incidence of iron deficiency anemia after dialysis was more than 60%^[3]. However, iron deficiency anemia causes tissue and organ ischemia, and further induces decreased appetite, fatigue, and sleepiness, decreased sleep quality and cognitive function, and emotional apathy, which seriously affects the physical and mental

health of patients^[4]. Several evidence-based data show that iron deficiency anemia results in poor prognosis in patients with end-stage renal disease (ESRD), and it is one of the main reasons for the high rates of hospitalization and mortality in patients with ESRD^[5]. There are nearly 800,000 dialysis patients in China, and standardized renal anemia treatment is imperative to slow down exacerbation of complications in patients with CKD post dialysis. The diagnosis and treatment of renal anemia has shaped clinical practice guidelines^[6].

Iron supplementation is an important treatment method to improve symptoms of anemia. The 2020 edition of the guidelines recommends that hemoglobin levels and iron metabolism status should be identified first and addressed with potential causes of iron deficiency, before starting iron therapy^[6]. Whether or not they are treated with erythropoiesis-stimulating agents (ESAs), patients with absolute iron deficiency should be treated with iron supplements. Also, patients with functional iron deficiency should be treated with iron supplements after weighing the benefits and risks of treatment. Commonly used iron agents are intravenous iron and oral iron. However, iron overload still exists in clinical intravenous iron therapy. In 2011, the Japanese Society for Dialysis first warned about the potential toxicity of intravenous iron maintenance therapy^[7]. The issue of iron overload continues to be addressed in several guidelines around the world^[8]. Oral iron can avoid iron overload, but the first and second generation of oral iron have obvious gastrointestinal side effects, poor compliance, and other significant problems. Polysaccharide iron complex (PIC) capsule, is a third generation of oral iron agent that has been widely used in clinical practice due its advantages of little or no stimulation of gastrointestinal tract, few side effects, stable coordination, good solubility, and high iron content.

Iron therapy is still a challenge in the clinical treatment of renal anemia, hence it is necessary to conduct clinical studies to explore optimal treatment of renal anemia. This study is the first multicenter clinical study of PIC in CKD patients with maintenance hemodialysis. It aims to evaluate the clinical efficacy and safety of oral iron and to provide additional drug options in the treatment of anemia in CKD patients. This clinical trial drug PIC, produced by SPH Qingdao Growful Pharmaceutical Co. Ltd, has been approved by the CFDA (national medicine permission number H20030033) and is a new oral iron supplement.

Methods

Objective

The objective of this study is to compare the efficacy of oral PIC and intravenous ferric sucrose infusion in maintenance hemodialysis patients with corrected anemia, and to evaluate the safety and cost-effectiveness ratio of the two treatment regimens.

Trial design

This study is a multi-center, parallel controlled, randomized, open clinical trial (Version 1.1; Date 11 Dec., 2019, phase IV post-marketing) in China, which has been registered with the Chinese Clinical Trial

Registry (<http://www.chictr.org.cn/index.aspx>) on March 23rd, 2020. Trial registration number is ChiCTR2000031166. The detailed flowchart is shown in Figure 1. All eligible patients will be randomly divided into two groups in a 1:1 ratio: experimental group (conventional drug therapy + PIC) and control group (conventional drug therapy + iron sucrose injection). Patients will complete the study visit at baseline (within 7 days before the first treatment), weeks 4, 8, 12, 16, 20, and 24 after the first treatment or when the visit is terminated early. We used the SPIRIT reporting guidelines^[9] in the current study.

Sample size

This clinical trial set has a non-inferiority threshold of 7 (%) and a variance of 11 (%) for the positive control group. The real difference between the tested drug and positive control is 2 (%). Unilateral significance level is 2.5%, with an assurance of 80%. In the case of 1:1 sample size between the control group and the experimental group, a total of 154 samples will be collected (77 of which will be in the control group and the experimental group, respectively). Considering 20% shedding rate, the actual planned inclusion number will be 186 cases.

