A MULTICENTRIC TRIAL TO EVALUATE THE SAFETY AND LIPID LOWERING EFFECTS OF AN INVESTIGATIONAL DRUG.

Clinical Protocol Title

A multicentric trial to evaluate the safety and lipid lowering effects of an investigational drug.

Investigator

Study monitor

Director General, CCRS, Chennai.

Investigational Drug

XXX

Co- Investigator(s):

Study Centre

CCRS Institutes

1. Introduction:

Hyperlipidemia is a common health problem that tends to affect more often the elderly population in developed countries. It is a major cause of disease burden globally as a risk factor for cardiovascular and cerebrovascular diseases.[1]

Worldwide, the prevalence of hyperlipidemia is about 39,000 per 100,000 patients. In developed countries, the prevalence of hyperlipidemia is about 51,000 per 100,000 patients. In developing countries, the prevalence of hyperlipidemia is about 26,000 per 100,000 patients. The prevalence of hyperlipidemia increases with age. It may be present in children and young adults but is seen more frequently in later life. The prevalence of hyperlipidemia among men is about 37,000 per 100,000 and among women is about 40,000 per 100,000. Thus gender is not much associated with an increased risk of hyperlipidemia. However, hyperlipidemia is more common in men less than 55 years of age and in women more than 55 years. People in the developed countries have a higher prevalance of hyperlipidemia. The prevalence also increases noticeably according to the income level of the country. In high-income countries, over 50% of adults have raised total cholesterol; more than double the level of the low-income countries. In the past, the incidence and prevalence of hyperlipidemia were low in developing countries in comparison to developed countries. But with the westernization of developing regions in Middle East, India and Central and South America, the incidence of hyperlipidemia is increasing.

1.1 Background:

Siddha system, the oldest traditional system, describes the ways and means of maintaining a healthy life style and emphasizes the importance of physical, emotional, psychological, social wellbeing. Siddha system explains about cycles of birth and death and the need to maintain one's harmony within to achieve Motcham or Eternal Bliss. A Strong belief in the community for the treatment of Non - communicable diseases in Siddha Medicine fetches more number of patient visits in our hospital which offers proper treatment modalities for life style disorders such as hyperlipidaemia

1.2 **Rationale:**

The study drug has been subjected to pilot level clinical trials (Sujatha et al, 2010) and has shown some significant efficacy .Multicentric trials involving large sample size have not been under taken so far. The efficacy of the investigational drug in hyperlipidemia has been proved in animal studies.

2 **Clinical study objective:**

2.1 ***Primary objective:***

To assess the efficacy of Siddha formulation – xxx in Hyperlipidemia .

2.2 ***Secondary objective:***

To draw the toxicological profile of Siddha formulation –xxx

2.3 **Objective destiny:**

Standardization of the trial drug as per PLIM guidelines.

Efficacy and chronic toxicity study as per OECD guidelines.

Phase III clinical trials as per GMP guidelines.

3 **Study design:**

Open labelled clinical trial, multi centric OPD level study

3.1 **Study design schematic:**

4 **Subject selection:**

4.1 **Criteria for inclusion:**

1) The subject 30-60 years of age of either sex with established hyperlipidemia

2) Free of obvious health problems as established by medical history and physical examination.

3) The subject willing to give written informed consent and willing to comply with study protocol.

4) The subject with following primary selection criteria:

LDL-C concentration > 130 mg %; Triglyceride level > 150 mg/dl, Total cholesterol more than 220mgs (fasting), HDL less than 35 mg.

5) The subject not taken lipid lowering drugs at least 3 months prior to the recruitment.

4.2 **Criteria for exclusion:**

1) Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, thyroid dysfunction as determined by medical history, physical examination or laboratory test, which in the opinion of the investigator, might interfere with the study objectives.

2) Subject participating in other clinical trials or planned to participate in another clinical trial during the present trial period.

3) The subject taking anti-inflammatory or lipid-lowering medication such as statins or finofibrates.

