

# Research on the improvement of allergic rhinitis in asthmatic children after reducing dust mite exposure: a randomized, double-blind, cross-placebo study protocol

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## Study protocol

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# Abstract

**Background:** Allergic rhinitis (AR) in children has become a major respiratory inflammatory disease with a high incidence that is increasing yearly. In China, 54.93% of children with asthma have AR, which often requires synchronous treatment. House dust mites (HDMs) are common allergens that often cause attacks of AR and asthma. Reducing allergen exposure is one of the most important measures to control and treat AR and asthma attacks. Hestelia Mite Bait, containing 0.1% emamectin, is a new tool for trapping and killing dust mites that can reduce the number of dust mites on mattresses, thereby potentially reducing stimulation by allergens and ultimately improving asthma and rhinitis symptoms. This single-centre, randomized double-blind cross-a-placebo trial will explore the improvement of allergic rhinitis in asthmatic children after reducing dust mite exposure.

**Methods:** We will recruit 60 children (aged 3-12 years) who have been diagnosed with allergic rhinitis and asthma and are allergic to dust mites as confirmed by a serum allergen test. Participants will randomly receive the Hestelia Mite Bait intervention for 8 weeks and the placebo intervention for 8 weeks. There will be a 4-week washout period between the two interventions. The primary outcome is the visual analogue scale (VAS) score of AR symptoms; the secondary outcomes include the Rhinitis Control Assessment Test (RCAT) score, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score, changes in the dust mite level, drug usage for asthma and AR, Asthma Control Questionnaire-5 (ACQ-5) score, and frequencies of acute asthma attacks, emergency visits, and hospitalization.

**Discussion:** This study will scientifically and objectively evaluate the improvement effects on rhinitis and asthma after reducing dust mite exposure and will provide a convenient means for the prevention and treatment of children's airway allergic diseases in the future.

**Trial registration:** ChiCTR1900024688 ([www.chictr.org.cn](http://www.chictr.org.cn)) registration date: July 21, 2019

## Introduction

### Background and rationale

Allergic rhinitis (AR) is a non-infectious disease of the nasal mucosa mediated by immunoglobulin E (IgE) after exposure to allergens. It is a common allergic disease in children. The incidence of AR may be increased by 10-30% in adults and by 40% in children <sup>[1]</sup>. AR manifests as sneezing, rhinorrhoea, sinus itch, and other symptoms, which have an adverse effect on quality of life, leading to sleep disordered breathing and increased attention deficit disorder <sup>[2-3]</sup>.

AR often coexists with organ-complicated allergic diseases, among which asthma is one of the most common conditions. In a Chinese epidemiological study, the incidence of asthma in children with AR was 35.01%, and the prevalence of AR in children with asthma was 54.93% <sup>[4]</sup>. There are common pathophysiological elements in AR and asthma. The immunopathologies of AR and asthma are quite similar regarding their cellular influxes of eosinophils, mast cells, and T-helper type 2 (Th2) cells. A similar

array of mediators can also be found in the lavages of patients with AR and asthma [5]. Therefore, AR and asthma are proposed as "the same respiratory tract, the same disease". In the presence of asthma, the treatment of allergic rhinitis is often overlooked, and poor control of AR has also been shown to be one of the causes of refractory and recurrent asthma [6-8]. The control of allergic rhinitis reduces the incidence of and hospitalization for asthma attacks [9].

Dust mites are a common trigger for AR [10]. The prevalence of house dust mites (HDMs) in AR patients in southern China is 95% [11]. Avoiding allergen exposure is an important measure to treat AR. Currently, reduced HDM exposure measures include keeping the room humidity below 50%, wrapping mattresses and pillows with impervious covers, regularly cleaning bedding with hot water, removing carpets and plush toys, and regularly using high-efficiency particulate air filters and acaricide. A systematic review of randomized controlled trials was conducted in which HDM control measures were evaluated in comparison with placebo or other HDM avoidance measures in patients with clinically proven AR. In this review, seven of the nine trials reported that compared with the control, the interventions studied resulted in significant reductions in HDM load. However, of the interventions studied to date, acaricides appear to be the most promising [12]. Hestelia Mite Bait, containing 0.1% emamectin, induces dust mites into the mite trapping bag through the combined action of an oligomeric aromatic factor and dust-mite atopic agents; then, it kills the dust mites, thereby achieving the goal of reducing allergens. Whether this new, safe and effective tool to trap and kill dust mites can improve rhinitis and asthma symptoms has not been verified.

