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Development of Clinical Trial Guidelines for Using Korean Herbal Medicine in Treatment of Common Cold

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감기 치료를 위한 한약제제 임상시험 가이드라인 개발

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Abstract

목적 : 본 연구는 감기에 대한 한약제제 임상시험을 수행하고 평가하는 데 보편적인 원칙을 제공하는 가이드라인 개발 과정 및 내용을 소개하여 가이드라인 활용성 및 접근성을 높이고자 한다.

방법 : 임상시험 가이드라인 개발을 위해 총 9인으로 이루어진 위원회를 구성하고, 전반적인 절차를 수립하였다. 먼저, 가이드라인 집필위원회에서 관련된 국내외 가이드라인을 고찰하고, 감기에 대한 최신 임상시험 논문을 분석하여 초안을 완성하였다. 이후 대한한방내과학회 소속 전문가 자문위원회 검토 및 8인의 전문가로 구성된 협의회 자문을 통해 최종 가이드라인을 도출하였다.

결과 : 본 가이드라인은 (1) 일반적 사항 (2) 유효성 평가 기준 (3) 유효성 평가 방법 (4) 시험 대상자 선정 (5) 임상시험 설계 (6) 안전성 평가 (7) 감기 치료에서의 병용요법 (8) 한의학적 고려 사항의 8가지 범주로 나뉘어진다. 최종 개발된 가이드라인은 한의약임상시험센터 협의회와 대한한방내과학회의 인증을 득하였다.

결론 : 본 가이드라인은 감기 치료를 위한 임상시험을 수행하고 평가하는 데 유용하게 사용될 것이며, 이를 통해 신뢰할 수 있는 결과를 이끌어내고 정확한 해석을 용이하게 할 수 있을 것이라 기대된다. 또한 추후 해당 가이드라인 개정 및 관련된 호흡기질환 가이드라인 개발 과정에 도움을 줄 수 있을 것으로 사료된다.

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Ⅰ. Introduction

The common cold is an acute upper respiratory infection caused by various pathogens, including viruses, and is characterized by clinical symptoms such as runny nose, nasal congestion, sneezing, and sore throat.[1] It is the most common cause of human illness, with adults experiencing it four to six times annually, and children under 6 years old typically getting infected six to eight times a year.[2] In 2022 in South Korea, 4,198,152 people out of a health insurance recipient population of 47 million received medical care for acute rhinopharyngitis (common cold), with relevant medical costs reaching 189 billion Korean won.[3] Although the common cold is a mild disease, it has a considerable impact on people's daily lives or social activities, while also posing a socioeconomic burden.[4,5] Great interest has been directed towards the discovery of a medication or natural treatment that relieves cold symptoms.

More than 200 different viruses can cause a cold, and it is well known that identifying the specific viral pathogen is inefficient to treat a cold.[1,2] The therapeutic efficacy of antibiotics and anti-histamines, which are commonly used for the treatment of colds, is unclear and associated with multiple side effects.[6,7] Therefore, the need for safe and effective pharmacotherapy for the cold is increasing. There is a long history of treating the common cold using Korean medicine, called *gammo*. Several traditional Korean medicine (TKM) prescriptions have been used to effectively treat the common cold. However, the treatments have little scientific basis.

Although the demands for clinical trials to establish objective evidence for the efficacy and safety of clinically used herbal medicines are increasing, there is no specific guideline for clinical trials on herbal medicines for the common cold. A good clinical study design is the most important component of a study that will result in a good quality clinical trial. In addition to the general methodology employed in the clinical trials of Western medicines, the unique features of herbal medicine should be considered during a clinical trial. Protocol guidelines or reporting guidelines enhance the quality of the trial and contribute to producing significant outcomes. Investigators may refer to the Consolidated Standards of Reporting Trials (CONSORT) for reports on herbal medicine clinical trials[8,9] and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[10] for writing protocols; however, these guidelines cannot provide detailed and specific information about common cold. Moreover, they do not take into account the unique characteristics of the TKM theory and herbal medicines. The Ministry of Food and Drug Safety (MFDS) in South Korea has attempted to present a clinical trial guideline for herbal medicine, but only six guidelines have been developed with no guideline for the common cold or diseases related to the common cold.[11] Clinical trials related to the treatment of colds are being actively encouraged, and a clinical trial guideline is required for corporate personnel and researchers who strive to improve study quality and initiate clinical trials.

Therefore, the Korean Pharmaceutics Clinical Trial Team at the Kyung Hee Korean Medicine Hospital Korean Medicine Clinical Trial Center aimed to develop a guideline that would provide the general principles for performing and assessing clinical trials on Korean medication used to

treat colds. Here, we share our discussions throughout the process of developing the guideline.

II. Methods

1. Development process

Utilizing the expertise of professionals associated with the Korean Medicine Clinical Trial Center, experienced in developing clinical trial guidelines for using Korean herbal medicine, the guideline development process was meticulously planned. This involved forming a guideline committee, consisting of a guideline development team and an expert panel, as well as establishing the Korean Medicine Clinical Trial Center Council review board. Initially, the development team conducted an investigation into domestic and international clinical trials and treatment guidelines related to Korean herbal medicine for the common cold, based on which a draft guideline was formulated. This draft underwent revisions following review by the expert panel. Subsequently, through two face-to-face meetings with the Korean Medicine Clinical Trial Center Council review board, consisting of eight relevant experts, and written review by a relevant academic society, the guideline was finalized. Certification by a relevant academic society was conducted by the Society of Internal Korean Medicine, the largest internal Korean medicine society in South Korea. Ultimately, the guideline obtained certification from the Society of Internal Korean Medicine and the Korean Medicine Clinical Trial Center Council. The development process is illustrated in Figure 1.

2. Guideline Committee

The guideline committee comprised a guideline development team and expert panel. The guideline development team was in charge of the administrative duties and the writing of the guideline. Administrative duties included planning the development, recruiting experts, collecting expert opinions, facilitating the general process of development, providing administrative support, and performing publishing-related tasks. Writing the guideline involved writing the content based on the results of a literature review and cross-checking the references. The structure of the guideline was established through the consensus of a team of five experts: one professor of Respiratory Medicine in Korean Medicine with over 3 years of experience, one professor of Sasang Constitutional Medicine within a Korean Medicine Clinical Trial Center with over 5 years of experience, one professor of Clinical Medicine in Korean Medicine with over 3 years of experience, one research methodologist with over 3 years of experience, and one statistician with a doctoral degree and over 3 years of experience.

The expert panel consisted of external experts who reviewed the outline, method of preparation, and contents of this guideline. The board consisted of two professors of Respiratory Medicine in Korean Medicine with over 5 years of experience each, one professor of Respiratory Medicine in Korean Medicine with over 10 years of experience, and one research professor of Gastroenterology in Korean Medicine with over 3 years of clinical trial experience.

