Efficacy and safety of two Ayurvedic dosage forms for Allergic rhinitis: Study protocol for an open-label randomized controlled trial

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Study protocol

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Abstract

Background Allergic rhinitis (AR) is an immune response of the nasal mucosa to airborne allergens and involves nasal congestion, watery nasal discharge, itching of the nose and sneezing. The symptoms of allergic rhinitis may significantly affect a patient's quality of life and can be associated with conditions such as fatigue, headache, cognitive impairment and sleep disturbances. Various complementary and alternative medicine treatments have been used for this condition in clinical practice. The Ayurveda system of medicine is the most common complementary medicine system in Sri Lanka. The aim of this study is to find out whether the use of two preparations (decoction and its freeze dried powder) over a period of 4 weeks is able to cure the symptoms of allergic rhinitis. Study design This is a three arm open label non-inferiority randomized controlled clinical trial in patients with AR. The study duration is 28 days oral administration of the two Ayurvedic dosage forms (Decoction and freeze dried) and the antihistamine loratidine into the 3 arms allocated randomly. After a 1 week run-in period, eligible subjects are randomly assigned to the TMD12 decoction group, TMD12 freeze dried group and the antihistamine group. Total Nasal symptom Score (TNSS) of the patients are used as the primary efficacy outcome. TNSS is recorded and compared in all 3 arms prior to visit 1, at the end of 28 days, end of the first month of follow up and second month of follow up. Symptom scores of daytime nasal symptoms, night time nasal symptoms, non-nasal symptoms and Health Related Quality of Life questionnaire are used as secondary end points. Discussion This clinical trial will be able to provide supportive evidence based scientific data on classical Ayurvedic dosage forms and the new dosage forms developed as freeze dried powder in the treatment of allergic rhinitis. Also by this trial, it is expected to develop capacity to scientifically evaluate Ayurvedic treatments that may help patients having conditions such as allergic rhinitis.

Background

Allergic rhinitis is an IgE-mediated immunological response of nasal mucosa to air borne allergens and is characterized by nasal congestion, watery nasal discharge, itching of the nose and sneezing. It is commonly defined as seasonal or perennial, depending upon whether symptoms are manifested at defined yearly intervals or throughout the year, respectively [1]. Allergic rhinitis is not life threatening, but for the patient it is an annoying and disturbing disease due to its chronicity and aggravation in case of exposure to allergic agents. Furthermore allergic rhinitis is a considerable cause of widespread morbidity, medical treatment costs, reduced work productivity and lost school days. The symptoms of Allergic rhinitis may significantly affect a patient's quality of life and can be associated with conditions such as fatigue, headache, cognitive impairment and sleep disturbances. Appropriate management of allergic rhinitis is an important component in effective management of coexisting or complicated respiratory conditions such as asthma, sinusitis and sleep apnea [2].

According to the information of World Allergy Organization (WAO) the prevalence of rhinitis symptoms in the International Study on Asthma and Allergies in Childhood (ISAAC) varied between 0.8% and 14.9% in

6–7 year olds and between 1.4% and 39.7% in 13–14 year olds [3]. Also in US an estimated 20% of cases are seasonal allergic rhinitis and 40% of cases are perennial rhinitis [4].

In Sri Lanka many people suffer from this condition. A survey of six thousand patients attending the OPD at the Teaching Hospital, Ragama, Sri Lanka revealed allergic manifestations in 8.8% patients, and 22% of them had rhinitis [5]. Another survey conducted in Sri Lanka also revealed that the children in grade 5 in 17 schools of Western province, Sri Lanka, 21.4 % children had allergic rhinitis and it showed a statistically significant difference between the two sexes, being more common in boys [6].

