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Efficacy and safety of GHX02 in the treatment of acute bronchitis: protocol of a phase 2, double-blind, randomized placebo-controlled trial

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ABSTRACT

Introduction: Acute bronchitis is a self-limiting infection of the large airways; cough is the primary symptom, usually lasting for about 3 weeks. Annually, approximately 5% of adults develop acute bronchitis, and its economic burden is substantial. There are also problems of antibiotic abuse associated with the treatment of acute bronchitis in public health systems, despite up to 90% of acute bronchitis cases being caused by viruses. Symptomatic therapies are commonly prescribed, for which there is insufficient supporting evidence. GHX02 contains four herbs originating from *gualouhengryunhwan*, which has been used in the treatment of acute bronchitis patients in Korea. The objective is to compare the GHX02 and placebo in terms of efficacy and safety, and to determine the appropriate dosage.

Methods and analysis: We planned a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial of two different doses of GHX02 compared with placebo. A total of 150 patients, aged between 17 and 75, with a Bronchitis Severity Score (BSS)≥5 due to acute bronchitis starting within 2 weeks of study enrolment will be recruited from three university-affiliated hospitals across Korea. Participants will be randomly assigned to either a high-dose GHX02 group(1,920mg/day), a standard-dose GHX02 group(960mg/day), or a placebo group according to a 1:1:1 allocation ratio using stratification block randomization with pattern identification. Patients will take medications three times daily for 7 days, with 3 visiting days. The primary outcome measure is a change in BSS from day 0 to day 7. The secondary outcomes are the Questionnaire of Clinical Symptoms of Cough and Sputum, Leicester Cough Questionnaire, frequency of coughing fits, Integrative Medicine Outcome Scale and the Integrative Medicine Patient Satisfaction Scale.

Ethics and dissemination: The study has been approved by our Institutional Review Board. (No. DJDSKH-17-DR-14) The trial results will be disseminated via peer-reviewed journals and the Clinical Research Information Service. Trial registration: NCT03310385

KEY WORDS: acute bronchitis, herbal medicine, GHX02, randomized controlled trial

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study will provide new evidence for the efficacy and safety of GHX02 in a standard

research design

- We will use the Korean Standard Tool of Pattern Identifications of Cough and Sputum, via stratified block randomization
- This is a well-designed study and the outcome measures are well balanced between patients' subjective and objective outcomes
- Multicentre study
- Limitation is that this trial protocol only targets adults

INTRODUCTION

Acute bronchitis is the most common disease seen in outpatient departments (OPDs) across South Korea; about 5% of the general population have acute bronchitis.[1] In 2016, the Health Insurance Review & Assessment Service of South Korea estimated that more than 1500 million people visited OPDs for acute bronchitis and that the rate of increase in medical expenses, compared to that over the previous year, also rose.[2] Thus, acute bronchitis represents a substantial economic burden on the public health system, and effective therapeutic agents are urgently required.[3]

Acute bronchitis is a self-limiting infection of the large airways, with cough as the primary symptom, usually lasting for about 3 weeks.[4] It is characterized by acute onset of cough, accompanied by the production of sputum and dyspnea or chest discomfort.[5] As there are no specific diagnostic criteria for acute bronchitis, diagnosis is primarily clinical and requires a thorough assessment to differentiate from pneumonia, common cold, and asthma.[6] Up to 90% of acute bronchitis is caused by viruses; bacterial infection accounts only for less than 10%. Nevertheless, 60–80% of patients, despite evidence of little or no benefit, are treated with antibiotics, contributing to bacterial resistance associated with multiple adverse effects.[7] Several guidelines and meta-analyses of randomized controlled trials(RCTs) have concluded that antibiotic treatment is mostly ineffective in acute bronchitis, unless the infection is of bacterial origin.[8]

As antibiotics are generally not recommended for acute bronchitis, symptomatic therapy such as antitussives, expectorants, beta-2 agonists, and alternative therapies are commonly prescribed, despite insufficient evidence to support such treatments. There have been the lack of consistent evidence for their use of antitussives on acute bronchitis,[9] and the evidence regarding the use of expectorants is also questionable.[10] Beta-2 agonists are reported to be effective for patients with airflow obstruction, but adverse events like tremor and nervousness are widely observed.[11]

Alternative therapies, like *Pelargonium sidodes* or ivy leaf extracts are used in various European countries, with variable results.[12 13]

Thus, there have been substantial efforts worldwide to develop effective therapeutic agents for treating acute bronchitis. In this study, we focused on herbal medicines that have been used for centuries in Oriental countries; we sought to evaluate the efficacy and safety of GHX02, which contains four herbs originating from *gualouhengryunhwan* (GLHRH) in Donguibogam (Principles and Practice of Eastern Medicine) (Table 1). GHX02 has been used for the treatment of patients with acute bronchitis in the Dunsan Korean Medicine Hospital, Daejeon University, and its effectiveness against acute cough has already been demonstrated. We planned a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial of two different doses of GHX02 compared with placebo. The objective is to compare the GHX02 and placebo in terms of efficacy and safety, and to determine the appropriate dosage of GHX02 required for the treatment of acute bronchitis. We chose a placebo as the control, as this is the most rigorous test for evaluating the efficacy of new medical therapy in a double-blind RCT.[14] In addition, as acute bronchitis is a self-limiting disorder, placebo control is ethically justifiable.

Table 1. Components of GHX02

Herb	Latin name	Family name	Part of plant	Amount
Gualouin	*Trichosanthis Semen*	Cucurbitaceae	seed	351mg
Hengin	*Armeniacae Semen*	Rosaceae	seed	175.5mg
Hwangryun	*Coptidis Rhizoma*	Ranunculaceae	root stock	175.5mg
Hwangkum	*Scutellariae Radix*	Labiatae/Lamiaceae	root	351mg

METHODS AND ANALYSIS

Trial Design

This study is a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial to evaluate the efficacy and safety of two different doses of GHX02, compared with placebo, for acute bronchitis. The trial will be conducted at three university-affiliated hospitals, including the Dunsan Korean Medicine Hospital, Daejeon University; the Kyunghee University Korean

Medicine Hospital; and the Pusan National University Korean Medicine Hospital which have been listed on advertising posters. One-hundred and fifty patients will be included in this trial and randomly assigned to either a high-dose GHX02 group (1920mg/day), standard-dose GHX02 group (960mg/day), or control group (placebo) in a 1:1:1 allocation ratio. Patients will take one of the medications three times a day for 7 days, with 3 visiting days (screening, day0, day7). On the screening day, we will use the Korean Standard Tool of Pattern Identification of Cough and Sputum, a diagnostic system that determines therapy in Traditional Korean Medicine, to allocate patients into three groups of *wind-heat, wind-cold* or *others* (Figure1, Table2). This follows the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[15], Reporting Randomized, Controlled Trials of Herbal Interventions[16] and the trial will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Table2. Timetable of study period

	STUDY PERIOD			
	Enrolment	**Allocation**	**Post-allocation**	
TIMEPOINT	screening	Day 0	Day 0	Day 7
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Demographic data	X			
Vital signs	X		X	X
Past history	X			
Concomitant medication	X		X	X
Physical examination & radiography	X			
Laboratory examination	X			X
Pattern identification of cough & sputum	X			
Allocation		X		
INTERVENTIONS:				
High-dose GHX02			←	→
Standard-dose GHX02			←	→
Placebo			←	→
ASSESSMENTS:				
BSS	X		X	X
QCSCS			X	X
LCQ-K-acute			X	X
Frequency of cough fits			←	→
IMOS, IMPSS				X
Concomitant therapy			X	X

Adverse events			X	X
Compliance				X

BSS, Bronchitis Severity Score; QCSCS, Questionnaire on Clinical Symptoms of Cough & Sputum; LCQ-K-acute, Leicester Cough Questionnaire-Korean version-acute; IMOS, Integrative Medicine Outcome Scale; IMPSS, Integrative Medicine Patient Satisfaction Scale

Study Drug and Placebo

GHX02 is a combination of the following four herbs: Gualouin (*Trichosanthis Semen*, 351 mg/tablet), Hengin (*Armeniacae Semen*, 175.5 mg/tablet), Hwangryun (*Coptidis Rhizoma*, 175.5 mg/tablet), Hwangkum (*Scutellariae Radix*, 351 mg/tablet) (Table 1). One GHX02 tablet (500mg/tablet) contains 160.0mg of dry extract of the four herbs (obtained by boiling in water and then dehydrating) mixed with 340.0mg of starch and lactose. The placebo tablet does not contain any of these active ingredients but is matched in terms of colour, smell, and taste. The dosage was determined according to the Pharmacologically Active Dose (PAD) in expectorant effective tests. Both tablets are green and round and will be provided by Hankookshinyak Corporation (Nonsan, Korea). The manufacturer complies with the provisions of the Regulations on the Safety of Pharmaceuticals and will manage the quality appropriately. Safety and toxicological tests of GHX02 will be conducted simultaneously. All allocated patients will be prescribed 4 tablets of either the clinical medicine or placebo to be administered three times daily for 7 days, and the number of remaining tablets will be recorded on day7 to calculate compliance. To improve compliance, participants will be asked to record their daily dosage in the cough diary. The overall medication compliance during the trial should be at least 75%; if the medication compliance is less than 75%, the participant will be considered inadequate and excluded from the per-protocol (PP) analysis group.

Sample size

According to the previous study, the estimated sample size required for this study is 150 patients (50 patients per group). This estimation is based on the Bronchitis Severity Score (BSS) of 2.3 ± 3.2 (mean ± standard deviation; day 0-day 7), obtained from an earlier study.[17] Moreover, to provide 90% power with a two-tailed level of significance of 5% at a ratio of 1:1:1 and dropout rate of 20%, we plan to include 150 patients.

Recruitment

Participants will be recruited from the outpatient departments (OPDs) of the affiliated hospitals and through poster advertisements. Recruitment will commence in January 2018.

Participants

Inclusion criteria

Potential participants who meet the following criteria will be included in this trial: (1) age 19–75 years; (2) BSS ≥ 5 points at day0 due to acute bronchitis; (3) symptoms starting within 2 weeks before study inclusion; (4) patients who consent to participate. Diagnoses of acute bronchitis will be based on patients' medical history, physical examinations, and BSS, including cough, sputum, dyspnea, chest pain during coughing, and rales on auscultation.

Exclusion criteria

Patients with any of the following criteria will be excluded from this trial: (1) pregnant or breast-feeding; (2) treatment with antibiotics, bronchodilators, glucocorticoids, immune-depressants, or other clinical trial medicines during the last 4 weeks before study inclusion; (3) treatment with antitussives or expectorants during the last 7 days before study inclusion; (4) history or presence of confounding respiratory disease that may affect evaluation of the efficacy of clinical medicine (e.g. chronic bronchitis, chronic obstructive pulmonary disease (COPD), bronchiectasis, asthma, pneumonia, cystic fibrosis, lung cancer, or active pulmonary tuberculosis); (5) liver or renal impairment (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] ≥ 2 times the normal upper limit, or creatinine> 3.0 mg/dL at screening); (6) history or presence of clinically relevant cardiovascular, renal, metabolic, haematological, neurological, psychiatric, systemic, infectious disease, or malignant tumour (except where there is no recurrence for more than 5 years after surgery); (7) history of alcoholism or substance abuse; (8) participation in other clinical medicine trials during the last 30 days before study inclusion; (9) judged by the investigators to be inappropriate for the clinical trial. Additional treatment will not

be permitted during the trial, and participants are recommended not to alter their exercise pattern or diet. Drugs that may affect bronchitis symptoms or that have a similar therapeutic purpose to the trial medication will not be permitted, including antibiotics, bronchodilators, glucocorticoids, immune-depressants, antitussives, expectorants, antihistamines, or any other clinical trial medicine. Other medications will only be permitted at the discretion of the investigators. All drug information (name of product, purpose of administration, dosage, duration of administration, etc.) will be recorded on the patient case report form (CRF).

Randomization and allocation concealment

Randomization will be conducted by an independent statistician, using a computer random number generator of SAS® Analytics Pro (SAS Institute, Inc., Cary, North Carolina, USA). The generated randomization numbers will be concealed using sequentially numbered, opaque, sealed envelopes. Stratified block randomization using the Korean Standard Tool of Pattern Identifications of Cough and Sputum will be performed in this trial. We will allocate three groups (*wind-heat, wind-cold,* or *others*) at a 1:1:1 ratio of high-dose, standard-dose, and placebo treatment. Allocation will be implemented by a management pharmacist with no other trial involvement to ensure that neither the participants nor the investigators can foresee group allocation. After participants are deemed eligible, investigators will inform the management pharmacist. Participants will then be given an envelope according to their screening sequential number and assigned to either the intervention or control group.

Korean Standard Tool of Pattern Identifications of Cough and Sputum

The Korean Standard Tool of Pattern Identifications of Cough and Sputum is used to identify patterns of acute bronchitis patients. It was proposed in the Traditional Korean Medicine Clinical Practice Guidelines for Antitussives and Expectorants for Korean Medical Diagnostic Standards. This comprises 56 items to classify cases into three patterns: *wind-cold, wind-heat* or *others*. We will investigate the correlation between the patterns and the efficacy of GHX02.

Blinding

This is a double-blind trial, thus neither participants nor investigators (including outcome assessors) will be aware of group assignment until the end of the study period. Placebo tablets will be matched to GHX02 tablets in terms of colour, taste, and smell, as well as outer packaging. Elimination of blindness will only be considered in cases of serious medical emergencies.

Outcome measures

Primary outcome

Bronchitis Severity Score

The BSS was developed as an evaluation tool for acute bronchitis in 1996 and was recently shown to be valid and reliable by the European Medicines Agency's Committee on Herbal Medicinal Products (HMPC).[15] It has been used successfully in many clinical trials for acute bronchitis. BSS comprises the sum of five major symptom scores for acute bronchitis: cough, sputum, dyspnea, chest pain during coughing, and rales on auscultation. Each symptom is scored on a 4-point-scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe), with a maximum total score of 20 points. The investigator assesses symptom scores on the basis of the patient's subjective symptoms, and this correlates highly with the patient's actual improvement, as acute bronchitis mainly involves subjective complaints.[18] BSS will be evaluated three times, at screening, day 0 and day 7. The change in BSS between day 0 and day 7 will be the primary outcome of this trial.

