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STUDY PROTOCOL **OPEN ACCESS**

Evaluation of efficacy and safety of Ayush-HR in the management of Pre- Hypertension: A Study protocol for a double-blind randomized controlled clinical study

Babita Yadav[1], Neha Dubey[1], Sumeet Goel[1], Sakshi Sharma[1], Varsha Sumedhan[1], Dr. Rakesh Rana[2], Richa Singhal[3], BCS Rao[4], N. Srikanth[5] and K. S. Dhiman[6]

[1]Research Officer (Ay.), Central Council for Research in Ayurvedic Sciences, New Delhi India,
[2]Statistical Officer, Central Council for Research in Ayurvedic Sciences, New Delhi, India
[3]Senior Statistical Asst, Central Council for Research in Ayurvedic Sciences, New Delhi, India
[4]Asst. Director (Ay.), Central Council for Research in Ayurvedic Sciences, New Delhi, India
[5]Deputy Director General, Central Council for Research in Ayurvedic Sciences, New Delhi, India
[6]Former Director General, Central Council for Research in Ayurvedic Sciences, New Delhi, India
****Corresponding Author's: Email Id:** ayuneha312@gmail.com
[ORCID Id -https://orcid.org/0000-0001-7204-3200]

ABSTRACT

Ayush-HR' is an Ayurvedic polyherbal formulation, developed by the Central Council of Research in Ayurvedic Sciences (CCRAS). The contents of this trial drug are found to be effective in hypertensive cases, therefore to generate research-based evidence; this study will be conducted to assess the clinical efficacy and safety of 'Ayush-HR' in the management of pre-hypertension. A multicentric, randomized, double-blinded, controlled clinical trial will be conducted at three peripheral centres of CCRAS. A total of 140 participants diagnosed with pre-hypertension will be selected and randomly allocated between two groups in the ratio of 1:1, meeting the following inclusion criteria: patients of either sex aged 30-50 years, diagnosed patients of prehypertension as per the 7th report of JNC (120-139 mm of Hg SBP or 80-89 mm of Hg DBP) , willing and able to participate for 3 months. The intervention group will be treated with the trial drug Ayush-HR and the control group will be treated with a placebo for 12 weeks. Outcome measures for assessment are the proportion of participants in whom blood pressure control was achieved, changes in mean Systolic Blood Pressure (mSBP) and changes in mean Diastolic Blood Pressure (mDBP). The trial drug of the study may be used as a safer drug for treating pre-hypertensive patients and therefore further preventing progression into essential hypertension. Other complications of increased blood pressure may also be prevented.

Keywords: *Ayush-HR, Pre-hypertension, Ayuvedic intervention, Protocol.*
Trial registration: Registered in Clinical Trial Registry of India, CTRI/2019/09/021266, dated 17/09/2019.

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INTRODUCTION

The seventh ***report*** of the ***Joint National Committee*** (JNC-7) report (1) has introduced a new classification that includes the term Prehypertension for those individuals with blood pressure ranging from 120-139 mm Hg systolic and /or 80-89 mm Hg diastolic. Prehypertension is not a disease category, JNC-7 states that it is a designation chosen to identify individuals at high risk of developing hypertension so that both the patient and clinician are altered to this risk and can work to intervene and prevent or delay the development of the disease (2).

As per WHO,(3) an estimated 1.28 billion adults aged 30-79 years worldwide have hypertension, most (two-thirds) living in low- and middle-income countries and an estimated 46% of adults with hypertension are unaware that they have the condition, only less than half of adults (42%) with hypertension are diagnosed and treated.

In addition, suboptimal blood pressure (BP) is an attributable risk factor for death throughout the world. National Heart, Lung, and Blood Institute suggests that people with hypertension are at a higher risk for developing hypertension or high blood pressure, compared to people with normal blood pressure (4). Prehypertension can increase the risk for heart attacks, strokes, congestive heart failure, and kidney failure (5). Prehypertension is associated with multiple additional cardiovascular risk factors, such as obesity, diabetes mellitus, dyslipidemia and inflammatory markers and evidence of organ damage for example

retinal arterial narrowing, left ventricular hypertro phy, microalbuminuria and coronary artery disease. Because of its high prevalence and long-term complications, prehypertension has been estimated to decrease the average life expectancy by as much as five years.