In Ayurveda and Sri Lankan Traditional System of Medicinethere are effective therapeutic methods for allergic rhinitis which include internal as well as external treatment methods. Tamalakyadi decoction which includes 12 ingredients (TMD12) is a herbal decoction used for allergic rhinitis in Ayurveda. [7] Decoctions are liquid dosage forms prepared freshly from herbs with a 24 hour Shelf life. Therefore patients on treatments with decoctions need to prepare it daily, which causes difficulties in their busy lifestyles. No scientific studies have been published that had evaluated the efficacy and safety of TMD12 decoction in allergic rhinitis. Hence this study plans to develop a ready to use dosage form, a freeze dried powder in sachets using TMD12 and investigate the efficacy and safety of the traditional TMD12 decoction and that of the freeze dried preparation in comparison to a non-sedating antihistamine loratidine used in allopathic system, in patients with allergic rhinitis.

Methods

Study design

This is a three arm open label non-inferiority randomized controlled clinical trial that is conducting at the National Ayurveda Teaching Hospital in Colombo, Sri Lanka. The study duration is 28 days oral administration of the two Ayurvedic dosage forms and the antihistamine loratidine into the 3 arms allocated randomly. The study consists of two week run-in period, four visits at weekly intervals and two months follow up period. This study protocol was developed as required by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Additional file 1).

Ethics approval has been obtained from Ethics Review Committee, Institute of Indigenous Medicine (ERCIIM), University of Colombo, Sri Lanka (ERC 18/76). The trial was registered in ISRCTN registry (Trial number ISRCTN18149439) (Additional file 2)

Participants

Patients will be selected from those seeking treatment for allergic rhinitis at Ayurveda teaching hospital, Borella, Sri Lanka. Participation in this research project is voluntary. Patients' recruitment is done by screening for eligibility criteria (inclusion and exclusion criteria). After a 2 week run-in period, eligible

subjects are randomly assign to the TMD12 decoction group, TMD12 freeze dried group (TMD12-FD) and the antihistamine group.

Inclusion and exclusion criteria

The inclusion criteria include (1) age group of 18–65 years at the time of enrollment, of either sex; (2) presence of two or more nasal symptoms (watery rhinorrhea, nasal obstruction, sneezing and nasal itching); (3) Total Nasal Symptom Score (TNSS) > 6 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms); (4) have given written, informed consent to participate in this study.

The exclusion criteria include: (1) Patients with deviated nasal septum/ nasal polyps/ nasal growth/ adenoids/ asthma; (2) Patients with impaired liver and kidney functions, anaemia, and unstable cardiovascular conditions or cerebrovascular conditions; (3) currently or previously treated for any malignancy; (4) patients on steroid therapy; (5) Already on treatment with TMD12 decoction or antihistamines; (6) Pregnant or lactating mothers; (3) those who have known systemic disorders; (4) those who have any history of drug allergy to any of the investigational products; (7) Illiterate patients without a literate relative/guardian who can explain the procedures and maintain the patient diary (8) any other patients who are considered unsuitable for recruitment by the investigators.

Sample size

Sample size was calculated based on the primary outcome measurement of TNSS (Total Nasal Symptom Score) and for a non-inferiority clinical trial. This study is designed to evaluate the comparative clinical efficacy and safety of two Ayurvedic dosage forms with the antihistamine loratidine, assuming non-inferiority-between the 3 interventions. Sample size was calculated as specified by Hampel and team [8]

According to a previous study done among patients with allergic rhinitis using loratidine, clinically significant standardized effect sizes of TNSS are reported in the range of 0.57 to 0.67. Therefore, a standardized effect size of 0.5 was considered as the non-inferiority margin using the effect reported by Hampel and team [8].

Sample size was calculated for a significance level (α) of 5 % and power of 80 %. The sample size calculated using these values is 64 per group. With an expected dropout rate of 10 %, minimum sample size was calculated as 70 for one arm.

Recruitment

People who are interested in participating in this clinical study will be provided with a detailed Patient Information Sheet supplemented by verbal explanation of the study procedures. If the participants agree

with the Information Sheet, asked to complete the screening questionnaire. Informed written consent will be obtained from each participant by the investigators prior to initial interview. The activities in the initial interview will include haematological and biochemical investigations (IgE level, FBS, FBC, ESR, ALT/AST, serum creatinine, UFR), complete history taking and physical examination. Diagnosis will be done according to the Allergic Rhinitis and its Impact of Asthma criteria (ARIA). The participants meeting the inclusion criteria will recruit for the study. All baseline assessment forms (Total Nasal Symptom Score, Quality of life questionnaire and Allergic rhinitis symptom score) will be completed by the investigator. The study design flow chart is shown in figure 1.

