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Efficacy of the Traditional Chinese Medicine, Qingganhewei Decoction, in Treating Refractory Non-Erosive Reflux Patients with Stagnated Heat in the Liver and Stomach: a Study Protocol for a Prospective Randomized Double-Blind Clinical Trial

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Clinical Trial Registration: Chinese Clinical Trial Registry (ChiCTR 2100054125).

Abstract: Non-erosive reflux disease (NERD) is characterized by typical gastroesophageal reflux symptoms and the absence of esophageal mucosal damage during upper gastrointestinal endoscopy. Almost 40% of NERD patients who fail to respond to double-dose proton pump inhibitor (PPI) treatment are characterized as having refractory non-erosive reflux (R-NERD). Traditional Chinese medicine (TCM) can effectively relieve the symptoms of this condition. We are conducting a clinical trial to assess the effectiveness of the Qingganhewei decoction in treating R-NERD among patients with stagnated heat in the liver and stomach. Ethics and Discussion: This clinical trial was approved by the Ethics Committee of Pinggu District Hospital of Traditional Chinese Medicine. It is the first randomized double-blinded trial to compare the effectiveness of the Qingganhewei decoction combined with PPI in treating R-NERD patients with stagnated heat in the liver and stomach. This novel protocol is expected to reduce symptom recurrence, lessen the physical and psychological burden of R-NERD, and provide good social benefits for patients.

Keywords: Refractory non-erosive reflux, protocol, randomized controlled trials, stagnated heat in liver and stomach, qingganhewei decoction

1. Introduction

Gastroesophageal reflux disease (GERD) occurs when stomach acid repeatedly leaks up into the esophagus resulting in symptoms such as heartburn and regurgitation. GERD can reduce quality of life and put patients at risk of developing esophageal carcinoma. This condition is a public health problem worldwide[1] and in China, recent changes in lifestyle and dietary structure are contributing to a rising incidence. GERD can be grouped into three basic phenotypes: erosive esophagitis (EE), non-erosive reflux disease (NERD), and Barrett's esophagus (BE)[2-3], of which NERD is the most prevalent.

Proton pump inhibitors (PPIs) are currently the most effective treatment for GERD. However, up to 40% of patients fail to respond well to one or two standard daily PPI doses.[4-5] Recent efforts to develop new treatments for GERD have been unsatisfactory. Indeed, refractory non-erosive reflux (R-NERD) is one of the most common treatment issues in gastroenterology. PPI remains the primary and preferred treatment for patients with this condition. Causes of failed treatment include poor treatment compliance, nocturnal acid breakthrough, weakly acidic and weakly alkaline reflux, metabolic differences, and psychophysiological factors.[6-11] One meta-analysis found that[12] 8 weeks of standard-dose esomeprazole treatment had a 5% higher R-NERD cure rate than other types of PPI. However, another meta-analysis showed that[13] this treatment had little advantage over other PPI. It remains unclear why differences in the efficacy of specific PPI preparations exist. In addition, different types of PPI can be affected by CYP2C19.[14] Numerous studies have shown that non-PPI drugs such as H2 receptor antagonists, anti-reflux drugs, neuroregulators, and prokinetic agents combined with PPIs cannot guarantee the clinical effectiveness of R-GERD treatment[15-17]. These therapeutic regimens increase the risk of drug resistance and adverse reactions and can have negative physical, psychological, and economic effects on patients after long-term use. There are two main reasons why R-GERD can be difficult to treat. First, large doses of PPI have a limited impact on weak acid and non-acid reflux. Second, long-term use of PPIs combined with other drugs may cause adverse reactions and increase a patient's risk of infections and tumors.[18]

R-GERD pathogenesis is complex, PPI treatment provides limited benefits and surgical treatment carries risks. The combination of PPI with other drugs not only increases medical costs but also elevates the risk of adverse reactions. In recent years, several studies have evaluated the clinical effectiveness of Traditional Chinese Medicine (TCM) herbs in the treatment of NERD.