Secondary outcomes

Acute bronchitis predominantly depends on subjective tools, but more reliable data can be derived if appropriate objective variables are used together. Symptom and quality of life (QOL) questionnaires will be used as subjective tools, whereas cough frequency will be used as an objective tool; among outcome measures of cough symptoms, only cough frequency and quality of life questionnaires have been shown to be valid.[19]

Questionnaire of Clinical Symptoms of Cough and Sputum

The Questionnaire of Clinical Symptoms of Cough and Sputum was proposed as a primary outcome measure in the Traditional Korean Medicine Clinical Practice Guidelines for Antitussives and Expectorants and was developed by remodelling the Clinical Asthma Measurement Scale in Oriental Medicine-V for cough and sputum.[20] It is also appropriate for preparing clinical trials of GHX02 as an IND(Investigational New Drug), as it is the suggested tool in Clinical Practice Guidelines from the Ministry of Food and Drug Safety in Korea. Questionnaire items are as follows: (1) cough –frequency, intensity, sensitivity; (2) sputum –frequency, volume, difficulty to cough-up, appearance, colour; (3) activities of daily living; (4) night-time sleeping. Each item is scored on a 4-point-scale, with a total maximum score of 40 points. This questionnaire can evaluate symptoms of cough and sputum more specifically and in more detail than the BSS.

Leicester Cough Questionnaire

The Leicester Cough Questionnaire (LCQ-K-acute) evaluates quality of life associated with cough. It consists of 19 items divided into three parts, physical, psychological, and social, each scored from 1 to 7. The total score is the sum of the average scores(1–7 points) for each part. The higher the score, the better the quality of life. Although it was initially developed as an assessment tool for chronic cough, it has also been found to be useful for acute cough, by changing the time criteria from 2 weeks to 24 hours.[21] In addition, the validity and reliability of the Korean version of the LCQ(LCQ-K) has already been verified.[22]

Frequency of coughing fits

Coughing frequency is an objective measurement tool for evaluating coughing. In this trial, we will ask participants to record how often they cough each day. A cough diary will be given to record their everyday coughing frequency, and participants will be classified into one of the following scales: 0 = 0 time/day, 1 = 1time/day, 2 = 2-3 times/day, 3 = 4-5 times/day(sometimes), 4 = 6-10 times/day(frequent), 5 = over 15 times/day(consistently).[23]

Integrative Medicine Outcome Scale and Integrative Medicine Patient Satisfaction Scale

The Integrative Medicine Outcome Scale is a 5-point-scale for evaluating improvement after treatment (where, 1=complete recovery, 2=major improvement, 3=slight-to-moderate improvement, 4=no change, 5=deterioration), either by the patient or investigator (the investigator in this trial). The Integrative Medicine Patient Satisfaction Scale is a 5-point-scale for evaluating patient satisfaction with the treatment (where, 1=very satisfied, 2=satisfied, 3=neutral, 4=dissatisfied, 5=very dissatisfied).[15] Both will be measured at the patients' final visit (day7). As many other clinical trials of acute bronchitis use these tools to measure overall improvement and satisfaction, using them will enable us to make direct comparisons with other medicines.

Safety assessment

Safety will be assessed in terms of adverse events (AEs), vital signs, and laboratory examinations (liver function test and routine blood and urine tests). AEs and vital signs will be recorded on a CRF at every visit, and laboratory examinations will be conducted before and after taking the medication. AEs will be defined as every unexpected sign or symptom during the trial period. All information about AEs will be recorded in detail, such as the duration and extent of the AE, relationship with the trial medicine, name of the suspected drug, etc. Common adverse events may include gastrointestinal side-effects, such as anorexia, stomach discomfort, nausea, and diarrhoea, which are not expected to be severe. However, if serious AEs occur that may lead to death or require extended hospitalization, the patient will be removed from the clinical trial as soon as possible and proper treatment will be provided (Table 2).

Data management and monitoring

The investigators will follow the Standard Operating Procedures (SOP) of the trial for a better quality of assessment and collection of outcome data. The investigators should be restricted to only physicians who have attended training meetings and can evaluate outcome measures, except for questionnaires. All assessment data and case reports will be collected at baseline (day 0) and at the end of the trial (day 7) in both the intervention and control groups. Collected documents and data will be managed by electronic CRF and encrypted using double data entry. Only the

principle investigator, or those who have permission, will be able to access the data. The original paper versions of the CRFs and other documents will be stored at a separate and secure location for 10 years after trial completion.

Multicentre clinical trial monitoring will be conducted via regular visits (every one-fourth of recruitment) and occasional telephone calls. The information collected will be reported to the data monitoring committee (DMC), comprising specialists in pulmonology and medical statistics who are unrelated to the trial. At visits, a monitor will confirm whether the trial is being conducted in accordance with the protocol and AEs are being properly reported and recorded on CRFs. The monitor will check the whole progress of the clinical trial and problems will be discussed with the investigator as and when they occur.

Statistical analysis

Data analysis will be performed by an independent statistician using SAS® Analytics Pro. Efficacy evaluation will be based on intention-to-treat (ITT) analysis, according to PP analysis. ITT analysis will be conducted for all randomized participants who took the trial medicine at least once, and PP analysis will be conducted for those who completed the entire trial without violating the protocol. To handle missing values when processing ITT analysis, the last-observation-carried-forward (LOCF) method and multiple imputation will be used. For primary outcome analysis, the change in BSS between day0 and day7 will be evaluated using analysis of covariance. Significance will be accepted at a two-sided α-level of 0.05. For continuous variables, 95% confidence intervals (CIs) will be calculated. Analyses of secondary outcomes will follow the same methods.

Safety assessment will be performed by ITT analysis; all participants will be included. Comparison between the number of adverse events associated with intervention and the control treatments will be performed using Kruskal-Wallis tests. Demographic and baseline data will be analysed using independent two-sample *t*-tests for continuous variables, and Pearson's chi-squared or Fisher's exact tests for categorical variables.

ETHICS AND DISSEMINATION

The trial protocol (version 1.0) has been approved by the Institutional Review Board (IRB) of the Dunsan Korean Medicine Hospital, Daejeon University. (No. DJDSKH-17-DR-14) If the protocol needs modifications, the investigators are required to inform the IRB (as well as participants) and receive re-approval. Before the trial, investigators are required to provide all information related to the clinical trial, including the possible benefits and risks, other therapeutic choices, and right to withdraw, via a written consent form approved by the IRB. After being provided with sufficient time and opportunity to ask questions and decide whether to participate, all participants are required to provide written consent before study inclusion. All patient identifiable data will be kept confidential, even when the results of the trial are published and participant information will be stored in a secure file, and only the primary investigator (including those who have permission) and the monitor will have access to the data. To ensure confidentiality, all clinical trial documents, such as CRFs, will be recorded and distinguished by the participant identification number throughout the trial. At the end of the trial, the study results will be disseminated via peer-reviewed journals, conference presentation and the Clinical Research Information Service; the participants will also be informed of the results, even unpublished data, including missing data.

DISCUSSION

Despite problems associated with antibiotic abuse in public health systems and the substantial economic burden associated with acute bronchitis, currently no definitive medication is recommended. There are many studies exploring the efficacy of herbal medicines; a systematic review concluded that there was insufficient evidence to support the use of Chinese herbs for acute bronchitis because of the high risk of bias and lack of toxicological evidence.[24] This study is a multicentre, double-blind, randomized placebo-controlled trial to evaluate the efficacy and safety of two different doses of GHX02, compared with placebo, for acute bronchitis, and we followed strict quality control methods. To ensure a well-designed trial, we conducted a systemic review of randomized controlled trials for acute bronchitis in the last 10 years.[25]

There are some strengths and limitations to this protocol. Contrary to other trials, we will use the Korean Standard Tool of Pattern Identifications of Cough and Sputum, which is a Korean Medical Diagnostic Standard for categorizing cases, to obtain additional information as to whether a certain categories of patients respond better than others to treatment. In this way, we will be able

to investigate the efficacy of GHX02 for a more specific groups of people suffering from acute bronchitis. Another strength is that the outcome measures we will use in this trial is well balanced between patients' subjective and objective outcomes; thus, the effectiveness of GHX02 will be demonstrated from various aspects. As GHX02 is an herbal prescription which has already been used for acute bronchitis, there is little risk of side-effects and the efficacy of GHX02 is already proven by empirical evidence. This study will provide new evidence for the efficacy and safety of GHX02 in a standard research design and is expected to be presented as a recommended alternative medicine for acute bronchitis.

A limitation of this trial protocol is that we will only target adults, despite most acute bronchitis patients being children under 5 years. As clinical drug trials are recommended to be first applied to adults, we selected adults aged between 17 and 75 years. Further studies among children will need to be conducted after completion of this study.

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Contributors

YRL drafted the research protocol and wrote the manuscript. WKY, SJP, SHK were involved in the protocol development. WK contributed to the statistical design and analysis. ICJ and YCP supervised this protocol. All authors contributed to the conception and implementation of this clinical trial.

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Competing interests

None declared.

Ethics approval

The protocol was approved by the Institutional Review Board of Dunsan Korean Medicine Hospital, Daejeon University.

Provenance and peer review

Not commissioned; externally peer reviewed.

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FIGURE LEGENDS

Figure 1. Flowchart of the study procedure

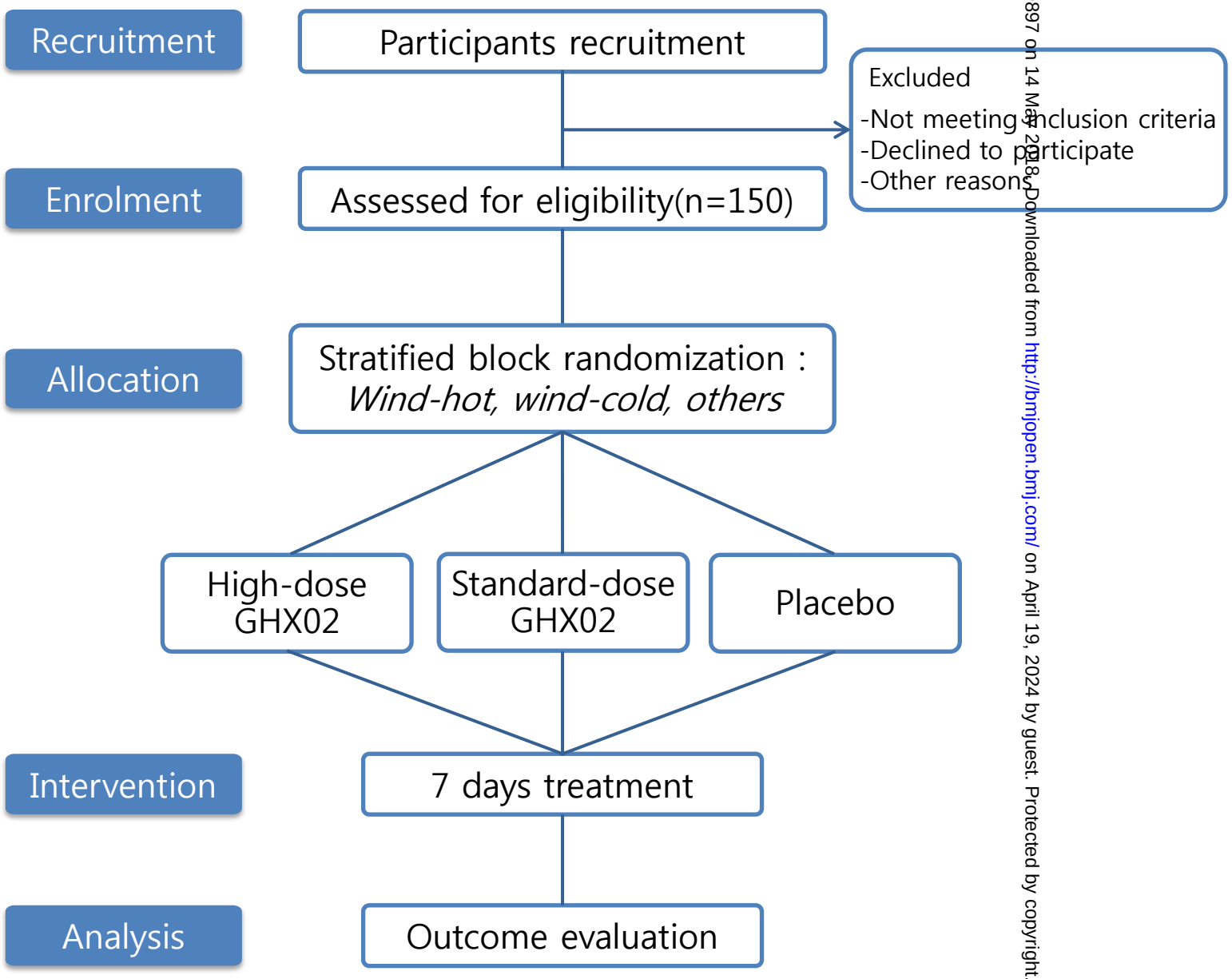

Figure1. Flowchart of the study procedure

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____p.1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ p.12-13___
	2b	All items from the World Health Organization Trial Registration Data Set	_____ p.1_____
Protocol version	3	Date and version identifier	_____p.12_____
Funding	4	Sources and types of financial, material, and other support	_____ p.14_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____ p.14_____
	5b	Name and contact information for the trial sponsor	_____ p.14_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____ p.14_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____p.11-12____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____p.3-4_____
	6b	Explanation for choice of comparators	____p.4 _____
Objectives	7	Specific objectives or hypotheses	____p.4_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____p.4-5_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____ p.4-5_ ____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____ p.7-8_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____p.6_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____p.9, 11 ___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____p.6, 11_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____p.7-8_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____p.9-11_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____p.4-6_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____p.6_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____p.7_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____p.8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____p.8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____p.8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____p.8-9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____p.8-9 ____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____p.11-12___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____p.11_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____p.11-12___
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___ p.12 _____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____p.12_ ____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____p.12_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____p.12_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____p.12____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____p.11-12__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____p.12_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____p.12-13_ _
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____p.12-13___

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____p.13_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____p.13_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____p.13_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____p.13_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____p.13_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____p.13_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ p.13_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____ p.13_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____p.13_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____p.12____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____p.10-11_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy and safety of GHX02 in the treatment of acute bronchitis: protocol of a phase 2, double-blind, randomized placebo-controlled trial

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Efficacy and safety of GHX02 in the treatment of acute bronchitis: protocol of a phase 2, double-blind, randomized placebo-controlled trial

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ABSTRACT

Introduction: Acute bronchitis is a self-limiting infection of the large airways; cough is the primary symptom, usually lasting for about 3 weeks. Annually, approximately 5% of adults develop acute bronchitis, and its economic burden is substantial. There are also problems of antibiotic abuse in public health systems and symptomatic therapies are commonly prescribed, for which there is insufficient supporting evidence. GHX02 contains four herbs originating from *gwaruhaengryeon-hwan*, which has been used in the treatment of acute bronchitis patients in Korea. The objective is to compare the GHX02 and placebo in terms of efficacy and safety, and to determine the appropriate dosage.