4) The subject with diseases demanding continuous administration of

B-blockers, calcium antagonists, hypoglycemic agents or diuretics.

5) History of a previous severe allergic reaction (generalized utricaria; angioedema or anaphylaxis).

6) History of chronic alcohol consumption and/or intravenous drug abuse.

7) Pregnant and lactating women.

8) History of contraceptive, hormone replacement therapy (HRT) or steroids since last 3 months.

9) Subjects with history of tuberculosis, HIV or malignancy.

10) Hypersensitivity to any component of the drug

5. **Study drug:**

The trial drug is xxx and it is an official Siddha formulation.

Dose:

Duration of the medication: 120 days

5.1 **Study drug Compliance / Adherence:**

Drug compliance form will be issued to assess the Compliance.

5.1.1 **Withdrawal of subjects due to non-compliance/ adherence**

The investigator shall withdraw the patients from the study if

- fasting total cholesterol rises to > 300 mg. /dl. Or LDL level increases > 190mg/dl and Triglyceride more than 250 mg/dl are not controllable within 30 days.

- Development of any serious complication which requires urgent treatment with any other drug / therapy.

The investigator will mention the probable cause of withdrawal and provide possible medical treatment to manage the illness

5.2 **Supply of Study Drug:**

Drug will be supplied by SCRI Pharmacy.

5.2.1 **Formulation and Packaging**

The sponsor will supply the trial drug 100 gms of investigational drug in the form of powder.

5.2.2 **Preparing and dispensing**

A plastic container can be given to the study subject, consisting of 30 pockets of 2 gms each for two times a day for 15 days. The study subject has to visit once in 15 days for 120 days. Prospective assessment without trial drug will be observed after a month.

5.2.3 **Drug administration**

2 Gms before food in the morning and evening with luke warm water.

5.3 **Concomitant medication:**

The study subject should not use any hypolipidemic agents. Without prior consultation of the investigator, the trial subject should not consume any medication for any other illness.

6. **Research Study Procedures**

6.1 **Screening procedures**

The full details of history and physical examination of the patients will be recorded as per the proforma. Fasting Lipid Profile is the main investigation for this study and based on this the screening will be done.

6.2 **Follow up procedure**

After the duration of trial drug administration, a follow up study for a period of 1 month will be undertaken and the measurement will be recorded.

7. **Safety and Effectiveness Assessments**

Routine assessment of investigations including lipid profile, liver function test, renal function test and electrolytes are done to assess the safety of the drug.

8. **Adverse Event Reporting**

If any adverse drug reaction or adverse event reported, the study subject should be referred to the Pharmacovigilance cell of the study centre. According to the advice of the Pharmacovigilance cell withdrawal or continuation of the study will be determined.

9. **Statistical Methods / Data Analysis**

9.1 **Study endpoints**

Reduction of hyperlipidemia to normal limits.

9.1.1 **Primary endpoint**

Reversal to Normal / Near normal lipid levels

9.1.2 **Secondary endpoints**

No alterations in LFT / KFT before and after drug administration.

9.2 **Sample size determination**

30 per centre is the sample size of the study.

9.3 **Statistical Analysis**

Data on Lipid profile, LFT /KFT will be analyzed by using appropriate statistical methods.

10. **Criteria for success of treatment**

If , during treatment or after treatment fasting total cholesterol become < 200mg/dl, fasting LDL < 130 mg/dl. and Serum triglyceride < 150 mg/dl and HDL > 35mg/dl it will be treated as successful outcome of the treatment.

11. **Trial monitoring and data analysis**

The progress of the trial will be monitored by CCRS. Data analysis will be undertaken at SCRI, Chennai.

12**. Ethical Review**

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

Multicentric trial to study the safety and lipid lowering effects of a poly-herbal formulation

CONSENT FORM

CERTIFICATE BY INVESTIGATOR

I certify that I have disclosed all the 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 physician, 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 have been informed about the possible side effects and procedures to report when encountered. 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 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 on ‘’A Multicentric trial to study the safety and lipid lowering effects of a poly-herbal formulation’’

Date: _____ Name of the Subject: _____

Signature or Thumb impression_____

Date: _____ Name of the witness: _____

Signature or Thumb impression: _____

Relationship _____

PATIENT INFORMATION SHEET

A Multicentric trial to study the safety & lipid lowering effects of poly-herbal formulation.

