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## • Study Protocol

# The add-on effect of a Chinese herbal formula for patients with resistant hypertension: study protocol for a pilot cohort study



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### ABSTRACT

**BACKGROUND:** Despite a recent American Heart Association (AHA) consensus statement emphasizing the importance of resistant hypertension (RH), its control is still a challenge for conventional medicine. The Chinese herbal formula, Qutan Huayu Fang, has been used effectively to assist antihypertensive agents in blood pressure control, but its effect for RH patients is still unclear. This pilot study aims to explore the effects of taking the formula in addition to antihypertensive medication in the management of RH.

**METHODS/DESIGN:** A prospective cohort study will be conducted in two first-class hospitals of traditional Chinese medicine (TCM). Eligible RH patients will be classified as the experimental group ( $n = 100$ ) and the control group ( $n = 100$ ) based on the interventions they receive. Participants taking antihypertensive agents and the Chinese herbal formula will be in the experimental group and those taking antihypertensive agents alone will be in the control group. The whole study will last 24 weeks, including an 8-week observation and follow-up at 24 weeks. The primary outcomes, assessed against patient baseline conditions, will be the reduction of systolic blood pressure and diastolic blood pressure as well as changes in TCM symptoms and signs. These outcomes will be assessed at weeks 2, 4, 6, and 8. The reductions of blood pressure will also be assessed at week 24. Cardiac events and mortality rate will be secondary outcomes and will be assessed at weeks 8 and 24. Any adverse reactions will be recorded during the study. The causal inference method will be used to assess the effectiveness of the inclusion of TCM herbal medicine in the management of patients with RH.

**DISCUSSION:** This study will determine whether the Chinese herbal formula is helpful for RH patients treated with antihypertensive agents and the findings will provide a basis for further confirmatory studies.

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**Keywords:** resistant hypertension; cohort study; medicine, Chinese traditional; Complementary therapies; study protocol

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## 1 Introduction

Resistant hypertension (RH) is defined as the failure to achieve target blood pressure despite concurrent use of 3 antihypertensive agents of different classes<sup>[1]</sup>. Research has shown that 1 in 50 patients receiving treatment for incident hypertension will develop RH<sup>[2]</sup>. It is estimated that there are more than 16 million patients with RH in China<sup>[3]</sup>. The incidence of RH is likely to increase as the population ages and grows heavier, as older age and obesity are two of the strongest risk factors for uncontrolled hypertension<sup>[1]</sup>. Great efforts are needed to control blood pressure for RH patients who are at increased risk of stroke, cardiovascular diseases and chronic kidney diseases<sup>[2,4,5]</sup>. However, the recommendations for the pharmacological treatment of RH largely depend on clinical experience due to the lack of systematic assessment of 3 or 4 drug combinations. Conventional treatments for RH, including lifestyle modification, baroreflex activation therapy and multidrug regimens, are rarely effective and some pharmacological therapies have the potential to cause adverse side effects<sup>[1]</sup>. Thiazide diuretics can provoke hyperglycaemia and diabetes<sup>[6]</sup>,  $\beta$ -blockers increase the risks of fatigue and sexual dysfunction<sup>[7]</sup> and angiotensin-converting enzyme (ACE) inhibitor may cause coughing, dizziness, headache, asthenia and nausea<sup>[8]</sup>. Studies have shown beneficial effects of renal nerve ablation on RH patients, however, long-term controlled data are still needed to explore the efficacy or sustainability of the treatment. Similarly, preliminary data set has shown potentially positive outcomes in reduction of blood pressure in response to renal denervation<sup>[9]</sup>. Effective treatment for improving the long-term clinical management of RH remains an urgent need.

In traditional Chinese medicine (TCM), RH is categorized as “dizziness” or “headache”. Recent years, 6 trials (690 participants) conducted in China suggested that use of TCM in conjunction with antihypertensive drugs generated additional positive effects<sup>[10-15]</sup>, such as reduced blood pressure, and improved TCM signs and symptoms. Although most of these trials were non-randomized and had small sample size, the results indicated a potential role for TCM in RH management.

Phlegm combined with blood stasis is the main pathogenesis for RH in TCM<sup>[16]</sup>. Therefore, removing both phlegm and blood stasis is an important approach for treating RH<sup>[17]</sup>. To design this treatment approach, two senior TCM doctors (Shao-gong Shen, and Xue-jie Han), composed a Chinese herbal formula, named Qutan Huayu Fang (aliased as the formula). A clinical study demonstrated that Qutan Huayu Fang, combined with antihypertensive agents significantly improved the efficacy of blood pressure control for patients with chronic hypertension (5-year and 10-year)<sup>[18]</sup>. However, it is not clear whether the formula is effective for RH patients.

We hypothesized that the formula could enhance the efficacy of antihypertensive agents in relieving high blood pressure, improving symptoms and signs, as well as reducing cardiac events and the overall mortality rate of patients with RH. With this purpose, we designed this trial to explore the additional effects of the formula for RH patients.

## 2 Methods and design

### 2.1 Design

This is a prospective pilot cohort study with two arms. Two-hundred participants will be recruited and divided into two groups, with 100 individuals per group. The study began in August 2013 and will last until March 2015. The first participant was recruited on August 23, 2013. Figure 1 shows the trial design.

### 2.2 Participants

#### 2.2.1 Diagnosis criteria

Patients with RH are prescribed 3 or more antihypertensive medications at doctor-recommended doses, including, if possible, a diuretic. Patients will have an office blood pressure  $>140/90$  or  $130/80$  mmHg when accompanied with diabetes or chronic kidney diseases. Patients requiring 4 or more antihypertensive medications may be deemed to have RH even if blood pressure is controlled<sup>[1]</sup>.

#### 2.2.2 Inclusion criteria

Patients will be eligible to participate if they are suffering from RH; aged 18–70 years; have a TCM diagnosis of phlegm accumulating with blood stasis pattern<sup>[19]</sup>; are currently taking (within the last week) antihypertensive agents or antihypertensive agents combined with the formula and are willing to continue taking the same agents throughout the entire observation period.

#### 2.2.3 Exclusion criteria

Patients will be excluded from the study for any of the following conditions: enrolled in other clinical trials within the previous month; pregnant, breast-feeding or preparing for pregnancy; suffering from serious complications, such as renal diseases, pheochromocytoma, stroke, coronary atherosclerotic heart diseases, diabetes or mental diseases.

### 2.3 Ethical consideration

The study was approved by the Institutional Review Board of the Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing, China (approval number 2012NO6).

### 2.4 Participant recruitment

RH patients will be recruited from outpatient and inpatient departments of two first-class TCM hospitals (Guang'anmen Hospital, and Xiyuan Hospital of China Academy of Chinese Medical Sciences) by means of posters. The patient screening will be conducted by clinicians who are not involved in the study.

If a patient meets the study criteria, the clinician who

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