# Central Council for Research in Siddha

# PROTOCOL FOR DOUBLE BLIND CLINICAL TRIAL FOR THE TREATMENT OF OSTEOPOROSIS

## I. INTRODUCTION:

Pommer coined the term osteoporosis in 1885, which literally means increased porosity of Bones. It is described as a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissues with a consequent increase in bone fragility and susceptibility to fracture. The magnitude of the problem has not been fully understood and the incidence of osteoporosis is highly increased due to increased life span and greater awareness of the disease since 1980 (Rosen et al, 1997). In recent study the following observations were made.

1) Osteoporosis occurs both in males and females in India.
2) Osteoporotic fractures occur more commonly in Indian males than females.
3) Osteoporotic fractures occur 10-20 years earlier in Indian men and women compared to west (Wali, T.P. etal)

Certain factors like Genetic, personal life style factors like smoking, alcoholism lower intake of calcium, non-exposure to sunlight and certain diseases predispose this disease.

In Siddha system also under the heading "Vatha Sronitham" many signs and symptoms described can closely be correlated with this clinical entity. (Yugimuni, 1985) This has also been treated with herbal and herbo minerals since very remote past. In recent years the advancement in the field of Phytochemistry and clinical trials, it has been evinced the role of certain herbals like *Cissus quadrangularis* in the treatment of bone fracture. The phytochemical studies have also established the presence of phytosterol, phytoestrogen and calcium, which will be more useful in the treatment of osteoporosis.

In modern medicine this disease is managed with, Hormone replacement therapy and also with calcium and Vitamin 'D' which is considered as anti resorptive and stimulator of Bone turn over. But these drugs do have side effects like nausea, vomiting and diarrhea. In this contest the natural calcium, which is safe, less toxic, and does not have any side effect will be taken for study.

## II. AIM

To assess the therapeutic efficacy of a Siddha coded trial drug **OPI** in the treatment of osteoporosis in comparison with standard control drug "**Calcium with Vitamin- D3".**

## III. TRIAL DESIGN:

Double blind randomized controlled clinical study.

## IV. PLACE OF STUDY:

CCRS centres.

## V. SAMPLE SIZE: 100 CASES

Groups: Two – trial and control [50(25 male and 25 female) cases in each group]

## VI. TREATMENT

**Control drug :** Calcitrol, which contains Calcium 500mg and Vitamin D3 (1.25 dihydroxy Cholecalciferal) 0.25 Microgram twice daily.

**Group-I** **:** Coded drug OP 1 500 mg twice a day in capsules.
**Group-II** **:** Standard control with calcitrol twice a day.

## VII. DURATION OF TREATMENT: One year

## VIII. CRITERIA FOR INCLUSION

1. Age: Patients of both sexes above 45 years and up to 70 years.
2. B.M.D. T. Score below – 1.5

The cases for carrying out BMD T Score will be screened with the following targeted patients:

1. Postmenopausal woman with early menopause (40 years and below) and familial prevalence.
2. Patients with osteopenia or spinal deformities on spine-x-rays.
3. Patients on long-term cortico steroids for more than six months.
4. Patients with history of osteoporosis related fractures.

## IX. CRITERIA FOR EXCLUSION

1. Age below 45 and above 70
2. T. Score below –1.5
3. Primary Hyper parathyroidism
4. Thyrotoxicosis
5. Addison's disease
6. Caushing syndrome
7. Rheumatoid arthritis
8. Mal absorption syndrome
9. Chronic liver diseases
10. Organ transplantation
11. Chronic renal failure
12. Prolonged immobilization
13. Diabetes (Uncontrolled)
14. Cases undergoing treatment for osteoporosis
15. Cases undergoing treatment for any other serious illness.

## X. CRITERIA FOR WITHDRAWAL

During the course of the trial there may be certain potential adverse threats like Kidney stones, hypercalcemia with renal insufficiency (milk alkali syndrome) and interference of calcium with other essential nutrients. If any other side effects and other symptoms are observed then the trial drugs will be withdrawn and will be treated symptomatically.