Methods and analysis: We planned a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial of two different doses of GHX02 compared with placebo. A total of 150 patients, aged 19-75 years, with a Bronchitis Severity Score (BSS)≥5 due to acute bronchitis starting within 2 weeks of study enrolment will be recruited from three university-affiliated hospitals across Korea. Participants will be randomly assigned to either a high-dose GHX02 group(1,920mg/day), a standard-dose GHX02 group(960mg/day), or a placebo group according to a 1:1:1 allocation ratio using stratification block randomization with pattern identification. Patients will take medications three times daily for 7 days, with 2 visiting days. The primary outcome measure is a change in BSS from day0 to day7. The secondary outcomes are the Questionnaire of Clinical Symptoms of Cough and Sputum, Leicester Cough Questionnaire, frequency of coughing fits, Integrative Medicine Outcome Scale, Integrative Medicine Patient Satisfaction Scale and withdrawal rate of patients with exacerbation. Safety will be assessed by adverse events, vital signs, and laboratory examinations.

Ethics and dissemination: The study has been approved by our Institutional Review Board (No. DJDSKH-17-DR-14). The trial results will be disseminated via peer-reviewed journals and the Clinical Research Information Service.

Trial registration number: NCT03310385

KEY WORDS: acute bronchitis, herbal medicine, GHX02, randomized controlled trial

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study will provide new evidence for the efficacy and safety of GHX02 in a standard research design

- We will use the Korean Standard Tool of Pattern Identifications of Cough and Sputum, via stratified block randomization
- This is a well-designed study and the outcome measures are well balanced between patients' subjective and objective outcomes
- Limitation is that this trial protocol only targets adults
- The trial period is brief to check the complete recovery form the disease

INTRODUCTION

Acute bronchitis is the most common disease seen in outpatient departments (OPDs) across South Korea; about 5% of the general population have acute bronchitis.[1] In 2016, the Health Insurance Review & Assessment Service of South Korea estimated that more than 1500 million people visited OPDs for acute bronchitis and that the rate of increase in medical expenses, compared to that over the previous year, also rose.[2] Thus, acute bronchitis represents a substantial economic burden on the public health system, and effective therapeutic agents are urgently required.[3]

Acute bronchitis is a self-limiting infection of the large airways, with cough as the primary symptom, usually lasting for about 3 weeks.[4] It is characterized by acute onset of cough, accompanied by the production of sputum and dyspnea or chest discomfort.[5] As there are no specific diagnostic criteria for acute bronchitis, diagnosis is primarily clinical and requires a thorough assessment to differentiate from pneumonia, common cold, and asthma.[6] Up to 90% of acute bronchitis is caused by viruses; bacterial infection accounts only for less than 10%. Nevertheless, 60–80% of patients, despite evidence of little or no benefit, are treated with antibiotics, contributing to bacterial resistance associated with multiple adverse effects.[7] Several guidelines and meta-analyses of randomized controlled trials (RCTs) have concluded that antibiotic treatment is mostly ineffective in acute bronchitis, unless the infection is of bacterial origin.[8]

As antibiotics are generally not recommended for acute bronchitis, symptomatic therapy such as antitussives, expectorants, beta-2 agonists, and alternative therapies are commonly prescribed, despite insufficient evidence to support such treatments. There have been the lack of consistent evidence for their use of antitussives on acute bronchitis,[9] and the evidence regarding the use of expectorants is also questionable.[10] Beta-2 agonists are reported to be effective for patients with airflow obstruction, but adverse events like tremor and nervousness are widely observed.[11] Moreover, the Cochrane Reviews suggested a lack of evidence to recommend the use of Chinese

herbs in the treatment of acute bronchitis[12] and other alternative therapies, like *Pelargonium sidodes* or ivy leaf extracts are used in various European countries, with variable results.[13 14]

Thus, there have been substantial efforts worldwide to develop effective therapeutic agents for treating acute bronchitis. In this study, we focused on herbal medicines that have been used for centuries in Oriental countries; we sought to evaluate the efficacy and safety of GHX02, which contains four herbs originating from *gwaruhaengryeon-hwan* (GRHRH) in Donguibogam (Principles and Practice of Eastern Medicine) (Table1). GHX02 has been used for the treatment of patients with acute bronchitis in the Dunsan Korean Medicine Hospital, Daejeon University, and its effectiveness against acute cough has already been demonstrated. We planned a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial of two different doses of GHX02 compared with placebo. The objective is to compare the GHX02 and placebo in terms of efficacy and safety, and to determine the appropriate dosage of GHX02 required for the treatment of acute bronchitis. We chose a placebo as the control, as this is the most rigorous test for evaluating the efficacy of new medical therapy in a double-blind RCT.[15] In addition, as acute bronchitis is a self-limiting disorder, placebo control is ethically justifiable.

Table1. Components of GHX02

Herb	Latin name	Family name	Part of plant	Amount
Gwaruin	*Trichosanthis Semen*	Cucurbitaceae	Seed	351mg
Haengin	*Armeniacae Semen*	Rosaceae	Seed	175.5mg
Hwangryeon	*Coptidis Rhizoma*	Ranunculaceae	Root stock	175.5mg
Hwangkeum	*Scutellariae Radix*	Labiatae/Lamiacea	Root	351mg

METHODS AND ANALYSIS

Trial Design

This study is a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial to evaluate the efficacy and safety of two different doses of GHX02, compared with placebo, for acute bronchitis. The trial will be conducted at three university-affiliated hospitals, including the Dunsan Korean Medicine Hospital, Daejeon University; the Kyunghee University Korean

Medicine Hospital; and the Pusan National University Korean Medicine Hospital. One-hundred and fifty patients will be included in this trial and randomly assigned to either a high-dose GHX02 group (1920mg/day), standard-dose GHX02 group (960mg/day), or control group (placebo) in a 1:1:1 allocation ratio. Patients will take one of the medications three times a day for 7 days, with 2 visiting days (day0, day7). On the screening day, we will use the Korean Standard Tool of Pattern Identification of Cough and Sputum, a diagnostic criterion that determines therapy in Traditional Korean Medicine, to allocate patients into three groups of *wind-heat, wind-cold* or *others* (Figure1, Table2). This follows the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[16], Reporting Randomized, Controlled Trials of Herbal Interventions[17] and the trial will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and Consolidated Standards of Reporting Trials (CONSORT) guidelines.[18]

Table2. Timetable of study period

	STUDY PERIOD			
	Enrolment	**Allocation**	**Post-allocation**	
TIMEPOINT	screening	Day 0	Day 0	Day 7
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Demographic data	X			
Vital signs	X		X	X
Past history	X			
Concomitant medication	X		X	X
Physical examination & radiography	X			
Laboratory examination	X			X
Pattern identification of cough & sputum	X			
Allocation		X		
INTERVENTIONS:				
High-dose GHX02			←	→
Standard-dose GHX02			←	→
Placebo			←	→
ASSESSMENTS:				
BSS	X		X	X
QCSCS			X	X
LCQ-K-acute			X	X
Frequency of cough fits			←	→
IMOS, IMPSS				X

Withdrawal rate of patients with exacerbation				X
Concomitant therapy			X	X
Adverse events			X	X
Compliance				X

BSS, Bronchitis Severity Score; QCSCS, Questionnaire on Clinical Symptoms of Cough & Sputum; LCQ-K-acute, Leicester Cough Questionnaire-Korean version-acute; IMOS, Integrative Medicine Outcome Scale; IMPSS, Integrative Medicine Patient Satisfaction Scale

Study Drug and Placebo

GHX02 is a combination of the following four herbs: Gwaruin (*Trichosanthis Semen*, 351 mg/tablet), Haengin (*Armeniacae Semen*, 175.5 mg/tablet), Hwangryeon (*Coptidis Rhizoma*, 175.5 mg/tablet), Hwangkeum (*Scutellariae Radix,* 351 mg/tablet) (Table1). One GHX02 tablet (500mg/tablet) contains 160.0mg of dry extract of the four herbs (obtained by boiling in water and then dehydrating) mixed with 340.0mg of starch and lactose. The placebo tablet does not contain any of these active ingredients but is matched in terms of colour, smell, and taste. The dosage was determined according to the Pharmacologically Active Dose (PAD) in expectorant effective tests. Both tablets are pink and round and will be provided by Hankookshinyak Corporation (Nonsan, Korea). The manufacturer complies with the provisions of the Regulations on the Safety of Pharmaceuticals and will manage the quality appropriately. Safety and toxicological tests of GHX02 will be conducted simultaneously. All allocated patients will be prescribed 4 tablets of either the clinical medicine or placebo to be administered three times daily for 7 days, and the number of remaining tablets will be recorded on day 7 to calculate compliance. To improve compliance, participants will be asked to record their daily dosage in the cough diary. The overall medication compliance during the trial should be at least 75%; if the medication compliance is less than 75%, the participant will be considered inadequate and excluded from the per-protocol (PP) analysis group.

Sample size

The estimated sample size required for this study is 150 patients (50 patients per group).[19] The estimation of the number of subjects is based on whether there is a difference in the change from baseline (day 0) to post-dose (day 7) BSS, between the control and standard-dose GHX02 group.

In an earlier comparable clinical study, the difference was reported to be 2.3, and the standard deviation of the changes in BSS, was estimated to be 3.2.[20] The power to detect the difference was assumed to be 0.8, and the two-sided significance level was 0.05. The ratio of allocation of subjects between the groups was 1:1:1, and dropout rate was presumed to be 0.2.

Recruitment

Participants will be recruited from the outpatient departments (OPDs) of the affiliated hospitals. Recruitment will commence in January 2018.

Participants

Inclusion criteria

Potential participants who meet the following criteria will be included in this trial: (1) age 19–75 years; (2) BSS ≥ 5 points at day 0 due to acute bronchitis; (3) symptoms starting within 2 weeks before study inclusion; (4) patients who consent to participate. Diagnoses of acute bronchitis will be based on patients' medical history, physical examinations, and BSS, including cough, sputum, dyspnea, chest pain during coughing, and rales on auscultation.

Exclusion criteria

Patients with any of the following criteria will be excluded from this trial: (1) pregnant or breast-feeding; (2) treatment with antibiotics, bronchodilators, glucocorticoids, immune-depressants, or other clinical trial medicines during the last 4 weeks before study inclusion; (3) treatment with antitussives or expectorants during the last 7 days before study inclusion; (4) history or presence of confounding respiratory disease that may affect evaluation of the efficacy of clinical medicine (e.g. chronic bronchitis, chronic obstructive pulmonary disease (COPD), bronchiectasis, asthma, pneumonia, cystic fibrosis, lung cancer, or active pulmonary tuberculosis); (5) liver or renal impairment (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] ≥ 2 times the normal upper limit, or creatinine> 3.0 mg/dL at screening); (6)

history or presence of clinically relevant cardiovascular, renal, metabolic, haematological, neurological, psychiatric, systemic, infectious disease, or malignant tumour (except where there is no recurrence for more than 5 years after surgery); (7) genetic problems such as galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption; (8) history of alcoholism or substance abuse; (9) participation in other clinical medicine trials during the last 30 days before study inclusion; (10) judged by the investigators to be inappropriate for the clinical trial. Additional treatment will not be permitted during the trial, and participants are recommended not to alter their exercise pattern or diet. Drugs that may affect bronchitis symptoms or that have a similar therapeutic purpose to the trial medication will not be permitted, including antibiotics, bronchodilators, glucocorticoids, immune-depressants, antitussives, expectorants or any other clinical trial medicine. Those who require or take these concomitant medicines during the trial will be excluded from this study. Other medications will only be permitted at the discretion of the investigators. All drug information (name of product, purpose of administration, dosage, duration of administration, etc.) will be recorded on the patient case report form (CRF).

Randomization and allocation concealment

An independent statistician will conduct randomization, using a computer random number generator of SAS® Analytics Pro (SAS Institute, Inc., Cary, North Carolina, USA). Allocation will be implemented by the manufacturers who collectively label serial numbers, by generating randomized numbers and handing over the sealed set to the management pharmacist. When the investigator requests for medication, the management pharmacist gives the participant a test drug or a placebo corresponding to the participant's identification code. We will allocate three groups (*wind-heat, wind-cold,* or *others*) at a 1:1:1 ratio of high-dose, standard-dose, and placebo treatment. Stratified block randomization using the Korean Standard Tool of Pattern Identifications of Cough and Sputum will be performed in this trial.

Korean Standard Tool of Pattern Identifications of Cough and Sputum

The Korean Standard Tool of Pattern Identifications of Cough and Sputum is used to identify patterns of acute bronchitis patients. This pattern identification is an important diagnostic criterion

in Korean medicine which is used for deciding medication and other therapies. It was proposed in the Traditional Korean Medicine Clinical Practice Guidelines for Antitussives and Expectorants for Korean Medical Diagnostic Standards.[21] This comprises 56 items to classify cases into three patterns: *wind-cold, wind-heat* or *others*. We will investigate the correlation between the patterns and the efficacy of GHX02; the *wind-heat* patterns group is expected to show greater response than the other groups to the therapeutic effects of GHX02.

Blinding

This is a double-blind trial, thus neither participants nor investigators (including outcome assessors) will be aware of group assignment until the end of the study period. Placebo tablets will be matched to GHX02 tablets in terms of colour, taste, and smell, as well as outer packaging. Elimination of blindness will only be considered in cases of serious medical emergencies.

Outcome measures

Primary outcome

Bronchitis Severity Score

The BSS was developed as an evaluation tool for acute bronchitis in 1996 and was recently shown to be valid and reliable by the European Medicines Agency's Committee on Herbal Medicinal Products (HMPC).[20] It has been used successfully in many clinical trials for acute bronchitis. BSS comprises the sum of five major symptom scores for acute bronchitis: cough, sputum, dyspnea, chest pain during coughing, and rales on auscultation. Each symptom is scored on a 4-point-scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe), with a maximum total score of 20 points. The investigator assesses symptom scores on the basis of the patient's subjective symptoms, and this correlates highly with the patient's actual improvement, as acute bronchitis mainly involves subjective complaints.[22] The change in BSS between day 0 and day 7 will be the primary outcome of this trial.