## **Objectives**

The purpose of this study is to evaluate the improvement in rhinitis and asthma symptoms after reducing dust mite exposure with an acaricide, Hestelia Mite Bait, through a randomized, double-blind, cross-placebo clinical trial.

## **Trial design**

This is a randomized, double-blind, cross-placebo clinical trial to determine the improvement of rhinitis and asthma symptoms after reducing dust mite exposure. Participants will be randomly divided into 2 groups (Group 1 and Group 2), with intervention by mite bait or the placebo package, respectively; for the first 8 weeks, parents will fill out the questionnaires three times (V1-V3, V1 = the first day after enrolment; V2 = the fourth week plus or minus 3 d after enrolment; V3 = the eighth week plus or minus 3 d after enrolment). House sampling must be conducted twice (V1 and V3) during this period. Then, the children will undergo a washout period for 4 weeks and cross over to the mite bait or the placebo package for 8 weeks. Questionnaires will be completed three times (V4-V6, V4 = the twelfth week plus or minus 3 d after enrolment, V5 = the sixteenth week plus or minus 3 days after enrolment, V6 = the twentieth week plus or minus 3 d after enrolment), and house sampling (V4 and V6) will need to be completed twice again. Finally, we will conduct the questionnaire survey 4 weeks after the end of the intervention (V7, V7 = the twenty-fourth week plus or minus 3 d after enrolment). Throughout the study, the children will receive

standard treatment in accordance with asthma and AR guidelines<sup>[13-14]</sup>. The efficacy of mite bait in AR and asthma symptoms will be assessed by a visual analogue score (VAS) for rhinitis symptoms, RACT score, RQLQ score, changes in the level of dust mites, drug usage for asthma and AR, ACQ-5, and frequencies of acute asthma attacks, emergency visits, and hospitalization.

## Methods

### Participants, interventions and outcomes

#### Study setting

The target population for this trial will be recruited from the respiratory clinic of Shanghai Children's Medical Center, a tertiary first-class paediatric hospital with a large number of outpatients with asthma and rhinitis and a professional respiratory medical team.

#### Eligibility criteria

##### *Participants:*

##### *Inclusion criteria:*

1. Age 3 -12 years, male or female.
2. Children diagnosed with AR in accordance with the 2019 guidelines for the diagnosis and treatment of allergic rhinitis<sup>[13]</sup>. At the same time, the diagnosis will conform to the diagnostic criteria for childhood asthma formulated by the National Children's Asthma Prevention and Treatment Cooperation Group in 2016<sup>[14]</sup>.
3. Maintained use of guide-based rhinitis and asthma control drugs for the past 1 month. Inhaled drugs such as budesonide suspension, fluticasone aerosol, salmeterol dry powder inhalation and budesonide formoterol dry powder inhalation can be chosen to control the condition according to age characteristics.
4. Performance of the serum-specific allergen test, with the level of dust mite allergen sIgE > 0.35 IU/mL considered positive.
5. Informed consent signed by the guardians of all subjects (approved by the Ethics Committee of Shanghai Children's Medical Center affiliated with Shanghai Jiao Tong University School of Medicine).
6. Agreement to collect dust mites from indoor mattresses.

##### *Exclusion criteria:*

1. Basic diseases such as congenital heart disease, immune deficiency, gastroesophageal reflux, bronchopulmonary dysplasia, and obliterative bronchiolitis.
2. Inability to sleep in a separate bed.

3. Participation in other clinical studies within the past 3 months.

### **Who will take informed consent ?**

Hui Li, a staff member hired by the trial sponsor, will post recruitment information on the WeChat official account "Respiratory Angel" of the Department of Respiratory Medicine of the Shanghai children's medical center and collect the information of the participants through Wenjuanxin, a platform providing functions equivalent to Amazon Mechanical Turk. Finally, Li Hui contacted the qualified patient's guardian through WeChat and got their paper consents.