Study Drugs: Rationale and benefits

Non-pharmacological treatment of prehypertension includes lifestyle modification such as weight loss, dietary modification, and increased physical activities whereas pharmacological treatment is indicated for some patients who have specific co-morbidities such as Diabetes mellitus, chronic kidney disease, coronary artery disease. Lifestyle advocacies are effective to a certain extent in managing, but alone are not much effective in the management of prehypertensive and prevention of essential hypertension and none of the antihypertensive drugs provides a complete cure and has limitations owing to their unwanted effects.

Here in this trial 'Ayush-HR', a polyherbal ayurvedic formulation, along with lifestyle advocacies will be used as an intervention in the management of Prehypertension. The trial drug **'**Ayush-HR' is a coded drug, developed by the Central Council of Research in Ayurvedic Sciences (CCRAS). The contents of this trial drug are found to be effective in hypertensive cases, therefore to generate research-based evidence; this study will be conducted to assess the clinical efficacy and safety of 'Ayush-HR' in the management of pre-hypertension.

Previous studies description

Ayurvedic drugs, used in various clinical trials (6) on hypertension are *M sarpgandha Mishran,* (7), *Sarpagandha Ghan Vati,* (8) *Brahmi* Vati (8) and *Arjuna Vachadi Yoga* (9) etc. are found to be safe and effective in hypertensive cases.

The primary and secondary objective of this trial is to assess the clinical efficacy and clinical safety of Ayush-HR in the management of pre-hypertension respectively.

Trial design

Multicentric (involving three centres), prospective double-blind (participant and investigator blinded) randomised placebo-controlled clinical trial with 90 days intervention period.

This study protocol follows the Standard Protocol Items for Clinical trials 2013 (SPIRIT 2013) guideline. The study flow-chart figure has been given in Figure no I.

MATERIAL AND METHODS

Methods: Participants, interventions and outcomes

Study setting

Participants diagnosed with pre-hypertension will be recruited from the outpatient department of Central Ayurveda Research Institute, located in Delhi, Guwahati and Regional Ayurveda Research Institute, Thiruvananthapuram. Participants who are willing to participate and meet the inclusion and exclusion criteria will be provided with Patient Information Sheet (PIS) in the language understandable by the participant. PIS contains information related to the purpose, methods and intervention details of the study. Written informed consent will be taken from all the participants by the investigator itself.

Eligibility criteria

Inclusion Criteria:

Inclusion criteria are as follows: patients of either sex aged 30- 50years, diagnosed patients of Prehypertension as per 7th report of JNC (120-139 mm of Hg SBP or 80-89 mm of Hg DBP), willing and able to participate for 3 months.

Exclusion Criteria:

Exclusion criteria are as follows: patients who have a history of Cardiac Arrhythmia, Acute Coronary Syndrome, Myocardial Infarction, congestive cardiac failure, Stroke or Severe Arrhythmia in the last 6 months; essential Hypertension / Secondary hypertension; patients with concurrent Hepatic Dysfunction (defined as AST and/or ALT > 2 times of the upper normal limit) or Renal Dysfunction (defined as S. creatinine > 1.2 mg/dl); uncontrolled Pulmonary Dysfunction (asthmatic and COPD patients); major systemic illness necessitating long term drug treatment (Rheumatoid arthritis, Neurological disorders, Endocrinal disorders, etc.); known cases of malignancy**, u**ncontrolled Diabetes Mellitus(HbA1C>8)**,** women who are planning for conception / pregnant or lactating; history of hypersensitivity to any of the trial drugs or their ingredients; patient taking participation in any other clinical trial**;** any other condition which the P.I. thinks may jeopardize the study.

Who will take informed consent?