Secondary outcomes

Assessment of acute bronchitis predominantly depends on subjective tools, but more reliable data can be derived if appropriate objective variables are used together. Symptom and quality of life (QOL) questionnaires will be used as subjective tools, whereas cough frequency will be used as an objective tool; among outcome measures of cough symptoms, only cough frequency and quality of life questionnaires have been shown to be valid.[23]

Questionnaire of Clinical Symptoms of Cough and Sputum

The Questionnaire of Clinical Symptoms of Cough and Sputum (QCSCS) was proposed as a primary outcome measure in the Traditional Korean Medicine Clinical Practice Guidelines for Antitussives and Expectorants[21] and was developed by remodelling the Clinical Asthma Measurement Scale in Oriental Medicine-V for cough and sputum.[24] It is also appropriate for preparing clinical trials of GHX02 as an Investigational New Drug (IND), as it is the suggested tool in Clinical Practice Guidelines from the Ministry of Food and Drug Safety in Korea. Questionnaire items are as follows: (1) cough – frequency, intensity, sensitivity; (2) sputum – frequency, volume, difficulty to cough-up, appearance, colour; (3) activities of daily living; (4) night-time sleeping. Each item is scored on a 4-point-scale, with a total maximum score of 40 points. This questionnaire can evaluate symptoms of cough and sputum more specifically and in more detail than the BSS. The changes in QCSCS from day0 to day7 will be analysed for a secondary outcome.

Leicester Cough Questionnaire

The Leicester Cough Questionnaire (LCQ-K-acute) evaluates quality of life associated with cough. It consists of 19 items divided into three parts, physical, psychological, and social, each scored from 1 to 7. The total score is the sum of the average scores (1–7 points) for each part. The higher the score, the better the quality of life. Although it was initially developed as an assessment tool for chronic cough, it has also been found to be useful for acute cough, by changing the time criteria from 2 weeks to 24 hours.[25] In addition, the validity and reliability of the Korean version of the LCQ(LCQ-K) has already been verified.[26] The changes of LCQ-K-acute between day0 and day7 will be evaluated.

Frequency of coughing fits

Coughing frequency is an objective measurement tool for evaluating coughing. In this trial, we will ask participants to record how often they cough each day. A cough diary will be given to record their everyday coughing frequency, and participants will be classified into one of the following scales: 0 = 0 time/day, 1 = 1 time/day, 2 = 2-3 times/day, 3 = 4-5 times/day(sometimes), 4 = 6-10 times/day(frequent), 5 = over 15 times/day(consistently).[27] We will evaluate the frequency of coughing fits daily from day0 to day7 and analyse the changes in frequency of coughing fits after 1-7days from the baseline. (change in frequency of coughing fits after k days of study = frequency of coughing fits after k days of study - frequency of coughing fits at day0, where k = 1, 2, ..., 7)

Integrative Medicine Outcome Scale and Integrative Medicine Patient Satisfaction Scale

The Integrative Medicine Outcome Scale is a 5-point-scale for evaluating improvement after treatment (where, 1=complete recovery, 2=major improvement, 3=slight-to-moderate improvement, 4=no change, 5=deterioration), either by the patient or investigator (the investigator in this trial). The Integrative Medicine Patient Satisfaction Scale is a 5-point-scale for evaluating patient satisfaction with the treatment (where, 1=very satisfied, 2=satisfied, 3=neutral, 4=dissatisfied, 5=very dissatisfied).[20] Both will be measured at the patients' final visit (day7) and will be analysed for a secondary outcome.

Withdrawal rate of patients with exacerbation

Exacerbation in this trial means progression of acute bronchitis to bacterial bronchitis or pneumonia, requiring concomitant medicine such as antibiotics, bronchodilators, glucocorticoids, etc. During the trial, patients will be asked to inform about any signs of worsening symptoms, and investigators will evaluate appropriate measures if they need additional therapy. Those who require concomitant medicines will be excluded from the trial and provided the necessary medicine. We will calculate this withdrawal rate in each intervention and control group to check

the relevance with drug effects.

Safety assessment

Safety will be assessed in terms of adverse events (AEs), vital signs, and laboratory examinations (liver function test and routine blood and urine tests). AEs and vital signs will be recorded on a CRF at every visit, and laboratory examinations will be conducted before and after taking the medication. AEs are defined as every unexpected sign or symptom during the trial period and participants are asked to inform about any of these AEs during medication. All information about AEs will be recorded in detail, such as the duration and extent of the AE, relationship with the trial medicine, name of the suspected drug, etc. Common adverse events may include gastrointestinal side-effects, such as anorexia, stomach discomfort, nausea, and diarrhoea, which are not expected to be severe. However, if serious AEs occur that may lead to death or require extended hospitalization, the patient will be removed from the clinical trial as soon as possible and proper treatment will be provided (Table2).

Data management and monitoring

The investigators will follow the Standard Operating Procedures (SOP) of the trial for a better quality of assessment and collection of outcome data. The investigators who evaluate outcome measures should be restricted to only physicians who have attended the training meetings. All assessment data and case reports will be collected at baseline (day0) and at the end of the trial (day7) in both the intervention and control groups. Collected documents and data will be managed by electronic CRF and encrypted using double data entry. Only the principle investigator, or those who have permission, will be able to access the data. The CRFs and other documents will be stored at a separate and secure location for 10 years after trial completion.

Multicentre clinical trial monitoring will be conducted via regular visits (every one-fourth of recruitment) and occasional telephone calls. The information collected will be reported to the data monitoring committee (DMC), comprising specialists in pulmonology and medical statistics who are unrelated to this trial. At visits, a monitor will confirm whether the trial is being conducted in accordance with the protocol and especially AEs are being properly reported and recorded on

CRFs. The monitor will check the whole process of the clinical trial and problems will be discussed with the investigator as and when they occur.

Statistical analysis

Data analysis will be performed by an independent statistician using SAS® Analytics Pro. Continuous variables will be summarized by Mean±SD, and categorical variables will be reported with frequencies and percentages according to three treatment groups. Efficacy evaluation will be primarily based on the intention-to-treat (ITT) analysis, and per-protocol (PP) analysis will be used as a secondary analysis. ITT analysis will be conducted for all subjects randomized, and PP analysis will be conducted for those who completed the entire trial without violating the protocol. For primary outcome analysis, the changes in BSS between day0 and day7 will be evaluated using analysis of covariance (ANCOVA) which contains the day0's BSS and the treatment group as covariates. Significance will be accepted at a two-sided test with α-level of 0.05. For effects of GHX02 treatments compared with the control group, 95% confidence intervals (CIs) will be calculated. Analyses of secondary outcomes will be carried out as follows: QCSCS and LCQ-K-acute by ANCOVA including its baseline value respectively; frequency of coughing fits by linear mixed models (LMMs); IMOS and IMPSS by analysis of variance (ANOVA); and withdrawal rate of patients with exacerbation by Pearson's chi-squared or Fisher's exact tests. To handle missing values when processing ITT analysis, the last-observation-carried-forward (LOCF) method will be used except for frequency of coughing fits analysed with LMMs in which missing values need not to be imputed.

Safety assessment will be performed by ITT analysis; all participants randomized will be included. Comparison of the number of adverse events between three treatment groups will be performed using Kruskal-Wallis tests. Demographic and baseline data will be analysed using ANOVA for continuous variables, and Pearson's chi-squared or Fisher's exact tests for categorical variables.

ETHICS AND DISSEMINATION

The trial protocol (version 1.0) has been approved by the Institutional Review Board (IRB) of the Dunsan Korean Medicine Hospital, Daejeon University (No. DJDSKH-17-DR-14) and has been

registered through the clinical trials registry (NCT03310385). If the protocol needs modifications, the investigators are required to inform the IRB (as well as participants) and receive re-approval. Before the trial, investigators are required to provide all information related to the clinical trial, including the possible benefits and risks, other therapeutic choices, and right to withdraw, via a written consent form approved by the IRB. After being provided with sufficient time and opportunity to ask questions and decide whether to participate, all participants are required to provide written consent before study inclusion. All patient identifiable data will be kept confidential, even when the results of the trial are published and participant information will be stored in a secure file, and only the primary investigator (including those who have permission) and the monitor will have access to the data. To ensure confidentiality, all clinical trial documents, such as CRFs, will be recorded and distinguished by the participant identification number throughout the trial. At the end of the trial, the study results will be disseminated via peer-reviewed journals, conference presentation and the Clinical Research Information Service; the participants will also be informed of the results, even unpublished data, including missing data.

DISCUSSION

Despite problems associated with antibiotic abuse in public health systems and the substantial economic burden associated with acute bronchitis, currently no definitive medication is recommended. There are many studies exploring the efficacy of herbal medicines; a systematic review concluded that there was insufficient evidence to support the use of Chinese herbs for acute bronchitis because of the high risk of bias and lack of toxicological evidence.[12] This study is a multicentre, double-blind, randomized placebo-controlled trial to evaluate the efficacy and safety of two different doses of GHX02, compared with placebo, for acute bronchitis, and we followed strict quality control methods. To ensure a well-designed trial, we conducted a systematic review of randomized controlled trials for acute bronchitis in the last 10 years.[28]

There are some strengths and limitations to this protocol. Contrary to other trials, we will use the Korean Standard Tool of Pattern Identifications of Cough and Sputum, which is a Korean Medical Diagnostic Standard for categorizing cases, to obtain additional information as to whether a certain categories of patients respond better than others to treatment. In this way, we will be able to investigate the efficacy of GHX02 for more specific categories of people suffering from acute

bronchitis. Another strength is that the outcome measures we will use in this trial is well balanced between patients' subjective and objective outcomes; thus, the effectiveness of GHX02 will be demonstrated from various aspects. As GHX02 is an herbal prescription which has already been used for acute bronchitis, there is little risk of side-effects and the efficacy of GHX02 is already proven by empirical evidence. This study will provide new evidence for the efficacy and safety of GHX02 in a standard research design and is expected to be presented as a recommended alternative medicine for acute bronchitis.

A limitation of this trial protocol is that we will only target adults, despite most acute bronchitis patients being children under 5 years. As clinical drug trials are recommended to be first applied to adults, we selected adults aged between 19 and 75 years. Further studies for children will need to be conducted after completion of this study.

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Contributors

YRL drafted the research protocol and wrote the manuscript. WKY, SJP, SHK were involved in the protocol development. WK contributed to the statistical design and analysis. ICJ and YCP supervised this protocol. All authors contributed to the conception and implementation of this clinical trial.

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Competing interests

None declared.

Ethics approval

The protocol was approved by the Institutional Review Board of Dunsan Korean Medicine Hospital, Daejeon University.

Provenance and peer review

Not commissioned; externally peer reviewed.

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FIGURE LEGENDS

Figure 1. Flowchart of the study procedure

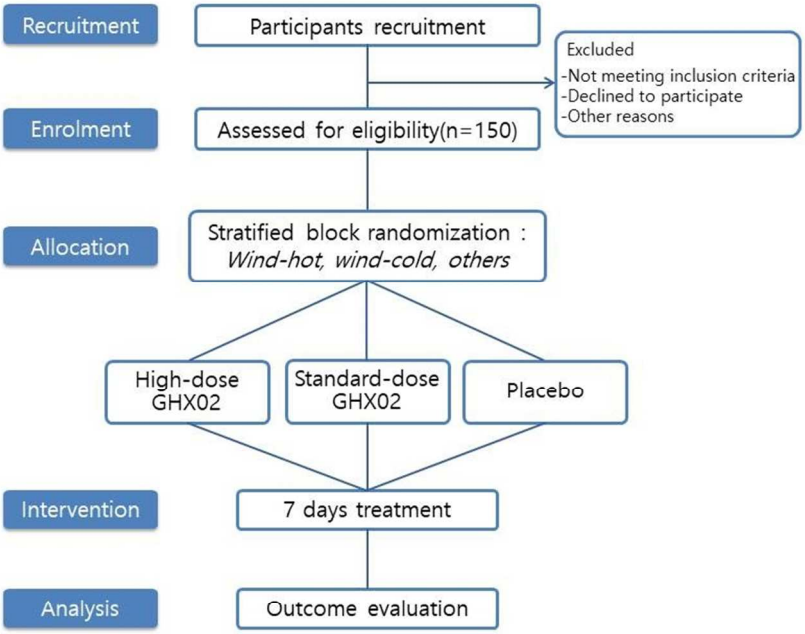

Figure1. Flowchart of the study procedure

Figure1. Flowchart of the study procedure

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____p.3_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ p.2,13___
	2b	All items from the World Health Organization Trial Registration Data Set	____p.2,5____
Protocol version	3	Date and version identifier	____p.13_____
Funding	4	Sources and types of financial, material, and other support	____p.16_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____p.16_____
	5b	Name and contact information for the trial sponsor	____p.16_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____p.16_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____p.12-13____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____p.3-4_____
	6b	Explanation for choice of comparators	____p.4 _____
Objectives	7	Specific objectives or hypotheses	____p.4_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____p.4-5_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____ p.4-5_ ____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____ p.7-8_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____p.6_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____p.8,9,11 ___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____p.6, 11_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____p.7-8_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____p.9-12_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____p.4-6_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____p.6-7_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____p.7_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____p.8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____p.8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____p.8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____p.8-9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____p.8-9 ____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____p.12-13___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____p.12-13___

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____p.11-12___
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___ p.13_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____p.13 _____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____p.13_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____p.12_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____p.12____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____p.12____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____p.12_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____p.13-14___
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____p.13-14___

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____p.14_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____p.14_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____p.14_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____p.14_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____p.14_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____p.14_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____p.14_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____ p.14_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____p.14_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____p.14____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____p.12____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy and safety of GHX02 in the treatment of acute bronchitis: protocol of a phase 2, double-blind, randomized placebo-controlled trial

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Primary Subject Heading:	Complementary medicine
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Keywords:	acute bronchitis, Herbal medicine < THERAPEUTICS, GHX02, randomized controlled trial

Efficacy and safety of GHX02 in the treatment of acute bronchitis: protocol of a phase 2, double-blind, randomized placebo-controlled trial

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ABSTRACT

Introduction: Acute bronchitis is a self-limiting infection of the large airways; cough is the primary symptom, usually lasting for about 3 weeks. Annually, approximately 5% of adults develop acute bronchitis, and its economic burden is substantial. There are also problems of antibiotic abuse in public health systems and symptomatic therapies are commonly prescribed, for which there is insufficient supporting evidence. GHX02 contains four herbs originating from *gwaruhaengryeon-hwan*, which has been used in the treatment of acute bronchitis patients in Korea. The objective is to compare the GHX02 and placebo in terms of efficacy and safety, and to determine the appropriate dosage.