### **Additional consent provisions for collection and use of participant data and biological specimens**

On the consent form, participants will be asked if they agree to use of their data should they choose to withdraw from the trial. Participants will also be asked for permission for the research team to share relevant data with people from the Universities taking part in the research or from regulatory authorities, where relevant. This trial does not involve collecting biological specimens for storage. The informed consent form is available from the corresponding author on request.

### **Interventions**

#### **Explanation for the choice of comparators**

We will compare Hestelia Mite Bait containing 0.1% emamectin with a placebo that has a consistent appearance and odour but no acaricidal effect to investigate the change of dust mite exposure and the improvement in asthma and rhinitis symptoms after using mite bait indoors.

#### **Intervention description**

After recruitment (V0), the baseline medical characteristics of name, age, sex, diagnosis of asthma and rhinitis and allergen test report will be collected. The subjects will be randomly grouped. We stipulate that the children randomly assigned to Group 1 are first placed with package A for an 8-week intervention. All HDM species reach adulthood within 3 to 4 weeks. Once mature, adult mites have a life expectancy of between 4 and 6 weeks<sup>[15]</sup>. To avoid the impact of the previous intervention on the second intervention, we have established a 4-week washout period according to the growth cycle of dust mites. Then, package B will be placed for an 8-week intervention after a 4-week washout period. In Group 2, package B will be placed for an 8-week intervention, followed by a 4-week washout period, and then package A placed for an 8-week intervention. Each child will undergo a total intervention period of 16 weeks, a washout period of 4 weeks, and a follow-up period of 4 weeks after the end of the second intervention. The flow chart of the study is shown in Figure 1.

At V1, V3, V4 and V6, the staff will collect indoor samples from mattresses with a glass fibre membrane mite-clearing vacuum cleaner. The components of dust mite antigens in the collected samples will be

detected by ELISA. Parents will be asked to evaluate the AR and asthma symptom scores and clinical event records at V1-V7 (see the outcome indicators for details), as shown in Table 1.

### **Criteria for discontinuing or modifying allocated interventions**

If the research physician feels that it is not in the child's best interest to continue participating in the study, for example, if there is an allergic reaction to the mite bait or placebo used, he/she may decide to withdraw the child from the study at any time. If the subjects' parents fail to complete the questionnaire after 3 reminders or fail to cooperate with the indoor sample collections, the subjects will be considered poorly compliant and will be excluded from the study.

### **Strategies to improve adherence to interventions**

First, we will explain our study to each child's parents as follows: The enrolled children can receive regular follow-up, a questionnaire evaluation and standardized treatment by respiratory specialists at Shanghai Children's Medical Center. The detection of the HDM antigen concentration in the bedroom mattress is free of charge, and the mite bait and placebo package are safe. This is the only hygienic product for dust mite removal certified by the Ministry of Agriculture in China and has a product registration certificate (registration certificate number: WP20180004). During the study, professional staff will enter the room four times to clean the mattress with a mite-removing vacuum cleaner and collect attractors. The whole process requires the cooperation of the subjects' family members, and the subjects' parents will be able to complete the questionnaires in 10-20 minutes.

Second, during the implementation process, we will regularly remind parents to fill out the questionnaire via WeChat. The research team will also provide help and detailed answers to parents' questions during the trial.

### **Relevant concomitant care permitted or prohibited during the trial**

The original asthma medication can be maintained during the trial. When acute asthma attack symptoms occur,  $\beta_2$  agonists will be used to relieve bronchospasm, and oral or intravenous corticosteroids will be used, depending on the clinical severity, until the symptoms are relieved. However, during the test, the children who go outside for long periods of time or who cannot guarantee living indoors in a room with mite bait or placebo will not be allowed.

### **Provisions for post-trial care**

There is no anticipated harm and compensation for trial participation.

### **Outcomes**

#### *Primary outcome*

- VAS of clinical symptoms of AR

- In 1988, Linder first applied VAS to the assessment of AR symptoms, demonstrating its sensitivity and specificity <sup>[17]</sup>. Patients will be scored with a VAS score for symptoms occurring in the past week, including sneezing, rhinorrhoea, nasal itching, nasal congestion, itchy eyes, teary eyes, foreign body sensation and red eyes, for a total of eight symptoms. The VAS uses a 10-cm-long ruler, 0 ~ 10, to show the severity of the patient symptoms ("0" for no such symptoms and "10" representing the heaviest of such symptoms), instructs the patients according to the symptoms, and directs the patients to mark the symptom scores on the scale.