Study Doctor:

Site of Investigation:

Contact No: (Mobile No.) –

You are being asked to participate in a clinical research study. However, before you decide to be a part in this study, you need to understand the risks and benefits as well as what is expected of you as a study participant. Please read the following information carefully. This consent form may contain word (s) that you do not understand. Do not hesitate to ask the doctor and/or doctor's staff any questions you may have. You should not sign this form until you understand all the information presented in the following pages and until all your questions about the research have been answered to your satisfaction.

What is the study about?

Research is going on to find a suitable natural product for the treatment of hyperlipidemia. You are invited to participate in such a study in which you will receive Siddha trial drug.

The aim of the present study is to clinically evaluate the efficacy of a polyherbal formulation in the management of hyperlipidemic patients.

Totally 30 patients from this hospital 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 three months to complete. After this period, you are expected to visit the hospital every fortnight. The interval between the first and second visit will be around 14 days.

Before you start treatment, during the first visit to the clinic, you will undergo a complete physical examination. Blood and urine samples will also be taken. This is to make sure that you are eligible for the study.

One week later, at your second visit, if you are eligible, you would be put on trial treatment for 120 days. You may receive trial drug for 120 days. You should follow life style modifications (diet advice, exercise) as given along with information Sheet. A prospective

assessment will be made after 1 month without trial drug but with lifestyle modification to assesses the efficacy of trial drug.

From the first visit onwards, you will be required to fast overnight before attending each visit. Blood and urine samples will be taken at Baseline, First and Fourth month. In each visit, you will be supplied with sufficient quantity of drug to last until your next visit.

How is blood tested?

A small sample of blood will be drawn from your arm. If your doctor has ordered other tests to be run at the same time as your cholesterol test, all the samples will usually be taken at the same time. Your blood sample is then analyzed by a laboratory.

Your doctor will tell you if you should fast (avoid consuming food, beverages and medications, usually for nine to 12 hours) before your blood test. If you aren't fasting when the blood sample is drawn, only the values for total cholesterol and HDL cholesterol will be usable. That's because the amount of LDL (bad) cholesterol level and triglycerides can be affected by what you've recently consumed.

What happens at the end of the study?

The trial treatment will be stopped at the end of 120 days. You will be referred to the General OPD.

Are there any risks?

In the earlier pilot study no adverse events were recorded and if anything adverse happens to any one of the participant it will be duly informed to all the other participants also.

What are the alternatives?

Your doctor will be pleased to explain to you the available alternative treatment for your impaired Lipid levels.

When can you leave the study?

Your participation in the study is entirely voluntary. You can choose to leave the study at any time. Your decision to leave the study will not affect your medical care or relationship with your doctor.

Your doctor may decide that you should not continue in the study if, a) your blood lipid level becomes very high or very low, b) you start on Statins or other medication c) you take part in any other trial.

What is the cost of the study?

All medication and tests to be done during the study will be free of charge.

If you do not want to participate, you are free to do so. It will not affect your medical care or relationship with your doctor in any way.

What happens now if you decided to take part?

You will be asked to sign a consent form saying that you have been given information about the study and you voluntarily agree to take part.

It is important to follow all the instruction given by your doctor or doctor's assistant carefully.

What about the confidentiality?

The study data in your name or address will be coded with initials and number in your records. The confidentiality will be maintained. Unless required by law, only the study Doctor, the study team and its authorized agents and the Institutional Ethics Committee will have access to confidential data which identifies you by name.

Any other additional information regarding this trial?

If you have any questions regarding the research study or if you need emergency medical treatment while you are participating in this study, or have questions or additional concerns about the study, you should contact the study doctor.