Setting and recruitment

A total of 186 subjects will participate in the study and will be recruited in a competitive manner from 9 participating research centers. Prior to recruitment, the investigator will carefully study the past condition, including but not limited to disease diagnosis and previous dialysis status of each patient. Researchers will fully consider the compliance of the patients within 24 weeks. Informed consent forms (ICF) will be obtained before collecting any patient data and patient information. After the patients sign the ICFs, the investigators will also sign the ICFs and record the informed consent process in the medical records. Patients eligible for inclusion in the trial will receive intravenous infusion (100 mg total) of iron sucrose for two weeks after initial screening. If they still meet the inclusion criteria, they will be formally enrolled and started on medication. The treatment follow-up period of each patient is 24 weeks; the follow-up point of screening and treatment period are shown in Figure 2.

Eligibility Criteria

The target population in this study are patients undergoing maintenance hemodialysis, and who can meet the following eligibility criteria.

Inclusion criteria:

Patients must meet all the following criteria to be enrolled in the clinical trial^[10]:

1. Age 18-75, either gender.
2. Maintenance hemodialysis patients (≥ 3 months), dialysis frequency 3 times/week.
3. Hemoglobin concentration 110–130 g/L (excluding 130 g/L).
4. Transferrin saturation 20%–50% (excluding threshold value).

5. Serum ferritin 200–500 µg/L (excluding threshold value).
6. Used recombinant human erythropoietin (EPO) and iron at least 12 weeks before enrollment.
7. Signed ICF voluntarily.

Exclusion criteria:

Patients who meet any of the following criteria will not be eligible to participate in this clinical trial:

1. Iron allergy, allergic history, or intolerance to test drugs.
2. Having erythrocyte aplastic anemia, other hematopoietic and hemolytic diseases,
3. Acute and chronic bleeding.
4. Serum albumin < 35g/L.
5. Hypersensitive C-reactive protein >10 mg/L.
6. Severe secondary hyperparathyroidism (iPTH \geq 800 pg/mL).
7. Severe cardiac dysfunction (NYHA score > 3) and poor control of hypertension (systolic blood pressure \geq 180 mmHg or diastolic blood pressure \geq 100 mmHg).
8. Severe liver disease (ALT, AST, and TBIL \geq 2 times the upper limit of normal) or hepatitis B surface antigen positive, or hepatitis C antibody positive.
9. Malignant tumor.
10. Severe bacterial or viral infection that occurred in the last 1 month, prior to signing consent.
11. History of blood transfusion history in the last 1 month.
12. Admitted to hospital or planned a kidney transplant during the trial.
13. History of chronic alcohol abuse, substance abuse or any factors affecting compliance.
14. Pregnant or breastfeeding woman.
15. Life expectancy less than 12 months.
16. Participating or has participated in clinical trials of other drugs within the last 3 months.
17. Gastric and duodenal ulcers and ulcerative colitis.
18. Presence of conditions that the investigator believes may affect patient compliance or test results.

Randomization and allocation

A central randomization method will be adopted in this study, and the principles of open and randomized control will be followed. All eligible patients will be randomly divided into an experimental group or the control group in a ratio of 1:1. An interactive web response system (IWRS) of the electronic data acquisition system (EDC) will be used to allocate and manage the random number, and the experimental drug (PIC or iron sucrose injection) will be distributed according to the group corresponding to the random number. All information, including failure and success of patient screening, will be recorded, registered, and managed in the EDC system.

Intervention

Experimental group

PIC will be taken orally, 2 capsules per day, for 24 weeks. Patients will be treated with EPO intravenously with a single dose of 10,000U once a week during the maintenance period. At the same time, EPO dosage will be adjusted according to the measured hemoglobin concentration, as follows^[6].

1. Discontinue EPO if Hb \geq 130 g/L. Hb levels will be checked once every two weeks. If the Hb level drops to 110–130 g/L, the original EPO dose will be reduced by 25% or extended to once in 10 days for continuation.
2. If Hb < 110 g/L, TSAT, and SF are met, EPO will be administered as a single dose of 10,000U at least three times, every two weeks. Also, the Hb values of patients will be evaluated once every two weeks. The maximum dose of EPO will be 10,000U twice a week. If TSAT and SF fail to meet the standard, the iron deficiency will be corrected first, and the EPO treatment regimen will be adjusted once TSAT and SF are normal.