Randomization

Randomization sequence was generated using an online randomization website (www.randomisation.com). Block randomization was done using blocks of 12 to generate the randomization schedule for 240 patients. The patients are allocating to treatments based on the randomization sequence generated. One week's supplies of the assigned investigational products are hand over to the patients according to the randomization number.

Intervention

Investigational products

Product I - Tamalakyadi decoction (TMD12)

This is a brown colour liquid prepared using 12 plant materials: *Phyllanthus niruri* L., *Terminalia chebula* Retz., *Premna herbacea* Roxb., *Piper retrofractum*Vahl, *Piper longum* L., *Solanum trilobatum* L., *Tinospora cordifolia (*Thunb.) Miers, *Zingiber officinale* Roscoe, *Piper nigrum* L., *Solanum indicum* L., *Solanum xanthocarpum* L., *Adhatoda vasica* L. (5 g from each ingredient). Five grams of each ingredient of the TMD 12 decoction is ground separately to make a coarse powder and to prepare a packet weighing 60 g containing all 12 ingredients. This packet of ingredients is use to prepare decoction need for one day. This pre-prepared dried herbs pack is supply to the patient. They are informed to put the supplied herbal pack into pot, add 1920 ml of water and simmer under low flame until the volume is reduced to 240 ml. The process of preparation under standard conditions is demonstrate to the group of patients who are randomly selected for TMD12 group at the Department of Dravyaguna Vignana of Institute of Indigenous Medicine using a video. Daily dose is 120 ml twice a day after meals.

Product II - Freeze dried Tamalakyadi decoction (TMD12-FD)

This is a freeze-dried powder of 240 ml of TMD12 decoction (TMD 12- FD) which contains 6 g of TMD12-FD packed in triple laminated bags under room temperature 19^0 C to minimize the moisture absorbance.

Preparation was done at the Research and Development Complex, Herbal Technology Section, Institute of Industrial Technology, Malabe, Sri Lanka under standard laboratory conditions.

The powder should be dissolved in 240 ml of hot water and should take 120 ml twice a day after meals. This reconstituted powder also contains the above mentioned 12 ingredients in almost the same quantities. In order to develop a ready to use formulation of the TMD 12, with composition similar to the TMD12 after preparation, three different formulations were developed and analyzed [9]. These included freeze dried formulation, spray dried formulation and Gnanasara formulation and detailed physicochemical and phytochemical analysis were performed. The results are now published and showed the freeze dried formulation to be quantitatively and qualitatively closest to TMD 12 [9]. Therefore the freeze-dried formulation was selected for evaluation of clinical efficacy and safety in this clinical trial.

Product III - Loratidine 10 mg

Non-sedating antihistamine-loratidine 10 mg was selected as the comparator for this clinical trial. Total quantity of loratidine required for the clinical trial, from one of the leading brands of Loratidine was purchased from one single batch, directly from the State Pharmaceuticals Corporation, Sri Lanka for the purpose of the trial. The certificate of analysis of the batch was obtained to check and ensure the quality of the product used. The purchased products were stored under 25^{o}C in an air-conditioned environment at the IIM. Patients allocated loratidine arm are requested to take one tablet daily at night with 240 ml of water. Details of the investigational drugs are shown in Table 1.

Storage, Packaging and dispensing of investigational drugs

All three investigational products (herbal materials of decoction, freeze dried powder and loratidine) are packed for 7 days and labeled which would indicate the batch number, dose, time of administration, mode of administration. These are stored in the clinic/Ayurveda Teaching Hospital, Sri Lanka. Drugs are dispensing to the study participants at each visit with instructions.