### *Secondary outcomes*

- **Change in RCAT**

- The RCAT demonstrated adequate reliability, validity, and responsiveness and was deemed acceptable and appropriate by the patients. This tool can facilitate the detection of AR symptom-control problems, and its brevity supports its usefulness in clinical care. The RCAT has 6 items that include nasal congestion, sneezing, watery eyes, sleep problems caused by rhinitis, activity avoidance, and rhinitis symptom control. Responses are measured on 5-point Likert-type scales. RCAT scores range from 6 to 30, with higher scores indicating better rhinitis control. <sup>[18]</sup>

- **Change in ACQ-5**

- ACQ-5 is a scale composed of 5 simple multiple choice questions. The results are obtained by adding the total points and averaging them. It plays a significant role in evaluating whether asthma is controlled and can rapidly assess asthma control. The child will be asked to evaluate the level of asthma control in the past 1 week. The lower the score is, the better the control level.

- **RQLQ for children with AR <sup>[19]</sup>**

- In this study, children with rhinitis in the past 1-2 weeks will be evaluated on their own symptoms, psychological status, mental status, social communication and other aspects of 14 problems caused by rhinitis, 0 points: normal; 1 point: slight; 2 points: mild; 3 points: serious; 4 points: very serious. The higher the score is, the more severe the rhinitis effect on quality of life.

- **Changes in levels of dust mite antigen in children's beds**

- Three sampling points will be randomly selected for each mattress, and each sampling point will have a range of 30 cm<sup>2</sup>. Each sampling point needs to be vacuumed 10 times repeatedly with a glass fibre membrane mite-clearing vacuum cleaner (the bed area will be recorded at the same time). Dust on the glass fibre membrane in the vacuum cleaner will be put into a plastic bag and stored at -20°C (killing the dust mites). Allergens will be extracted from samples from each family after weighing. The ELISA method (Indoor Biotechnologies, Charlottesville, VA, USA) will be adopted to detect dust mite antigens Der p2 (*Dermatophagoides pteronyssinus*) and Der f2 (*farinae*) in the extracted solution.

- **Use of medicines for children's AR and asthma**

- For children who, over the past 4 weeks, used anti-asthma drugs frequently for the control of rhinitis, the percentages are as follows: no use ever: 0%; a total of 1 week of use: 25%; and use every day: 100%. Specific drugs include physiological saline, nasal spray hormone (Mometasone Furoate Aqueous Nasal Spray, Fluticasone Propionate Nasal Spray, Budesonide Nasal Spray, etc.), oral allergy drugs (cetirizine, loratadine, levocetirizine, desloratadine, etc), Sinupret Drops, montelukast, traditional Chinese medicine (Tongqiao Biyan Granule, Biyuanshu Oral Liquid, Xinqin Granule), nasal allergy medications (levocabastine, azelastine hydrochloride), desensitization treatment (Dermatophagoides Farinae Drops), and inhaled hormones to control asthma (Budesonide Suspension For Inhalation, Seretide, Flixonase, Symbicort Turbuhaler).
- **Number of asthma attacks, emergency visits, frequency of hospitalization**

## **Sample size**

On the assumption that a reduction of 25% in VAS scores would be of clinical significance, 44 patients in each group are required at the 5% significance level (two-tailed), with a power of 90% to detect this difference between the two groups <sup>[16]</sup>. Considering a 10% possible dropout, each group needs to enrol at least 49 people.

In this experiment, we will recruit 60 people for a placebo-controlled, double-blind crossover trial. After crossover, the placebo and experimental groups will each be increased to 60 people.

## **Recruitment**

Recruitment information will be posted on WeChat official account "Respiratory Angel" of the Department of Respiratory Medicine of the Shanghai children's medical center.

## **Assignment of interventions: allocation**

## **Sequence generation**

Random sequences will be generated by the random number table.

## **Concealment mechanism**

Random sequences will be successively assigned to the subjects according to the enrolment order.