Study investigators will obtain written informed consent from eligible participants. We will provide a model consent form on request.

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

Not applicable

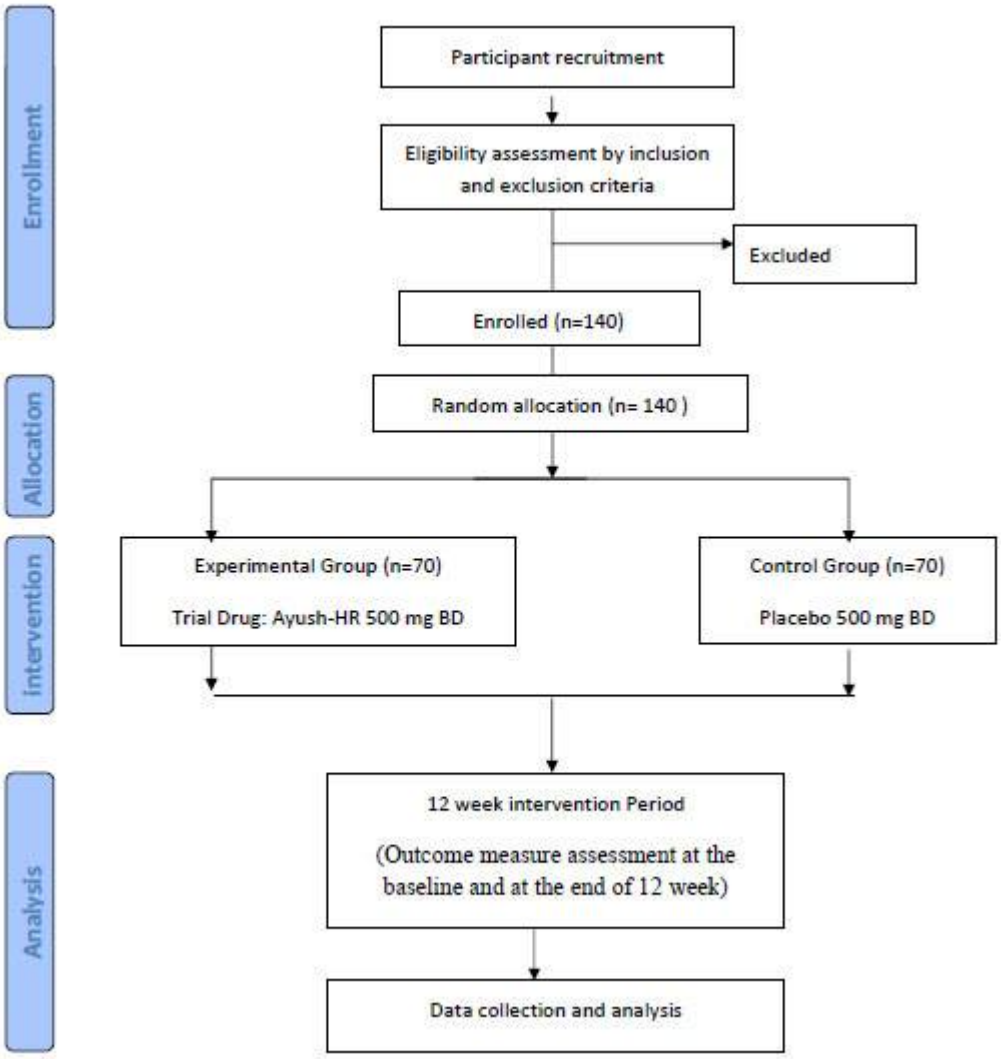

Figure No I: Study Flow-chart

Diagnostic Criteria for Pre-hypertension:

As per the 7th Report of JNC, participants having Systolic Blood pressure (SBP) of 120-139 mm Hg OR Diastolic blood pressure (DBP) of 80-89 mm Hg will be diagnosed as Pre-hypertension.