Do not sign this form unless you have had a chance to ask questions and have received satisfactory answers to all your questions.

A Multicentric trial to evaluate the safety and lipid lowering effects of poly-herbal formulation

FORM I - SCREENING PROFORMA

1. Code No (of clinical trial)

2. Centre:

3. Name of the Patient _____

4. S. No. of Patient _____

5. Gender Male (1) Female (2)

6. Date of Birth Age (Years)

7. Address _____

_____

Mobile: Phone no:

CRITERIA FOR INCLUSION Yes (1) No (0)

8) The subject 30-60 years of age of either sex with established hyperlipidemia

9) Free of obvious health problems as established by medical history and physical examination.

10) The subject willing to give written informed consent and willing to comply with study protocol.

11) The subject with the following primary selection criteria:

LDL- C concentration > 130 mg %; Triglyceride level > 150 mg/dl, Total cholesterol more than 220 mgs (fasting), HDL less than 35 mg.

12) The subject not taken lipid lowering drugs at least 3 months prior to the recruitment.

CRITERIA FOR EXCLUSION

13) Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, thyroid dysfunction as determined by medical history, physical examination or laboratory test, which in the opinion of the investigator, might interfere with the study objectives.

14) Subject participating in other clinical trials or planned to participate in another clinical trial during the present trial period.

15) The subject taking anti-inflammatory or lipid-lowering medication such as statins or finofibrates.

16) The subject with diseases demanding continuous administration of

B-blockers, calcium antagonists, hypoglycemic agents or diuretics.

17) History of a previous severe allergic reaction (generalized utricaria; angioedema or anaphylaxis).

18) History of chronic alcohol consumption and/or intravenous drug abuse.

19) Pregnant and lactating women.

20) History of contraceptive, hormone replacement therapy (HRT) or steroids since last 3 months.

21) Subjects with history of tuberculosis, HIV or malignancy.

22) Hypersensitivity to any component of the drug

If 'yes' to S.No.8-12 admit the patient into the study and if 'yes' to 13-22 exclude the patient.

If admitted subject _____ No. _____

Date: _____ Signature of the Doctor _____

A Multicentric trial to evaluate the safety and lipid lowering effects of poly-herbal formulation .

FORM I A – SELECTION PROFORMA

1. Code No. (Clinical trial)

2. Centre :

3. Name of the Patient _____

4. S. No. of Patient _____

5. Gender Male (1) Female (2)

6. Date of Birth Age (Years)

7. Address _____

_____

_____

8. Educational status

Illiterate (1) Read & Write (2)

Educational qualifications_____ (3)

9. Occupation

Desk Work (1) Field Work (2) Others specify_____

10. Income per capita per month in _____

Chief complaint with duration (if any) in days (mostly asymptomatic)

Absent (0) Present (1)

11. Dyspnoea

If present, duration in days_____

12. Fatigue

If present, duration in days _____

13. Polydipsia (Excessive Thirst)

If present, duration in days _____

14. Exhaustion/Tiredness

If present, duration in days _____

15. Body ache

If present, duration in days _____:

Personal History

16. Diet Veg (1) Non-veg (2) Lacto-veg (3)

17. Presence of anxiety No (0) Yes (1)

18. Constipation No (0) Yes (1)

Addiction

19. Smoking No (0) Yes (1)

If yes specify:

(a) Quantity [packs] _____ (b) Total duration in years _____

20. Tobacco No (0) Yes (1)

If yes, specify: (a) quantity_____ b) Total duration in years_____

21. Alcohol No (0) Yes (1)

22. If yes, specify: quantity (ml)_____

23. Total duration in years_____

24. Any other (specify)_____

25. Yakkaiyin Ilakkanam (Type of body constitution)

VITAL SIGNS

26. Pulse rate/min

27. Heart rate/min

28. BP(mmof Hg)

29. Temperature ºF

		PRESENT (1)	ABSENT (2)
30.	Cyanosis		
31.	Anaemia		
32.	Jaundice		
33.	Clubbing		
34.	Lymphadenopathy		
35.	Oedema		
36.	Height/cm		
37.	Weight/Kgs		
38.	BMI		

