Central Council for Research in Siddha

PROTOCOL FOR PLACEBO CONTROLLED CLINICAL TRIAL OF AN SIDDHA FORMULATION IN THE MANAGEMENT OF CHRONIC STABLE ANGINA

I. BACKGROUND:

Coronary artery disease is an important cause of morbidity and mortality. The incidence and prevalence of the disease is gradually rising in our country and a substantial part of adult population is affected. Some of the *Siddha* drugs investigated so far have shown encouraging cardio-protective action. The investigational drug in prevention and treatment of *Thamaraga noi* (cardiac angina specially related to Ischemic heart diseases) and the efficacy of the drug in the management of ischemic heart disease and has been proved in preventive cardiology. They lower lipids in patients and prevent the increase in lipids in experimental animals.

Keeping in view the references with the ancient classical literature of *Siddha* and the leads obtained in the recent studies, the investigational drug has been selected for trial in prevention of cardiac risk factors in cases of Chronic Stable Angina .

II. AIM

Effect of the investigational drug on Chronic Stable Angina.

III. SAMPLE SIZE AND METHODS

Sample Size:- 100 Subjects

Run-in Period- one week

Groups : Two – trial and control (50 subjects in each group)

Treatment :

Group-I Trial drug

(i) Drug : Coded formulation – CRIS CARD

(ii) Dosage: Two capsules of 500 mg each twice a day.

(iii) Duration : 90 days

Group II- Placebo in the same dose

Design of the study: Randomised Double–blind Placebo controlled study.

Duration of the study: **One week run-in period** and **three months drug therapy** with **follow up for three months** without drug.

IV. INCLUSION CRITERIA:

1. Age between 35 – 60 years of either sex
2. Diagnosed cases of Chronic Stable Angina.
3. TMT positive cases

V. EXCLUSION CRITERIA:

1. Age below 35 years
2. Recent M.I. less than three months
3. Patients with conduction problem
4. Patients with uncontrolled hypertension
5. Unstable Angina
6. Serious concomitant disease of liver and/or kidney
7. Any malignancy
8. Undergoing treatment for any other serious illness

VI. CRITERIA FOR WITHDRAWAL

During the course of the trial treatment, subjects showing the following:

Any serious toxicity due to intolerance,acute myocardial infarction, stable angina progressing to unstable angina and / or undergoing Coronary re-vascularisation will be withdrawn from the study. If any other serious condition develops during the course of study, which requires urgent treatment, such subjects will also be withdrawn from the trial and managed by the Principal Investigator accordingly.

VII. ROUTINE EXAMINATION AND ASSESSMENT

The full details of history and physical examination of the patients will be recorded as per the proformae (Forms I & IA). Clinical assessment will be done before drug administration (0), after one week of Run-in period, every six weeks during treatment and at the end of follow up (Form II) (after three months of completion of treatment). The laboratory investigations and TMT will be recorded before drug administration, after one week of Run-in period and after completion of treatment (Form-III). All the patients will be provided a 'Diary of Events' for keeping record of angina attacks and consumption of nitrate tablets.

VIII. PERIOD OF STUDY

Period of study will be six months in each case. Total duration will be two and half years to complete the trial.

IX. FOLLOW - UP

Follow-up will be carried out after three months of completion of treatment.

X. STATISTICAL ANALYSIS

Data on frequency of angina, consumption of nitro-glycerine tablets, duration of exercise tolerance on TMT (end point), time taken for 1 mm ST depression, maximum double product, lipid profile at the end of run-in period and at the end of treatment will be analyzed using appropriate statistical methods.

XI. ETHICAL REVIEW

Institutional Ethical Committee (IEC) of each participating centres should give a clearance certificate before the project is initiated. Patient's information sheet and informed consent form should be submitted along with the project proposal for approval by IEC. Both should be maintained in duplicate with one copy given to the patient at the time of entry to the trial.

Central Council for Research in Siddha

PROTOCOL FOR PLACEBO CONTROLLED CLINICAL TRIAL OF A SIDDHA FORMULATION IN THE MANAGEMENT OF CHRONIC STABLE ANGINA

CONSENT FORM

CERTIFICATE BY INVESTIGATOR

I certify that I have disclosed all details about the study in the terms easily understood by the patient.

Date:_____ Signature_____

Name_____

CONSENT BY SUBJECT

I have been informed to my satisfaction, by the attending doctor, the purpose of the clinical trial and the nature of drug treatment and follow-up, including the laboratory investigations to be performed to monitor and safeguard my body functions.

I am also aware of my right to opt out of the trial at any time during the course of the trial without having to give the reasons for doing so.

I, exercising my free power of choice, hereby give my consent to be included as a subject in the clinical trial of xxx in the cases of Chronic Stable Angina.