Withdrawal Criteria:

Participant not willing to continue or non-compliant (less than 80% compliance) with the study procedure; participant developing life-threatening complication or any other severe illness because of other pathology which requires urgent treatment; Adverse effect (AE)/ Adverse drug reaction (ADR) necessitating hospitalization includes withdrawal criteria. The decision to withdraw a participant from the trial will be informed to the sponsor and the Ethics Committee within two working days with detailed justification.

Interventions

Explanation for the choice of comparators {6b}

This trial is placebo-controlled in which there are two groups. One group gets the active treatment and the other gets the placebo. Everything else is held the same between the two groups so that any difference in their outcome can be attributed to the active treatment.

Intervention description {11a}

Intervention Group (Goup-I):

In this group, participants will be treated with the Ayurvedic trial drug, Ayush-HR tablet, 500 mg twice daily, after taking food for 12 weeks.

Control Group (Group-II)

In this group, participants will be treated with a placebo, 500 mg, twice daily after food for 12 weeks.
Both groups will follow the same diet and lifestyle advice.
The trial drugs are being procured from a GMP certified pharmaceutical company.

Criteria for discontinuing or modifying allocated interventions

Treatment will be stopped in the case of any adverse events occurring which are considered serious or intolerable in the judgment of the investigators and the data safety and monitoring committee (DSMB) and under medical consent. Individuals who declare they no longer wish to participate at any time will be discontinued from the study.

Strategies to improve adherence to interventions

Strategies to be adapted for making participants adherent to interventions are as follows: Face-to-face adherence reminder sessions will take place at the initial product dispensing and each study visit thereafter. In these sessions, the participant will be informed about the importance of following study guidelines, instructions about taking the trial drug including dose timing, storage, and importance of taking the trial drug and what to do in the event of a missed dose, information that there will be a pill count at every study visit. Participants will be asked about any problems they are having taking their trial drug. There will be a brief discussion of reasons for missed doses and simple strategies for enhancing adherence, eg, linking pill-taking to meals or other daily activities.

Assessment of adherence: To enhance the validity of data, questionnaire items including two weeks of compliance assessments will be given to participants. Participants will return the unused tablets and drug strips at each follow-up visit. Unused tablets will be counted and recorded on the appropriate case record form (CRF).

Relevant concomitant care and rescue medication permitted or prohibited during the trial

Participants registered under the trial will be instructed to avoid the use of any other drugs on their own for any ailment and to consult the investigators for any symptoms or complaints, or if they feel anything unusual. The investigator will record any medication(s) he/she may prescribe to alleviate their ailments. To alleviate any emergency medical condition, the use of any rescue medication will be permitted as per the discretion of the Investigators. However, the same will have to be documented in the Case Record Form.

Provisions for post-trial care

No such provision is included in the trial.

Outcomes

Timelines:

The participant will be assessed at two-time points, at baseline and the end of 12 weeks.

Primary Outcome Measures:

The primary outcome measure of the study includes the proportion of participants in whom blood pressure control was achieved, changes in mean Systolic Blood Pressure (mSBP) and changes in mean Diastolic Blood Pressure (mDBP).

Secondary Outcome Measures:

Secondary outcome measure includes, the number of participants with adverse events will be assessed continuously throughout 12 weeks, changes in quality of life -assessment by SF-36 Health Survey Questionnaire, changes in echocardiography parameters of Left ventricular Ejection fraction (LVEF) and Left Ventricular Mass Index and assessment of safety parameters (Liver Function Test and Kidney Function test)

Participant timeline {13}:

Participant timelines and study schedule of enrolment, interventions and assessments are given in detail in Table no 1.