Methods and analysis: We planned a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial of two different doses of GHX02 compared with placebo. A total of 150 patients, aged 19-75 years, with a Bronchitis Severity Score (BSS)≥5 due to acute bronchitis starting within 2 weeks of study enrolment will be recruited from three university-affiliated hospitals across Korea. Participants will be randomly assigned to either a high-dose GHX02 group(1,920mg/day), a standard-dose GHX02 group(960mg/day), or a placebo group according to a 1:1:1 allocation ratio using stratification block randomization with pattern identification. Patients will take medications three times daily for 7 days, with 2 visiting days. The primary outcome measure is a change in BSS from day0 to day7. The secondary outcomes are the Questionnaire of Clinical Symptoms of Cough and Sputum, Leicester Cough Questionnaire, frequency of coughing fits, Integrative Medicine Outcome Scale, Integrative Medicine Patient Satisfaction Scale and withdrawal rate of patients with exacerbation. Safety will be assessed by adverse events, vital signs, and laboratory examinations.

Ethics and dissemination: The study has been approved by our Institutional Review Board (No. DJDSKH-17-DR-14). The trial results will be disseminated via peer-reviewed journals and the Clinical Research Information Service.

Trial registration number: NCT03310385

KEY WORDS: acute bronchitis, herbal medicine, GHX02, randomized controlled trial

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study will provide new evidence for the efficacy and safety of GHX02 in a standard research design

- We will use the Korean Standard Tool of Pattern Identifications of Cough and Sputum, via stratified block randomization
- This is a well-designed study and the outcome measures are well balanced between patients' subjective and objective outcomes
- Limitation is that this trial protocol only targets adults
- This clinical trial was limited in that complete remission of acute bronchitis could not be observed due to the short trial period

INTRODUCTION

Acute bronchitis is the most common disease seen in outpatient departments (OPDs) across South Korea; about 5% of the general population have acute bronchitis.[1] In 2016, the Health Insurance Review & Assessment Service of South Korea estimated that more than 1500 million people visited OPDs for acute bronchitis and that the rate of increase in medical expenses, compared to that over the previous year, also rose.[2] Thus, acute bronchitis represents a substantial economic burden on the public health system, and effective therapeutic agents are urgently required.[3]

Acute bronchitis is a self-limiting infection of the large airways, with cough as the primary symptom, usually lasting for about 3 weeks.[4] It is characterized by acute onset of cough, accompanied by the production of sputum and dyspnea or chest discomfort.[5] As there are no specific diagnostic criteria for acute bronchitis, diagnosis is primarily clinical and requires a thorough assessment to differentiate from pneumonia, common cold, and asthma.[6] Up to 90% of acute bronchitis is caused by viruses; bacterial infection accounts only for less than 10%. Nevertheless, 60–80% of patients, despite evidence of little or no benefit, are treated with antibiotics, contributing to bacterial resistance associated with multiple adverse effects.[7] Several guidelines and meta-analyses of randomized controlled trials (RCTs) have concluded that antibiotic treatment is mostly ineffective in acute bronchitis, unless the infection is of bacterial origin.[8]

As antibiotics are generally not recommended for acute bronchitis, symptomatic therapy such as antitussives, expectorants, beta-2 agonists, and alternative therapies are commonly prescribed, despite insufficient evidence to support such treatments. There have been the lack of consistent evidence for their use of antitussives on acute bronchitis,[9] and the evidence regarding the use of expectorants is also questionable.[10] Beta-2 agonists are reported to be effective for patients with airflow obstruction, but adverse events like tremor and nervousness are widely observed.[11]

Moreover, the Cochrane Reviews suggested a lack of evidence to recommend the use of Chinese herbs in the treatment of acute bronchitis[12] and other alternative therapies, like *Pelargonium sidodes* or ivy leaf extracts are used in various European countries, with variable results.[13 14]

Thus, there have been substantial efforts worldwide to develop effective therapeutic agents for treating acute bronchitis. In this study, we focused on herbal medicines that have been used for centuries in Oriental countries; we sought to evaluate the efficacy and safety of GHX02, which contains four herbs originating from *gwaruhaengryeon-hwan* (GRHRH) in Donguibogam (Principles and Practice of Eastern Medicine) (Table1). GHX02 has been used for the treatment of patients with acute bronchitis in the Dunsan Korean Medicine Hospital, Daejeon University, and its effectiveness against acute cough has already been demonstrated. We planned a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial of two different doses of GHX02 compared with placebo. The objective is to compare the GHX02 and placebo in terms of efficacy and safety, and to determine the appropriate dosage of GHX02 required for the treatment of acute bronchitis. We chose a placebo as the control, as this is the most rigorous test for evaluating the efficacy of new medical therapy in a double-blind RCT.[15] In addition, as acute bronchitis is a self-limiting disorder, placebo control is ethically justifiable.

Table1. Components of GHX02

Herb	Latin name	Family name	Part of plant	Amount
Gwaruin	*Trichosanthis Semen*	Cucurbitaceae	Seed	351mg
Haengin	*Armeniacae Semen*	Rosaceae	Seed	175.5mg
Hwangryeon	*Coptidis Rhizoma*	Ranunculaceae	Root stock	175.5mg
Hwangkeum	*Scutellariae Radix*	Labiatae/Lamiacea	Root	351mg

METHODS AND ANALYSIS

Trial Design

This study is a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial to evaluate the efficacy and safety of two different doses of GHX02, compared with placebo, for acute bronchitis. The trial will be conducted at three university-affiliated hospitals, including

the Dunsan Korean Medicine Hospital, Daejeon University; the Kyunghee University Korean Medicine Hospital; and the Pusan National University Korean Medicine Hospital. One-hundred and fifty patients will be included in this trial and randomly assigned to either a high-dose GHX02 group (1920mg/day), standard-dose GHX02 group (960mg/day), or control group (placebo) in a 1:1:1 allocation ratio by stratification block randomization of pattern identification. By using the Korean Standard Tool of Pattern Identifications of Cough and Sputum, participants are classified into three patterns: *wind-heat, wind-cold*, or *others* (Figure1, Table2). Patients will take one of the medications three times a day for 7 days, with 2 visiting days (day0, day7). This follows the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[16], Reporting Randomized, Controlled Trials of Herbal Interventions[17] and the trial will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and Consolidated Standards of Reporting Trials (CONSORT) guidelines.[18]

Table2. Timetable of study period

	STUDY PERIOD			
	Enrolment	**Allocation**	**Post-allocation**	
TIMEPOINT	screening	Day 0	Day 0	Day 7
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Demographic data	X			
Vital signs	X		X	X
Past history	X			
Concomitant medication	X		X	X
Physical examination & radiography	X			
Laboratory examination	X			X
Pattern identification of cough & sputum	X			
Allocation		X		
INTERVENTIONS:				
High-dose GHX02			←	→
Standard-dose GHX02			←	→
Placebo			←	→
ASSESSMENTS:				
BSS	X		X	X
QCSCS			X	X
LCQ-K-acute			X	X
Frequency of cough fits			←	→

IMOS, IMPSS				X
Withdrawal rate of patients with exacerbation				X
Concomitant therapy			X	X
Adverse events			X	X
Compliance				X

BSS, Bronchitis Severity Score; QCSCS, Questionnaire on Clinical Symptoms of Cough & Sputum; LCQ-K-acute, Leicester Cough Questionnaire-Korean version-acute; IMOS, Integrative Medicine Outcome Scale; IMPSS, Integrative Medicine Patient Satisfaction Scale

Study Drug and Placebo

GHX02 is a combination of the following four herbs: Gwaruin (*Trichosanthis Semen*, 351 mg/tablet), Haengin (*Armeniacae Semen*, 175.5 mg/tablet), Hwangryeon (*Coptidis Rhizoma*, 175.5 mg/tablet), Hwangkeum (*Scutellariae Radix,* 351 mg/tablet) (Table1). One GHX02 tablet (500mg/tablet) contains 160.0mg of dry extract of the four herbs (obtained by boiling in water and then dehydrating) mixed with 340.0mg of starch and lactose. The placebo tablet does not contain any of these active ingredients but is matched in terms of colour, smell, and taste. The dosage was determined according to the Pharmacologically Active Dose (PAD) in expectorant effective tests. Both tablets are pink and round and will be provided by Hankookshinyak Corporation (Nonsan, Korea). The manufacturer complies with the provisions of the Regulations on the Safety of Pharmaceuticals and will manage the quality appropriately. Safety and toxicological tests of GHX02 will be conducted simultaneously. All allocated patients will be prescribed 4 tablets of either the clinical medicine or placebo to be administered three times daily for 7 days, and the number of remaining tablets will be recorded on day 7 to calculate compliance. To improve compliance, participants will be asked to record their daily dosage in the cough diary. The overall medication compliance during the trial should be at least 75%; if the medication compliance is less than 75%, the participant will be considered inadequate and excluded from the per-protocol (PP) analysis group.

Sample size

The estimated sample size required for this study is 150 patients (50 patients per group).[19] The estimation of the number of subjects is based on whether there is a difference in the change from

baseline (day 0) to post-dose (day 7) BSS, between the control and standard-dose GHX02 group. In an earlier comparable clinical study, the difference was reported to be 2.3, and the standard deviation of the changes in BSS, was estimated to be 3.2.[20] The power to detect the difference was assumed to be 0.8, and the two-sided significance level was 0.05. The ratio of allocation of subjects between the groups was 1:1:1, and dropout rate was presumed to be 0.2.

Recruitment

Participants will be recruited from the outpatient departments (OPDs) of the affiliated hospitals by posting brochures in a well visible place in front of the clinic and distributing it to every patient visiting OPDs of pulmonology. Recruitment will commence in January 2018.

Participants

Inclusion criteria

Potential participants who meet the following criteria will be included in this trial: (1) age 19–75 years; (2) BSS ≥ 5 points at day 0 due to acute bronchitis; (3) symptoms starting within 2 weeks before study inclusion; (4) patients who consent to participate. Diagnoses of acute bronchitis will be based on patients' medical history, physical examinations, and BSS, including cough, sputum, dyspnea, chest pain during coughing, and rales on auscultation.

Exclusion criteria

Patients with any of the following criteria will be excluded from this trial: (1) pregnant or breast-feeding; (2) treatment with antibiotics, bronchodilators, glucocorticoids, immune-depressants, or other clinical trial medicines during the last 4 weeks before study inclusion; (3) treatment with antitussives or expectorants during the last 7 days before study inclusion; (4) history or presence of confounding respiratory disease that may affect evaluation of the efficacy of clinical medicine (e.g. chronic bronchitis, chronic obstructive pulmonary disease (COPD), bronchiectasis, asthma, pneumonia, cystic fibrosis, lung cancer, or active pulmonary tuberculosis); (5) liver or renal

impairment (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] ≥ 2 times the normal upper limit, or creatinine> 3.0 mg/dL at screening); (6) history or presence of clinically relevant cardiovascular, renal, metabolic, haematological, neurological, psychiatric, systemic, infectious disease, or malignant tumour (except where there is no recurrence for more than 5 years after surgery); (7) genetic problems such as galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption; (8) history of alcoholism or substance abuse; (9) participation in other clinical medicine trials during the last 30 days before study inclusion; (10) judged by the investigators to be inappropriate for the clinical trial. Additional treatment will not be permitted during the trial, and participants are recommended not to alter their exercise pattern or diet. Drugs that may affect bronchitis symptoms or that have a similar therapeutic purpose to the trial medication will not be permitted, including antibiotics, bronchodilators, glucocorticoids, immune-depressants, antitussives, expectorants or any other clinical trial medicine. Those who require or take these concomitant medicines during the trial will be excluded from this study. Other medications will only be permitted at the discretion of the investigators. All drug information (name of product, purpose of administration, dosage, duration of administration, etc.) will be recorded on the patient case report form (CRF).

Randomization and allocation concealment

An independent statistician will conduct randomization, using a computer random number generator of SAS® Analytics Pro (SAS Institute, Inc., Cary, North Carolina, USA). Allocation will be implemented by the manufacturers who collectively label participant's identification code on the packages of the test drug or a placebo using generated random numbers. This labeled drug will be given to the management pharmacist. When the investigator requests medication, the management pharmacist gives the participant the drug corresponding to the participant's identification code. Only the statistician and manufacturer have access to the random numbers, and they will sign and submit a written non-disclosure agreement. After that, just the identification code is used to identify which drug to give to which participant. We will allocate three groups (*wind-heat, wind-cold,* or *others*) at a 1:1:1 ratio of high-dose, standard-dose, and placebo treatment. Stratified block randomization using the Korean Standard Tool of Pattern Identifications of Cough and Sputum will be performed in this trial.

Korean Standard Tool of Pattern Identifications of Cough and Sputum

The Korean Standard Tool of Pattern Identifications of Cough and Sputum is used to identify patterns of acute bronchitis patients. This pattern identification is an important diagnostic criterion in Korean medicine which is used for deciding medication and other therapies. It was proposed in the Traditional Korean Medicine Clinical Practice Guidelines for Antitussives and Expectorants for Korean Medical Diagnostic Standards.[21] This comprises 56 items to classify cases into three patterns: *wind-cold, wind-heat* or *others*. We will investigate the correlation between the patterns and the efficacy of GHX02; the *wind-heat* patterns group is expected to show greater response than the other groups to the therapeutic effects of GHX02.

Blinding

This is a double-blind trial, thus neither participants nor investigators (including outcome assessors) will be aware of group assignment until the end of the study period. Placebo tablets will be matched to GHX02 tablets in terms of colour, taste, and smell, as well as outer packaging. Elimination of blindness will only be considered in cases of serious medical emergencies.

Outcome measures

Primary outcome

Bronchitis Severity Score

The BSS was developed as an evaluation tool for acute bronchitis in 1996 and was recently shown to be valid and reliable by the European Medicines Agency's Committee on Herbal Medicinal Products (HMPC).[20] It has been used successfully in many clinical trials for acute bronchitis. BSS comprises the sum of five major symptom scores for acute bronchitis: cough, sputum, dyspnea, chest pain during coughing, and rales on auscultation. Each symptom is scored on a 4-point-scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe), with a maximum total score of 20 points. The investigator assesses symptom scores on the basis of the patient's subjective symptoms, and this correlates highly with the patient's actual improvement, as acute bronchitis mainly involves subjective complaints.[22] The change in BSS between day 0 and day 7 will be the

primary outcome of this trial.

