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## Study Protocol

## Herbal medicines (Eunkyosan and Samssoeum) for treating the common cold: a protocol for a randomized, placebo-controlled, multicenter clinical trial

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## ABSTRACT

**Background:** The common cold is the most frequent acute respiratory illness that places a burden on society, both personally and economically. There is no standard therapy; only symptomatic therapy remains the mainstay of common cold treatment. Thus, interest in herbal medicines is on the rise. Eunkyosan and Samssoeum are used for the common cold in East Asian countries. Although Eunkyosan and Samssoeum are clinically used for the treatment of the common cold, their effectiveness and safety have yet to be studied. Therefore, we aimed to evaluate their effectiveness and safety.

**Methods:** This study is a randomized, patient-assessor blind, controlled, parallel, and multicenter clinical trial. A total of 375 participants diagnosed with the common cold will be enrolled via four hospitals. The common cold patients will take a daily dose of Eunkyosan or Samssoeum or a placebo, three times a day for eight days. The primary outcome is the change in total Wisconsin Upper Respiratory Symptom Scale-21-Korean version (WURSS-21-K) score between baseline and six days. The secondary outcome includes the visual analogue scale (VAS). Safety is evaluated and adverse events are assessed throughout the trial. Written informed consent will be obtained from all study participants before enrollment.

**Discussion:** This results will be published in a peer-reviewed journal and disseminated in related conferences.

**Trial Registration:** ClinicalTrials.gov, registration number: NCT04073511.

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## Introduction

The common cold is a syndrome that involves coughing, sputum, a runny nose, a stuffy nose, sneezing, soreness, or fever; it is generally cured naturally, but it is the most common illness in everyday life that places a burden on society in terms of personal pain and economic loss.<sup>1–4</sup>

Since common colds do not have any standard treatment, symptomatic therapy is mainly used.<sup>5</sup> However, antihistamines and nonsteroidal anti-inflammatory drugs used for symptomatic therapy may not demonstrate effectiveness,<sup>6,7</sup> and cause side effects, such as drowsiness or gastrointestinal bleeding.<sup>4</sup> Antibiotics have also been reported to cause adverse events, such as an increased resistance rate.<sup>8,9</sup> Therefore, interest in herbal medicine treatment for colds is increasing in many countries.

Samssoeum is a prescription written in 『Dongui Bogam』 and is used for weak or elderly individuals who are negatively affected by wind and cold and have a fever, sore head, nasal congestion, coughing, sputum, stuffy chest, nausea, cold body, and cold sweat. The number of patients who visited Korean medicine clinics in Korea with acute pharyngitis [common cold] (Korean Standard Classifica-

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tion of Diseases, KCD: J00) was between 350,000 and 450,000 per year from 2010 to 2016, and the proportion of patients receiving Samsoeum was 22–27%.<sup>10</sup> This shows that Samsoeum is frequently used in the treatment of adult cold patients in Korea and has high utility in the clinical field.

Eunkyosan is a prescription written in 『Onbyeongjobyeon』 and is used for symptoms of a cold, feverish without sweat, pain in the head and throat, and coughing due to wind-heat cold type. It can be used for influenza, cold, acute tonsillitis, acute bronchitis, pneumonia, acute parotitis etc. In China, various clinical studies have evaluated the effectiveness of Eunkyosan on colds. Hu et al. administered Eunkyosan and ribavirin to 60 adult patients for three to five days.<sup>11</sup> The Eunkyosan-administered group showed a statistically significant improvement of an risk ratio (RR) of 1.40 [CI 1.05–1.89] greater than the general medicine group, as well as a statistically significant decrease in the time it took for patients' fever, cough, and nasal symptoms to subside than the general medicine group. In a study by Jiao et al., Eunkyosan and general medicine (antivirus, paracetamol) were administered to 192 adult patients with colds.<sup>12</sup> The improvement rate of symptoms was a RR of 1.24 [CI 1.12–1.39], which showed a statistically significant effect.<sup>12</sup>

Eunkyosan is frequently used in Korea, but it is a non-reimbursed Korean medicine, and clinical studies have only been conducted in other countries. Samsoeum is actively prescribed for colds as a reimbursed Korean medicine, but there are no clinical studies at the local or global level, and it is recommended only as a GPP (good practice point, professional joint recommendation grade). For these reasons, both prescriptions require clinical evidence. Therefore, we aimed to conduct a multicenter clinical trial to verify the effectiveness and safety of the administration of Eunkyosan and Samsoeum in cold patients.