3. Preparation of the first draft

This guideline adhered to the Korean Good Clinical Practice. We referred to the respiratory tract-related guidelines (asthma, chronic obstructive pulmonary disease) by the European Medicines Agency (EMA),[12] clinical trial guideline for herbal medicines published by the MFDS,[11] existing cases of clinical trials related to the common cold, and Chinese guidelines for common cold.[13] The table of contents and lists of contents were

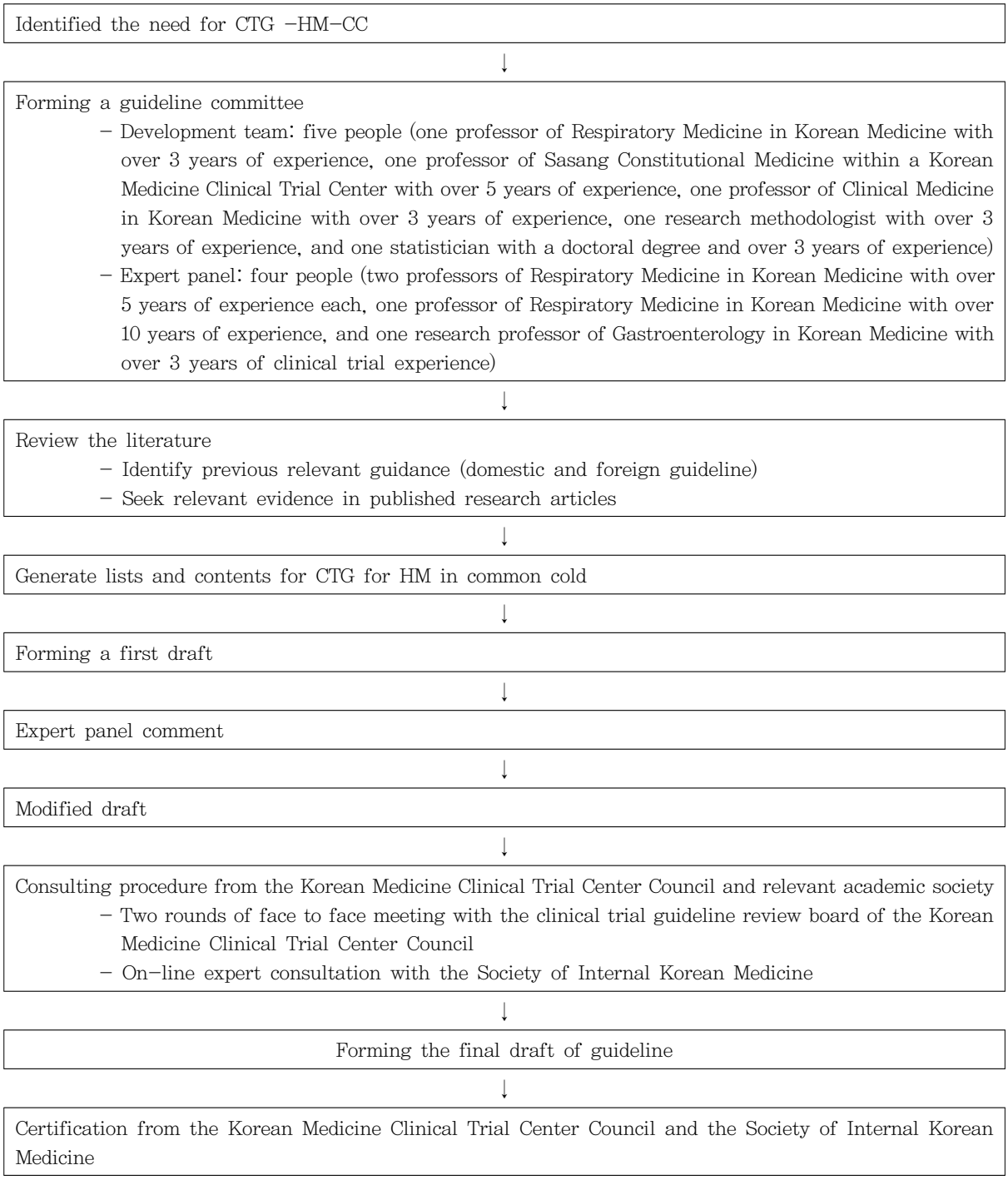

Figure 1. The Process of Development of Clinical Trial Guidelines for Using Korean Herbal Medicine in Treatment of Common Cold (CTG–HM–CC).

determined under the supervision of the expert panel, and the first draft was written to reflect the current state of affairs in Korea and Korean medicine clinical trials.

We searched for the latest clinical trials on the common cold in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) using the keywords *common cold, upper respiratory tract infection, rhinovirus, and corona virus*. The period of search was set to the last 10 years, subjects to human subjects, and language to English in the title and abstract

category. The selected papers were reviewed and the following were analyzed: the general outline, aims, sample size, intervention and control groups, treatment duration, and assessment tools. We reported the results of literature process to the journal.[14] Relevant contents were reflected in the guideline. The expert panel reviewed, edited, and revised the contents of the first draft.

4. Review process and certification by Korean Medicine Clinical Trial Center Council and relevant academic society

After completing the first draft, we requested a review from the Korean Medicine Clinical Trial Center Council and the Society of Internal Korean Medicine. The Korean Medicine Clinical Trial Center Council has a clinical trial guideline review board consisting of 8 experts. This includes one member from the Clinical Research Department of the Korea Institute of Oriental Medicine (as the chairperson), one pharmaceutical personnel, one contract research organization worker, one professor of Korean Pharmaceutical Science, and four Korean Medicine clinical professors (including one professor specializing in Sasang Constitutional Medicine from the Korean Medicine Clinical Trial Center, one professor of Gastroenterology in Korean Medicine, one professor of Respiratory Medicine in Korean Medicine, and one professor of Psychiatry from the Korean Medicine Clinical Trial Center). Two rounds of face-to-face meetings were conducted with the review board to review the first draft and revise accordingly. A written expert consultation was performed by the Society of Internal Korean Medicine per the society's certification procedures. We completed the final draft based on the expert opinions of the Korean Medicine Clinical Trial Center Council and Society of Internal Korean Medicine and obtained approval.

Ⅲ. Results

The guideline includes background information, the definition of a common cold, trial design, inclusion and exclusion criteria, efficacy evaluation tool, interventional drug, placebo, safety evaluation, analysis method and pattern differentiation. The list of contents is shown in Table 1 and the full version of the guideline is presented in the Appendix.

We shared several major concerns and discussions from our experience during the development to help the understanding of other researchers.