Secondary outcomes

Assessment of acute bronchitis predominantly depends on subjective tools, but more reliable data can be derived if appropriate objective variables are used together. Symptom and quality of life (QOL) questionnaires will be used as subjective tools, whereas cough frequency will be used as an objective tool; among outcome measures of cough symptoms, only cough frequency and quality of life questionnaires have been shown to be valid.[23]

Questionnaire of Clinical Symptoms of Cough and Sputum

The Questionnaire of Clinical Symptoms of Cough and Sputum (QCSCS) was proposed as a primary outcome measure in the Traditional Korean Medicine Clinical Practice Guidelines for Antitussives and Expectorants[21] and was developed by remodelling the Clinical Asthma Measurement Scale in Oriental Medicine-V for cough and sputum.[24] It is also appropriate for preparing clinical trials of GHX02 as an Investigational New Drug (IND), as it is the suggested tool in Clinical Practice Guidelines from the Ministry of Food and Drug Safety in Korea. Questionnaire items are as follows: (1) cough – frequency, intensity, sensitivity; (2) sputum – frequency, volume, difficulty to cough-up, appearance, colour; (3) activities of daily living; (4) night-time sleeping. Each item is scored on a 4-point-scale, with a total maximum score of 40 points. This questionnaire can evaluate symptoms of cough and sputum more specifically and in more detail than the BSS. The changes in QCSCS from day0 to day7 will be analysed for a secondary outcome.

Leicester Cough Questionnaire

The Leicester Cough Questionnaire (LCQ-K-acute) evaluates quality of life associated with cough. It consists of 19 items divided into three parts, physical, psychological, and social, each scored from 1 to 7. The total score is the sum of the average scores (1–7 points) for each part. The higher the score, the better the quality of life. Although it was initially developed as an assessment tool for chronic cough, it has also been found to be useful for acute cough, by changing the time criteria

from 2 weeks to 24 hours.[25] In addition, the validity and reliability of the Korean version of the LCQ(LCQ-K) has already been verified.[26] The changes of LCQ-K-acute between day0 and day7 will be evaluated.

Frequency of coughing fits

Coughing frequency is an objective measurement tool for evaluating coughing. In this trial, we will ask participants to record how often they cough each day. A cough diary will be given to record their everyday coughing frequency, and participants will be classified into one of the following scales: 0 = 0 time/day, 1 = 1 time/day, 2 = 2-3 times/day, 3 = 4-5 times/day(sometimes), 4 = 6-10 times/day(frequent), 5 = over 15 times/day(consistently).[27] We will evaluate the frequency of coughing fits daily from day0 to day7 and analyse the changes in frequency of coughing fits after 1-7days from the baseline. (change in frequency of coughing fits after k days of study = frequency of coughing fits after k days of study - frequency of coughing fits at day0, where k = 1, 2, ..., 7)

Integrative Medicine Outcome Scale and Integrative Medicine Patient Satisfaction Scale

The Integrative Medicine Outcome Scale is a 5-point-scale for evaluating improvement after treatment (where, 1=complete recovery, 2=major improvement, 3=slight-to-moderate improvement, 4=no change, 5=deterioration), either by the patient or investigator (the investigator in this trial). The Integrative Medicine Patient Satisfaction Scale is a 5-point-scale for evaluating patient satisfaction with the treatment (where, 1=very satisfied, 2=satisfied, 3=neutral, 4=dissatisfied, 5=very dissatisfied).[20] Both will be measured at the patients' final visit (day7) and will be analysed for a secondary outcome.

Withdrawal rate of patients with exacerbation

Exacerbation in this trial means progression of acute bronchitis to bacterial bronchitis or pneumonia, requiring concomitant medicine such as antibiotics, bronchodilators, glucocorticoids, etc. During the trial, patients will be asked to inform about any signs of worsening symptoms, and

investigators will evaluate appropriate measures if they need additional therapy. Those who require concomitant medicines will be excluded from the trial and provided the necessary medicine. We will calculate this withdrawal rate in each intervention and control group to check the relevance with drug effects.

Safety assessment

Safety will be assessed in terms of adverse events (AEs), vital signs, and laboratory examinations (liver function test and routine blood and urine tests). AEs and vital signs will be recorded on a CRF at every visit, and laboratory examinations will be conducted before and after taking the medication. AEs are defined as every unexpected sign or symptom during the trial period and participants are asked to inform about any of these AEs during medication. All information about AEs will be recorded in detail, such as the duration and extent of the AE, relationship with the trial medicine, name of the suspected drug, etc. Common adverse events may include gastrointestinal side-effects, such as anorexia, stomach discomfort, nausea, and diarrhoea, which are not expected to be severe. However, if serious AEs occur that may lead to death or require extended hospitalization, the patient will be removed from the clinical trial as soon as possible and proper treatment will be provided (Table2).

Data management and monitoring

The investigators will follow the Standard Operating Procedures (SOP) of the trial for a better quality of assessment and collection of outcome data. The investigators who evaluate outcome measures should be restricted to only physicians who have attended the training meetings. All assessment data and case reports will be collected at baseline (day0) and at the end of the trial (day7) in both the intervention and control groups. Collected documents and data will be managed by electronic CRF and encrypted using double data entry. Only the principle investigator, or those who have permission, will be able to access the data. The CRFs and other documents will be stored at a separate and secure location for 10 years after trial completion.

Multicentre clinical trial monitoring will be conducted via regular visits (every one-fourth of recruitment) and occasional telephone calls. The information collected will be reported to the data

monitoring committee (DMC), comprising specialists in pulmonology and medical statistics who are unrelated to this trial. At visits, a monitor will confirm whether the trial is being conducted in accordance with the protocol and especially AEs are being properly reported and recorded on CRFs. The monitor will check the whole process of the clinical trial and problems will be discussed with the investigator as and when they occur.

Statistical analysis

Data analysis will be performed by an independent statistician using SAS® Analytics Pro. Continuous variables will be summarized by Mean±SD, and categorical variables will be reported with frequencies and percentages according to three treatment groups. Efficacy evaluation will be primarily based on the intention-to-treat (ITT) analysis, and per-protocol (PP) analysis will be used as a secondary analysis. ITT analysis will be conducted for all subjects randomized, and PP analysis will be conducted for those who completed the entire trial without violating the protocol. For primary outcome analysis, the changes in BSS between day0 and day7 will be evaluated using analysis of covariance (ANCOVA) which contains the day0's BSS and the treatment group as covariates. Significance will be accepted at a two-sided test with α-level of 0.05. For effects of GHX02 treatments compared with the control group, 95% confidence intervals (CIs) will be calculated. Analyses of secondary outcomes will be carried out as follows: QCSCS and LCQ-K-acute by ANCOVA including its baseline value respectively; frequency of coughing fits by linear mixed models (LMMs); IMOS and IMPSS by analysis of variance (ANOVA); and withdrawal rate of patients with exacerbation by Pearson's chi-squared or Fisher's exact tests. To handle missing values when processing ITT analysis, the last-observation-carried-forward (LOCF) method will be used except for frequency of coughing fits analysed with LMMs in which missing values need not to be imputed.

Safety assessment will be performed by ITT analysis; all participants randomized will be included. Comparison of the number of adverse events between three treatment groups will be performed using Kruskal-Wallis tests. Demographic and baseline data will be analysed using ANOVA for continuous variables, and Pearson's chi-squared or Fisher's exact tests for categorical variables.

ETHICS AND DISSEMINATION

The trial protocol (version 1.0) has been approved by the Institutional Review Board (IRB) of the Dunsan Korean Medicine Hospital, Daejeon University (No. DJDSKH-17-DR-14) and has been registered through the clinical trials registry (NCT03310385). If the protocol needs modifications, the investigators are required to inform the IRB (as well as participants) and receive re-approval. Before the trial, investigators are required to provide all information related to the clinical trial, including the possible benefits and risks, other therapeutic choices, and right to withdraw, via a written consent form approved by the IRB. After being provided with sufficient time and opportunity to ask questions and decide whether to participate, all participants are required to provide written consent before study inclusion. All patient identifiable data will be kept confidential, even when the results of the trial are published and participant information will be stored in a secure file, and only the primary investigator (including those who have permission) and the monitor will have access to the data. To ensure confidentiality, all clinical trial documents, such as CRFs, will be recorded and distinguished by the participant identification number throughout the trial. At the end of the trial, the study results will be disseminated via peer-reviewed journals, conference presentation and the Clinical Research Information Service; the participants will also be informed of the results, even unpublished data, including missing data.

DISCUSSION

Despite problems associated with antibiotic abuse in public health systems and the substantial economic burden associated with acute bronchitis, currently no definitive medication is recommended. There are many studies exploring the efficacy of herbal medicines; a systematic review concluded that there was insufficient evidence to support the use of Chinese herbs for acute bronchitis because of the high risk of bias and lack of toxicological evidence.[12] This study is a multicentre, double-blind, randomized placebo-controlled trial to evaluate the efficacy and safety of two different doses of GHX02, compared with placebo, for acute bronchitis, and we followed strict quality control methods. To ensure a well-designed trial, we conducted a systematic review of randomized controlled trials for acute bronchitis in the last 10 years.[28]

There are some strengths and limitations to this protocol. Contrary to other trials, we will use the Korean Standard Tool of Pattern Identifications of Cough and Sputum, which is a Korean Medical

Diagnostic Standard for categorizing cases, to obtain additional information as to whether a certain categories of patients respond better than others to treatment. In this way, we will be able to investigate the efficacy of GHX02 for more specific categories of people suffering from acute bronchitis. Another strength is that the outcome measures we will use in this trial is well balanced between patients' subjective and objective outcomes; thus, the effectiveness of GHX02 will be demonstrated from various aspects. As GHX02 is an herbal prescription which has already been used for acute bronchitis, there is little risk of side-effects and the efficacy of GHX02 is already proven by empirical evidence. This study will provide new evidence for the efficacy and safety of GHX02 in a standard research design and is expected to be presented as a recommended alternative medicine for acute bronchitis.

A limitation of this trial protocol is that we will only target adults, despite most acute bronchitis patients being children under 5 years. As clinical drug trials are recommended to be first applied to adults, we selected adults aged between 19 and 75 years. Further studies for children will need to be conducted after completion of this study.

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Contributors

YRL drafted the research protocol and wrote the manuscript. WKY, SJP, SHK were involved in the protocol development. WK contributed to the statistical design and analysis. ICJ and YCP supervised this protocol. All authors contributed to the conception and implementation of this clinical trial.

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Competing interests

None declared.

Ethics approval

The protocol was approved by the Institutional Review Board of Dunsan Korean Medicine Hospital, Daejeon University.

Provenance and peer review

Not commissioned; externally peer reviewed.

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FIGURE LEGENDS

Figure 1. Flowchart of the study procedure

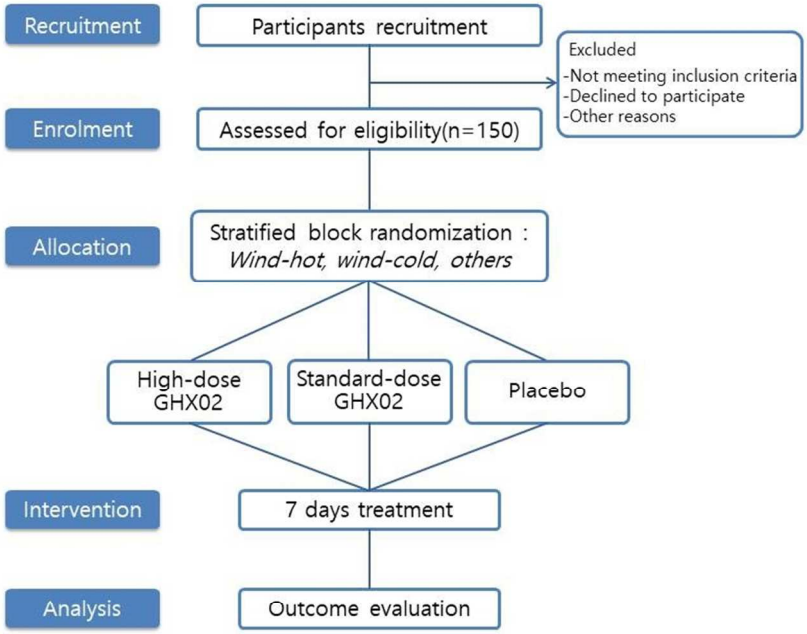

Figure1. Flowchart of the study procedure

Figure1. Flowchart of the study procedure

81x60mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p.1,line1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p.2,line26/ p.14,line5
	2b	All items from the World Health Organization Trial Registration Data Set	p.5,line8-12
Protocol version	3	Date and version identifier	p.14,line2
Funding	4	Sources and types of financial, material, and other support	p.16,line18-22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p.16,line13-16
	5b	Name and contact information for the trial sponsor	p.16,line18-22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	-
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	p.14,line1-4

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p.3,line10-p.4,line16
	6b	Explanation for choice of comparators	p.4,line14-16
Objectives	7	Specific objectives or hypotheses	p.4,line12-14
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p.4,line27-29
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p.4,line29-p.5,line2, p.7,line9-11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p.7,line13-p.8,line18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p.6,line22-24
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p.8,line10-14/ p9,line15/ p11,line25-p.12,line4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p.6,line25-26
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p.8,line10-16
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p.9,line18-p.12,line4

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p.5,line13-p.6,line9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p.6,line30-p.7,line5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p.7,line7-10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p.8,line19-20/25-27/29-30
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p.8,line20-23
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p.8,line23-27
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p.9,line12-13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	p.9 ,line15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	p.12,line20-24

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p.6,line25-26
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p.12,line24-26
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p.13,line10-21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p.13,line18-21
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p.13,line21-24
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p.12,line28-p.13,line5
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	p.12,line15-17/ p.11,line25-p.12,line4
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p.12,line11-17 / p.13,line2-4
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	p.12,line28-p.13,line5
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p.14,line2-4

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p.14,line4-5
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p.14,line6-10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	p.14,line6-10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p.14,line10-15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p.16,line24-25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p.14,line12-13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	p.12,line15-17
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p.14,line15-17
	31b	Authorship eligibility guidelines and any intended use of professional writers	p.16,line13-16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	p.14,line15-17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	p.12,line26-27

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Efficacy and safety of GHX02 in the treatment of acute bronchitis: protocol of a phase 2, double-blind, randomized placebo-controlled trial

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Efficacy and safety of GHX02 in the treatment of acute bronchitis: protocol of a phase 2, double-blind, randomized placebo-controlled trial

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ABSTRACT

Introduction: Acute bronchitis is a self-limiting infection of the large airways; cough is the primary symptom, usually lasting for about 3 weeks. Annually, approximately 5% of adults develop acute bronchitis, and its economic burden is substantial. There are also problems of antibiotic abuse in public health systems and symptomatic therapies are commonly prescribed, for which there is insufficient supporting evidence. GHX02 contains four herbs originating from *gwaruhaengryeon-hwan*, which has been used in the treatment of acute bronchitis patients in Korea. The objective is to compare the GHX02 and placebo in terms of efficacy and safety, and to determine the appropriate dosage.