Outcome measurements

Primary outcome

Total Nasal symptom Score (TNSS) of the patients are used as the primary efficacy outcome which has been previously used in allergic rhinitis clinical trials. The mean difference in TNSS is compared between the 3 arms as the primary end point. TNSS is recorded and compared in all 3 arms prior to visit 1, at the end of 28 days, end of the first month of follow up and second month of follow up. The TNSS assesses the symptoms of watery rhinorrhea, nasal obstruction, sneezing and nasal itching on a four point scale. The total score range from 0 to 12 where 0 = absent symptoms (no sign/symptom evident), 1 = mild

symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated), 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable), 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

Secondary outcomes

The following four symptom scores are using as secondary end points.

1. Mean score of daytime nasal symptom score
2. Mean score of night time nasal symptom score
3. Mean score of non-nasal symptoms

Patient's self-rated symptom scores (daily rhinitis diary card) and allergic rhinitis grading symptoms are using as secondary measures of the efficacy in the clinical trial. Such symptom scores are collected on a weekly basis during the assessment period. The measurement of symptoms on a 4-point rating scale with the following definitions is used.

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

4. Mean score of Health Related Quality of Life score—Health related quality of life is measured using allergic rhinitis symptoms at the baseline and end of the intervention (after four weeks, one month of follow up and two months of follow up).

Changes in the serum IgE level and eosinophil count will be studied by comparing before and after treatment values. Procedures related to the study are shown in Table 2.

Safety assessment

Each patient is undergo hematological and biochemical investigations (FBS, FBC, ESR, AST/ALT, and Serum Creatinine/GFR), Urine full report before and after the treatment, which are done primary for safety assessment.

All adverse events experienced by patients are record weekly during treatment. Patients are advised to come for assessment if they have any unexpected symptoms complaints. If any serious adverse events occur they will be carefully assessed and reported to the ERCIIM and regulatory authority within 5 working days.

Data handling and recordkeeping

The data is retain with the researchers alone and will not be handed over to any other party under any circumstance. The study participant's information are securely stored at each clinical visit for internal use during the study. At the end of the study, all records continue to be kept in a secure location for six months period.

Study participants research data, which is for purposes of statistical analysis and scientific reporting, is transmitted to and stored at the department of DravyagunaVignana, Institute of Indigenous Medicine. This will not include the participant's contact or identifying information. Rather, individual participants and their research data is identified by a unique study identification number. At the end of the study, all study databases will be de-identified and archived.

Ethical consideration

The approval of the research protocol was obtained from the Research approval committee of the Faculty of Graduate Studies, University of Colombo and the Ethics Review Committees of Institute of Indigenous Medicine. The trial was registered in ISRCTN registry (Trial number ISRCTN18149439 https://doi.org/10.1186/ISRCTN18149439). The study will be conducted adhering to GCP guidelines.

Selected patients are provided with an information sheet with the details of the research given in all three languages (Sinhala/Tamil/English) and written consent are obtained before participation. The information will include about the nature, duration and possible consequences of the trial. Patient may withdraw his or her consent to participate in this study at any time, with no penalty or effect on medical care or loss of benefits. The questionnaire is interviewer administrated and anonymous. Minimal amount of data needed to assess the socio demographic data is gathered. This will include occupation and nature of health condition. Researchers do not collect any other personal data.

Method of data analysis

For primary and secondary outcome measures, the mean values at baseline and at the end of the study and the mean differences will be compared between the three arms using ANOVA (analysis of variance) or the non-parametric Kruskal-Wallis test, depending on the normality of the data. Within each treatment arm, the before and after difference in primary and secondary outcome measures will be compared using paired samples T test or non-parametric Wilcoxan Signed rank test, depending on the normality of the data. Categorical variables will be compared between groups using chi square test. Possible confounders will be adjusted using ANCOVA. Statistical analysis will be performed using the SPSS statistical package program (ver. 18.0), and the level of significance will be established at $\alpha = 0.05$.