1. Definition of the common cold and *gammo*

In Korean medicine, the common cold is referred to as *gammo*, and is considered a disease caused by pulmonary dysfunction as a result of the wind (*pungsa*) infiltrating the pulmonary system (nasal cavity, pharynx, bronchus), causing pulmonary dysfunction. *Gammo* has been classified into several pattern types, including wind-cold *gammo*, wind-heat *gammo*, complicated dampness *gammo*, epidemic *gammo*, qi-deficiency *gammo*, blood-deficiency *gammo*, yin-deficiency *gammo*, and yang-deficiency *gammo*, depending on the pattern of the diagnostic system used. Among these, epidemic *gammo* falls under today's definition of influenza and epidemic infectious disease and is in a different category than that of the common cold. Hence, in this guideline, the common cold was defined as acute rhinopharyngitis (KOICD diagnosis code J00), which only accounts for a part of the conditions included in *gammo*, according to the latest views on the disease. We included the patterns of Korean medicine diagnosis that

Table 1. Contents of the Guideline

Number	Title	Main Content
1.	Introduction	The basis and purpose of this guideline.
2	General Information	
2.1.	Definition and classification of common cold	Definition of the common cold in Western medicine and traditional Korean medicine, as well as several pattern differentiation systems of the common cold.
2.2.	Pathophysiology of common cold	Types of viruses that cause the common cold and the transmission routes of the virus.
2.3.	Diagnostic criteria of common cold	Clinical symptoms indicative of the common cold, differential diagnoses, and complications.
2.4.	Clinical significance of common cold	The role of traditional Korean medicine and the necessity of clinical trials for Korean herbal medicine in the treatment of the common cold.
2.5.	Standard treatment methods	Clinical recommendations that were published by the Society of American Family Physicians.
3.	Assessment tools	
3.1.	Wisconsin Upper Respiratory Symptom Survey (WURSS)	As a tool developed to measure symptom severity and quality of life, WURSS is recommended as a primary assessment tool in clinical studies.
3.2.	Severity of symptoms	Introduction of Jackson Cold Index, Symptom Severity According to Korean Medicine, and Visual Analogue Scale (VAS).
3.3.	Symptom duration	Symptom duration can be used as a primary assessment tool.
3.4.	Nasal airway resistance (NAR)	NAR can be used as a primary assessment tool.
3.5.	Quality of Life measurement tools	General quality of life measurement questionnaires can be used as a secondary assessment tool.
4.	Validity assessment methods	
4.1.	Wisconsin Upper Respiratory Symptom Survey (WURSS)	Introduction of WURSS-44, WURSS-21, WURSS-11, and WURSS-K.
4.2.	Total daily symptom score (TDSS)	TDSS measures cold symptoms, which were first characterized by Jackson and colleagues, using a 4 point Likert scale.
4.3.	Symptom duration	Symptom duration is assessed per hour or per day, from the initial date of intervention to the last day that the cold symptoms are observed.
5.	Participant selection	
5.1.	General considerations	Considerations for setting or reporting inclusion criteria.

Number	Title	Main Content
5.2.	Main inclusion criteria	1) Children or adolescents that are below 18 years of age, or adults above 19 years of age. 2) (If applicable) Diagnosed with common cold. 3) Perceived to have had common cold symptoms within 24 to 48 hours. 4) (If applicable) Presenting common cold symptoms that correspond with cold criteria. 5) (If applicable) Diagnosed according to Korean Medicine pattern differentiation. 6) Signed informed consent form prior to any study-related procedures.
5.3.	Main exclusion criteria	1) Paranasal sinusitis, allergic rhinitis, pneumonia, flu, bronchitis, acute otitis media, acute tonsillitis. 2) Chronic respiratory diseases (COPD, interstitial lung disease), asthma. 3) Subjects who have taken medication that can suppress cold symptoms, such as antibiotics, antiviral medication, steroids, decongestants, antihistamines, and more. 4) (If applicable) Subjects with diseases that are not known to affect common cold but is currently progressing such as systemic diseases, and autoimmune disorders. 5) (If applicable) Subjects diagnosed with Korean Medicine pattern differentiation that does not coincide with common cold. 6) Subjects with diabetes, tumor, congestive heart failure. 7) Subjects who are pregnant. 8) Other subjects that are deemed inappropriate to participate by the researcher.
6.	Clinical trial design	
6.1.	Therapeutic trial	Recommendations about therapeutic exploratory studies, therapeutic confirmatory studies, and control group.
7.	Safety evaluation	Safety evaluation items, classification and analysis methods.
8.	Administration of combined therapy and complex medicines during treatment of common cold	While participating in the clinical trial, any consumption of medication that can alleviate the common cold symptoms should be restricted.
9.	Points to consider in Korean Medicine	
9.1.	Classification criteria for pattern differentiation in Korean Medicine	The pattern differentiation of the Guiding principles of clinical research on new drugs of traditional Chinese medicine, Chinese guidelines on common cold, and evidence-based clinical guidelines of common cold.
9.2.	Points to consider regarding herbal medicine used in clinical trials	Considerations during investigational product manufacturing and information to be included on the container for investigational medicinal products.
10.	References	

falls under the definition of the common cold in this guideline.

Since the common cold is a syndrome that is based on the clinical symptoms reported by the patient and not a disease definitively diagnosed by test results, the scope of the common cold was a major issue throughout the process of developing this guideline. Using other guidelines, the most recent inclusion and exclusion criteria used by common cold clinical trials, and expert opinions as references, we defined the common cold as a type of upper respiratory tract infection syndrome characterized by mild and self-limiting clinical symptoms of a viral infection, such as nasal obstruction, nasal drainage, sore throat, and cough. We excluded conditions with symptoms that overlapped with those of the common cold, but are not diagnostically classified as common cold, such as sinusitis, allergic rhinitis, pneumonia, influenza, bronchitis, acute otitis media, and acute tonsillitis.

Based on this process, we developed the inclusion and exclusion criteria listed in Table 2.

2. Efficacy assessment

We recommended practical evaluation parameters as the primary and secondary endpoints based on their use in common cold clinical trials and established their validity and reliability. We recommended the Wisconsin upper respiratory symptom survey,[15-17] Jackson score[18], and duration of symptoms as the primary endpoints and quality of life and visual analogue scale (VAS) as the secondary endpoints. The instruments for efficacy assessment were listed with detailed explanations to help investigators use them. The forms for the assessment scales were attached as appendices. There was not much disagreement during the review of the efficacy assessment instruments. To ensure a wide range of options for researchers, we did present the relative importance of each tool but included a variety of tools in the guideline. In consideration of TKM assessments, we also included a tool for evaluating the severity of Korean medical symptoms.

3. Korean medicine pattern diagnosis

Pattern differentiation is a unique diagnostic system in TKM. The use and prescription of Korean medicine are fundamentally performed based on pattern diagnosis. Thus, pattern differentiation should be carefully dealt with in clinical trials for Korean medicine. Indeed, it is possible to conduct a clinical trial without regard to the concept of pattern diagnosis, as done in clinical trials for Western medicine, simply by using Korean medicine as the trial drug. However, pattern differentiation should be considered in the study design in order to reflect the clinical setting in which Korean medicine is used. When considering a clinical trial based on pattern differentiation, the concept of pattern should be reflected in the study design, selection of inclusion/exclusion criteria, selection of outcome measures and interpretation of the data, etc.[19]

The pattern has been developed through generations based on the key pattern diagnostic systems at the time. Based on the decision that it is not only impossible but also not useful to include all of the diverse pattern diagnoses related to the common cold, we reviewed and organized the types of pattern diagnoses for the common cold based on the pattern diagnostic systems established through systematic reviews and research conducted by countries that generally use herbal medicine, such as China and Korea.[13,20] Clinically, the wind-cold and wind-heat types seem to hold significance, but other patterns may be added depending on the nature of the clinical trial. We explained pattern differentiation in the separate part named “Point to consider in Korean Medicine”. We also reflected pattern differen-