## XI. METHODS OF ASSESSMENT

Clinical assessment will be done (O), at the end of $1^{st}$, $2^{nd}$ and every subsequent month till the completion of treatment (Form 2). The Lab investigations (Biochemical markers) will be recorded before drug administration (O month) and after every two months till the completion of trial (0, $2^{nd}$, $4^{th}$, $6^{th}$, $8^{th}$, $10^{th}$ and $12^{th}$ months i.e. the end of the treatment). The B.M.D. will be done before and after the completion of the treatment.

## XII. PERIOD OF STUDY

One year for each case. Total duration will be Two years to complete the study.

## XIII. STATISTICAL ANALYSIS

30% or more in B.M.D. T. Score (above –1.5 level) increase will be considered as significant improvement. .

## XIV. TRIAL MONITORING AND DATA ANALYSIS

Siddha Central Research Institute, Chennai, Department of Orthopedic, KMC, Chennai and CCRS, HQ's Office, Chennai will monitor the progress of the trial. Siddha Central Research Institute, Chennai, will undertake data analysis.

## XV. ETHICAL REVIEW

Clearance certificate from Institutional Ethical Committee (IEC) or Head of the Institution should be obtained before the Project is initiated. IEC/Head of the Institution should submit patient's information sheet and informed consent form along with project proposal for approval. Both of these forms should be maintained in duplicate with one copy given to the patient at the time of entry to the trial.

---

The change between two BMD can be expressed in the form of (%) percentage between two measurements or by absolute change in gm/cm between two measurements.

Percentage change is calculated as $\frac{\text{I BMD} - \text{II BMD}}{\text{I BMD}} \times 100$

= (%) Percentage change.

Absolute change is calculated as I BMD – II BMD

Absolute change

**Central Council for Research in Siddha**

## 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

The attending physician, the purpose of the clinical trial and the nature of drug treatment and follow-up have informed me to my satisfaction,, 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 am willing to undergo any risk for inclusion in this study.

I, exercising my free power of choice, hereby give my consent to be included as a subject in the clinical trial of Siddha Formulation on Osteoporosis.

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 DOUBLE BLIND CLINICAL TRIAL FOR THE TREATMENT OF OSETOPOROSIS

### PATIENT INFORMATION SHEET

**What is the study about?**

Osteoporosis is characterized by increased fragility and susceptibility to fracture. It is a disease very common and there is increase in its incidence due to increased life span and advancement in health delivery system. Osteoporotic fractures occur 10-20 years earlier in Indian men and women compared to west. The life style changes have also bearing on the predisposition of this disease. In Siddha system also the management is done through herbal medicines and this clinical entity can be correlated with vatha suronitham. The drugs, which are used for the treatment of Osteoporosis, some time causes side effects. In Siddha system the efficacy of herbal drugs have been observed in clinical trials in the union of bones in the treatment of Bone fractures. So, a new formula, OPI is to be tried with modern medicine calcitrol in 100 cases (50 each group)

**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 one year to complete. During this period, you are expected to visit the hospital thirteen times. The interval between the first and second visit will be around one month. After it, you are required to visit once in a month till the completion of the treatment.

Before you start treatment, during the first visit to the clinic, you will undergo a complete physical examination, BMD Test (Bone mineral density). This is to make sure that you are eligible for the study.

If you were found eligible, you would be put on trial treatment for one year. The daily dosage will be 500mg twice. At each visit, you will be supplied with sufficient quantities of drugs to last until your next visit. On completion of the treatment B.M.D. will be done again to asses the effect of the treatment. Bio-chemical investigations will also be carried out one in every two months.