R-GERD is associated with symptoms such as acid regurgitation, gastric upset, pyretic esophagus, dysphagia, and hiccups (2017 TCM diagnosis and treatment expert consensus opinion). This condition can be classified into different syndromes, including stagnant heat of the liver and stomach, gallbladder heat invading the stomach, qi stagnation and phlegm obstruction, blood stasis card, reverse syndrome of qi deficiency, and dampness-heat due to spleen deficiency.[19] Research on TCM syndrome differentiation has shown that 42.13–51.67% of patients have stagnant heat in the liver and stomach.

The QingganHewei prescription used in this study is one that Professor Shengsheng commonly uses to treat non-erosive R-GERD patients with liver and stomach stagnation. Our study will assess the short- and mid-term efficacy of the TCM Qingganhewei decoction and PPI treatment, and its impact on subjective patient feelings and objective disease indicators. Evidence-based medical data will be obtained to inform the use of TCM to treat non-erosive R-GERD, improve the clinical cure rate of the disease, and effectively relieve symptoms.

2. Methods and Analysis

2.1 Study Design

This trial is adopting a double-blind, randomized controlled trial (RCT) with two parallel groups to explore the efficacy of the Qingganhewei decoction in treating R-GERD patients with stagnated heat in the liver and stomach. This double-blind RCT is being conducted at the Pinggu District Hospital of Traditional Chinese Medicine. A total of 60 participants are being recruited from the hospital's outpatient and inpatient departments. Patient recruitment commenced in August 2022 and will continue until July 2024. Participants are being randomly divided into an intervention and a control group at a 1:1 ratio. Study design details are shown in **Figure1**.

2.2 Eligibility Criteria

All participating patients are being evaluated by TCM physicians to determine whether they meet the inclusion and exclusion criteria.

2.2.1 Inclusion Criteria

Patients are included in the study if they are (1) 18–65 years of age, (2) have a clinical diagnosis of non-erosive R-GERD according to the consensus of Chinese experts on gastroesophageal reflux disease (2014),(3) have TCM syndrome differentiation that aligns with the syndrome of stagnation of heat in liver and stomach in the consensus on traditional Chinese Medicine diagnosis and treatment of gastroesophageal reflux disease (2017) and the consensus on Integrated traditional Chinese and Western Medicine diagnosis and treatment of gastroesophageal reflux disease (2017),(4) have normal gastroscopy findings, with an allowance for superficial or atrophic gastritis, and (5) agree to undergo 24-hour esophageal pH-impedance monitoring and sign an informed consent form.

2.2.2 Exclusion Criteria

Patients are excluded if they (1) have a history of gastric, esophageal, and duodenal surgery, (2) have drug-induced esophagitis, fungal esophagitis, corrosive esophagitis, achalasia, hiatal hernia, eosinophilic esophagitis, and immune-related esophageal diseases, (3) have a suspected or confirmed malignancy or early warning symptoms, and previous examinations have revealed organic lesions of the digestive tract, (4) have used PPI or H2 receptor blockers within 2 weeks of enrollment, (5) have severe primary heart, liver, lung, kidney, pancreas, or liver diseases that affect survival, (6) have any disabilities specified by law, (7) have a suspected or confirmed history of alcohol or drug abuse, (8) have an allergic constitution, (9) have a mental illness, (10) are a woman who is pregnant, lactating, or planning to become pregnant in $\leqslant$ 3 months, or (11) have R-GERD due to poor treatment compliance.

2.3 Intervention

To improve treatment compliance and vigilance, health education on R-GERD etiology, harm, and treatment is provided to each participant. Patients are encouraged to exercise properly while avoiding strenuous exercises, that include frequent bending and exertion. They are required to avoid sleeping pills and replace drugs such as nifedipine and verapamil with other medications. Psychological counseling is encouraged for any patient with anxiety or depression.