Control group

100 mg of iron sucrose injection dissolved in 100 mL 0.9% sodium chloride solution will be intravenously administered at the end of dialysis once every two weeks for 24 weeks. During this period, patients will continue to receive intravenous EPO treatment in the same way as the experimental group. For the first intravenous infusion of iron sucrose injection, a small test dose will be performed. The test method refers to the drug instructions of iron sucrose injection, which are as follows.

1. Dosage: 1–2.5 ml (20–50 mg iron content) for adults. Children should be given 1 mL (iron content 20 mg) each time with body weight > 14 kg and given half of the daily dose (body weight kg \times 1.5 mg/kg) each time with body weight < 14 kg.
2. Caution: cardiopulmonary resuscitation equipment should be available during the test. If no adverse reactions occur after 15 minutes of administration, the remaining administration can be continued.

Dose adjustment during the trial

If TSAT < 20% occurs during the test, the dosage of iron agent will be adjusted as follows.

1. PIC: The PIC prescription will be adjusted from one capsule daily to two capsules twice daily.
2. Iron sucrose injection: the prescription of iron sucrose injection will be adjusted from "100 mg/time, intravenous drop, once every two weeks" to "100 mg/time, once a week". If SF \geq 500 μ g/L and/or TSAT \geq 50% after the above treatment, iron supplementation therapy will be stopped and SF and TSAT will be reevaluated twice a week. If SF < 200 μ g/L and/or TSAT < 20%, or SF 200–500 μ g/L and/or TSAT 20%–50% are found twice consecutively, iron supplementation therapy will be

restarted. Iron supplementation therapy is iron sucrose injection 100 mg/time, intravenous drip, once a week

Endpoints

Primary endpoint

1. TSAT will be measured at 12 weeks after patients receive either PIC or iron sucrose injection.

Secondary endpoints

1. TSAT of patients at 24 weeks of treatment.
2. Hb, SF, Hct, and Hs-CRP values of patients before and at 12 and 24 weeks of treatment.
3. Drug costs for patients at 24 weeks of treatment (including rHuEPO and iron supplementation).
4. Quality of life scale scores EQ5D-5L of patients prior to treatment and at 24 weeks of treatment^[11].
5. Indicators of oxidative stress, including malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px), will be measured in patients before and at 12 and 24 weeks of treatment^[10].

Withdrawal and drop-out

Patients can withdraw from the clinical trial at any time for any reason without prejudice to the investigator's right to treat their disease. After fully considering the benefit of the patient, the investigator has the right to request the patient to withdraw for any reason, such as the occurrence of concomitant disease, adverse events, or treatment failure. The ethics committee reserves the right to request withdrawal of the patient for program violation, administrative reasons, or other valid and ethical reasons. All patients withdrawing from the clinical trial must complete a final trial evaluation. And the reason for withdrawal will be stated in the eCRF with all other appropriate and valuable information. Specific discontinuation and exit criteria are listed below.

Discontinuation criteria:

1. Patients with serious non-compliance to discharge criteria.
2. Patients not having used the drug even once.
3. Without any test records or follow-up data, no safety and efficacy data records.
4. Affecting the trial evaluation by using prohibited treatments and drugs in the protocol during the trial.
5. Other serious breaches of the scheme.

Exit criteria:

1. Exit requested by the patient.
2. Recurring intolerable adverse reactions.

3. SF \leq 200 μ g/L or TSAT \leq 20% within 2 consecutive months.
4. Hb concentration $<$ 90 g/L or $>$ 130g/L within 2 consecutive months.
5. Poor compliance, failure to comply to protocol thus affecting efficacy.
6. Study observations could not be continued due to unforeseen circumstances occurring during the test.

Statistical methods

The detailed contents of the statistical analysis methods of this clinical trial are as follows.

Data Set Category

1. Full Analysis Set (FAS): The case of using drugs at least once and main analyzing efficacy indexes after drug administered.
2. Per Protocol Set (PPS): Good compliance case data that meets the main inclusion and exclusion criteria without affecting the main curative effects of prohibiting drugs during the trial.
3. Safety Set (SS): Case data involving usage of investigational drug product at least once, including safety evaluation.