Odd-numbered subjects will be entered into Group 1, and even-numbered subjects will be entered into Group 2. Three copies of the generated distribution sequence table will be distributed among the designer, pharmacist and statistician. Each copy should be sealed with an opaque envelope and kept with a lock.

## **Implementation**

A special person who is not involved in the subsequent grouping and intervention is responsible for enrolling the test subject according to the selection and exclusion criteria. A random sequence is

generated by the statistician. The test designer decides that odd-numbered subjects will be entered into Group 1, and even-numbered subjects will be entered into Group 2.

## **Assignment of interventions: Blinding**

### **Who will be blinded**

The placebo used in the study looks and smells indistinguishable from mite bait and will be labelled either A or B. The identities of Tag A or Tag B will be known only to the pharmacists and unknown to the subjects and researchers.

### **Procedure for unblinding if needed**

When the trial is over, the number of each subject and the treatment plan received need to be checked, and the sealed distribution sequence needs to be decrypted. When unblinding, the intervention measures recorded in the assigned serial number were checked with the drug delivery record sheet, and the result data were classified for analysis by the test group and the control group.

### **Data collection and management**

Baseline data and questions related to the outcome indicators will be designed into questionnaires at <https://www.wjx.cn/> and will be regularly pushed to parents to fill out via WeChat. Parents who fill out questionnaires are usually a fixed one who is mainly responsible for the daily life of the child. During the follow-up period, once the questionnaire is completed and submitted, no one has the right to modify the contents of the questionnaire. In addition, there will be a fixed staff member to check whether the parents fill in the questionnaire and whether the questionnaire is completed. The staff member will not know the parent grouping and intervention. After the end of the whole experiment, all data will be exported in the form of EXCEL and analysed by SPSS 2.0 software.

### **Statistical methods**

#### **Statistical methods for primary and secondary outcomes**

SPSS 2.0 will be used to analyse the experimental data. Descriptive statistics will be used for the following data analysis: the categorical variables RCAT scores, ACQ-5 scores, drug usage for asthma and AR, and frequencies of acute asthma attacks, emergency visits and hospitalizations by frequency tables (i.e., number of evaluable subjects, frequency and percentage for categorical values) and the continuous variables VAS scores and RQLQ scores (i.e., mean, SD, minimum, median and maximum). One-way analysis of variance and two sample T-test will be adopted for normally distributed data, and the non-parametric rank-sum test will be adopted for non-normally distributed data. Fisher's exact chi-square test will be used to compare classified data, and  $P < 0.05$  will be considered statistically significant.

### **Interim analyses**

At the end of the first phase of the test (V3), an interim analysis of the data from the previous stage will be conducted by the biostatistician of the data monitoring committee. Mainly analyze the size of the estimated effect in advance and the incidence of adverse events. If there is a lack of treatment effect or the incidence of adverse events is high, consider terminating the trial early. These results will be fed back to the trial sponsor, and he or she will decide whether to terminate the experiment.

### **Methods for additional analyses**

When evaluating factors affecting rhinitis and asthma control, multiple linear regression or logistics regression is used.

### **Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data**

For those that are randomised to the intervention but do not adhere to the intervention, if they completed first phase of the trial before the cross, we will retain the data and perform the shortest distance filling method or multiple filling method on the missing data, else, we will delete the observed samples.

### **Plans to give access to the full protocol, participant level-data and statistical code**

The datasets analysed during the current study are available from the corresponding author on reasonable request.

### **Oversight and monitoring**

#### **Composition of the coordinating centre and trial steering committee**

In this trial, the sponsor hired staff member Li Hui to publish recruitment information through the WeChat and collect the basic information of participants. The information will be aggregated to Yufen Wu in order to select qualified research objects. After confirming the eligibility, Hui Li will contact the child's guardian and get their paper consent form. Throughout the trial, we will have two professional staffs who are responsible for collecting samples indoor and replacing mite bait or placebo. At the same time, one staff is responsible for regularly pushing electronic questionnaires to the enrolled subjects to follow up the symptoms of the children and summarize the adverse events during the trial. Ming Chen evaluated the reliability of each follow-up questionnaire uploaded. During the trial, Trial Steering Committee is composed of Lirong Jiang and Yijiong Ren. They will review the progress and safety of the trial.