Table 2. Inclusion/Exclusion Criteria

Criteria	
Inclusion criteria	
	1. Children or adolescents that are below 18 years of age, or adults above 19 years of age
	2. (If applicable) Diagnosed with common cold
	3. Perceived to have had common cold symptoms within 24 to 48 hours
	4. (If applicable) Presenting common cold symptoms that correspond with cold criteria
	5. (If applicable) Diagnosed according to Korean Medicine pattern differentiation
	6. Signed informed consent form prior to any study-related procedures
Exclusion criteria	
	1. Paranasal sinusitis, allergic rhinitis, pneumonia, flu, bronchitis, acute otitis media, acute tonsillitis
	2. Chronic respiratory diseases (COPD, interstitial lung disease), asthma
	3. Subjects who have taken medication that can suppress cold symptoms, such as antibiotics, antiviral medication, steroids, decongestants, antihistamines, and more.
	4. (If applicable) Subjects with diseases that are not known to affect common cold but is currently progressing such as systemic diseases, and autoimmune disorders
	5. (If applicable) Subjects diagnosed with Korean Medicine pattern differentiation that does not coincide with common cold
	6. Subjects with diabetes, tumor, congestive heart failure
	7. Subjects who are pregnant
	8. Other subjects that are deemed inappropriate to participate by the researcher

tiation in the inclusion/exclusion criteria.

4. Treatment duration

Since the common cold is a self-limiting disease, we recommended that subjects be recruited within 1 to 2 days after the onset of cold and medicine be administered for at least three days. This guideline was determined based on existing clinical trial protocols and expert opinions. We specified that medicine administration should not exceed eight days.

5. Combination therapy & Safety

With regard to combination therapies, all types of drugs that may mitigate cold symptoms were prohibited during the clinical trial period. It is because common cold is a mild and self-limiting disease and there is no established, recommended standard therapy for the common cold. However, the use of rescue drugs was permitted if the clinical trial included the frequency of rescue medication as an evaluation parameter.

Safety assessment adhered to the general principles of Korean medicine clinical trials, encompassing adverse reactions, physical evaluation, laboratory tests, and internal symptom tests.

6. Others

When considering a clinical trial using Korean herbal medicine, researchers have to consider the qualifications of the herbal medicine. For example, in order to manufacture herbal medicinal products that use raw herbs as their main ingredients, the origin of the herbs must be checked with at least two herb analysts. The manufacture process must be recorded with utmost precision and standardization must be established prior to conducting the clinical trial.

The common difficulties in the clinical trials

of Korean herbal medicine are as follows. First, there is few validated and reliable pattern differentiation tool so researchers don't use appropriate pattern diagnosis or evaluation tool while designing the trial with pattern. Second, the provision of matching placebo in herbal medicine is not simple since herbal medication has unique taste and unusual odour.

Ⅳ. Discussion

Although the common cold is a self-limiting, mild respiratory syndrome, it is highly prevalent and affects the quality of life by hindering the affected individuals from carrying on with their social activities and daily lives.[4,5] In particular, identifying the cause of the cold would be ineffective due to the diverse pool of pathogenic viruses for the common cold.[1,2] Drug therapies, such as treatment with antibiotics, are unsatisfactory with no solid basis.[7] This adds to the need for herbal agents to treat the common cold.[21] Herbal agents have been widely used to treat the common cold for a long time and currently, it is reported to be very popular in South Korea.[22]

The demand for clinical trials to verify the efficacy and safety of clinically used herbal medicines is increasing, yet there are no specific clinical trial guidelines for using herbal medicines in treatment of common cold.[14] Although references such as CONSORT and SPIRIT are available,[8,9,10] these guidelines are the general methodology and do not address the specificities of the common cold, nor do they consider the unique characteristics of herbal medicine and TKM theory. In Korea, the importance of well-designed clinical trials has been recognized and some guidelines for TKM prescriptions have been established, but guidelines specifically for clinical trials related to herbal medicines for the common cold have not yet been established.[11]

Therefore, we aimed to develop guidelines that provide the general principles for performing and assessing clinical trials on the treatment of common cold using herbal medicine. In this study, we introduce the process of developing a guideline that reflects the protocol commonly used in Western medicine and the distinct properties of the herbal agents, as well as share the contents of the developed guideline. Ultimately, this study aims to provide a guideline for clinicians seeking to conduct clinical trials by introducing the issues they should consider in the design and overall process of the clinical trial in order to produce quality data.

This study has many strengths. First, this study presented the scope of the common cold included in clinical trials by reflecting the latest evidence and expert opinions on the nature of the common cold, which is usually diagnosed based on clinical symptoms, as opposed to objective tests, is short-lasting, and is difficult to differentiate from other diseases. Second, this study presented pattern differentiation, a unique diagnostic system in Korean medicine, which is the basis for prescribing herbal medicine, and the pattern differentiation system that has been used for the common cold in an easily comprehensible format. Third, this study presented tools for efficacy assessment and considered the importance of each tool. Most of all, the investigators strived to develop an unbiased, reliable guideline by collecting data through a systematic review of the clinical trials of the common cold from the past ten years in collaboration with a methodology expert. In addition, the contents were reviewed by experts from relevant fields in order to prepare the outline of the guideline based on these data. One shortcoming of this guideline is that it was developed for use in Korea and its use in other countries would be limited. Nevertheless, the development protocol or contents presented in this study would be helpful for developing guidelines for similar

topics.

V. Conclusions

As shown here, this study developed the "Guideline for clinical trials of Korean herbal medicine for the common cold treatment" with sound scientific grounds and adherence to international standards by reviewing the latest domestic and global data, while also considering the unique features of Korean medicine. We expect this guideline to be used in various clinical trials for developing herbal agents that treat the common cold, improving the safety and efficacy of herbal agents, and ultimately contributing to the development of new herbal agents. Furthermore, this guideline will be revised and modified to keep abreast with the latest trends and situations. We hope this guideline proves to be widely useful.

List of abbreviations

CENTRAL: Cochrane Central Register of Controlled Trials

CONSORT: Consolidated Standards of Reporting Trials

CTG -HM-CC: Clinical Trial Guidelines for Using Korean Herbal Medicine in Treatment of Common Cold

EMA: European Medicines Agency

MFDS: Ministry of Food and Drug Safety

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

TKM: traditional Korean medicine

VAS: visual analogue scale

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The guideline will be presented in an appendix. Other data related to this study will be available from the corresponding author upon reasonable requests.

Conflicts of interest

The authors declare that they have no competing interests.

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Appendix. Clinical Trial Guidelines for Using Korean Herbal Medicine in Treatment of Common Cold

Clinical Trial Guidelines for Using Korean Herbal Medicine in Treatment of Common Cold

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Contents

1. Introduction

This guideline has been developed based on other clinical guidelines and research papers that were published in South Korea, China, USA, etc. in order to: 1. provide general recommendations in the development of Korean herbal medicine for treatment/alleviation of symptoms related to common cold; 2. be used for assessing already developed Korean herbal medicine products for common cold.