The effectiveness of Eunkyosan and Samsoeum for acute nasopharyngitis [common cold] compared to a placebo will be evaluated by giving a daily dose of Eunkyosan or Samsoeum or a placebo, three times per day for eight days to patients diagnosed with acute nasopharyngitis [common cold] (International Statistical Classification of Diseases and Related Health Problems, ICD-10 : J00).

## Methods

### Trial registration

This trial has been registered at 'ClinicalTrials. Gov' and the registration number is NCT04073511.

### Study design

The study is conducted as a randomized, patient-assessor blind, controlled, parallel, and multicenter trial.

### Recruitment

The study will be conducted in four hospitals, and the posters will be posted on each institution's bulletin board to recruit subjects.

### Participants

#### Inclusion criteria

- 1) Male and female aged between 19 and 60 years as of the screening date
- 2) Onset of cold symptoms within 48 h before screening
- 3) Those who have one or more of the symptoms and related symptoms of a runny nose and sore throat (Related symptoms: nasal

congestion, sneezing, cough, sore throat, headache, chest tightness, fatigue)

- 4) Those who demonstrate an understanding of the study details and have a willingness to participate, as evidenced by voluntary written informed consent
- 5) Those who can be followed up during the clinical trial
- 6) Those who do not meet the exclusion criteria

#### Exclusion criteria

- 1) Those who have sinusitis (when the sinus is opaque at the time of examination through the transillumination of the maxillary sinus and the frontal sinus), allergic rhinitis, pneumonia, flu (when coughing or sore throat with sudden fever above 38 °), bronchitis, otitis media, tonsillitis (paranasal sinus [PNS] view, chest x-ray test if an accurate test is needed)
- 2) Those who have a chronic respiratory disease (chronic obstructive pulmonary disease, interstitial lung disease) and asthma
- 3) Those who have taken or should be taking or are taking antibiotics, antivirals, steroids, nasal decongestants, antihistamines, or other medications that are expected to alleviate cold symptoms, or those who have taken food that is expected to relieve cold symptoms within one week of the start of the study
- 4) Those who are being treated for liver cancer or cirrhosis, chronic renal failure, congestive heart failure, etc.
- 5) Those who have a systemic disease or autoimmune disease that does not affect cold symptoms
- 6) Those who have severe mental illnesses, such as depression or anxiety disorders, or those who are currently taking psychoneurological drugs, such as antidepressants
- 7) Drug addicts or alcoholics
- 8) Alanine transaminase (ALT) or aspartate transaminase (AST) exceeds three times the upper limit of normal
- 9) Creatinine exceeds twice the upper limit of normal of the research institute
- 10) Weak person (less than body mass index [BMI] of 18.5, clinically judged by a Korean medical doctor through physical examination)
- 11) Those who have a weak stomach and are considered unfit to take an investigational drug (clinically judged by a Korean medical doctor through physical examination)
- 12) Those who have a high blood pressure (vital signs measured at sitting position for at least five minutes at screening: systolic blood pressure  $\geq$  160 mmHg or diastolic blood pressure  $\geq$  100 mmHg) or elderly
- 13) Those who have a cardiac disorder or renal disorder (clinically judged by a Korean medical doctor through physical examination, electrocardiogram [ECG], and serum biochemistry)
- 14) Those who have histories of hives, rashes, or itching while taking medicine
- 15) Participants in other clinical trials within one month of the start of the trial (30 days prior to the screening visit) or plan to participate in other clinical trials during the trial
- 16) Pregnant women or women who may be pregnant
- 17) Those who do not agree to contraception in the case of women of childbearing age
- 18) Those who are being held in group facilities, such as social welfare facilities
- 19) Those who are deemed inappropriate to participate in the trial by the investigator's judgment
- 20) Those who have hypersensitivity to the investigational drug (main ingredient and its components)
- 21) Those who have genetic problems, such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
- 22) Those who have hypokalemia

- 23) Those who have difficulty in daily life due to sweats (excessive sweating, general weakness, etc.)
- 24) Those who have difficulty in daily life due to anorexia, nausea, or vomiting
- 25) Those who are suspected of having pneumonia and need antibiotic treatment or those who are receiving medical treatment (those receiving other medications)