Date: Signature of Investigator/ Medical Officer

FORM III - LABORATORY INVESTIGATIONS (Before Treatment)

1. Code No. (of clinical trial)

1. Centre:

3. S. No. of the Patient _____

4. Name of the Patient _____

5. Address _____

_____

6. Gender Male (1) (1) Female (2)

7. Date of Birth 8. Age (Years)

9. Date of assessment

Urine examination

Routine

10. Sugar_____ 11.a) Albumin_____ b) Microalbumin_____

12. Deposits_____

Microscopic

13. Pus cell _____ (HPF)

14. RBC_____ (HPF)

15. Cast_____ (HPF)

Stool examination

16. Routine _____

Microscopic

17. Ova_____ 18. Cyst_____19. Occult Blood_____

Blood

20. TC (Cells/Cumm) _____

Differential Count

21. P (%) _____ 22. L (%) _____ 23. E (%) _____ 24. M (%) ____ 25.B (%) ___

26. Hb (g/dl) _____.

27. ESR (1/2 hour.) _____ ESR (1 hour.) _____

30. Glycated Hemoglobin (HbA1c) _____ (to be done before treatment and at the end of treatment)

31. Blood Urea (mg/dl) _____

32. S. Creatinine (mg/dl) _____

33. Uric acid (mg/dl) _____

LIPID PROFILE

34. Serum total Cholesterol (mg/dl) _____

35. S. Triglycerides (mg/dl) _____

36. HDL (mg/dl) _____

37. LDL (mg/dl) _____

38. VLDL (mg/dl) _____

LIVER FUNCTION TESTS

Serum bilirubin

39. Total (mg/dl) _____

40. Direct (mg/dl) _____

41. SGOT (IU/L) _____

42. SGPT (IU/L) _____

43. Alk. Phosphatase (KA units) _____

44. Total proteins (gm/dl) _____

45. Albumin (gm/dl) _____

46. Globulin (gm/dl) _____

47. A/G Ratio _____

Serum Electrolytes

48. Sodium (mEq/L) _____

49. Potassium (mEq/L) _____

50. Chloride (mEq/L)_____

Sl.No.10-50 will be done before and after treatment except Sl.No.34-38 (Lipid profile) which will be done before treatment, and consequently every month and a month after prospective observation with out trial drugs.

Date: Signature of Investigator/ Medical Officer

FORM IV A

DRUG COMPLIANCE REPORT FORM – I

(To be filled by the trial participant)

(To be issued on 1st visit – 0th day and taken back on 2nd visit – 30th day)

Registration No. of the participant _____

Name of the participant _____

Please come for next visit on (Date and time is to be filled by the Investigator)

(அடுத்த முறை மருத்துவமனைக்கு வரவேண்டிய தேதி மற்றும் நேரம்)

Instructions to trial participant:

• **Please take four tablets twice a day before food**

(4 மாத்திரைகளை உணவுக்கு முன்பு காலை மாலை இருவேளை எடுத்துக்கொள்ளவும்)

• **Please return the unused tablets along with the drug compliance report form duly filled.**

(பூர்த்தி செய்யப்பட்ட இப்படிவத்துடன் உபயோகப்படுத்தாமல் மீதமிருக்கும் மாத்திரைகளையும் கொண்டுவரவும்)

S.no	Date	காலை - மருந்து உடகொண்ட பின் முறையாக நேரம் குறிதுகொள்ளவுய Morning dose (Around 9 AM)		மாலை - மருந்து உடகொண்ட பின் முறையாக நேரம் குறிதுகொள்ளவுய Evening dose (Around 8 PM)	
		Please put mark after taking the Medicine	Please enter the time	Please put mark after taking the Medicine	Please enter the time
1.					
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Name of the Participant: _____ Date: _____

Signature or
Thumb impression of the participant
(பங்குபெறுபவரின் கையொப்பம்)

Signature of the Investigator
with date