2. General information

2.1. Definition and classification of common cold

Common cold is a self-limiting disease caused by a virus that produces acute respiratory tract infection with mild symptoms ranging from nasal obstruction, runny nose, sore throat, cough and more [1].

In East Asian Medicine, common cold is referred to as 'gam mo'(感冒) and several pattern differentiation systems have been developed. In his book Shanghanlun (Treatise on Cold Damage Disorders), Zhang Zhongjing (Han dynasty, China) explained the changing symptoms and the pathology of the exogenous pathogens according to the six channel theory (六經), and later on, the concept of ba gong (八綱) was added to include syndromes such as wind-cold gam mo, or wind-heat gam mo. Overall, gam mo is described to be caused by the wind pathogen invading the Lung system (nasal cavity, throat, bronchial tube) and hence harming Lung Qi. The main symptoms include chilliness, fever, headache, malaise, nasal obstruction, runny nose, sneezing, tickly throat, and cough [2].

2.2. Pathophysiology of the Common Cold

The common cold is caused by a virus invading the respiratory organs and the mucous membranes. About 200 kinds of viruses with different antigenicity are known to cause inflammation, and among them, the most frequently identified viruses are rhinovirus, corona virus, and respiratory syncytial virus (RSV). Rhinovirus is known to have more than a hundred serotypes, responsible for approximately 30-50% of the colds and up to 80% of the colds caused in autumn. In general, an average adult is expected to experience 2-4 common cold bouts per year with the cold being clearly seasonal. The viruses are transmitted via different routes including ① skin contact ② direct nasal droplets and ③ airborne viruses circulating in the air for considerably long periods of time [1, 3, 4].

Virus	
Rhinoviruses	30-50%
Coronaviruses	10-15%
Influenza viruses	5-15%
Respiratory synctial virus	5%
Parainfluenza viruses	5%
Adenoviruses	〈5%
Enteroviruses	〈5%
Metapneumovirus	Not known
Unknown	20-30%

〈Reference: Heikkinen T, Järvinen A. The common cold. Lancet. 2003;361(9351):51-9〉

2.3. Diagnostic Criteria of the Common Cold

The common cold is primarily diagnosed based on the symptoms experienced and observed in the clinic. Symptoms such as runny nose, nasal obstruction, cough, and mild fever can be diagnosed as acute infectious rhinitis, acute rhinopharyngitis, acute coryza, acute cold, or grouped into nonspecific acute upper respiratory infection, also known as the common cold [5,6]. The disease has an incubation period that is different depending on the type of virus causing the symptoms. Most symptoms will naturally subside in 7 to 10 days but if the symptoms persist, further diagnosis should be made to check if there are accompanying bacterial infections. Tympanitis and rhinosinusitis are important complications [1,4].

2.4. Clinical Significance of the Common Cold

The common cold is a frequently occurring disease that affects social and daily life, leading to frequent absence from work or school. According to the Medical Cost Care Index in 2014, the common cold was ranked the 17th (124,430 people) most frequently claimed medical condition, and the 2nd (307,528 people) most frequently claimed medical condition when the claims for 'unspecified acute respiratory tract infection' were included [7].

Importantly, the need for Korean Medicine treatment for common colds is increasing. Since it is caused by many different viruses, focusing treatment on eradication of a specific virus is ineffective, and the benefits of using conventional medicine for the common cold is limiting. For a long period of time, Korean Medicine has played an important role in the treatment of the common cold and with time-tested efficacy, doctors have diagnosed patients using pattern differentiation and by prescribing herbal treatment accordingly. If more clinical trials can verify the therapeutic effects of Korean herbal medicine, we believe that this may in effect, reduce medical costs related to therapies that overly emphasize the Western medical viewpoint in the treatment of the common cold.

2.5. Standard Treatment Methods

There is no established standard treatment method for the common cold. The following table shows a few clinical recommendations that were published by the Society of American Family Physicians [8]. The recommendations were based on results of randomized controlled trials and systematic reviews that explored the use of medicine or alternative medicine as a treatment intervention. The included systematic reviews were those published by the Cochrane Review Group. Despite a few limitations (not clearly identifying the selection criteria and the research methodology, analysis that is limited to only those that used conventional medicine and alternative medicine, and the omission of several latest reviews), the recommendations outline several key guidelines for practice.

Clinical recommendation	Evidence rating
Antibiotics should not be used for the treatment of cold symptoms in children or adults.	A
Over-the-counter cough and cold medications should not be used in children younger than four years because of potential harms and lack of benefit.	B
Treatment with buckwheat honey, Pelargonium sidoides (geranium) extract (Umcka Coldcare), nasal saline irrigation, vapor rub, or zinc sulfate may decrease cold symptoms in children.	B

Clinical recommendation	Evidence rating
Codeine is not effective for cough in adults.	A
Antihistamine monotherapy (sedating and nonsedating) does not improve cold symptoms in adults	A
Decongestants, antihistamine/decongestant combinations, and intranasal ipratropium (Atrovent) may improve cold symptoms in adults	B
Nonsteroidal anti-inflammatory drugs reduce pain secondary to upper respiratory tract infection in adults.	A
Andrographis paniculata (Kalmcold) and P. sidoides may reduce severity and duration of cold symptoms in adults	B

A = consistent, good-quality patient-oriented evidence
B = inconsistent or limited-quality patient-oriented evidence
C = consensus, disease-oriented evidence, usual practice, expert opinion, case series

〈Reference: Fashner J, Ericson K, Werner S. Treatment of the common cold in children and adults. Am Fam Physician. 2012;86(2):153-9.〉

3. Assessment Tools

3.1. Wisconsin Upper Respiratory Symptom Survey (WURSS)

While conducting a randomized controlled trial in 1999, Barrett and colleagues felt a strong need to develop an assessment tool that could additionally measure quality of life. In 2000, he developed WURSS, a new assessment tool consisting of 44 items and evaluated for validity [9]. Consequently, he further selected 21 items with high internal validity and developed a short form, WURSS-21, which was also evaluated for credibility and validity [10]. An even simpler version with only 11 items (WURSSS-11) [11], and a version for kids (WURSS-K) was also developed.

In Korea, Yang et al. completed validation of WURSS-44-K, the Korean version of WURSS [12]. WURSS-21-K (Korean version of WURSS-21) has been used in a Korean clinical trial and the results have been published [13]. As a tool developed to measure symptom severity and quality of life, WURSS is recommended as a primary assessment tool in clinical studies.

3.2. Severity of symptoms

3.2.1. Jackson Cold Index

The Jackson Cold Index uses a Likert scale to quantify the severity of cold symptoms which were first identified by Jackson and colleagues in 1958 [14]. It is frequently used as a diagnostic tool as well as a tool to measure symptom severity. It has been used in many randomized controlled clinical trials and there have been no negative reports. As it is generally well accepted in trials, the Jackson Cold Index is recommended as a primary and secondary assessment tool.

3.2.2. Symptom Severity According to Korean Medicine

Based on the Guiding principles of Clinical Research on New drugs of traditional Chinese Medicine, the symptom severity for the common cold defined in East Asian Medicine is as follows. It may be utilized in trials when appropriate [15].