#### Subject withdrawal and discontinuation

- 1) Violation of inclusion/exclusion criteria
- 2) Subject's request
- 3) Adverse events (including serious adverse events) that have made it impossible to participate the trial
- 4) Non-compliance (less than 80%) or not followed up
- 5) Protocol violations which could have a significant impact on the trial
- 6) Those who have taken or have to take medications or nutraceuticals that may affect this trial
- 7) Investigator's decision for other reasons
- 8) Those whose pregnancy is confirmed during the trial

#### Randomization and allocation

The randomization table should be commissioned by an independent statistician and sent directly to the sub-investigator (clinical trial pharmacist). The sub-investigator will treat subjects sequentially according to the randomization. Subjects who participate in the study will be assigned to each group according to the randomization number generated in advance according to the assigned randomization number. The number of subjects in each group should be the same, at a ratio of 1: 1: 1. A three-digit identification code (randomized number) shall be assigned in the order in which the subjects enrolled according to the randomization table, and the investigational or control drug packaged according to the code will be distributed to the subjects. The randomization table is generated by a statistician using nQuery Advisor 7.0 (or SAS 9.0 or SPSS 21.0), delivered to the sponsor. The sponsor will provide randomization details of each subject in each non-transparent envelope sealed to trial institutions.

#### Blinding

This study is blinded to all subjects, investigators, and pharmacists. To maintain double blinding, subjects should not be gathered in the waiting room but be individually contacted via phone to control the visit. In this study, Eunkyosan, Samssoeum, and a placebo are all packed in the same package. Apparently, Eunkyosan and Samssoeum may be recognized as different drugs, but it is difficult for subjects to distinguish which drug is used. The placebo can be recognized as a Korean medicine with brown granules. The subjects will complete a questionnaire about whether the medicine they took was a common cold medication or a placebo at the end of the clinical trial. The assignment of randomized code is kept sealed by the study director and is not released until the end of the study. Even if it is necessary to break the blinding due to the occurrence of serious adverse drug reactions, it is managed in the form of a separate blind envelope for each study subject so that only the randomization of the study subjects can be read.

#### Interventions

##### Eunkyosan

We use Eunkyosan Ext. Granule Hanpoong of Hanpoong Pharm and Foods Co., Ltd. Hanpoong Pharm is a good manufacturing practice (GMP)-certified facility. This drug is a commercially available drug, manufactured according to the Preparation of granules, Gen-

**Table 1**

Composition of *Eunkyosan* and *Samssoeum* per one dose.

<i>Eunkyosan</i>	
Ingredients (Latin name)	Amount (g)
Lonicerae Flos	0.41
Forsythiae Fructus	0.41
Menthae Herba	0.24
Platycodonis Radix	0.24
Glycyrrhizae Radix et Rhizoma	0.24
Lophatheri Herba	0.16
Schizonepetae Spica	0.16
Glycine Semen Preparatum	0.20
Arctii Semen	0.20
Antelopsis Cornu	0.01
<i>Samssoeum</i>	
Ingredients (Latin name)	Amount (g)
Ginseng Radix	0.30
Perillae Folium	0.20
Angelicae Decursivae Radix	0.36
Menthae Herba	0.31
Puerariae Radix	0.56
Poria Sclerotium	0.03
Citri Unshius Pericarpium	0.30
Platycodonis Radix	0.40
Aurantii Fructus Immaturus	0.29
Glycyrrhizae Radix et Rhizoma	0.25
Zingiberis Rhizoma Crudus	0.03
Zizyphi Fructus	0.34

eral rule of formulation, Korean Pharmacopoeia. The dosage is one packet, 2.3 g, three times daily, for a 6.9 g total daily dose. The total duration of administration is up to eight days. The composition of Eunkyosan is presented in [Table 1](#).

##### Samssoeum

We use Samssoeum Hanpoong (sweetened Ext. powder mixture) of Hanpoong Pharm and Foods Co., Ltd. This drug is a commercially available drug, manufactured according to Ministry of Food and Drug Safety (MFDS) regulations and the Preparation of granules, General rule of formulation, Korean Pharmacopoeia. 3.37 g of a packet, three times a day, total daily dose is 10.11 g. The total duration of administration is up to eight days. The composition of Samssoeum is presented in [Table 1](#).

##### Placebo

The placebo was manufactured by Hanpoong Pharm. It is composed of lactose carb, corn starch, caramel pigment, and ginseng-flavored powder. It appears as brown granules and is made to be recognized as Korean medicine. The dosage is 9.0 g–3.0 g each, three times a day. The total duration of administration is up to eight days.