Intervention group: One bag of TCM Formula Granules Qingganhewei decoction, mixed with 150–200 ml boiling water before breakfast and dinner. The decoction, which is formulated into granules by a third-party pharmaceutical company, includes 6 g Coptidis rhizoma, 6 g Menthae haplocalycis herba, 3 g Euodiae fructus, 10 g Perillae folium, 25 g Arcae concha,9 g Pinelliae rhizoma praeparatum cum alumine, 15 g Paeoniae radix alba, 10 g Aucklandiae radix, 10 g Citri reticulatae pericarpium, and 10 g Bletillae rhizoma. Sodium Rabeprazole Enteric-coated tablets (20 mg; Jiangsu Hansoh Pharmaceutical Co., Ltd., National Drug Approval Number H20020330) are administered every morning on an empty stomach.

Control group: One bag of TCM Formula Granules Simulation of Qingganhewei decoction, mixed with 150–200 ml boiling water before breakfast and dinner. This decoction is also formulated into granules by a third-party pharmaceutical company. While the simulated agent is similar to the intervention decoction in appearance, smell, and packaging the formula contains only a 5% concentration of the original drug. Sodium Rabeprazole Enteric-coated tablets (20 mg Jiangsu Hansoh Pharmaceutical Co., Ltd., National Drug Approval Number H20020330) are administered each morning on an empty stomach.

Duration of treatment: Both groups are receiving 8 weeks of treatment.

2.4 Sample Size Estimation

$$n_2 = \frac{\left(Z_{1-\alpha}+Z_{1-\beta}\right)^2 \sigma^2 \left(\frac{1+k}{k}\right)}{\left(\delta-\Delta\right)^2}$$

$$n_1 = kn_2$$

The sample size was estimated by comparing the means of two samples using a superiority test. In preliminary clinical studies, the overall mean DeMeester score was obtained from 24-hour esophageal pH-impedance monitoring of R-GERD patients after TCM combined with PPI treatment ($\mu 1 = 21.95$). The mean DeMeester score of R-GERD patients after 8 weeks of simple PPI treatment was $\mu 2 = 24.43$. The standard deviations of the two groups were $\sigma = 5.07$. If a subject's DeMeester score was 2 points lower than that of a control group participant,

it was considered to have clinical significance ($\Delta = 2$). Considering $\alpha = 0.025$ and $\beta = 0.1$, both are one-sided. Using the Z critical value table, $Z_{1-\alpha} = 1.960$, $Z_{1-\beta} = 1.282$, and $k = 1$. By substituting these values into the above formula, $n_1 = n_2 = 27$. Assuming a 10% shedding rate, N = 30. Thus, 30 patients are required in both the experimental and control groups, for a total of 60 participants.

2.5 Randomization and Blinding

2.5.1 Randomization

The cases are divided into intervention and control groups at a ratio of 1:1. A random assignment table is generated by a third-party biostatistician with treatment allocation corresponding to the serial numbers, 001-060. An investigator is responsible for issuing random numbers in the order each patient is enrolled in the trial.

2.5.2 Blind Design and Implementation

This study uses a double-blind single-simulation technology. A random number table is generated by a computer and sealed and opaque envelopes are used for random concealment to ensure that each subject is fully enrolled and prescribed the corresponding treatment. The generation of random numbers, coding of investigational drugs, subject enrollment and medication, recording and evaluation of research results, monitoring research process, data management, and statistical analysis are all blinded. The Qingganhewei formula simulation agents are prepared according to the control and blinding requirements. The study and control drugs are packaged uniformly to ensure that they are indistinguishable in appearance and that the usage and dosage are the same for each. After the drugs are prepared, a third-party person not involved in the clinical research is responsible for packaging and blinding the drugs. The study drugs are then distributed by drug number to each subject who signs the informed consent form. Neither the subjects themselves nor the researchers know whether the medications used by the subjects are study or control drugs. Thus, the patients, patient recruiters, clinical investigators, drug managers, outcome assessors, data managers, and statisticians are blinded to the study.

