RESEARCH PROPOSAL

ON

CLINICAL EVALUATION OF *AN INVESTIGATIONAL DRUG IN* THE MANAGEMENT OF *KALLADAIPPU* (UROLITHIASIS)

1. INTRODUCTION

1.1. Background

Medicinal plants are widely used worldwide as an alternative for primary health care. Traditional herbal medicine is an important part of the health care system in India. Since most of the plants are claimed to be non-toxic, low-cost, available in rural areas and culturally acceptable, their effectiveness in the treatment of urinary stones has been widely studied. Herbal medicines have been used to help in Urolithiasis through anti-inflammatory, diuretic, litholytic, antimicrobial and antispasmodic actions. *xxx* is a decoction form of polyherbal Siddha formulation indicated for the management of Urolithiasis[2].

***Kalladaippu* (Urolithiais)**

Kalladaippu is described well in the classical Siddha text Yugi Vaithiya Chintamani. It is classified into four types which is described by Yugi muni based on three vital life factors (*Mukkutram*) in our body. The clinical features of *Kalladaippu can be* correlated to those of Urolithiasis. Typical symptoms of acute renal colic are intermittent colicky flank pain that may radiate to the lower abdomen or groin, often associated with nausea and vomiting. Lower urinary tract symptoms such as dysuria, urgency and frequency may occur as the stone enters the ureter.

Aetiology and classification of Kalladaippu

As per the Siddha literature, *Kalladaippu* results owing to intake of turbid water, food contaminated with stones, bones, hair and sand; intake of putrified food stuff and starch substances; eating flatulence producing food while indigestion.

கலங்கின தோர்தண்ணீர்தான் குடித்த பேர்க்கும்
கல்லெலும்பு மயிர்மண்தான் கலந்தன்னத்தில்
அலங்கின தோரன்னங்க ளருந்த லாலும்
அழுகலோடு முற்றபண்ட மருந்தலாலும்
மலங்கின தோர்மாப்பண்ட மருந்தலாலும்
மந்தத்தில் வாய்வானப தார்த்தந் தன்னை
துலங்கின தோருசிதன்னிற் சுவைத்த லாலும்
சுருக்காய் கல்லடைப்புவந் துதோன்றுந் தானே

- Verse 727, Yugimuni Vaithiya Chintamani 800

TYPES OF KALLADAIPPU:

The Sage Yugi has classified *Kalladaippu* into four types – *Vaatha Kalladaippu, Pitha Kalladaippu, Slethuma Kalladaippu* and *Thontha Kalladaippu* based upon the clinical features and affected Mukkutram.

i. Vaatha *Kalladaippu* (வாதக்கல்லடைப்பு)

தரித்து நாபிக்குங்கீழ் சுருக்காய் குற்றிச்
சலமலந்தான் வீழாமற் றம்ப மாகி
வரித்துமே லிங்கத்தில் வலியு மாகி
மருவியதோர் பொத்தியெலாஞ் சுரந்து கட்டி
திரித்தியே கிடைகொடாப் பிரட்டலாகித்
தேம்பியே மூச்சுமாய் வயிறு முப்பும்
உரித்ததோர் சதைபோல உவர்ப்பு மாகும்
ஓங்கியதோர் வாதக்கல்லடைப்பு தானே

- Verse 729, Yugimuni Vaithiya Chintamani 800

In Vaatha Kalladaippu, pain is felt just below the umbilical region and penis. It is characterized by severe colic, dyspnoea, abdominal distension, oliguria and constipation.

ii. *Pitha Kalladaippu* (பித்தக் கல்லடைப்பு)

அடைப்பாகிச் சலந்தானுமருவ லாகி
அயங்காய்ச்சிச் சொருகினாற் போலே காணும்
புடைப்பாகப் பொற்றியெங் கும்பு ழுக்கமாகிப்
பூட்டுபோல் பிகுவாகிப் பிரட்டலாகும்
மடைப்பாகி உதிரநிற மாய்க்கல் லாகி
வந்திழிந்து லிங்கத்தில் மாட்டிக் கொள்ளும்
குடைப்பாகிக் குற்றலாய்க் கூச்ச லாகிக்
குதட்டுமே பித்தக்கல் லடைப்பு தானே

- Verse 730, Yugimuni Vaithiya Chintamani 800

In Pitha Kalladaippu, reduced urine output with characteristic burning sensation (similar to introducing a red-hot iron needle into the urethra), red-blood coloured stone which blocks the ureter causing gnawing and pricking pain and tenderness.

iii. *Slethuma Kalladaippu* (சிலேத்துமக் கல்லடைப்பு)