##### Concomitants

Combination with antibiotics, antivirals, steroids, nasal decongestants, antihistamines, and other drugs that are expected to alleviate cold symptoms, from the start of the study to visit 3, is prohibited.

##### Outcomes

##### Primary outcome

The primary objective is the change in the total Wisconsin Upper Respiratory Symptom Scale-21-Korean version (WURSS-21-K) score (symptom score + quality of life score) six days after baseline. Dairies of WURSS-21-K are provided to participants and they are asked to record every question from day 1 to day 8. Barrett et al. developed the assessment instrument, a questionnaire

	STUDY PERIOD						Close-out
	Enrollment	Allocation	Post-allocation				
Time point (Day)	-1-0	0	3±1	6±1	8+3	15±1	
Visit	Screening (Visit 1)	Visit 2	F/U 1	F/U 2	Visit 3	F/U 3	
<b>ENROLLMENT:</b>							
Informed consent	X						
Eligibility Screening:	X						
Demographics	X						
Medical history	X						
Physical examination	X						
Vital signs	X						
Blood test	X						
Electro-cardio-graphy test	X						
Allocation		X					
<b>INTERVENTIONS:</b>							
Eunkyosan		←	→				
Samsoeum		←	→				
Placebo		←	→				
<b>ASSESSMENTS:</b>							
Vital signs		X			X		
WURSS-21-K*		←	→				
VAS*		←	→				
Adverse event			←	→			
Concomitant drug		←	→				
Safety(Blood test)					X		
Compliance check					X		
Symptom check			←	→			
Database completed and locked							X

Fig. 1. Study process.

\* Evaluation diary: 8-day self-recording worksheets will be provided at baseline after registering the study subjects. The subjects will record data daily and return the worksheets to the investigators on from day 8 to day 11.

WURSS-21-K, Wisconsin Upper Respiratory Symptom Survey-21-Korean version; VAS, Visual Analogue Scale.

consisting of 44 questions that included symptomatic or functional impairment including quality of life related to experienced cold illness.<sup>13</sup> Subsequently, 21 questions with high importance and internal reliability in each domain of the questionnaire were selected to develop the short version, WURSS-21<sup>14</sup>; the reliability and validity of this version were tested and this is being used as an assessment instrument in the common cold. This study utilized the WURSS-21-K, which is validated in Korea.<sup>15,16</sup> The WURSS-21-K consists of 10 questions on disease symptoms, nine questions on functional quality of life, one question on overall severity of disease, and one question on improvement or deterioration, and responses are recorded on a seven-point Likert scale. The total score is used as a measure of symptom severity, and higher scores indicate higher severity of symptoms. We will evaluate the WURSS-21-K using a self-written diary.

The clinical trial process is presented in Fig. 1.

#### Secondary outcomes

Apart from the primary outcome, i.e., the change of total sum of WURSS-21-K, separate change values of symptom score and quality of life score of WURSS-21-K at day 6 from baseline, are secondary outcomes. Also, the duration of cold symptoms and the change in the VAS between day 6 and baseline will be evaluated. VAS will be evaluated using EuroQoL-visual analog scales (EQ-VAS). The EQ-VAS is a vertical visual analog scale that takes values between 100

(best imaginable health) and 0 (worst imaginable health), on which participants provide a global assessment of their health.

For the outcomes regarding WURSS-21-K and VAS, data collected at different times of other than day 6, can be used as a reference.

#### Safety

The subjects are those who have received the drug used in the clinical trial at least once and who have visited at least once thereafter to evaluate safety data, such as adverse events (AEs), vital signs, or changes in clinical test values. Safety is assessed by AEs, abnormal vital signs, and abnormal changes in hematological and biochemical tests. AEs are undesired and unintended signs, symptoms, or illnesses after taking investigational products used in a clinical trial. It is not necessary to have a causal relationship with the drug. Serious adverse events (SAEs) are defined as follows: 1) fatal or life-threatening AEs; 2) AEs requiring hospitalization or extension of hospital stay; 3) AEs leading to persistent or significant disability or dysfunction; 4) AEs leading to congenital deformity or abnormalities; 5) other medically significant AEs.

AEs are classified into three grades: 1) Mild = No impairment of daily activities; 2) Moderate = Impaired daily activities, requiring simple treatment; 3) Severe = Unable to perform daily activities, requiring a high level of treatment.