#### **Composition of the data monitoring committee**

The data monitoring committee includes a biostatistician, a respiratory professional physician, and a patient advocate, to advise the sponsors and principal investigators regarding the continuing safety of study patients and the continuing scientific merit of the study. It is independent from the sponsor and competing interests. The DMC is responsible for monitoring the recruitment of participants, compliance

with the protocol and data quality, as well as monitoring for serious adverse events and other safety questions.

### **Adverse event reporting and harms**

During the trial, we will collect and record the occurrence of adverse events, describe the date of onset and date of resolution, evaluate its severity, the causal relationship with the intervention, and other suspect drugs and the final outcome. And report it to the DMC and ethics committee.

The acute oral, transdermal and inhalation toxicity of the 0.1% emamectin in the mite bait slightly toxic, and the mite bait is placed under the mattress and is not in direct contact with the child. Therefore, it has high security. For some adverse events that may occur with emamectin, including skin and eye irritation, nausea, vomiting, headache and dizziness, as well as fatigue and chest tightness, excessive sweating, salivation, blurred vision, convulsions, tachycardia or bradycardia.

Severity should be defined according to the following criteria:

Mild : Awareness of signs or symptoms, but easily tolerated

Moderate : Discomfort enough to cause interference with normal daily activities

Severe : Inability to perform normal daily activities

Life threatening : Immediate risk of death from the reaction as it occurred

All adverse events will be tracked until the incident is resolved or the study is over.

### **Frequency and plans for auditing trial conduct**

Project Management Group meet to review trial once a month. The Trial Steering Group and the independent Data Monitoring and Ethics Committee meet to review conduct throughout the trial period 12 months after the trial is approved.

### **Dissemination plans**

Investigators and sponsor will communicate trial results to participants, healthcare professionals, the public, via WeChat Official Accounts "Respiratory Angel" and publication .

## **Discussion**

In recent years, the prevalence of allergic diseases has been increasing. In the past 20 years, China has conducted three national epidemiological surveys on asthma in children. The results show that in 1990, the average prevalence of asthma among children aged 0-14 years was 1.08%. In 2000, this number increased to 1.97%. In 2010, when 400,000 children were surveyed, the figure was 3.01%, up

approximately 50% from 2000<sup>[20]</sup>. Zhao Jing et al. adopted the multi-stage sampling method to conduct epidemiological investigations on children with AR in Beijing, Chongqing and Guangzhou and found that the incidence rates of AR were 14.46%, 20.42% and 7.83%, respectively. At the same time, it was found that the incidence level of AR in China was gradually increasing and that the gap with developed countries was narrowed <sup>[21]</sup>. Consequently, allergic diseases are increasingly affecting people's health and quality of life <sup>[1]</sup>.

Taking asthma as an example, the causes of allergic diseases are mostly related to indoor allergens, such as dust mites, moulds and animal dander, among which dust mites are the most closely involved <sup>[20]</sup>. A longitudinal population-based study, which included 29 centres (14 countries) mostly in western Europe, showed that AR with allergies to dust mites was associated with an increased risk of asthma independent of other allergens <sup>[23]</sup>.

There is still no ideal treatment for diseases caused by dust mite allergy. In clinical practice, dust mite antigen extract infusion or drug inhibition can be used to reduce the immune tolerance of the body and thereby alleviate or relieve symptoms. However, patients with an allergic constitution can reduce their symptoms through treatment, but this condition is difficult to completely cure <sup>[24-25]</sup>. Therefore, compared with expensive and long-cycle treatment, controlling the number of dust mites in the house and reducing the exposure of patients to allergens is an inexpensive and easy method to promote.

There are several common methods for physical mite removal in clinical practice <sup>[26]</sup>, such as anti-mite bed covers and anti-mite vacuum cleaners, but these measures cannot significantly reduce the number of live dust mites and cannot remove hidden allergens. Chemical control for different purposes can be divided into two types: acaricide and other types. Acaricide can quickly and effectively kill individual dust mites, but it cannot effectively remove dust mite carcasses, faeces and other allergens, and as a chemical agent, its safety cannot be guaranteed. Repellent only enables the avoidance of dust mites but cannot isolate allergens and is characterized by a bad odour, a thick and oily texture, no resistance to sweat or washing, and other defects. However, the mite bait used in this experiment enables the compound oligomeric aromatic factor and dust mite atopic agents to work together to induce dust mites to enter the bag and ingest only the effective agents against dust mites until they die, thus effectively achieving the purpose of blocking allergens.