Symptom	Light(經)	Moderate(中)	Heavy(重)
Chilliness(惡寒)	Feels slightly cold but does not necessarily wear more clothes.	Feels cold and wears more clothes.	Feels cold and wears a heavy coat or covers up with a thicker blanket.
Fever(發熱)	Body temperature between 37.1~37.9	Body temperature between 38.0~38.5	Body temperature above 38.6
Nasal obstruction(鼻塞)	Slight nasal obstruction with changes in voice.	Occasionally plugged nose.	Constantly plugged nose.
Myalgia(身體酸痛)	Mild body ache and soreness.	Body ache and soreness.	Severe body ache and soreness, difficult to move around.
Sore throat(咽痛)	Dry and slightly sore throat.	Sore throat.	Severely sore throat.
Runny nose(流涕)	Occasionally runny nose.	Slightly runny nose.	Constantly runny nose.
Perspiration(汗出)	Slight sweating.	Sweating.	Profuse sweating.
Headache(頭痛)	Mild, occasional headache.	Constant headache.	Severe headache that interferes with work.
Cough(咳嗽)	Occasional cough.	Intermittent cough.	Frequent cough. .
Dry mouth(口渴)	Slightly dry mouth.	Dry mouth.	Severely dry mouth.

3.2.3. Visual Analogue Scale (VAS)

The Visual Analogue Scale measures the subjective aspects of symptoms and its severity, thus can be used as a secondary assessment tool for measuring changes induced by treatment for relief of general common cold symptoms or specific symptoms (ex: nasal obstruction).

3.3. Symptom Duration

Symptom duration can be used as a primary assessment tool. It can be used to measure the period from initial treatment/intervention up to the last day of symptom presentation, as pre- defined by the researchers.

3.4. Nasal Airway Resistance (NAR)

If the study focuses on specific nasal symptoms of the common cold, nasal airway resistance can be used as a primary assessment tool.

3.5. Quality of Life Measurement Tools

The common cold affects patients' social and general quality of life, and treatment goals emphasize alleviating symptoms rather than reducing inflammation. Quality of life measurement tools can be used to compare the treatment effects before and after intervention. For this, general quality of life measurement questionnaires such as SF-8® Health Survey, EQ-5D (EuroQoL score) can be used as a secondary assessment tool.

4. Validity Assessment Methods

4.1. Wisconsin Upper Respiratory Symptom Survey (WURSS) (Appendix)

4.1.1 WURSS-44 [9]

WURSS-44 uses an 8 point Likert scale (0 to 7 points) to assess 32 items related to cold symptoms, 10 items related to quality of life, 1 item on general symptom severity, and 1 item assessing changes in symptom severity.

The last item measures changes in symptom severity by asking the participant to answer whether the symptoms have become "very much better – somewhat better – a little better - the same - a little worse - somewhat worse - very much worse" compared to yesterday. Since the last item measures a different aspect of the symptoms, the total score is calculated by adding only the first 43 items. The total score reveals the severity of the disease with 301 points being the most severe. If needed, scores of the items related to symptoms and scores of the items looking into the functional aspects of quality of life can be added separately to reveal different scores for each.

WURSS-44 is provided to the participants to be marked every day. The baseline scores and the scores measured after final application of intervention can be compared to assess whether there are statistically significant improvements, or the mean scores of the treatment group and the control group can be compared on the last day of intervention.

4.1.2. WURSS-21 [10]

WURSS-21 is a revised, short form of WURSS-44.

It uses an 8 point Likert scale (0 to 7 points) to assess 10 items related to cold symptoms, 9 items related to quality of life, 1 item on general symptom severity, and 1 item assessing changes in symptom severity.

The last item measures changes in symptom severity by asking the participant to answer whether the symptoms have become "very much better – somewhat better – a little better - the same - a little worse - somewhat worse - very much worse" compared to yesterday.

The last item in WURSS-21 is identical to the one in WURSS-44 and measures a different aspect of the symptoms. Thus, the total score is calculated by adding only the first 20 items. The total score reveals the severity of the disease with 140 points being the most severe. If needed, scores of the items related to symptoms and scores of the items looking into the functional aspects of quality of life can be added separately to reveal different scores for each.

WURSS-21 is also provided to the participants to be marked every day. The baseline scores and the scores measured after final application of intervention can be compared to assess whether there are statistically significant improvements, or the mean scores of the treatment group and the control group can be compared on the last day of intervention.

4.1.3. WURSS-11 [11]

WURSS-11 uses a 7 point Likert scale to measure 7 items related to cold symptoms, 2 items related to quality of life, 1 item on general symptom severity, and 1 item assessing changes in symptom severity.

The last item measures changes in symptom severity by asking the participant to answer whether the symptoms have become "very much better – somewhat better – a little better - the same - a little

worse - somewhat worse - very much worse" compared to yesterday.

The last item in WURSS-11 is identical to the one in WURSS-44 and WURSS-22, and measures a different aspect of the symptoms. Thus, the total score is calculated by adding only the first 10 items. The total score reveals the severity of the disease with 70 points being the most severe. If needed, scores of the items related to symptoms and scores of the items looking into the functional aspects of quality of life can be added separately to reveal different scores for each.

WURSS-11 is also provided to the participants to be marked every day. The baseline scores and the scores measured after final application of intervention can be compared to assess whether there are statistically significant improvements, or the mean scores of the treatment group and the control group can be compared on the last day of intervention.

4.1.4. WURSS-K

WURSS-K was developed for kids. To make it easier for kids to answer each item, images of different facial expressions are provided along a 4 point Likert scale to measure general symptom severity, and a 5 point scale to measure symptom changes. There are 6 items assessing cold symptoms and 7 items assessing quality of life, with a total of 39 points. To facilitate better understanding, a general information sheet with standard definition of symptoms is provided for the kids and having an education session prior to trial inclusion is recommended.

4.2. Total Daily Symptom Score (TDSS)

The Total Daily Symptom Score measures cold symptoms, which were first characterized by Jackson and colleagues, using a 4 point Likert scale (0-3 points; 0, absent; 1, slight; 2, moderate; 3, severe). In 1958, Jackson and colleagues identified 8 cold symptoms that included nasal obstruction, nasal discharge, sneezing, sore throat, cough, headache, muscle aching, and chilliness [14]. In 1962, the symptoms were amended to include a total of 12 symptoms ranging from nasal discharge, nasal obstruction, sniffing, sore throat, malaise, postnasal discharge, headache, cough, feverish feeling, chilliness, burning eyes and nasal membrane, muscle aching [16]. The succeeding studies mostly characterized the common cold into four symptoms (nasal obstruction, nasal discharge, sneezing, sore throat) or into eight symptoms (nasal obstruction, nasal discharge, sneezing, sore throat, cough, headache, muscle aching, chilliness). The items were measured on a scale of 0 - 3 with higher scores signifying more severe conditions.

The Total Daily Symptom Score is provided to the participants and is marked every day. The baseline scores and the scores measured after final application of intervention can be compared to assess whether there are statistically significant improvements, or the mean scores of the treatment group and the control group can be compared on the last day of intervention.