Statistical analysis technique

The number of patients selected and completing follow-up visits in the population and centers will be listed separately, and the three analysis data sets (FAS, PPS, SS) as specified above will be identified^[11]. Cases of protocol violation should also be listed and the reasons indicated. In terms of outcome indicators analysis, continuous variable indicators will count the number of cases (n), mean (\bar{x}), standard deviation (SMD), median (M), minimum (min), and maximum (max). The difference between groups will be analyzed using Student's-t-test. Counting and grading data will be used to calculate the frequency and composition ratio. χ^2 test / Chi-square test will be used for differences between groups. Unless otherwise stated, all statistical tests will be conducted in a bilateral manner. For example, if $P \leq 0.05$, the difference between groups is statistically significant. Results of this clinical trial will be analyzed using SAS version 9.2 or above software.

Harms

Intravenous iron has the risk of potentially fatal allergic reactions, so we will conduct a small dose test before the first administration to ensure the safety of the patients. Safety endpoints are related directly to changes in laboratory safety indicators and incidence of adverse events between the treatment and control groups during follow-up. These endpoints will be listed according to the treatment received and recorded in detail. Patients will be followed up in detail, if any complications arise, appropriate treatment will be provided in accordance with current routine medical procedures.

Ethics and dissemination

This clinical study has been approved by the Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University (approval number: 2019-048). Other participating sub-centers must also obtain ethics committee approval documents prior to the start of clinical trials. The Good Clinical Practice (GCP) principles and guidelines shall be strictly followed during the test implementation^[12]. At the same time, any problems related to the clinical trial must be reported to the ethics committee in a timely manner, such as changes in the trial protocol or patient information page, serious adverse events, termination or early termination of the clinical trial, etc. After the publication of study results, the study report will be published in a peer-reviewed journal and/or at a national or international conference. All researchers involved in the design, writing and discussion of this clinical trial protocol, are listed as the authors.

Discussion

Anemia is one of the complications in patients on maintenance hemodialysis. The deficiency of hematopoietic iron is an important reason for this complication. Therefore, iron supplements are important to correct renal anemia^[13]. Long-term iron deficiency anemia can cause serious consequences to the treatment and prognosis of patients with CKD. Normal hemoglobin levels will not only improve the quality of life of patients, but also reduce the probability of cardiovascular and cerebrovascular complications, thus reducing the hospitalization and mortality rate in patients^[14]. The commonly used iron preparations in clinical practice include intravenous and oral iron agents. Compared to oral iron, intravenous iron has the advantages of faster onset and better absorption. But it also has some limitations, such as an increase in the risk of infectious complications^[15] and increase in oxidative stress response. Moreover, intravenous iron dosage needs to be carried out in professional medical places, which require relatively high time and place of administration. At the same time, the health economics evaluation found that intravenous iron is more expensive than oral iron^[16]. Accordingly, intravenous iron agent is inferior to oral iron agent in terms of the economic and convenience aspect of the treatment. At present, the main oral iron agent is divalent iron agent, which has some shortcomings such as low iron absorption rate, large gastrointestinal stimulation response, and relatively slow onset effect, which affect the therapeutic effect to some extent^[17]. PIC, as an oral iron trivalent supplement, has the advantages of high iron content (46%), and gastrointestinal metabolism in the form of iron molecules without containing free iron ions.

The KDIGO Clinical Practice Guideline mentions that correction of iron deficiency with oral or intravenous iron supplementation can reduce the severity of anemia in patients with CKD. However, the guidelines do not explicitly mention the method of replacing intravenous iron with oral iron. The reason is the lack of high-quality comparative study on the efficacy of oral and intravenous iron^[18].