Table I: Spirit Table for study schedule of enrolment, interventions, and assessments*

		STUDY PERIOD							
		Allocation	**Post-allocation**						**Close-out**
VISITS	**Screening Visit 1**	**-**	**Baseline Visit 2**	**Treatment Period**					
				Visit 3	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
TIMEPOINT**	**-1 week**		**0 week**	***2nd week***	***4th week***	***6th week***	***8th week***	***10th week***	***At the end of 12th week***
ENROLMENT:									
Eligibility screen	✓								
Informed consent	✓								

Allocation		✓							
INTERVENTIONS:									
Intervention Group (Ayush-HR)				♦—	—	—	—	—	—♦
Control group (Placebo)				♦—	—	—	—	—	—♦
ASSESSMENTS:									
Demographics and medical history	✓		✓						
PRIMARY OUTCOME MEASURE ASSESSMENT									
Laboratory Investigations	✓								✓
Blood Pressure Measurement, mSBP, mDBP	✓								✓
SECONDARY OUTCOME MEASURE ASSESSMENT									
Assessment of ADRs				♦—	—	—	—	—	—♦
SF-36 Health Survey Questionnaire			✓						✓
Echocardiography	✓								✓
ASSESSMENT OF SAFETY PARAMETERS									
Routine examination	✓								✓
Bio-chemical Investigation	✓								✓
OTHER PARAMETERS									
Concomitant Medication				✓	✓	✓	✓	✓	✓
Rescue Medication				✓	✓	✓	✓	✓	✓
Assessment of drug compliance				✓	✓	✓	✓	✓	✓
Issue of Trial drugs			✓	✓	✓	✓	✓	✓	

Sample size

The total sample size of the study is 140, with 70 participants in each group. Based on the assumption of expecting a difference in Systolic Blood pressure of 5 mm Hg between the intervention group (22 mm Hg difference pre and post-treatment) and placebo group (14 mm Hg difference pre and post-treatment) as clinically relevant and specified such an effect to be detected with 80% power and a significance level alpha of 0.05. Experience with similar experiments, with similar measuring methods, suggests that the data will be approximately normally distributed with an SD of 15 mm Hg. The sample size needed for each group after taking into account a dropout rate of 20 % will be approximately 70 in number, 140 is the total sample size.

Recruitment

In this study a total of 140 patients will be recruited from the outpatient department of Central Ayurveda Research Institute, located in Delhi, Guwahati and Regional Ayurveda Research Institute, Thiruvananthapuram. and will be randomly assigned into two groups, intervention group and control group-placebo with 70 patients in each group. Both groups will undergo 12 week intervention period.

Assignment of interventions: allocation

Sequence generation

A randomization chart will be prepared using a random number table generated by the statistician. This random number table will be used for assigning the participants into two groups. This sequence will be sealed in an opaque envelope. Only the statistician who generated this random number table will be aware of the assignment of the group. When a participant will be found suitable for enrollment then the investigator will give them a random number.

Concealment mechanism

Allocation concealment will be done using sequentially numbered, opaque, sealed containers. Containers will be equal in weight, similar in appearance and tamper-proof. Allocation concealment will prevent the next assignment in the clinical trial from being known. This will ensure that investigators and participants do not know to which group participant will be allocated before he/she is entered into the study.

Implementation

All participants who will give consent for participation and who fulfil the inclusion criteria will be randomized. Participants will receive the intervention as per the randomization sequence. All the three participating centres will receive sequentially numbered, opaque, sealed containers of trial drugs. Participants will receive the intervention as per the randomization sequence.

Assignment of interventions: Blinding

Who will be blinded

This study is double-blinded i.e. investigator and participant both are blinded. The statistician will only know the allocation of the participant. Blinding can be obtained by keeping the treatment regimen identical in both arms (Test arm and control arm) in content (look, taste, doses etc.) except for active ingredients. It will improve compliance and retention of subjects by clearly demonstrating that all are being treated alike. Trial medicine and placebo will have possibly the same physical properties like packaging, labelling, handling, colour, shape, size, smell and taste.

Procedure for unblinding if needed

If any emergency condition appears then the study investigator will unblind the participant with an independent physician to maintain the blinding. the incidence will be recorded and reported to the competent authority.

Data collection and management

Plans for assessment and collection of outcomes

Plans to promote participant retention and complete follow-up

Data management

After informing the participants about the research study as per the Patient Information Sheet, written consent (in triplicate) will be taken from the participants before screening them. After screening the participants, the eligible participants will be included in the study and data will be collected in a case record form. The data will be subsequently recorded in an e-format for statistical analysis and record.