Methods and analysis: We planned a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial of two different doses of GHX02 compared with placebo. A total of 150 patients, aged 19-75 years, with a Bronchitis Severity Score (BSS)≥5 due to acute bronchitis starting within 2 weeks of study enrolment will be recruited from three university-affiliated hospitals across Korea. Participants will be stratified into three patterns using the Korean Standard Tool of Pattern Identifications of Cough and Sputum and randomly assigned to either a high-dose GHX02 group(1,920mg/day), standard-dose GHX02 group(960mg/day), or placebo group according to a 1:1:1 allocation ratio. Patients will take medications three times daily for 7 days, with 2 visiting days. The primary outcome measure is a change in BSS from day0 to day7. The secondary outcomes are the Questionnaire of Clinical Symptoms of Cough and Sputum, Leicester Cough Questionnaire, frequency of coughing fits, Integrative Medicine Outcome Scale, Integrative Medicine Patient Satisfaction Scale and withdrawal rate of patients with exacerbation. Safety will be assessed by adverse events, vital signs, and laboratory examinations.

Ethics and dissemination: The study has been approved by our Institutional Review Board (No. DJDSKH-17-DR-14). The trial results will be disseminated via peer-reviewed journals and the Clinical Research Information Service.

Trial registration number: NCT03310385

KEY WORDS: acute bronchitis, herbal medicine, GHX02, randomized controlled trial

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study will provide new evidence for the efficacy and safety of GHX02 in a standard research design

- We will use the Korean Standard Tool of Pattern Identifications of Cough and Sputum, via stratified block randomization
- This is a well-designed study and the outcome measures are well balanced between patients' subjective and objective outcomes
- Limitation is that this trial protocol only targets adults
- This clinical trial is limited in that complete remission of acute bronchitis could not be observed due to the short trial period

INTRODUCTION

Acute bronchitis is the most common disease seen in outpatient departments (OPDs) across South Korea; about 5% of the general population have acute bronchitis.[1] In 2016, the Health Insurance Review & Assessment Service of South Korea estimated that more than 1500 million people visited OPDs for acute bronchitis and that the rate of increase in medical expenses, compared to that over the previous year, also rose.[2] Thus, acute bronchitis represents a substantial economic burden on the public health system, and effective therapeutic agents are urgently required.[3]

Acute bronchitis is a self-limiting infection of the large airways, with cough as the primary symptom, usually lasting for about 3 weeks.[4] It is characterized by acute onset of cough, accompanied by the production of sputum and dyspnea or chest discomfort.[5] As there are no specific diagnostic criteria for acute bronchitis, diagnosis is primarily clinical and requires a thorough assessment to differentiate from pneumonia, common cold, and asthma.[6] Up to 90% of acute bronchitis is caused by viruses; bacterial infection accounts only for less than 10%. Nevertheless, 60–80% of patients, despite evidence of little or no benefit, are treated with antibiotics, contributing to bacterial resistance associated with multiple adverse effects.[7] Several guidelines and meta-analyses of randomized controlled trials (RCTs) have concluded that antibiotic treatment is mostly ineffective in acute bronchitis, unless the infection is of bacterial origin.[8]

As antibiotics are generally not recommended for acute bronchitis, symptomatic therapy such as antitussives, expectorants, beta-2 agonists, and alternative therapies are commonly prescribed, despite insufficient evidence to support such treatments. There have been the lack of consistent evidence for their use of antitussives on acute bronchitis,[9] and the evidence regarding the use of expectorants is also questionable.[10] Beta-2 agonists are reported to be effective for patients with airflow obstruction, but adverse events like tremor and nervousness are widely observed.[11]

Moreover, the Cochrane Reviews suggested a lack of evidence to recommend the use of Chinese herbs in the treatment of acute bronchitis[12] and other alternative therapies, like *Pelargonium sidodes* or ivy leaf extracts are used in various European countries, with variable results.[13 14]

Thus, there have been substantial efforts worldwide to develop effective therapeutic agents for treating acute bronchitis. In this study, we focused on herbal medicines that have been used for centuries in Oriental countries; we sought to evaluate the efficacy and safety of GHX02, which contains four herbs originating from *gwaruhaengryeon-hwan* (GRHRH) in Donguibogam (Principles and Practice of Eastern Medicine) (Table1). GHX02 has been used for the treatment of patients with acute bronchitis in the Dunsan Korean Medicine Hospital, Daejeon University, and its effectiveness against acute cough has already been demonstrated. We planned a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial of two different doses of GHX02 compared with placebo. The objective is to compare the GHX02 and placebo in terms of efficacy and safety, and to determine the appropriate dosage of GHX02 required for the treatment of acute bronchitis. We chose a placebo as the control, as this is the most rigorous test for evaluating the efficacy of new medical therapy in a double-blind RCT.[15] In addition, as acute bronchitis is a self-limiting disorder, placebo control is ethically justifiable.

Table1. Components of GHX02

Herb	Latin name	Family name	Part of plant	Amount
Gwaruin	*Trichosanthis Semen*	Cucurbitaceae	Seed	351mg
Haengin	*Armeniacae Semen*	Rosaceae	Seed	175.5mg
Hwangryeon	*Coptidis Rhizoma*	Ranunculaceae	Root stock	175.5mg
Hwangkeum	*Scutellariae Radix*	Labiatae/Lamiacea	Root	351mg

METHODS AND ANALYSIS

Trial Design

This study is a phase 2, multicentre, dose-finding, double-blind, randomized placebo-controlled trial to evaluate the efficacy and safety of two different doses of GHX02, compared with placebo, for acute bronchitis. The trial will be conducted at three university-affiliated hospitals, including

the Dunsan Korean Medicine Hospital, Daejeon University; the Kyunghee University Korean Medicine Hospital; and the Pusan National University Korean Medicine Hospital. One-hundred and fifty patients will be included in this trial and stratified into three patterns (*wind-heat, wind-cold*, or *others*) by using the Korean Standard Tool of Pattern Identifications of Cough and Sputum. Then, each pattern of patients will randomly assigned to either a high-dose GHX02 group (1920mg/day), standard-dose GHX02 group (960mg/day), or control group (placebo) in a 1:1:1 allocation ratio. Stratified block randomization using the pattern identification will be performed in this trial as above (Figure1, Table2). Patients will take one of the medications three times a day for 7 days, with 2 visiting days (day0, day7). This follows the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[16], Reporting Randomized, Controlled Trials of Herbal Interventions[17] and the trial will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and Consolidated Standards of Reporting Trials (CONSORT) guidelines.[18]

Table2. Timetable of study period

	STUDY PERIOD			
	Enrolment	**Allocation**	**Post-allocation**	
TIMEPOINT	screening	Day 0	Day 0	Day 7
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Demographic data	X			
Vital signs	X		X	X
Past history	X			
Concomitant medication	X		X	X
Physical examination & radiography	X			
Laboratory examination	X			X
Pattern identification of cough & sputum	X			
Allocation		X		
INTERVENTIONS:				
High-dose GHX02			←	→
Standard-dose GHX02			←	→
Placebo			←	→
ASSESSMENTS:				
BSS	X		X	X
QCSCS			X	X
LCQ-K-acute			X	X

Frequency of cough fits			←	→
IMOS, IMPSS				X
Withdrawal rate of patients with exacerbation				X
Concomitant therapy			X	X
Adverse events			X	X
Compliance				X

BSS, Bronchitis Severity Score; QCSCS, Questionnaire on Clinical Symptoms of Cough & Sputum; LCQ-K-acute, Leicester Cough Questionnaire-Korean version-acute; IMOS, Integrative Medicine Outcome Scale; IMPSS, Integrative Medicine Patient Satisfaction Scale

Study Drug and Placebo

GHX02 is a combination of the following four herbs: Gwaruin (*Trichosanthis Semen*, 351 mg/tablet), Haengin (*Armeniacae Semen*, 175.5 mg/tablet), Hwangryeon (*Coptidis Rhizoma*, 175.5 mg/tablet), Hwangkeum (*Scutellariae Radix,* 351 mg/tablet) (Table1). One GHX02 tablet (500mg/tablet) contains 160.0mg of dry extract of the four herbs (obtained by boiling in water and then dehydrating) mixed with 340.0mg of starch and lactose. The placebo tablet does not contain any of these active ingredients but is matched in terms of colour, smell, and taste. The dosage was determined according to the Pharmacologically Active Dose (PAD) in expectorant effective tests. Both tablets are pink and round and will be provided by Hankookshinyak Corporation (Nonsan, Korea). The manufacturer complies with the provisions of the Regulations on the Safety of Pharmaceuticals and will manage the quality appropriately. Safety and toxicological tests of GHX02 will be conducted simultaneously. All allocated patients will be prescribed 4 tablets of either the clinical medicine or placebo to be administered three times daily for 7 days, and the number of remaining tablets will be recorded on day 7 to calculate compliance. To improve compliance, participants will be asked to record their daily dosage in the cough diary. The overall medication compliance during the trial should be at least 75%; if the medication compliance is less than 75%, the participant will be considered inadequate and excluded from the per-protocol (PP) analysis group.

Sample size

The estimated sample size required for this study is 150 patients (50 patients per group).[19] The

estimation of the number of subjects is based on whether there is a difference in the change from baseline (day 0) to post-dose (day 7) BSS, between the control and standard-dose GHX02 group. In an earlier comparable clinical study, the difference was reported to be 2.3, and the standard deviation of the changes in BSS, was estimated to be 3.2.[20] The power to detect the difference was assumed to be 0.8, and the two-sided significance level was 0.05. The ratio of allocation of subjects between the groups was 1:1:1, and dropout rate was presumed to be 0.2.

Recruitment

Participants will be recruited from the outpatient departments (OPDs) of the affiliated hospitals by posting brochures in a well visible place in front of the clinic and distributing it to every patient visiting OPDs of pulmonology. Recruitment will commence in January 2018.

Participants

Inclusion criteria

Potential participants who meet the following criteria will be included in this trial: (1) age 19–75 years; (2) BSS ≥ 5 points at day 0 due to acute bronchitis; (3) symptoms starting within 2 weeks before study inclusion; (4) patients who consent to participate. Diagnoses of acute bronchitis will be based on patients' medical history, physical examinations, and BSS, including cough, sputum, dyspnea, chest pain during coughing, and rales on auscultation.

Exclusion criteria

Patients with any of the following criteria will be excluded from this trial: (1) pregnant or breast-feeding; (2) treatment with antibiotics, bronchodilators, glucocorticoids, immune-depressants, or other clinical trial medicines during the last 4 weeks before study inclusion; (3) treatment with antitussives or expectorants during the last 7 days before study inclusion; (4) history or presence of confounding respiratory disease that may affect evaluation of the efficacy of clinical medicine (e.g. chronic bronchitis, chronic obstructive pulmonary disease (COPD), bronchiectasis, asthma,

pneumonia, cystic fibrosis, lung cancer, or active pulmonary tuberculosis); (5) liver or renal impairment (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] ≥ 2 times the normal upper limit, or creatinine> 3.0 mg/dL at screening); (6) history or presence of clinically relevant cardiovascular, renal, metabolic, haematological, neurological, psychiatric, systemic, infectious disease, or malignant tumour (except where there is no recurrence for more than 5 years after surgery); (7) genetic problems such as galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption; (8) history of alcoholism or substance abuse; (9) participation in other clinical medicine trials during the last 30 days before study inclusion; (10) judged by the investigators to be inappropriate for the clinical trial. Additional treatment will not be permitted during the trial, and participants are recommended not to alter their exercise pattern or diet. Drugs that may affect bronchitis symptoms or that have a similar therapeutic purpose to the trial medication will not be permitted, including antibiotics, bronchodilators, glucocorticoids, immune-depressants, antitussives, expectorants or any other clinical trial medicine. Those who require or take these concomitant medicines during the trial will be excluded from this study. Other medications will only be permitted at the discretion of the investigators. All drug information (name of product, purpose of administration, dosage, duration of administration, etc.) will be recorded on the patient case report form (CRF).

Randomization and allocation concealment

An independent statistician will conduct randomization, using a computer random number generator of SAS® Analytics Pro (SAS Institute, Inc., Cary, North Carolina, USA). Allocation will be implemented by the manufacturers who collectively label participant's identification code on the packages of the test drug or a placebo using generated random numbers. This labeled drug will be given to the management pharmacist. When the investigator requests medication, the management pharmacist gives the participant the drug corresponding to the participant's identification code. Only the statistician and manufacturer have access to the random numbers, and they will sign and submit a written non-disclosure agreement. After that, just the identification code is used to identify which drug to give to which participant. We will allocate three groups (*wind-heat, wind-cold,* or *others*) at a 1:1:1 ratio of high-dose, standard-dose, and placebo treatment. Stratified block randomization using the Korean Standard Tool of Pattern Identifications of Cough and Sputum will be performed in this trial.

Korean Standard Tool of Pattern Identifications of Cough and Sputum

The Korean Standard Tool of Pattern Identifications of Cough and Sputum is used to identify patterns of acute bronchitis patients. This pattern identification is an important diagnostic criterion in Korean medicine which is used for deciding medication and other therapies. It was proposed in the Traditional Korean Medicine Clinical Practice Guidelines for Antitussives and Expectorants for Korean Medical Diagnostic Standards.[21] This comprises 56 items to classify cases into three patterns: *wind-cold, wind-heat* or *others*. We will investigate the correlation between the patterns and the efficacy of GHX02; the *wind-heat* patterns group is expected to show greater response than the other groups to the therapeutic effects of GHX02.

Blinding

This is a double-blind trial, thus neither participants nor investigators (including outcome assessors) will be aware of group assignment until the end of the study period. Placebo tablets will be matched to GHX02 tablets in terms of colour, taste, and smell, as well as outer packaging. Elimination of blindness will only be considered in cases of serious medical emergencies.

Outcome measures

Primary outcome

Bronchitis Severity Score

The BSS was developed as an evaluation tool for acute bronchitis in 1996 and was recently shown to be valid and reliable by the European Medicines Agency's Committee on Herbal Medicinal Products (HMPC).[20] It has been used successfully in many clinical trials for acute bronchitis. BSS comprises the sum of five major symptom scores for acute bronchitis: cough, sputum, dyspnea, chest pain during coughing, and rales on auscultation. Each symptom is scored on a 4-point-scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe), with a maximum total score of 20 points. The investigator assesses symptom scores on the basis of the patient's subjective

symptoms, and this correlates highly with the patient's actual improvement, as acute bronchitis mainly involves subjective complaints.[22] The change in BSS between day 0 and day 7 will be the primary outcome of this trial.