2.6 Outcomes

Table 1 shows the collected procedures, data, and outcomes.

2.6.1 Primary outcomes

The DeMeester score obtained from 24-hour esophageal pH-impedance monitoring is the main observation index. The number of refluxes with an esophageal pH < 4 within 24 h, the longest reflux time, the number of refluxes lasting > 5 min, and the percentage of monitoring time with an esophageal pH < 4 are used to calculate DeMeester point, and the patients are evaluated for esophageal reflux. A value of < 14.72 is considered normal reflux, 15–50 is considered mild acid reflux, 50–100 is considered moderate acid reflux, and > 100 is considered severe acid reflux.

2.6.2 Secondary outcomes

(1) 24-hour esophageal pH-impedance monitoring: total reflux time, long reflux time, acid reflux time, weak acid reflux time, and weak base reflux time. The main evaluation criteria for 24-hour esophageal pH-impedance monitoring is the number of proximal esophageal acid reflux events and the proportion of total time when the proximal esophageal pH value is < 4. The fewer the number of reflux events and the smaller the percentage of total time when the proximal esophageal pH value is < 4, the closer it is to a physiological state.

(2) Gastroesophageal Reflux Disease Questionnaire (GERD-Q): This scale assesses the frequency of heartburn, acid reflux, upper abdominal pain, nausea, sleep disturbance, and whether OTC drugs have been taken in the past weeks. The score decreases as the frequency of attacks increases. The other four items are positive symptoms, with scores that increase as the frequency of attacks increases. The GERD-Q score is the sum of the symptom scores, ranging from 0 to 18 points. A score of $\geqslant$ 8 points is indicative of GERD. Changes in patient GERD-Q scores are being observed at different treatment time points.

(3) TCM clinical symptom scale: This is a 15-item scale based on the Clinical Guidelines of New Drugs for Traditional Chinese Medicine and Expert consensus on quantitative standards for spleen and stomach disease-related symptoms. This scale evaluates changes in TCM symptoms of the digestive tract and the whole body, including flatulence, stomachache, poor appetite, heartburn, belching, acid reflux, pharyngeal paraesthesia, thirst, distention of the lateral lower

abdomen, fatigue, shortness of breath, unwillingness to speak, somatosensory heaviness, fear of cold, and loose stool. Each item is scored, from 1 (asymptomatic) to 4 (severe).

(4) Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA). Two specially trained evaluators jointly evaluate each patient through conversations and observations. The HAMD scale is divided into five structural factors: anxiety somatization, cognitive impairment, retardation, sleep disorder, and weight, while the HAMA scale is further divided into two structural factors: mental anxiety and somatic anxiety. Changes in the HAMD and HAMA scores of the enrolled patients are observed before and after treatment.

(5) Follow-up plan: Each patient's medication status, including maintenance treatment, intermittent use, and on-demand use of PPI or H2 receptor blockers, is assessed at 4 and 8 weeks after drug withdrawal.

2.7 Data Collection and Management

Professional statisticians are directly contributing to the project design, performing statistical processing on all data, and working with TCM experts to analyze and summarize the results and ensure consistency between the clinical and statistical research.

2.8 Statistical Methods

Non-normally distributed data are represented as medians (M) and quartiles (25th, 75th), and the rank sum test is used for evaluation (i.e. GERD-Q scores, HAMD scores, HAMA scores, total reflux times, long reflux times, acid reflux times, weak acid reflux times, and weak alkali reflux times obtained by 24-hour esophageal pH-impedance monitoring). Data that fit a normal distribution are represented as $\bar{x} \pm s$, and independent sample means are compared using a t-test (e.g. DeMeester score obtained by 24-hour esophageal pH-impedance monitoring). Grade data are expressed in tables using ratio analysis or the rank sum test (TCM symptom efficacy, post-treatment medication use, and DeMeester score grading). The main observation index is a statistical test of superiority. If the lower limit of the two-sided 95% confidence interval is greater than the superiority critical Δ value, the difference in the test results is considered statistically significant. The secondary observation index uses the two-sided test. A p-value of < 0.05 is considered statistically significant. All statistical analyses are performed using SPSS (Version 22.0).