Clinical laboratory tests shall be subject to the following items: glucose, white blood cells, red blood cells, hemoglobin, hematocrit, blood urea nitrogen, creatinine, AST, ALT, sodium, potassium, and chlorine. If it is uncertain of pregnancy for any participants, urine HCG shall be tested.

#### *Data collection, management, and monitoring*

Data will be managed by independent third parties. All documents related to clinical trials, such as case records, should be recorded and identified by identification code, not by subject name. Information relating to clinical trials is kept confidential and must have facilities and management standards for confidential storage. Only the principal investigator, and sub-investigators delegated by the principal investigator can access the data. Sponsors conduct monitoring during the trial. Monitoring should be done to ensure that the case records are complete and clear and to be reviewed with the records source in the presence of the investigator, who will cooperate with the sponsor at any time.

The monitor visits and conducts monitoring according to the monitoring plan and schedule. The monitor checks the protocol, case record form, and supporting documents to determine whether they are carried out scientifically in accordance with the institutional review board (IRB) approved plan and whether the subjects are being infringed on their safety and rights. If necessary, interviews with the principal investigator or sub-investigators can be conducted.

The sponsor manages and coordinates the trial progress of the institution with one or more monitors for this study. Clinical trial progress and management of the conducting institution will be overseen by the sponsor in charge of clinical trials. If any problem occurs in the institution, the monitor will report to the principal investigator, sub-investigators, and the sponsor.

#### *Ethics*

This trial is approved by the IRB of Pusan National University Korean Medicine Hospital (PNUKHIRB-2019001), the IRB of Kyung Hee University Korean Medicine Hospital (KOMCIRB 2019-01-003-002), the IRB of Daejeon University Korean Medicine Hospital (DJDSKH-19-DR-03), and the IRB of Semyung University Korean Medicine Hospital (SMJOH-2019-02-01). The protocol complied with the Helsinki Declaration and the Good Clinical Practice (GCP) Guidelines. Subject consent will be obtained in written form after informing those participating in the trial in advance so that they can easily understand the trial and compensation and procedures for the health damage that may occur to the subjects during the trial.

This trial is registered with the ClinicalTrials. Gov. (NCT04073511).

#### *Sample size*

This study is a superiority test to show the difference in changes in WURSS-21-K values measured at six days compared to baseline in three groups (control, Samssoeum, and Eunkyosan) (two-sided tests). Since there have been no clinical studies of Eunkyosan or Samssoeum using the WURSS-21-K, this protocol used similar trials that investigate the effectiveness of Korean medicine using the WURSS-21-K.<sup>15</sup> The allocation ratio of each group was 1: 1: 1. The clinical difference indicating the mean change of total WURSS-21-K in Socheongryongtang and the placebo was 6 in Byun et al.'s study,<sup>15</sup> and 10 in minimal important difference (MID) in that of Barrett et al.<sup>14</sup> In Andrey et al.'s study, the difference in variation considering the AUC difference of 30% was 18.<sup>17</sup> In this study, the clinical difference between the experimental and control groups

was set to 10 considering that the difference in the change amount of the WURSS-21-K was 6–18. The standard deviation was set to 30 based on the Byun et al.'s study.<sup>15</sup> As a result, 112 subjects for each group was needed. Considering the 10% dropout rate, total 375 patients were required, 125 in each group.

#### *Statistical analysis*

The subject for effectiveness assessment must have at least one primary or secondary effectiveness data endpoint obtained after the first visit for an intention-to-treat (ITT) analysis.

The following requirements must be met for per-protocol (PP) analysis: 1) Participants met eligibility criteria based on inclusion/exclusion criteria; 2) Participants who have not taken more than three consecutive days of investigational drug and who have taken more than 80% of the total. If the subject feels that the symptoms of the common cold have all improved for more than two consecutive days, the subject shall terminate the investigational drug administration and effectiveness evaluation at that time (early termination). But safety test will conduct at day 8 and adverse events also will be checked at day 8 and 15. Since the data of subjects who were terminated due to symptom improvement are missing from that point, the data for the later evaluation of effectiveness is replaced by the last observation carried forward (LOCF) analysis method.