The same is true at home. Most of the domestic clinical evidence against PIC in China are based on bivalent oral iron as a control, which cannot fully confirm the application value and advantages of PIC in the treatment of anemia in maintenance hemodialysis patients^[19-20]. Therefore, it is necessary to carry

out further clinical trials to clarify the efficacy and safety of PIC in correcting anemia in the maintenance of hemodialysis patients. In this study, intravenous injection of iron agent—iron sucrose will be used as the control group, and it is assumed that the efficacy and safety of PIC in anemia and in maintenance hemodialysis patients will be not inferior to that of iron sucrose injection. The purpose of this study is to increase the head-to-head data of oral iron compared with intravenous iron treatment and provide high-quality theoretical support for treatment of CKD patients with renal anemia. It is expected that this clinical trial will provide strong evidence as to the safety level and efficacy of PIC in the treatment of anemia in maintenance hemodialysis patients. Further it will provide a strong evidence-based basis for the development of guidelines in the treatment of chronic kidney disease complicated with renal anemia.

Abbreviations

PIC
Iron polysaccharide complex capsules
MHD
maintenance hemodialysis
TSAT
transferrin saturation
Hb
hemoglobin
Hct
hematocrit
HsCRP
hypersensitive C-reactive protein
CKD
chronic kidney disease
ESRD
end-stage renal disease
ESAs
erythropoiesis-stimulating agents
ICF
Informed consent forms
EPO
erythropoietin
IWRS
interactive web response system
EDC
electronic data acquisition system
MDA
malondialdehyde

SOD
superoxide dismutase
GSH-Px
glutathione peroxidase
DMC
data monitoring committee
FAS
Full Analysis Set
PPS
Per Protocol Set
SS
Safety Set
GCP
Good Clinical Practice

Declarations

Ethics approval and consent to participate

This study protocol has been approved by the ethics committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University (approval number: 2019-048). Informed consent to participate will be obtained from all participants.

Consent for publication

I will be willing to provide a model consent form on request.

Availability of data and materials

The investigator must properly handle all the data obtained during the clinical trial, and truthfully record all adverse events and serious adverse events during the clinical trial, to ensure the rights and privacy of the patients participating in the clinical trial. In accordance with the regulations, the right to access all test records belongs to National Medical Products Administration, hospital ethics committee, medical inspection authorities, project managers, clinical research associate, etc., who verify the accuracy of the original data and understand the progress of the test during the trial. If the original records cannot be effectively verified, the investigator must assist the inspector/auditor in further verifying the quality of the data.

The group leader of this study has set up a data monitoring committee (DMC) for the purpose of ensuring the safety of patients and the quality of study data. The DMC is composed of clinicians and biostatisticians from the Clinical Center for Investigation, Renji Hospital, and School of Medicine,

Shanghai Jiao Tong University who are not involved in this study. After publication of trial results, the trial report will be published in peer-reviewed journals and / or in national or international conferences.

Competing interests

None declared.

Funding

This research received no specific grant from any funding agency including from the public, commercial, or not-for-profit sectors.

Authors' contributions

ZN is responsible for the integrity of the whole research work, participation in the clinical trial protocol drafting, clinical trial concept design and evaluation, interpretation of trial data, revision, and submission of trial protocol manuscript. RL, XZ, XC, XW, HL and LW are responsible for drafting the test plan, research design, data interpretation, and participation in writing and modifying the test plan manuscript. YZ, JS, QL, and HZ are responsible for research management, data collection, coordination, and quality control. RL are in charge of writing the manuscript of the experimental schema. All authors have read and approved the final manuscript.

Acknowledgements

We would like to thank all patients and their families for participating in this clinical trial. We also thank Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital, Taixing People's Hospital, Ningbo Hospital of Traditional Chinese Medicine, Tongren Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Sir Run Shaw Hospital affiliated to the Zhejiang University School of Medicine, Shanghai Pudong New District Zhoupu Hospital, Wuxi People's Hospital, and Shandong Province Qianfoshan Hospital for their contributions to the Institute as participating research centers.

Trial status

The protocol version number is 1.1 and date is 11 Dec., 2019. The recruitment date is 1 Apr. 2021, and the approximate date when recruitment will be completed is 31 Dec. 2021.