**Central Council for Research in Siddha**

**DOUBLE BLIND CLINICAL TRIAL OF SIDDHA FORMULATIONS IN THE TREATMENT OF OSETOPOROSIS**

**FORM I - SCREENING PROFORMA**

1. Name of the Person _____

2. Gender Male ☐ (1) Female ☐ (2)

3. Date of Birth ☐☐ ☐☐ ☐☐ Age (.In Yrs) ☐☐
   D D M M Y Y

4. Address _____

_____

| **CRITERIA OF INCLUSION** | **Yes (1)** | **No (0)** |
|---|---|---|
| 5. Age between 45 and 70 years of either Sex | ☐ | ☐ |
| 6. Bone Mineral Density (B.M.D.) T. Score < – 1.5 and > -4 | ☐ | ☐ |
| **CRITERIA FOR EXCLUSION** | | |
| 7. Age below 45 and above 70 | ☐ | ☐ |
| 8. T. Score >-1.5 and <. 4 | ☐ | ☐ |
| 9. Primary hyper parathyroidism | ☐ | ☐ |
| 10. Thyrotoxicosis | ☐ | ☐ |
| 11. Addison's | ☐ | ☐ |
| 12. Caushing syndrome | ☐ | ☐ |
| 13. Rheumatoid Arthritis | ☐ | ☐ |

| | Yes (1) | No(2) |
|---|---|---|
| 14. Mal-absorption syndrome | ☐ | ☐ |
| 15. Chronic liver diseases | ☐ | ☐ |
| 16. Organ Transplantation | ☐ | ☐ |
| 17. Chronic renal failure | ☐ | ☐ |
| 18. Prolonged immobilization | ☐ | ☐ |
| 19. Uncontrolled Diabetes | ☐ | ☐ |
| 20. Cases undergoing treatment for osteoporosis | ☐ | ☐ |
| 21. Cases undergoing treatment for any other serious illness | ☐ | ☐ |

22. If **yes** to 5 and 6 and No to 9-21 above, admit the subject to the trial. If admitted, subject serial No. ____

No. of packets issued: _____

Date:_____ Signature of the Doctor _____

**CENTRAL RESEARCH INSTITTUE FOR SIDDHA, CHENNAI**

**DOUBLE BLIND CLINICAL TRIAL OF SIDDHA FORMULATIONS IN THE TREATMENT OF OSETOPOROSIS**

**FORM I A – HISTORY PROFORMA**

1. SL. No. of Subject _____
2. Name of the Subject _____
3. Gender Male ☐ (1) Female ☐ (2)
4. Date of Birth ☐☐ ☐☐ ☐☐ Age (In Yrs) ☐☐

   D D M M Y Y
5. Educational status

   Illiterate ☐ (1) Read & Write ☐ (2)

   Educational qualifications_____(3)

6. Past occupation

   Desk Work ☐ (1)

   Fieldwork with physical labour ☐ (2)

   Fieldwork Intellectual ☐ (3)

   Indicate nature of work_____(4)

7. Occupation: -

   Desk works ☐ (1)

   Fieldwork with physical labour ☐ (2)

   Fieldwork intellectual ☐ (3)

   Indicate nature of work_____ (4)