2.9 Adverse Event Reporting

Adverse events are evaluated according to the CTVAE V5.0 (Common Terminology Criteria for Adverse Events) issued by the U.S. Department of Health and Human Services. Any adverse events are recorded on an adverse event report form during the trial.

3. Discussion

The incidence of R-GERD is gradually increasing. Due to its complex pathogenic mechanism, modern medical treatment is limited, and simple Western medicine treatment remains ineffective. TCM has the unique advantage of alleviating the symptoms of this condition. Thus, a combination of traditional Chinese and Western medicine is recommended to improve the clinical efficacy of R-GERD treatment. This study uses a prospective, randomized, double-blind, single-dummy, placebo-controlled clinical trial to observe the clinical efficacy of the QingganHewei Recipe in the treatment of non-erosive R-GERD patients with liver and stomach stagnation heat syndrome by analyzing TCM symptoms, signs, and 24-hour esophageal pH-impedance monitoring. Byassessing treatment with TCM Formula Granules Qingganhewei decoction and PPI, this study will provide valuable insight into the treatment of R-GERD and inform directions for future research and clinical practice. We hope this trial will inspire new studies on the diagnosis and treatment of this condition.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics Statement

This clinical trial was approved by the Ethics Committee of Beijing Pinggu Traditional Chinese Medicine Hospital. Any amendments to a previously completed protocol will be resubmitted, approved, and documented. Based on the ethical principles and relevant regulations of the Declaration of Helsinki, a detailed explanation of the clinical trial process will be provided to the participants by the PI and authorized

researchers in accordance with legal procedures. The participants are required to sign an informed consent form of their own free will before participating in the clinical trial

Author Contributions

ZSN: Writing-original draft. WZQ: Conceptualization, Methodology, Writing – review & editing. ZSN, WBL: Data curation. GXL, ZC, DJY: Investigate. LW, WDM: Project administration. LHJ: Supervision.

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Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Consent for Publication

Not applicable.

Competing Interests

The authors declare no competing interests.

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Tables

Tables 1. Collected procedures, date, and outcomes.

Figure Legends

Figure 1. Flowchart of the proposed trial.

Research Stage / Inspection Item	Screening Period	The Day of Randomization	Visit 1	Visit 2	Visit 3	Visit 4
Access Window	**2 weeks before enrollment**	**Day 0**	**Week 4**	**Week 8**	**Week 9**	**Week 12/16**
History-taking						
Sign informed consent form	√					
Fill in general information	√					
Medicalhistory and previous treatment	√					
Concomitant diseases and treatment	√					
Check inclusion/exclusion criteria	√					
Filter Indicators						
GERD-Q	√					
TCM syndrome differentiation	√					
Electronic gastroscopy	√					
24h esophageal pH-impedance monitoring	√					
Observation Of Effectiveness						
DeMeester score	√				√	
24h esophageal pH-impedance monitoring	√				√	
Major TCM clinical symptoms scale		√	√	√		
GERD-Q		√	√	√		√
HAMD、HAMA		√	√	√		
Safety Observation						
Physical examination	√	√	√	√		
Blood routine, urine routine, stool routine	√			√		
Liver function（ALT, AST）	√			√		
Renal function（Scr, BUN）	√			√		
12-lead ECG	√			√		
Adverse event	√			√		
Other Items						
Concomitant medication/treatment	√	√	√	√		√
Randomization to enrollment		√				
Dispensing medications		√	√			
Issue "patient diary cards"		√	√			
Recovery of medicines			√	√		
Recovery of "patient diary cards"			√	√		
End of study summary						√

Table 1

Collected procedures, data, and outcomes.