Data Monitoring: The study will be monitored by Data and Safety Monitoring Board (DSMB). An Interim analysis, if required can be done when at least 25% of participants have completed their trial period.

Confidentiality

Personal information of all the participants will be protected before, during and after the trial by providing specific identification codes (ID) for each participant. These IDs were used further in all related data collection. All the personal and sensitive information related to the participant will be kept confidential. We will use the summary data in place of personal data to maintain confidentiality. Individual participant data will not be shared with any third party.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use

Not applicable

Statistical methods

Statistical methods for primary and secondary outcomes

- **Analysis Sets**

PP and ITT Analysis

The main analysis set will be defined as all subjects who receive at least one dose of any investigational medicinal product, i.e., the Intention-to-Treat (ITT) population. This population will be used for all efficacy evaluations. A secondary analysis set, the Per Protocol (PP) set, will also be defined, which will exclude all subjects found to have a major protocol deviation*.

*Deviation from the protocol will be determined by medical check.

- **Subgroup Analysis**

Subgroup analysis will be conducted within the subgroups.

- **Safety Analysis**

The set of subjects included in the safety analysis is those subjects who receive at least one dose of the trial drug and who have follow-up safety data.

Description of Statistical Analyses:

The categorical variables in the study data will be summarized as numbers (percentage) and compared using the chi-square test. The continuous data having normal distribution will be represented as mean (SD), and data not following normal distribution as median (min-max). Parametric data will be analyzed by paired t-test and independent sample t-test for within and between-group analysis respectively whereas non-parametric data will be calculated by Wilcoxon signed-rank test and Mann-Whitney test for within and between-group analysis respectively. All statistical tests will be performed at the 0.05 significance level. 95% confidence intervals will be calculated whenever appropriate. Only available data will be considered for analysis. Subjects who discontinue the study prematurely will be considered missing data and will be dropped from the statistical analysis. All the data analysis will be done using the SPSS software version 15.

Interim analyses

During the trial period, if the interim analysis is required then available data will be analysed and will be presented before Data Safety Management Board.

Methods for additional analyses (e.g., subgroup analyses)

Subgroup analysis will be conducted within the subgroups.

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

The primary analysis will use the intention-to-treat principle and per-protocol analysis will be undertaken to assess the robustness of the findings.

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

These plans were not yet decided.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee

This trial is conducted at the outpatient department of the three centres viz; Central Ayurveda Research Institute, located in Delhi, Guwahati and Regional Ayurveda Research Institute, Thiruvananthapuram. The trial steering committee consists of members from the Central Council for Research in Ayurvedic Sciences, responsible for the monitoring of trial protocol.

Composition of the data monitoring committee, its role and reporting structure

The independent DSMB committee is responsible for protocol adherence and the safety of participants. The members will be independent of the sponsor and have no financial or other conflicts of interest. The investigator of the study will send monthly reports containing the trial data along with reporting of adverse events.

Adverse event reporting and harms

The occurrence of adverse events will be recorded during the intervention period in a separate ADR reporting format. For each adverse event, the duration (starting and ending date), severity, and relationship to the trial will be recorded. In case of a serious adverse event, immediate protective action, and treatment will be provided.

Frequency and plans for auditing trial conduct

Trials will be audited by the competent authority from time to time to ensure the safety and well being of trial participants and the validity of data obtained as per the primary outcome of the project.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees)

Important protocol amendments will be communicated to Institutional Ethics Committee. After getting approval from the Institutional Ethics committee these changes will be implemented.

Ancillary and post-trial care

No such regime has been planned.

Dissemination plans

The results of this study will be communicated through publications in scientific journals as soon as the study is completed.

DISCUSSION

Hypertension is currently a major public health problem in India, where Ayurvedic medicines are often used for symptom relief and quality of life improvement. This study aims to examine the efficacy and safety of Ayush-HR-An Ayurvedic polyherbal formulation in the management of hyperuricemia.