Discussion

Allergic rhinitis is a chronic respiratory disease related with a significant health and psychological burden in patients due to its causes, prolong disease course and high incidence [10]. The symptoms of Allergic rhinitis may significantly affect a patient's quality of life and can be associated with conditions such as fatigue, headache, cognitive impairment and sleep disturbances.Previously findings introduce it as major risk factor for developing asthma and other respiratory disorders [11]. Therefore effective treatment would be important for treating this disease. At present pharmacotherapies consists of oral and intranasal antihistamines, mast cell stabilizers, decongestants, intranasal steroids, leukotriene inhibitors and allergy immunotherapy [12]. Due to fear of adverse effects of these allopathic pharmacotherapies, several patients now prefer to take herbal remedies as effective treatment method.

Tamalakyadi decoction is an herbal decoction prescribed for allergic rhinitis in Ayurveda and Sri Lankan Traditional system of medicine since long time. Decoctions are liquid dosage forms which have to be prepared everyday due to its short shelf life. Hence in this study an attempt was made to prepare ready to use modified dosage form from Tamalakyadi decoction as freeze dried powder.

Therefore our research team has designed this three arm open label non inferiority randomized control trial to compare and evaluate the effectiveness of these drugs for allergic rhinitis. This clinical trial will be able provide supportive evidence based scientific data on classical Ayurvedic dosage forms and the new dosage forms developed as freeze dried powder in the treatment of allergic rhinitis. Also by this trial, it is expected to develop capacity to scientifically evaluate Ayurvedic treatments that may help patients having conditions such as allergic rhinitis.

Strengths and limitations

To our knowledge, this is the first randomized clinical trial to investigate the efficacy of herbal decoction with its modified dosage form in Sri Lanka for allergic rhinitis. Results of this study will provide evidence regarding the use of herbal preparations for the treatment of allergic rhinitis.

Trial status

This protocol is version 1. The trial recruitment began in June 2019 after obtaining the ethics approval. It is expected that the recruitment will be completed by the end of May 2021. The recruitment is currently in progress.

Declarations

Ethics approval and consent to participate

The ethics approval for this clinical trial was obtained from Research approval committee of the Faculty of Graduate Studies, University of Colombo and the Ethics Review Committee of Institute of Indigenous

Medicine, University of Colombo, Sri Lanka. The trial was registered in ISRCTN registry (Trial number ISRCTN18149439 https://doi.org/10.1186/ISRCTN18149439). The study is conducting adhering to Good Clinical Practice (GCP) guidelines. Written informed consent will be obtained from each participant (Additional file 3). The participants will be given sufficient time to ask questions and to consider whether they wish to participate in this study.

Consent for publication

Not applicable

Availability of data and materials

Not applicable. This manuscript is a protocol for a randomized clinical trial and does not contain any data.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

All authors contributed to design this clinical study and approved the final version of the manuscript.

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Tables

Table 1: Investigational products

	Drug	Dose	Mode of administration	Route	Method of preparation
1	Tamalakyadi decoction (TMD12)	120 ml	Morning and evening before meals	Oral	60 g (1 packet) of dried powder of plant materials boiled with 1920 ml of water and reduced to 240ml
2	Freeze dried Tamalakyadi decoction	120 ml	Morning and evening before meals	Oral	6 g (1 sachet) of freeze dried powder dissolve in 240 ml of warm water.
3	Loratidine	10 mg	Evening after meals	Oral	Ingested with 240 ml of water

Table 2: Study procedures

	Study period													
	Screening	Recruitment	Treatment				Follow up							
Time point (weeks)	-1	0	1	2	3	4	5	6	7	8	9	10	11	12
Eligibility screening	♦													
Informed consent	♦													
Recruitment		♦												
ARMS														
Arm – 1(TMD12 decoction)			♦			♦	♦							♦
Arm – 2 Freeze dried preparation			♦			♦	♦							♦
Arm – 3 Loratidine			♦			♦	♦							♦
Investigations*	♦						♦							
Assessment														
TNSS	♦					♦				♦				♦
HRQoL			♦			♦				♦				♦
Adverse events			♦	♦	♦	♦								