**Addiction**

8. Smoking No ☐ (0) Yes ☐ (1)
9. if yes specify: (a) quantity[packs] _____

10. (b) Total Duration in years _____

11. Tobacco No ☐ (0) Yes ☐ (1)

12. If yes specify: (a) quantity_____

13. (b) Total Duration in years_____

14. Alcohol No ☐ (0) Yes ☐ (1)

15. If yes specify: (a) quantity (ml)_____

16. (b) Total Duration in years_____

17. Prakriti

(1)Vatham ☐ (2)Pitham ☐ (3) Kapham ☐

(4) Vatha-kapham ☐ (5)Vatha-pitham ☐ (6) Pitha-kapham ☐

(7)Mukkutram ☐

**Physical Examination**

18. Height (cm) _____

19. Weight (kg) _____

**MEDICAL HISTORY**

20. Pathological Fracture(After the age of 40 yrs or more) No ☐ (0) Yes ☐ (1)

21. If yes indicate : Date_____(22) Site_____ History of pain before fracture_____

23. Family History of Osteoporosis No ☐ (0) Yes ☐ (1)

24. If yes indicate relationship_____

25. Spinal Deformity No ☐ (0) Yes ☐ (1)

26. If yes indicate site_____ 27. Date from which suffering_____

---

**Menstrual History (For female patients):**

28. Age in years at Menarche ☐☐

☐

☐

☐

29. Duration of menstrual period in days ☐

30. Interval of menstrual period ☐

31. Age in years at onset of menopause ☐

**SURGICAL HISTORY**

32. Abdominal Surgery No ☐ (0) Yes ☐ (1)

33. Hysterectomy ☐ (0) ☐ (1)

34. Oophorectomy No ☐ (0) Yes ☐ (1)

35. Orthopedic Surgery No ☐ (0) Yes ☐ (1)

**Drugs used (having bearing on Osteoporosis)**

36. Steroids No ☐ (0) Yes ☐ (1)

37. If yes indicate duration (in months) _____(38) doses_____

39. Anti convulsive No ☐ (0) Yes ☐ (1)

40. If yes indicate duration (in months) _____(41) doses_____

42. 41. HRT Heparin/Warfarin No ☐ (0) Yes ☐ (1)

43. If yes indicate duration (in months) _____(44) doses_____

**Clinical Symptoms**

45. Skeletal Pain ☐ (0) Y ☐ (1)

46. If yes indicate Region_____(47) Duration in months _____

48. Type of pain Acute ☐ (1) Chronic ☐ (2)

49. Kyphosis No ☐ (0) yes ☐ (1)

50. Other clinical symptoms No ☐ (0) Yes ☐ (1)

51. If yes,
specify_____
_(2)
(Symptoms & Duration)

Date: Signature of Doctor_____

---

# Central Council for Research in Siddha

## DOUBLE BLIND CLINICAL TRIAL OF SIDDHA FORMULATIONS IN THE TREATMENT OF OSETOPOROSIS
## FORM II – CLINICAL ASSESMENTS

1. Serial No. of the Subject:_____

2. Name _____

3. Gender Male ☐ (1) Female ☐ (2)

4. Date of Birth ☐☐ ☐☐ ☐☐ Age (In yrs). ☐☐
D D M M Y Y

5. Date of Assessment _____

6. Month of Assessment : Initial ☐ (0) 1st month ☐ (1) 2nd month ☐ (3)
3rd month ☐ (4) 4th month ☐ (5) 5th month ☐ (6)
6th month ☐ (7) 8th month ☐ (9) 9th month ☐ (10)
10th month ☐ (11) 11thmont ☐ (12) 12th month ☐ (13)

**Clinical Symptoms**

7. Skeletal Pain No ☐ (0) Yes ☐ (1)

8. If yes indicate Region_____(9) Duration in months _____

10. Type of pain Acute ☐ (1) Chronic ☐ (2)

11. Kyphosis No ☐ (0) Yes ☐ (1)

12 Other clinical symptoms No ☐ (0) Yes ☐ (1)

13. If yes, specify
_____(2)
(Symptoms & Duration)

Date: Signature of Doctor_____

## Central Council for Research in Siddha

# DOUBLE BLIND CLINICAL TRIAL OF SIDDHA FORMULATIONS IN THE TREATMENT OF OSTEOPOROSIS
# FORM III – LABORATORY INVESTIGATIONS

1. Serial No. Of the Subject: _____
2. Name _____
3. Gender Male ☐ (1) Female ☐ (2)
4. Date of Birth ☐☐ ☐☐ ☐☐ Age (In yrs). ☐☐
   D D M M Y Y
5. Date of Assessment _____
6. Month of Assessment: Initial ☐ (0) 2nd month ☐ (1)
   4th month ☐ (2) 6th month ☐ (3)
   8th month ☐ (4) 10th month ☐ (5)
   12th month ☐ (6)
7. Serum Calcium_____(mg / 100 ml)

**BONE TURNOVER**

8. Alkaline phosphate_____( µg/L)
   (Bone specific)
9. Osteo calcin (BGP) _____( µg/L)
10. Procollagen peptides_____

**BONE RESORPTION**

11. Pyridinium cross links and some of_____
    Type – I Collagen Break down products in serum
12. Serum Tartarate resistant_____
    Acid phosphatase

Date: Signature of Doctor

_____