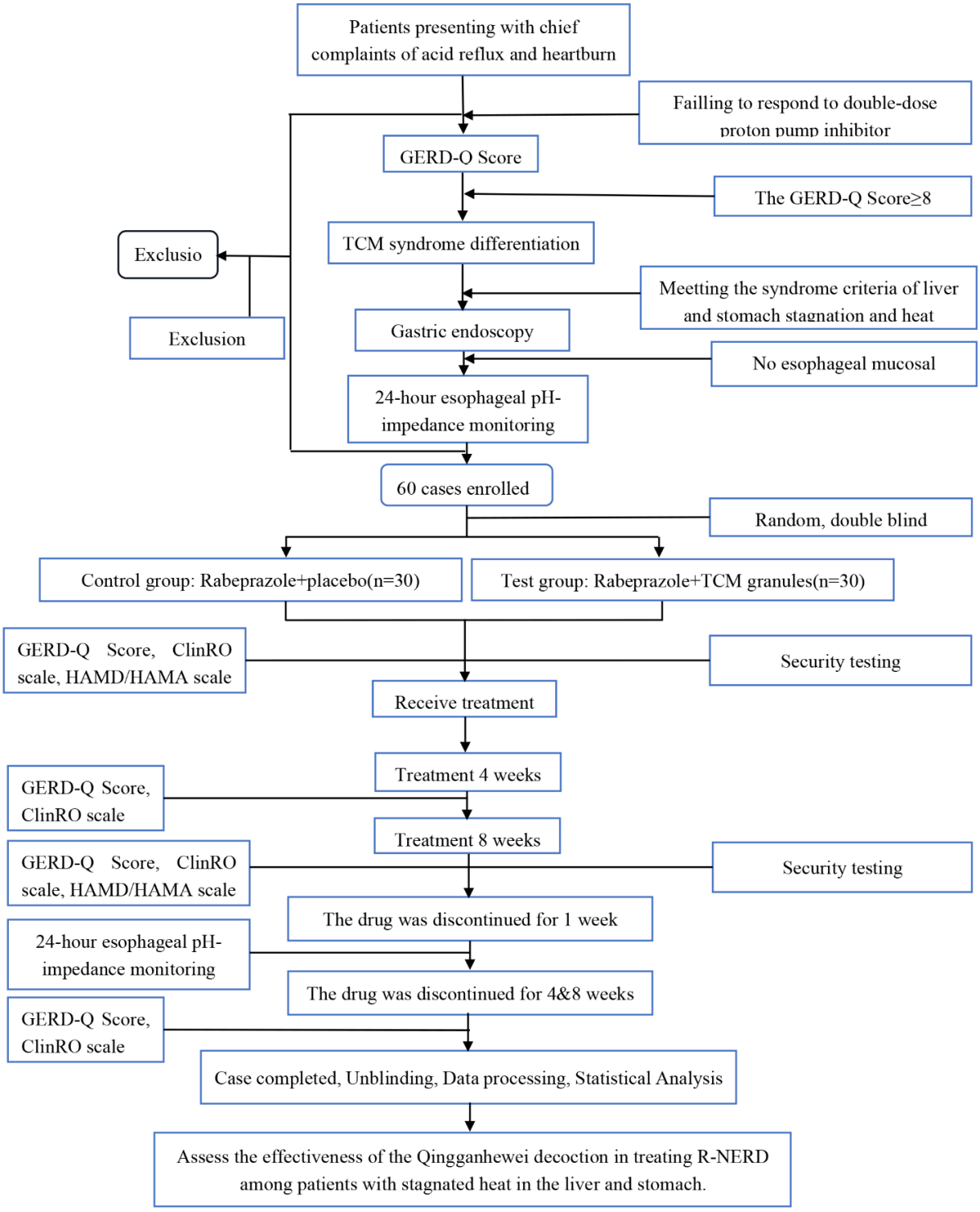

FIGURE 1
Flowchart of participants