The main effective components of the mite bait emamectin benzoate is a low-toxicity insecticide and acaricide. It is a highly effective biological agent synthesized on the basis of avermectin and has the characteristics of super-high efficiency, low toxicity (nearly non-toxic), no residue, and no pollution. Compared with that of avermectin, the insecticidal activity of emamectin benzoate is improved by 1-3 orders of magnitude, and it has very high activity against the larvae of lepidoptera insects, mites and many other injurious insects. Emamectin benzoate has both the gastric toxicity and action of a contact poison, with a good effect at a very low dose (0.084~2 g/ha) <sup>[27]</sup>. After testing, the 0.1% emamectin benzoate used in the mite bait has a slight toxicity through the skin, mouth and nose. It was found that

the product attracted 93% of dust mites, killed 74% of dust mites within 48 hours, and killed nearly 100% of dust mites within 72 hours.

At present, Chinese people with allergic diseases account for approximately 30% of the total population (approximately 400 million), with hundreds of millions of people, especially among those who are young [28]. Based on the prevalence of childhood asthma in 2010, there were 6.7 million children with asthma in China alone. Therefore, the potential consumer group for this product is very large. If the efficacy and safety of this product in allergic diseases can be further confirmed through this test, it will provide a new tool for the treatment of such allergic diseases in the future.

Additionally, the random grouping, double-blind, crossover test method is adopted in this experiment, which reduces the influence of selection bias, measurement bias and other errors on the test results. Each subject will receive two schemes successively, which has its own before-and-after comparison, eliminating individual differences and obtaining the results of inter-group comparison.

However, due to the long period of this study, problems such as loss to follow-up, exit and decline in compliance may easily occur. It is difficult to ensure that each case is in the same condition as it is at the beginning of the first phase of the trial when receiving the second phase of treatment.

To improve the compliance of the experiment, during the study, we will contact the parents through WeChat, receive the questions raised by the parents in real time, and record and answer them. They will receive regular questionnaires reviewed by clinical professionals. Workers who collect dust mite specimens indoors should receive training and assessment and complete specimen collection in strict accordance with sampling procedures with the consent of parents. In terms of trial safety, we will track all the events during the study until the incident is alleviated, the situation is stable, other explanations of the incident are obtained, or the subjects lose contact. Subjects can drop out of the study at any time and continue to receive standard treatment for rhinitis and asthma in the outpatient department.

In summary, this study will scientifically and objectively evaluate the improvement effect of mite bait on rhinitis and asthma and provide a convenient means for the prevention and treatment of children's airway allergic diseases in the future.

## **Trial status**

Protocol version and date: April 25, 2019

Start date: 28-7-2019

Planned end date: 28-6-2020

## **Abbreviations**

AR: Allergic rhinitis

HDMs: House dust mites

Th2 cells: T-helper type 2 cells

VAS: Visual analogue scale

RCAT: Rhinitis Control Assessment Test

RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire

ACQ-5: Asthma Control Questionnaire-5

## **Declarations**

### **Acknowledgements**

The Hestelia Mite Bait used in this experiment was provided by Shanghai Jianlida Medical Technology co., LTD

### **Authors' contributions**

Ming Chen and Yufen Wu are joint first authors. Yong Yin obtained funding. Ming Chen, Yufen Wu, and Jing Zhang designed the study. Jiande Chen, Luanluan Li and Jinhong Wu collected the data. Ming Chen and Yufen Wu analysed the data. Shuhua Yuan and Ming Chen drafted the manuscript, no professional writers have been involved. Jing Zhang contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript. Jing Zhang and Yong Yin are the study guarantors. All named authors adhere to the authorship guidelines of Trials. All authors have agreed to publication.

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### **Availability of data and materials**

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

### **Ethics approval and consent to participate**

This study was approved by the Institutional Review Board of Shanghai Children's Medical Center Affiliated with Shanghai Jiaotong University of Medicine. Prior to randomization, written informed consent will be obtained from the parents/caretakers of each participant.