The allopathic system of medicine is widely used for the treatment of hypertension, but many side effects are reported. To date, many targeted drugs have emerged for the treatment of hypertension, however, these drugs are limited by unsatisfactory long-term efficacy and their expensive price.
Various Ayurvedic drugs are frequently used for the prevention and treatment of hypertension, however, there is little research evidence to support the efficacy of these Ayurvedic drugs. Ayush-HR' is an Ayurvedic polyherbal formulation, developed by the Central Council of Research in Ayurvedic Sciences (CCRAS). The contents of this trial drug are found to be effective in hypertensive cases. The results of this trial will be useful for researchers, practitioners, and patients. This study has some limitations; this study has a small sample size so the results may not apply to other hospitals or regions. We plan to conduct a subsequent large-scale clinical study comprehensively evaluating the efficacy and safety of TMP in the treatment of PH based on the findings of the present study
Expected outcomes from this trial are better clinical outcomes and safety profile in Pre-hypertensive cases by the Ayurvedic intervention and a reduced relapse rate during the post-treatment period. If the study is found to be effective then, the selected drug will be listed in the management protocol of Pre-Hypertension at the clinical practice level in terms of better efficacy, safety and cost-effectiveness treatment and the selected drug may lead to a step ahead of better understanding and management in Hypertension.

Trial status
Participant enrollment has been started on 8 February 2022 and is expected to be completed by February 2023. The protocol version is CCRAS_IMR_Version 1.0, 14 June 2018.

Abbreviations
JNC: Joint National Committee, WHO: World Health Organization, BP (Blood Pressure), CCRAS: Central Council for Research in Ayurvedic Sciences, SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials, PIS: Patient Information Sheet, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, COPD: Chronic Obstructive Pulmonary Disease, SBP: Systolic Blood Pressure, DBP: Diastolic Blood pressure, AE: Adverse Event, ADR: Adverse Drug Reaction, GMP, DSMB: Data Safety and Management Board, CRF; Case Record form, mSBP: Mean Systolic Blood Pressure, mDBP: Mean Diastolic Blood Pressure, LVEF: Left Ventricular Ejection Fraction, SD: Standard Deviation, ITT: Intention to Treat, PP: Per Protocol

ACKNOWLEDGEMENTS
The study design was developed by BCSR, BY and SG, development of the protocol was done by SG, ND, SS and VS, and finalization of the protocol was done by inputs of BY, NS, and KSD. RR and RS developed the statistical plan, and drafting of the manuscript was done by ND followed by editing from BY and RS.

FUNDING
The project is funded by Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Government of India, New Delhi.

Availability of data and materials
Final data analysis may be shared with other researchers on request.

Ethics approval and consent to participate
The study was approved by Institutional Ethics Committee (IEC) and was registered prospectively in the Clinical Trials Registry of India CTRI/2019/09/021266, dated 17/09/2019. All the participants will sign the written informed consent.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

ADMINISTRATIVE INFORMATION
Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title{1}	Evaluation of efficacy and safety of Ayush-HR in the management of Pre-Hypertension – Study protocol for a double-blind randomized controlled clinical study.
Trial registration {2a and 2b}.	Registered in Clinical Trial Registry of India, CTRI/2019/09/021266, dated 17/09/2019
Protocol version {3}	CCRAS_IMR_Version 1.0, 14 June 2018
Funding {4}	Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Government of India, New Delhi.
Author details {5a}	SPIRIT guidance: Affiliations of protocol contributors.
Name and contact information for the trial sponsor {5b}	Central Council for Research in Ayurvedic Sciences, Jawahar Lal Nehru Bhartiya Chikitsa Evam Homoeopathy Anusandhan Bhawan, 61-65, Institutional Area, Opposite 'D' Block, Janakpuri, New Delhi-110058, INDIA.
Role of sponsor {5c}	The funding agency has designed this study and will analyse and interpret the data and publish the results.

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