#### *Analysis method*

ITT and PP were performed to compare the WURSS-21-K between the three groups. For continuous data, clinical laboratory tests, and vital sign variables, baseline, each visit, final evaluation, and changes from baseline to final evaluation are summarized by means of descriptive statistics and standard deviations. The change mean score from baseline to day 6 in Eunkyosan, Samssoeum, and control groups are compared using ANOVA. Additionally, since all primary (WURSS-21-K total score (symptom score + quality of life score)) and secondary (change in WURSS-21-K symptom score, change in WURSS-21-K quality of life score, duration of cold symptoms, change in the VAS) data are continuous variables, ANOVA is performed for the difference in the baseline and the difference between the baseline and subtracted baseline at each time point. If the differences between groups are statistically significant, multiple comparisons are performed using the Duncan method. A paired *t*-test is used to test the differences compared to baseline at each time point in each group. All analyses are performed using SPSS for Windows 17.0 (SPSS Inc., Chicago, IL, USA) and judged to be statistically significant when the *p*-value is less than 0.05.

The superiority is assessed by comparing the change in effectiveness. In the case of missing values for the endpoint or dropout before completion, the most recent measured data should be analyzed as though they were obtained at that time. This is because it is the simplest and most conservative method of use and the most commonly used method.

For the safety assessment, the number (%) of adverse events and abnormal vital signs in each group will be summarized and Fisher's exact test or Chi-square test will be performed if necessary. Also, the number (%) of each laboratory abnormality will be summarized in each group and ANOVA will be performed if needed.

#### **Discussion**

The present study is a randomized, patient-assessor blind, parallel-group, placebo-controlled, multicenter clinical trial conducted to investigate the effectiveness and safety of treatment with Eunkyosan and Samssoeum in the common cold. Eunkyosan, Sam-

soeum, or a placebo will be administered for eight days to patients with common cold.

The common cold is a mild, acute, self-limited viral syndrome; it is the most common syndrome worldwide. Although the disease is usually mild, episodes occur frequently, impair social life and daily activities, and cause considerable economic loss. When symptoms persist without any improvement, patients often develop further complications. There are over 200 species of viruses causing the common cold, making it difficult to identify the causative organism and to treat the condition. Conventional treatment generally consists of symptomatic therapy to alleviate symptoms; this makes it even more important to study the efficacy of Korean herbal medicines in the common cold. Herbal medicines are already widely used to treat the common cold in Korea. Due to the difficulties in diagnosis and its short duration, there have not been many large clinical trials on the common cold. Specifically, there is a severe shortage of large studies on the disease using traditional Korean medicine. Eunkyosan and Samsoeum used in this study are commonly used traditional Korean medicines for the common cold in Korea, but there is a lack of clinical evidence regarding their efficacy in the country and abroad. To provide clinical evidence for the therapeutic effects of these two drugs in the common cold, we designed the present study as a well-designed clinical trial based on SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and CONSORT (Consolidated Standards of Reporting Trials) guidelines. A multicenter design has been used to ensure an adequate sample size and a representative sample. We assumed the drop-out rate as 10% as the timeline of this trial is relative short (up to 16 days) and trial disease (common cold) is a mild condition. In a previous large scaled common cold trial, only 7 participants out of 480 randomized patients, were dropped out.<sup>16</sup>

It is anticipated that this study will demonstrate the therapeutic effects of the two drugs in the common cold and will expand the established treatment options available to clinicians and patients. Moreover, we hope that this study will provide a basis for implementing insurance claims for traditional Korean medicines prescribed for common diseases, increasing access to high-quality medical care.

### Conflicts of interest

The authors declare that they have no competing interests.

### Funding

This study was supported by the Traditional Korean Medicine R&D program funded by the Ministry of Health & Welfare through the Korea Health Industry Development Institute (KHIDI) (HB16C0006).

### Ethical statement

This trial has been authorized by the IRB of Pusan National University Korean Medicine Hospital (PNUKHIRB-2019001), the IRB of Kyung Hee University Korean Medicine Hospital (KOMCIRB 2019-01-003-002), the IRB of Daejeon University Korean Medicine

Hospital (DJDSKH-19-DR-03), and the IRB of Semyung University Korean Medicine Hospital (SMJOH-2019-02-01). Written informed consent will be obtained from all participants.

### Data availability

Due to ethical matters, supporting data can't be openly available.

### CRedit authorship contribution statement

**Kwan-Il Kim:** Methodology, Writing - original draft. **Minna Hong:** Writing - review & editing. **Yang-Chun Park:** Conceptualization, Investigation. **Beom-Joon Lee:** Conceptualization, Investigation. **Kitae Kim:** Conceptualization, Investigation. **Byung Kab Kang:** Conceptualization, Methodology, Data curation. **Jun-Yong Choi:** Conceptualization, Methodology, Investigation, Project administration, Supervision, Writing - review & editing.

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