Figures

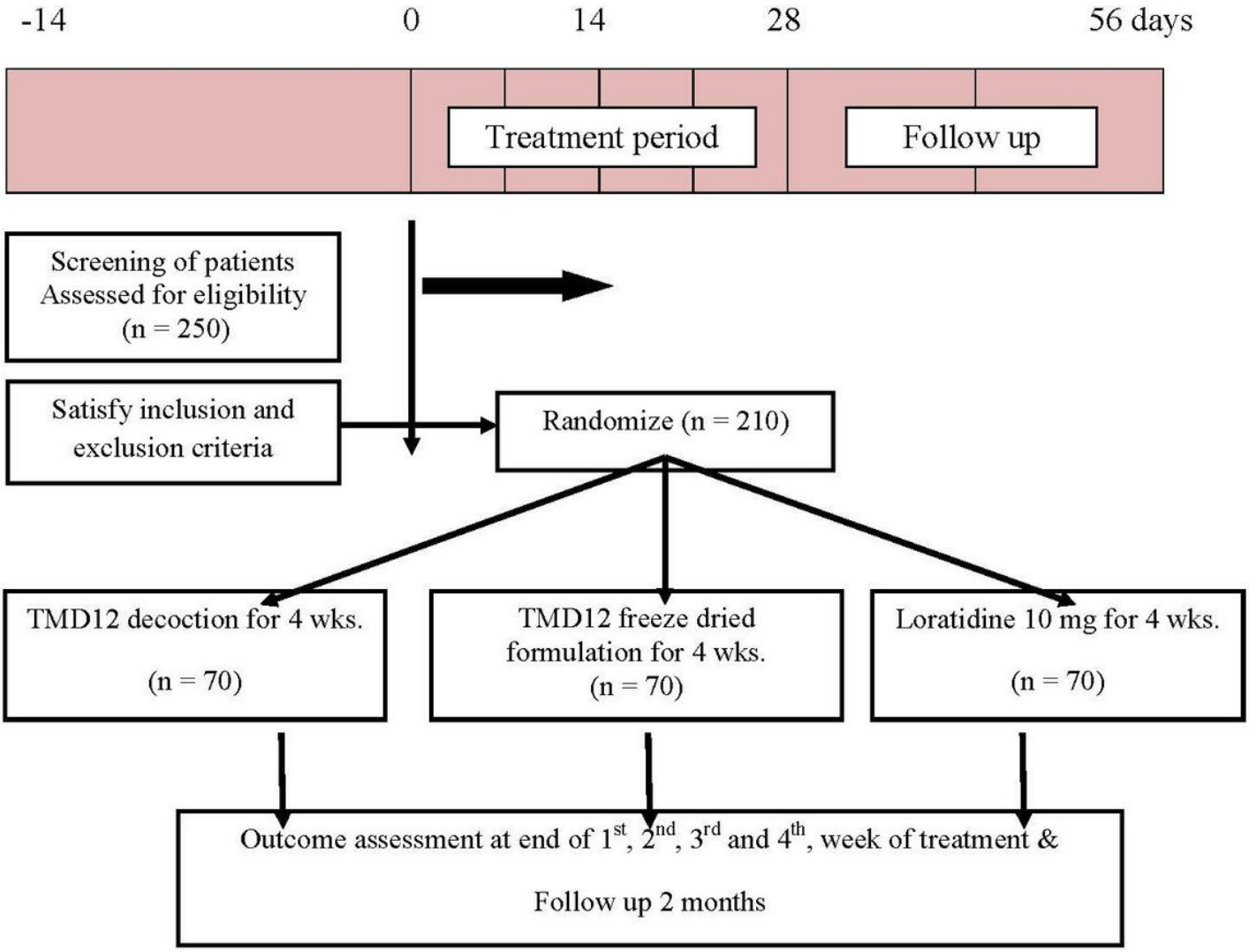

Figure 1

Flow chart of study design

Supplementary Files

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- supplement1.pdf
- supplement2.docx
- supplement3.doc