Secondary outcomes

Assessment of acute bronchitis predominantly depends on subjective tools, but more reliable data can be derived if appropriate objective variables are used together. Symptom and quality of life (QOL) questionnaires will be used as subjective tools, whereas cough frequency will be used as an objective tool; among outcome measures of cough symptoms, only cough frequency and quality of life questionnaires have been shown to be valid.[23]

Questionnaire of Clinical Symptoms of Cough and Sputum

The Questionnaire of Clinical Symptoms of Cough and Sputum (QCSCS) was proposed as a primary outcome measure in the Traditional Korean Medicine Clinical Practice Guidelines for Antitussives and Expectorants[21] and was developed by remodelling the Clinical Asthma Measurement Scale in Oriental Medicine-V for cough and sputum.[24] It is also appropriate for preparing clinical trials of GHX02 as an Investigational New Drug (IND), as it is the suggested tool in Clinical Practice Guidelines from the Ministry of Food and Drug Safety in Korea. Questionnaire items are as follows: (1) cough – frequency, intensity, sensitivity; (2) sputum – frequency, volume, difficulty to cough-up, appearance, colour; (3) activities of daily living; (4) night-time sleeping. Each item is scored on a 4-point-scale, with a total maximum score of 40 points. This questionnaire can evaluate symptoms of cough and sputum more specifically and in more detail than the BSS. The changes in QCSCS from day0 to day7 will be analysed for a secondary outcome.

Leicester Cough Questionnaire

The Leicester Cough Questionnaire (LCQ-K-acute) evaluates quality of life associated with cough. It consists of 19 items divided into three parts, physical, psychological, and social, each scored from 1 to 7. The total score is the sum of the average scores (1–7 points) for each part. The higher the

score, the better the quality of life. Although it was initially developed as an assessment tool for chronic cough, it has also been found to be useful for acute cough, by changing the time criteria from 2 weeks to 24 hours.[25] In addition, the validity and reliability of the Korean version of the LCQ(LCQ-K) has already been verified.[26] The changes of LCQ-K-acute between day0 and day7 will be evaluated.

Frequency of coughing fits

Coughing frequency is an objective measurement tool for evaluating coughing. In this trial, we will ask participants to record how often they cough each day. A cough diary will be given to record their everyday coughing frequency, and participants will be classified into one of the following scales: 0 = 0 time/day, 1 = 1 time/day, 2 = 2-3 times/day, 3 = 4-5 times/day(sometimes), 4 = 6-10 times/day(frequent), 5 = over 15 times/day(consistently).[27] We will evaluate the frequency of coughing fits daily from day0 to day7 and analyse the changes in frequency of coughing fits after 1-7days from the baseline. (change in frequency of coughing fits after k days of study = frequency of coughing fits after k days of study - frequency of coughing fits at day0, where k = 1, 2, ..., 7)

Integrative Medicine Outcome Scale and Integrative Medicine Patient Satisfaction Scale

The Integrative Medicine Outcome Scale is a 5-point-scale for evaluating improvement after treatment (where, 1=complete recovery, 2=major improvement, 3=slight-to-moderate improvement, 4=no change, 5=deterioration), either by the patient or investigator (the investigator in this trial). The Integrative Medicine Patient Satisfaction Scale is a 5-point-scale for evaluating patient satisfaction with the treatment (where, 1=very satisfied, 2=satisfied, 3=neutral, 4=dissatisfied, 5=very dissatisfied).[20] Both will be measured at the patients' final visit (day7) and will be analysed for a secondary outcome.

Withdrawal rate of patients with exacerbation

Exacerbation in this trial means progression of acute bronchitis to bacterial bronchitis or

pneumonia, requiring concomitant medicine such as antibiotics, bronchodilators, glucocorticoids, etc. During the trial, patients will be asked to inform about any signs of worsening symptoms, and investigators will evaluate appropriate measures if they need additional therapy. Those who require concomitant medicines will be excluded from the trial and provided the necessary medicine. We will calculate this withdrawal rate in each intervention and control group to check the relevance with drug effects.

Safety assessment

Safety will be assessed in terms of adverse events (AEs), vital signs, and laboratory examinations (liver function test and routine blood and urine tests). AEs and vital signs will be recorded on a CRF at every visit, and laboratory examinations will be conducted before and after taking the medication. AEs are defined as every unexpected sign or symptom during the trial period and participants are asked to inform about any of these AEs during medication. All information about AEs will be recorded in detail, such as the duration and extent of the AE, relationship with the trial medicine, name of the suspected drug, etc. Common adverse events may include gastrointestinal side-effects, such as anorexia, stomach discomfort, nausea, and diarrhoea, which are not expected to be severe. However, if serious AEs occur that may lead to death or require extended hospitalization, the patient will be removed from the clinical trial as soon as possible and proper treatment will be provided (Table2).

Data management and monitoring

The investigators will follow the Standard Operating Procedures (SOP) of the trial for a better quality of assessment and collection of outcome data. The investigators who evaluate outcome measures should be restricted to only physicians who have attended the training meetings. All assessment data and case reports will be collected at baseline (day0) and at the end of the trial (day7) in both the intervention and control groups. Collected documents and data will be managed by electronic CRF and encrypted using double data entry. Only the principle investigator, or those who have permission, will be able to access the data. The CRFs and other documents will be stored at a separate and secure location for 10 years after trial completion.

Multicentre clinical trial monitoring will be conducted via regular visits (every one-fourth of recruitment) and occasional telephone calls. The information collected will be reported to the data monitoring committee (DMC), comprising specialists in pulmonology and medical statistics who are unrelated to this trial. At visits, a monitor will confirm whether the trial is being conducted in accordance with the protocol and especially AEs are being properly reported and recorded on CRFs. The monitor will check the whole process of the clinical trial and problems will be discussed with the investigator as and when they occur.

Statistical analysis

Data analysis will be performed by an independent statistician using SAS® Analytics Pro. Continuous variables will be summarized by Mean±SD, and categorical variables will be reported with frequencies and percentages according to three treatment groups. Efficacy evaluation will be primarily based on the intention-to-treat (ITT) analysis, and per-protocol (PP) analysis will be used as a secondary analysis. ITT analysis will be conducted for all subjects randomized, and PP analysis will be conducted for those who completed the entire trial without violating the protocol. For primary outcome analysis, the changes in BSS between day0 and day7 will be evaluated using analysis of covariance (ANCOVA) which contains the day0's BSS and the treatment group as covariates. Significance will be accepted at a two-sided test with α-level of 0.05. For effects of GHX02 treatments compared with the control group, 95% confidence intervals (CIs) will be calculated. Analyses of secondary outcomes will be carried out as follows: QCSCS and LCQ-K-acute by ANCOVA including its baseline value respectively; frequency of coughing fits by linear mixed models (LMMs); IMOS and IMPSS by analysis of variance (ANOVA); and withdrawal rate of patients with exacerbation by Pearson's chi-squared or Fisher's exact tests. To handle missing values when processing ITT analysis, the last-observation-carried-forward (LOCF) method will be used except for frequency of coughing fits analysed with LMMs in which missing values need not to be imputed.

Safety assessment will be performed by ITT analysis; all participants randomized will be included. Comparison of the number of adverse events between three treatment groups will be performed using Kruskal-Wallis tests. Demographic and baseline data will be analysed using ANOVA for continuous variables, and Pearson's chi-squared or Fisher's exact tests for categorical variables.

Patient and Public Involvement

Patients and public are not actively involved in the process of this study. The participants will be informed of the study results via peer-reviewed journals, conference and the Clinical Research Information Service.

ETHICS AND DISSEMINATION

The trial protocol (version 1.0) has been approved by the Institutional Review Board (IRB) of the Dunsan Korean Medicine Hospital, Daejeon University (No. DJDSKH-17-DR-14) and has been registered through the clinical trials registry (NCT03310385). If the protocol needs modifications, the investigators are required to inform the IRB (as well as participants) and receive re-approval. Before the trial, investigators are required to provide all information related to the clinical trial, including the possible benefits and risks, other therapeutic choices, and right to withdraw, via a written consent form approved by the IRB. After being provided with sufficient time and opportunity to ask questions and decide whether to participate, all participants are required to provide written consent before study inclusion. All patient identifiable data will be kept confidential, even when the results of the trial are published and participant information will be stored in a secure file, and only the primary investigator (including those who have permission) and the monitor will have access to the data. To ensure confidentiality, all clinical trial documents, such as CRFs, will be recorded and distinguished by the participant identification number throughout the trial. At the end of the trial, the study results will be disseminated via peer-reviewed journals, conference presentation and the Clinical Research Information Service; the participants will also be informed of the results, even unpublished data, including missing data.

DISCUSSION

Despite problems associated with antibiotic abuse in public health systems and the substantial economic burden associated with acute bronchitis, currently no definitive medication is recommended. There are many studies exploring the efficacy of herbal medicines; a systematic review concluded that there was insufficient evidence to support the use of Chinese herbs for acute bronchitis because of the high risk of bias and lack of toxicological evidence.[12] This study is

a multicentre, double-blind, randomized placebo-controlled trial to evaluate the efficacy and safety of two different doses of GHX02, compared with placebo, for acute bronchitis, and we followed strict quality control methods. To ensure a well-designed trial, we conducted a systematic review of randomized controlled trials for acute bronchitis in the last 10 years.[28]

There are some strengths and limitations to this protocol. Contrary to other trials, we will use the Korean Standard Tool of Pattern Identifications of Cough and Sputum, which is a Korean Medical Diagnostic Standard for categorizing cases, to obtain additional information as to whether a certain categories of patients respond better than others to treatment. In this way, we will be able to investigate the efficacy of GHX02 for more specific categories of people suffering from acute bronchitis. Another strength is that the outcome measures we will use in this trial is well balanced between patients' subjective and objective outcomes; thus, the effectiveness of GHX02 will be demonstrated from various aspects. As GHX02 is an herbal prescription which has already been used for acute bronchitis, there is little risk of side-effects and the efficacy of GHX02 is already proven by empirical evidence. This study will provide new evidence for the efficacy and safety of GHX02 in a standard research design and is expected to be presented as a recommended alternative medicine for acute bronchitis.

A limitation of this trial protocol is that we will only target adults, despite most acute bronchitis patients being children under 5 years. As clinical drug trials are recommended to be first applied to adults, we selected adults aged between 19 and 75 years. Further studies for children will need to be conducted after completion of this study.

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Contributors

YRL drafted the research protocol and wrote the manuscript. WKY, SJP, SHK were involved in the protocol development. WK contributed to the statistical design and analysis. ICJ and YCP supervised this protocol. All authors contributed to the conception and implementation of this clinical trial.

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Competing interests

None declared.

Ethics approval

The protocol was approved by the Institutional Review Board of Dunsan Korean Medicine Hospital, Daejeon University.

Provenance and peer review

Not commissioned; externally peer reviewed.

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FIGURE LEGENDS

Figure 1. Flowchart of the study procedure

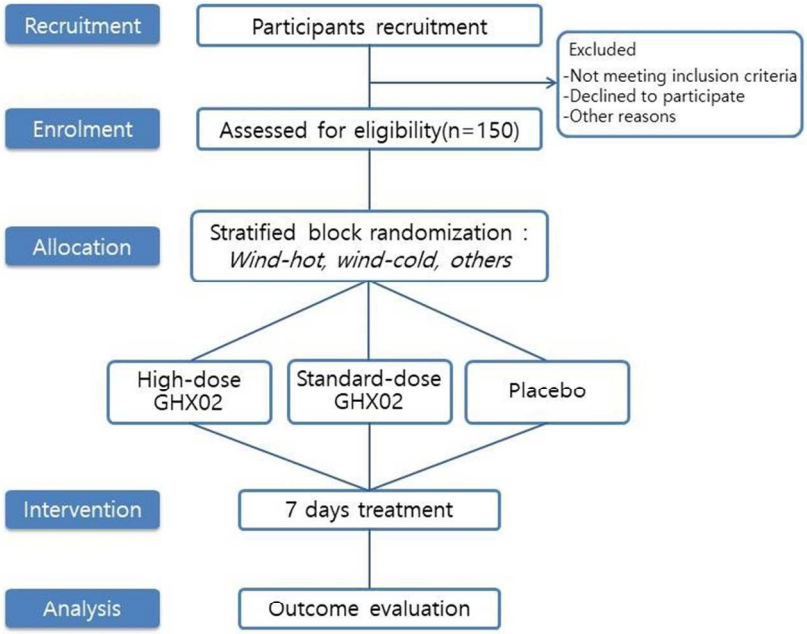

Figure1. Flowchart of the study procedure

Figure1. Flowchart of the study procedure

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p.1,line1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p.2,line26/ p.14,line5
	2b	All items from the World Health Organization Trial Registration Data Set	p.5,line8-12
Protocol version	3	Date and version identifier	p.14,line2
Funding	4	Sources and types of financial, material, and other support	p.16,line18-22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p.16,line13-16
	5b	Name and contact information for the trial sponsor	p.16,line18-22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	-
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	p.14,line1-4

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p.3,line10-p.4,line16
	6b	Explanation for choice of comparators	p.4,line14-16
Objectives	7	Specific objectives or hypotheses	p.4,line12-14
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p.4,line27-29
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p.4,line29-p.5,line2, p.7,line9-11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p.7,line13-p.8,line18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p.6,line22-24
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p.8,line10-14/ p9,line15/ p11,line25-p.12,line4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p.6,line25-26
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p.8,line10-16
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p.9,line18-p.12,line4

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p.5,line13-p.6,line9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p.6,line30-p.7,line5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p.7,line7-10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p.8,line19-20/25-27/29-30
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p.8,line20-23
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p.8,line23-27
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p.9,line12-13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	p.9 ,line15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	p.12,line20-24

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p.6,line25-26
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p.12,line24-26
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p.13,line10-21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p.13,line18-21
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p.13,line21-24
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p.12,line28-p.13,line5
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	p.12,line15-17/ p.11,line25-p.12,line4
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p.12,line11-17 / p.13,line2-4
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	p.12,line28-p.13,line5
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p.14,line2-4

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p.14,line4-5
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p.14,line6-10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	p.14,line6-10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p.14,line10-15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p.16,line24-25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p.14,line12-13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	p.12,line15-17
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p.14,line15-17
	31b	Authorship eligibility guidelines and any intended use of professional writers	p.16,line13-16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	p.14,line15-17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	p.12,line26-27

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.