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Figures

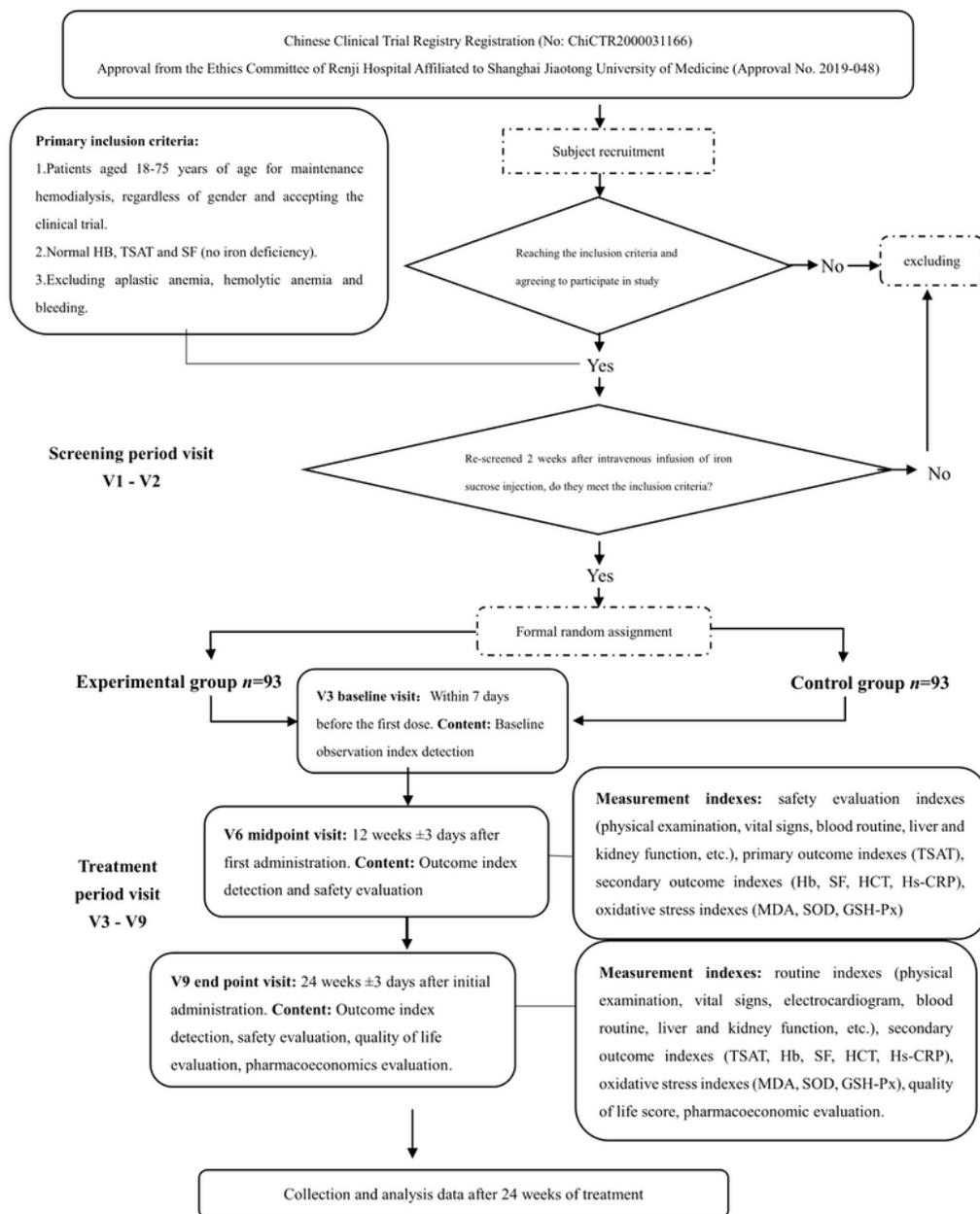


Figure 1

Flowchart of test scheme. Experimental group (routine treatment of CKD anemia + PIC), control group (routine treatment of CKD anemia + iron sucrose injection). Primary outcome: TSAT 12 weeks after treatment. Secondary outcomes: iron metabolism, oxidative stress, safety evaluation, pharmacoeconomic evaluation, quality of life score, etc.

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