Date:_____ Signature or Thumb impression

Name:_____

Date:_____ Signature of witness:_____

Name:_____

Relationship _____

:_____

TO BE TRANSLATED INTO REGIONAL LANGUAGE

Central Council for Research in Siddha

PROTOCOL FOR PLACEBO CONTROLLED CLINICAL TRIAL OF A SIDDHA FORMULATION IN THE MANAGEMENT OF CHRONIC STABLE ANGINA

PATIENT INFORMATION SHEET

What is the study about?

Siddha has a very comprehensive approach for the treatment of chronic stable angina. The present study is aimed to evaluate selected *Siddha* drugs for their efficacy in the treatment of Ischaemic heart disease. You are invited to participate in this study where you will be provided a investigational drug in a daily dose of three capsules BD. The previous observations in clinical and experimental studies have shown promising effect of these drugs in the treatment of **Ischaemic heart disease**. About 300 cases of **Ischaemic heart disease** from this and other hospitals around the country will be taking part in this study.

What will you have to do?

Your doctor will explain clearly what you have to do. It is important that you follow the instructions scrupulously. The study will take approximately six months to complete (three months for treatment and another three months for follow-up study). During this period, you are expected to visit the hospital five times (0, after one week, six weeks, 12 weeks and six months).

Before you start treatment, during the first visit to the clinic, you will undergo a complete physical examination, ECG, X-ray, TMT . Blood and urine samples will also be taken. This is to make sure that you are eligible for the study. Clinical assessment and lab investigations will be carried out during subsequent visits.

If you are found fit, you would be put on trial treatment for three months and on follow up for three months. The daily dosage will be three capsules twice a day. At each visit, you will be supplied with sufficient quantities of drugs to last until your next visit.

Central Council for Research in Siddha

PROTOCOL FOR PLACEBO CONTROLLED CLINICAL TRIAL OF A SIDDHA FORMULATION IN THE MANAGEMENT OF CHRONIC STABLE ANGINA

PROFORMA

FORM I - SCREENING OF THE CASES

1. Code No.(of clinical trial) ☐☐☐
2. Centre_____ ☐☐☐
3. Name of the Subject _____
4. Gender Male ☐ (1) Female ☐ (2)
5. Date of Birth ☐☐ ☐☐ ☐☐☐☐ Age (in years) ☐☐
6. Address _____

_____

CRITERIA OF SELECTION

		Yes(1)	**No(2)**
7.	Age between 35-60 years of either sex	☐	☐
8.	Diagnosed cases of chronic stable angina	☐	☐
9.	TMT positive case	☐	☐

CRITERIA FOR EXCLUSION

		Yes (1)	No(2)
10.	Age below 35 and above 60 years	☐	☐
11.	Recent M.I. less than three months	☐	☐
12.	Patients with conduction problem	☐	☐
13.	Uncontrolled hypertension	☐	☐
14	Unstable Angina	☐	☐
15.	Serious concomitant disease of liver / kidney	☐	☐
16	Malignancy	☐	☐
17	Patients undergoing treatment for any other serious illness	☐	☐

18. If "**Yes" to 7-9** above, admit the subject to the trial and if "**Yes" to 10-17** above, do not admit the subject to the trial.

If admitted, subject serial No. ☐☐☐

No. of packets issued: _____ ☐☐☐

Date:_____ Signature of the Doctor _____

Central Council for Research in Siddha

PROTOCOL FOR PLACEBO CONTROLLED CLINICAL TRIAL OF A SIDDHA FORMULATION IN THE MANAGEMENT OF CHRONIC STABLE ANGINA

FORM I A - HISTORY PROFORMA

1. Code No. (of clinical trial) ☐☐☐

2. Centre _____ ☐

3. Sl.No. of Subject: ☐☐☐

4. Name of the Subject _____

5 Gender Male ☐ (1) Female ☐ (2)

6. Date of Birth ☐☐ ☐☐ ☐☐☐☐ Age(In Yrs) ☐☐

Chief complaint with duration (if any) in days.

7. Chest pain Absent ☐ (0) Present ☐ (1)
[NYHA Criteria]

If present, Indicate:

9. Location_____

10. Radiation_____

11. Type of pain_____

12. Frequency of anginal attacks per week ☐☐

		Absent (0)	**Present(1)**
12.	Post-prandial pain	☐	☐
13.	Dyspnoea on exertion	☐	☐
14.	History of CAD if any in the Past	☐	☐

_____

History of present illness

15. Duration of disease(in months)_____ ☐☐

Treatment given so far		No (0)	Yes(1)
16.	Beta blockers	☐	☐
17.	Calcium channel blocker	☐	☐
18.	Nitrates	☐	☐
19.	Others	☐	☐
	if yes, specify_____		
20.	**FAMILY HISTORY of CAD**	☐	☐
	if yes, specify_____		