Symptom severity can be used during participant recruitment

〈Example of using symptom severity score in the inclusion criteria〉
Participants will be recruited after asking "Do you think you have the cold?" or "Do you have flu-like symptoms?" Among the participant who answered "Yes" to both questions, the participants must specifically have one or more symptoms of nasal obstruction, nasal discharge, sneezing, or sore throat and score an average of 2 and above in the total of eight symptoms (the rest being headache, malaise, chilliness, cough).
those who score average of 2 and above in the eight specific survey items
Each symptom is scored from 0 to 3. 0 : absent, 1 : mild, 2 : moderate, 3 : severe.

4.3. Symptom Duration

Symptom duration is assessed per hour or per day, from the initial date of intervention to the 'Last day' that the cold symptoms are observed. The 'Last day' can be defined as either the day that all of the cold symptoms are gone, or the day that one of the symptoms become 'mild' with a total survey score of 0–1. Depending on the research question, the 'Last day' can also be defined as the day that the total score of cold symptoms remain low (around 3 out of a total 24 points) for more than two to three days. There is no established definition for the endpoint and the 'Last day' can be defined by the researcher.

5. Participant Selection

5.1 General Consideration [17]

While designing a clinical trial, one of the first things that a researcher must consider is setting a clear inclusion criteria that is appropriate for the research question. The target disease and the diagnosis standards should follow the International statistical Classification of Diseases (ICD–10) and if the treatment intervention is Korean Herbal Medicine, the diagnosis criteria can further include Korean Medicine diagnostic criteria as well. Additional patient histories can be checked using a pre–established guideline for dealing with specific variables. Using a specified cut–off score that can be quantitatively recorded is highly desirable.

Moreover, participants that are recruited for the clinical trial must be able to represent the cohort of patients that is being researched. When publishing the research results, including descriptions of both conventional medicine and Korean Medicine diagnosis is advised. The credibility of the diagnostic criteria used for the clinical trial must also be stated in the paper.

5.2. Main Inclusion Criteria

The main inclusion criteria for recruiting cold patients in a clinical trial exploring the effectiveness of Korean Herbal Medicine must consider the following: First, the age of the participants. 'Children' are defined as the group of population ranging in age from birth to 19 years old, and 'adults' are those above 19. When testing Korean Herbal Medicine for clinical trials in children, the age groups can be further divided according to the standards established by the Korea Food and Drug Administration: neonates from 0 to 27 days, infants from 28 days to less than 23 months, children from the age of 2 to 11 years and adolescents from the age of 12 up to but not including those of 19 years of age. According to the details of the clinical trial, the study can include all ranges of children from infants to adolescents, or include only those that can sufficiently express themselves, or specify an age group (example: from 8 to 13 years of age) [18].

The second consideration should be how the common cold is going to be diagnosed. Since the common cold can be diagnosed by observing the clinical symptoms, a participating physician can provide the diagnosis (further laboratory results can be added if needed).

Third, since symptoms usually last from 7 to 10 days, subjects with symptom presentation of less than 24 to 48 hours must be recruited. It is strongly recommended to recruit patients in their early stages of disease so that treatment can be provided for at least 3 days. This criterion can be adjusted accordingly.

Fourth, the cold symptoms can be scored from recruitment and a minimum score for inclusion can be established. Other than using the scores, the number of presenting symptoms can also be set as a minimum standard for inclusion. Using at least one of the above two standards is recommended.

Fifth, the Korean Medicine Pattern Differentiation method can be used.

Sixth, those who provide informed consent must be included.

1) Children or adolescents that are below 18 years of age, or adults above 19 years of age
2) (If applicable) Diagnosed with common cold
3) Perceived to have had common cold symptoms within 24 to 48 hours
4) (If applicable) Presenting common cold symptoms that correspond with cold criteria
5) (If applicable) Diagnosed according to Korean Medicine pattern differentiation
6) Signed informed consent form prior to any study-related procedures

5.3. Main Exclusion Criteria

The following is the main exclusion criteria for recruiting cold patients in a clinical trial exploring the effectiveness of Korean Herbal Medicine.

1) Paranasal sinusitis, allergic rhinitis, pneumonia, flu, bronchitis, acute otitis media, acute tonsillitis
2) Chronic respiratory diseases (COPD, interstitial lung disease), asthma
3) Subjects who have taken medication that can suppress cold symptoms, such as antibiotics, antiviral medication, steroids, decongestants, antihistamines, and more.
4) (If applicable) Subjects with diseases that are not known to affect common cold but is currently progressing such as systemic diseases, and autoimmune disorders
5) (If applicable) Subjects diagnosed with Korean Medicine pattern differentiation that does not coincide with common cold
6) Subjects with diabetes, tumor, congestive heart failure
7) Subjects who are pregnant
8) Other subjects that are deemed inappropriate to participate by the researcher

6. Clinical Trial design

6.1. Therapeutic Studies

6.1.1. Therapeutic Exploratory Studies

Therapeutic Exploratory Studies are trials that look into dose-response rates, and conducted in a randomized, placebo controlled, double-blinded manner. It explores not only the optimum therapeutic dose but also the range of clinically effective dose ranges, exploring at least three different dosages. If the researchers decide to use the WURSS for assessing effectiveness of Korean Herbal Medicine in the common cold, possible systematic bias must be considered, and conducting a double- blinded, placebo-controlled study is recommended.

Generally, in a therapeutic exploratory study looking into the effectiveness of the cold treatment, a

parallel test is conducted by randomizing subjects (those presenting symptoms within 24 to 48 hours) into a fixed dosage group. The effectiveness must be proven separately for different dosages and the treatment must be provided for at least 3 days.

The inclusion and exclusion criteria, evaluation criteria, evaluation method, safety monitoring criteria and more should follow the general guidelines stated in this guideline.

6.1.2. Therapeutic Confirmatory Studies

Since there is no established, recommended treatment medication for the common cold, when conducting a randomized, placebo-controlled clinical trial, any placebo medication that is absent of the active ingredient can be used. However, in studies exploring specific symptoms of the common cold, medication that is known to alleviate the specific symptom can be used as a strong, active control.

Dosing schedule must be determined based on the dose-response rate test (or the therapeutic exploratory studies). If the medication is among the herbal medicines enlisted in the 10 main traditional medicine books, the dosage and dosing schedule should be based on the instructions mentioned in the books. If the medication is a licensed pharmaceutical product, the dosage that was licensed for use should be the optimum dosage used in the clinical trial. The administration period should depend on the research question, and to assess effectiveness, administration of the drug should persist for at least 3 days. Dosage can be increased accordingly, and the treatment period for each dosage should be sufficient to be able to correlate the treatment with the treatment effects.

The design of the therapeutic exploratory study can be similarly applied to the therapeutic confirmatory study. Also, the inclusion and exclusion criteria, evaluation criteria, evaluation method, safety monitoring criteria and more should follow the general guidelines stated in this guideline.