### **Consent for publication**

Not applicable

### **Competing interests**

The authors declare that they have no competing interests.

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## Figures

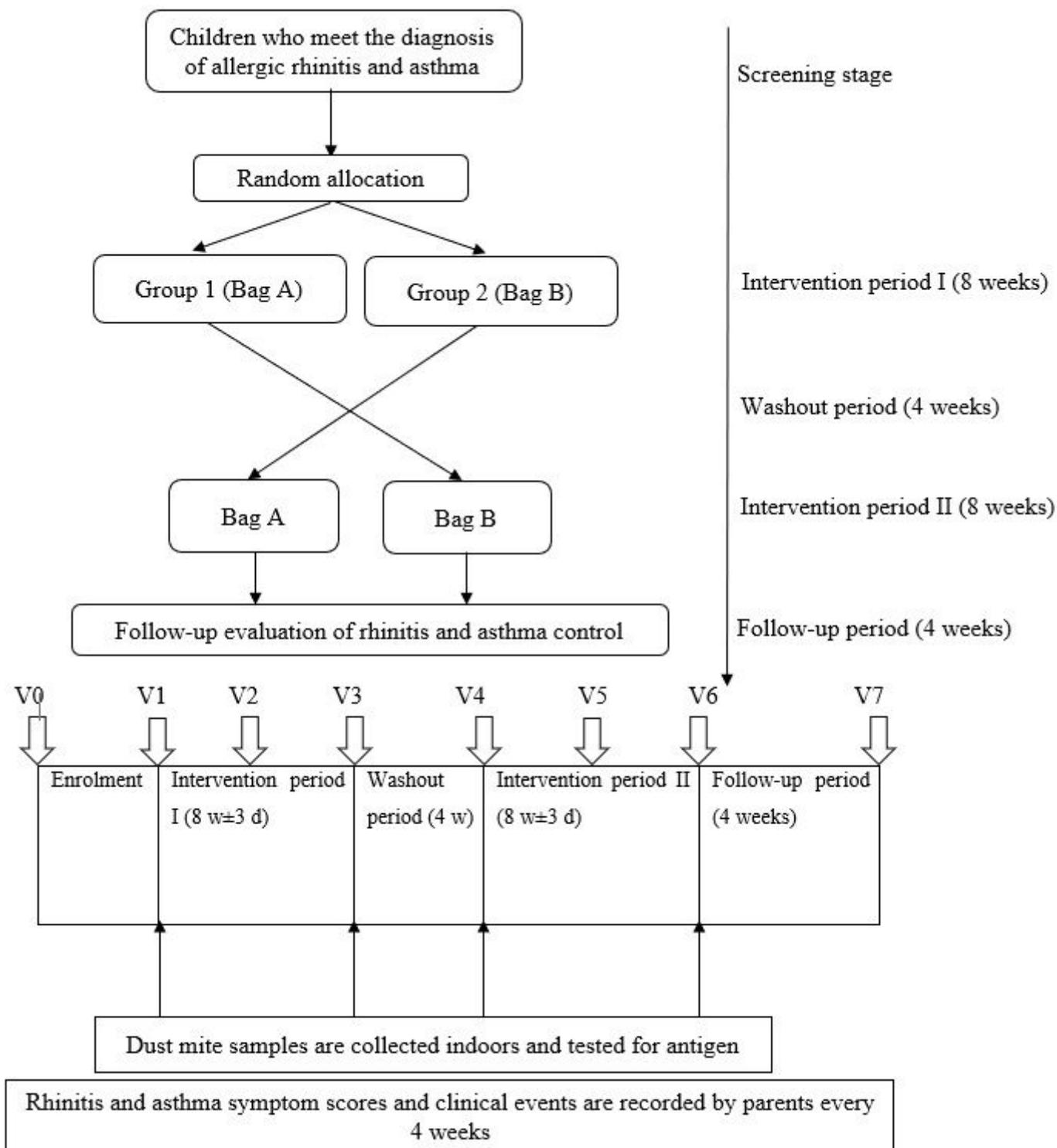


Figure 1

Study flow chart

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