PERSONAL HISTORY

21	Smoking/Tobacco/Pan masala	☐	☐
22.	Constipation	☐	☐

23. Udaliyal Vali ☐ (1) Azhal ☐ (2) Iyyam ☐ (3)
Vali Iyyam ☐ (4) Vali Azhal ☐ (5)
Azhal Iyyam ☐ (6)

PHYSICAL EXAMINATION

GENERAL

24	Body weight (Kg.)	☐☐☐
25.	Body height (in cm)	☐☐☐
26.	Resting Blood pressure (Systolic) mm of Hg	☐☐☐
27	Resting Blood pressure (Diastolic) mm of Hg	☐☐☐

SYSTEMIC EXAMINATION

CARDIOVASCULAR

28 Pulse Rate (per minute) ☐☐☐

29 Pulse Rhythm Regular ☐ (0) Irregular ☐ (1)

30 Apex beat Normal ☐ (0) Abnormal ☐ (1)

31 Heart sound Normal ☐ (0) Abnormal ☐ (1)

if abnormal, specify abnormalities_____

32 Jugular Venous pulse. Normal ☐ (0) Abnormal ☐ (1)

	Absent(0)	**Present(1)**
33. Congestive Cardiac Failure	☐	☐
35 Oedema	☐	☐

GASTRO INTESTINAL TRACT

36 Hepatomegaly	☐	☐
37 Splenomegaly	☐	☐

RESPIRATORY

38 Crepitation	☐	☐
39 Rhonchi/Wheezing	☐	☐

CENTRAL NERVOUS SYSTEM

40. Normal(Y/N)	☐	☐

41. Date:_____ 42.. Signature of the Doctor _____

_____

Central Council for Research in Siddha

PROTOCOL FOR PLACEBO CONTROLLED CLINICAL TRIAL OF A SIDDHA FORMULATION IN THE MANAGEMENT OF CHRONIC STABLE ANGINA

FORM II – CLINICAL ASSESSMENT
(0,1st,7th ,13th and 25th week)

1. Code No. (of clinical trial) ☐☐☐

2. Centre_____ ☐☐☐

3. Serial No. of the Subject : ☐☐☐

4. Name _____

5. Date of Assessment ☐☐ ☐☐ ☐☐☐☐

6 Stage of Assessment (in weeks) ☐☐

Clinical Parameters

A. Subjective

7. Chest pain Absent ☐ (0) Present ☐ (1)
[NYHA Criteria for Class II/III]

If present, Indicate :

8. Location_____

9. Radiation_____

10. Type of pain_____

11. Frequency of anginal attacks per week ☐☐

		Absent (0)	**Present(1)**
12.	Post-prandial pain	☐	☐
13.	Dyspnoea on exertion	☐	☐

B. Objective

14. Body weight (in kg) | | | |

15. Resting Blood pressure (Systolic) (mm of Hg) | | | |

16. Resting Blood pressure (Diastolic) (mm of Hg) | | | |

17. Date:_____ 18.Signature of the Doctor _____

Central Council for Research in Siddha

PROTOCOL FORPLACEBO CONTROLLED CLINICAL TRIAL OF A SIDDHA FORMULATION IN THE MANAGEMENT OF CHRONIC STABLE ANGINA

FORM III – LABORATORY INVESTIGATIONS
(0, 1st and 13th week)

1. Code No. (of clinical trial) | | | |
2. Centre_____ | | | |
3. Serial No. of the Subject : | | | |
4. Name _____
5. Date of Assessment | | | | | | | | | |
6 Stage of Assessment (in weeks) | | |

Urine Examination (Microscopic)

7. Sugar_____ 8.Albumin_____ 9. Deposits_____

Blood

10. Hb(g/dl) _____
11. Blood Sugar-Fasting(%) _____
12. Blood Sugar – PP(mg./dl) _____
13. S.Cholesterol(mg./dl) _____
14. HDL(mg./dl) _____
15. LDL(mg./dl) _____
16. Triglycerides (mg./dl) _____

---

17. B.urea (mg./dl) _____

18. S.creatinine (mg./dl) _____

19. Uric acid (mg./dl) _____

20. SGOT _____

21. SGPT _____

Radiological Investigations

22. X-ray Chest: [0 Month only] _____

_____

Special Tests

23. ECG (report all details) _____

_____

TMT(Bruce Protocol)

24. Duration of exercise (in minutes&seconds) (min.) ☐☐ (sec.) ☐☐
{Mets-…….]

25. Time to 1mm ST depression(in seconds) ☐☐

26. Maximum double product ☐☐☐☐☐

27. Maximum ST segment depression(in mm) ☐☐

28. Leads showing ST depression:

L_1 ☐ L_2 ☐ L_3 ☐ aVR ☐ aVL ☐ aVF ☐

V_1 ☐ V_2 ☐ V_3 ☐ ☐ ☐ ☐

If in other special leads, specify_____

29. Date: _____ 30. Signature of Doctor_____

_____