6.1.3. Control Group

In a clinical trial, the control group can be set up to explore different targets. If possible, using a placebo control group is recommended since this may increase the strength of evidence of the trial. The placebo medication should be similar in dosage form, size, color, weight etc. but most importantly, the active ingredient must be missing. The purpose of using a placebo control group is not to prove the value of using the Korean Herbal Medicine product, but to evaluate whether using the Korean Herbal Medicine product is of more value than using the control treatment. Therefore, by using a placebo control group, researchers can evaluate whether the specific herbal medicine treatment is adequate for use despite additional costs, safety, etc. If needed, a positive control group can be used to evaluate non inferiority or superiority of the treatment.

7. Safety Evaluation [17]

Safety evaluation should be conducted according to the characteristics of the herbal medicine product, to include adverse reactions, physical evaluation, laboratory tests, and internal symptom tests. These tests should be categorized and analyzed according to the internationally standardized classifications (WHO-ART). Adverse reactions that occur during the clinical trial period should be analyzed separately, including looking into herbal medicine reactions, dropouts, and laboratory results. These should be recorded meticulously. If there are potential adverse reactions or drug abuse, it

should be analyzed and reflected in the results. If a positive control group has been used, the amount of drug tolerance and adverse drug reaction should be checked, and evaluated if it has been effectively improved. If there are any side effects, the presenting events should be observed carefully in respect to the treatment period, dosage, blood concentration, recuperation period, age and any other possible influential factors.

8. Administration of Combined Therapy and Complex Medicines during Treatment of the Common Cold

While participating in the clinical trial, any consumption of medication that can alleviate the common cold symptoms should be strongly restricted. If there are symptoms such as high fever, or sever pain etc. that may reflect signs of other diseases, it must be reported to the principal investigator and measures must be taken to identify a clear etiology. If the researchers decide to allow the use of a rescue medication, and the number of rescue medication used is evaluated as one of the variables, consumption of medication can be allowed.

9. Points to consider in Korean Medicine

9.1. Classification criteria for pattern differentiation in Korean Medicine

Texts differ in the specific classification of Korean Medicine/East-Asian Medicine pattern differentiation, but according to the Guiding principles of Clinical Research on New drugs of traditional Chinese Medicine [15], Chinese guidelines on common cold [19], and Evidence-based Clinical Guidelines of Common Cold [20], the pattern differentiation can be categorized as follows.

1) 〈 Guiding principles of Clinical Research on New drugs of traditional Chinese Medicine 〉

(1) Wind-Cold Pattern

Main symptoms: Severe chilliness without high fever. Absence of sweating, headache, myalgia, nasal obstruction, changes in voice with intermittently runny nose. Floating pulse or floating, tight pulse.

Additional symptoms: Tickly throat and sneezing. Watery white sputum, lack of thirst or desire to drink hot water. Thin tongue coating with shiny white color.

(2) Wind-Heat Pattern

Main symptoms: High fever and less severe chilliness. Heavy sweating that does not relieve heat. Dry throat accompanied by pain or swollen tonsils. Nasal obstruction and yellow nasal discharge. Floating, tight pulse.

Additional symptoms: Severe, agonizing headache, cough with sticky yellow sputum. Increased thirst with a strong desire to drink water. White and yellow tongue coating, redder tip.

2) Guidelines on the Common Cold According to Traditional Chinese Medicine Pattern Differentiation

(1) Exterior Wind-Cold Pattern

Symptoms: Chilliness with slight fever. No sweating, headache, myalgia, feeling weak, nasal congestion accompanied by clear and runny nose, sneezing, cough, clear sputum, light tongue coating, floating pulse.

(2) Exterior Wind-Heat Pattern

Fever, agonizing headache, nasal congestion accompanied by sticky nose, severe throat pain and swollen throat with difficulties swallowing saliva, coughing with yellow sputum, dry mouth, dry throat, yellowy white tongue coating, floating, tight pulse.

(3) Exterior Summer-Heat and Dampness Pattern

Frequent during summer and autumn. Fever, no sweating or very slight sweating, feeling weak, dizziness, heaviness in head, nasal obstruction, runny nose, chest discomfort and stuffiness, nausea, vomiting, stomach distention. Light yellow tongue coating, fast pulse.

(4) Exterior Wind-Cold with Qi Deficiency Pattern

Chilliness and fever or slight fever, sudden sweating, headache, nasal congestion, coughing with white sputum, small voice, difficulty breathing, malaise, feeling weak, thirsty without desire to drink, frequent cold. Thick white tongue coating, floating, weak pulse.

3) Evidence-based Clinical Guidelines of Common Cold

(1) Wind-Cold Pattern

Chilliness with slight fever. No sweating, headache, body aches, weakness, clear nasal discharge with nasal obstruction, sneezing, cough. Sputum is white and clear. Light white tongue coating, floating and tight pulse, or floating and relaxed pulse.

(2) Wind-Heat Pattern

Severe fever with slight aversion for wind, agonizing headache, sticky nasal discharge with nasal obstruction, swollen throat and pain, cough with yellow sputum, sputum that is hard to expectorate, dry mouth, dry throat. Light yellow tongue coating, floating fast pulse.

(3) Summer-Dampness Pattern

Frequent during summer and autumn. Fever, slight aversion of wind, no sweating or slight sweating, body ache and weakness, agonizing headache with heaviness, nasal obstruction, chest discomfort, nausea, vomiting, stomach distention. Slimy yellow tongue coating, fast pulse.

(4) Qi Deficiency Pattern

Chilliness and fever or slight fever, chilliness, aversion of wind, aversion of cold, sweating, headache, nasal obstruction, cough with white sputum, small voice, short of breath, malaise, weakness, thirsty but without desire to drink, frequent cold, white tongue coating, floating weak pulse.

(5) Yin Deficiency Pattern

Fever, slight chilliness, slight aversion of wind, no sweating or slight sweating, night sweating,

headache, throat pain, dry mouth, dry throat, desire to drink water, heat in palms and soles of feet, chest discomfort, dry cough or cough without much sputum. Red tongue, thin fast pulse.

9.2. Points to Consider Regarding Herbal Medicine Used in Clinical Trials

In order to manufacture herbal medicinal products that use raw herbs as its main ingredients, the origin of the herbs must be checked with at least two herb analysts. The manufacture process must be recorded with utmost precision and standardization must be established prior to conducting the clinical trial. While submitting trial papers for approval and while conducting the clinical trial, herbal medicinal products and the manufacturing process should not be changed.

The following items, in accordance with the Regulations on the Manufacturing and Quality Control of Pharmaceuticals, should be printed on the package or container of the investigational new drug.

1. The statement indicating that it is for clinical trial purposes only.
2. The name or identification mark of the investigational product for clinical trials.
3. Batch number or code number that identifies the contents and packaging operation.
4. Name, address, and telephone number of the sponsor (or the person who approved the clinical trial plan).
5. Expiry date.
6. Storage conditions.
7. “Keep out of reach of children.”
8. Reference code that identifies the clinical trial.
9. Subject identification number, treatment number, visit number. However, if the sponsor recognizes unnecessary specificity considering the characteristics of the clinical trial, it can be documented and omitted.
10. Name of the investigator if deemed necessary by the sponsor of the clinical trial.
11. Directions for use if deemed necessary by the sponsor of the clinical trial.

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