தானான தொப்புளிலே வில்லு போலச்
சலியாமற் சுரந்துமே சற்றே குற்றும்
ஏனான காலோடு கைகள் சந்து
இடுப்புதான் குடைச்சலாயி சிவு காணும்
வேனான லிங்கத்தின் வெண்மை தன்னில்
விறுவிறென் றேகடுப்பாகி வியர்வை யாகும்
தேனான வெளுப்புக்கல் சிறுகல் லாகச்
சிக்கலாய் வந்திறங்குச் சேட்பந்தானே

- Verse 731, Yugimuni Vaithiya Chintamani 800

Slethuma Kalladaippu is characterized by excruciating pain in the umbilical region, pain in the joints of upper and lower extremities, low-backache, spasmodic pain, sweating and gradual passing out of white coloured stone granules in the urine.

iv. *Thontha Kalladaippu* (தொந்த கல்லடைப்பு)

வந்திறங்கும் நீர்த்தாரை யடியிற் றானும்
மாவருத்த முண்டாகி வலியு மாகி
நொந்திறங்கி நீர்தானு மருவி பாயும்
நொய்தான சிறுமணல் போல் நொறுங்கிக் கல்லான்
சந்திறங்கி நீர்வழியில் வந்து வீழும்
தாக்கான சிறங்கைக்கல் தினமொன்றுக்கு
துந்திறங்கித் தினந்தினமு மிழந்து கொல்லும்
தொந்தமாங் கல்லடைப்புச் சூட்டி டாயே

- Verse 731, Yugimuni Vaithiya Chintamani 800

In Thontha Kalladaippu, severe pain is felt ar the base of below the urethral region with excess urination. It is characterized by disintegration of stones in to small, sand like granules in the urine.

Incidence of urolithiasis

Urolithiasis is the third most common affliction of the urinary tract. Although the surgical techniques have taken greater strides, yet the common man in developing countries like India may not find it affordable. Hence the therapies described in traditional texts as that of Siddha Medicine have to be revived for the management of Urinary calculi. These traditional formulations are comparatively economical and also clinically effective.

Urinary stones affect 10–12% of the population in industrialized countries[4, 5]. The incidence of urinary stones has been increasing recently[6]. With a prevalence of> 10% and an expected recurrence rate of nearly 50%,stone disease has an important effect on the health care system[7]. Epidemiological studies revealed that nephrolithiasis is more common in men (12%) than in women (6%)and is more prevalent between the ages of 20 to40 in both sexes[8]. The etiology of this disorder is multifactorial and is strongly related to dietary lifestyle habits or practices[9]. Increased rates of hypertension and obesity, which are linked to nephrolithiasis, also contribute to an increase in stone formation[10].

1.2. Rationale of the study

Management of stone disease depends on the size and location of the stones. Large calculi associated with unbearable pain may require treatment with ureteroscopy, extracorporeal shock wave lithotripsy, percutaneous nephrostomy and surgery. Due to the advancement of modern science, stones larger than 5 mm or stones that fail to pass through are treated only by interventional procedures such as extra-corporeal shock wave lithotripsy (ESWL), ureteroscopy (URS), or percutaneous nephrolithotomy (PNL) [11]. Unfortunately, the tendency for stone recurrence is not

altered by removal of stones with ESWL. In addition, ESWL might show some significant side effectssuch as renal damage, ESWL induced hypertension or renal impairment [12].Though there are a few recent reports of beneficial effects of medical treatments in enhancing clearance of stones in the distal ureters [13], still there is no satisfactory drug especially for the prevention or the recurrence of stones. But the traditional Siddha system uses many herbs to treat kidney stones and they have been shown to be effective for long years.

Recent study on SK reveals that this polyherbal formulation is a potent antioxidant, biologically safe and the LD(50) was found to be greater than 50 ml/kg b.wt in fasted female Sprague Dawley rats[26].Moreover subacute toxicity evaluation of SK did not show much alteration in haematological, biochemical and histological observations. The study confirmed that SK is safe upto a dose of 9 ml/kg which is the rat dose derived from the maximum recommended human dose of 100 ml confirming the traditional claims[27].

Based on the safety and toxicity studies, a maximum human dose of SK will also be definitely safe. Since the trial drug SK is a classical formulation indicated for the management of Urolithiasis and found to be safe in toxicity studies, a Phase 2 clinical study is proposed. This will be done by recruiting Urolithiasis patients of either sex in the age group of 18 to 65 years reporting to the OPD. The patients with 3 to 10 mm calculi only will be inducted to the study.

2. CLINICAL STUDY OBJECTIVES

2.1. Primary Objective:

To evaluate the efficacy of the trial drug SK to remove or reduce the renal stones in human subjects.

2.2. Secondary Objective:

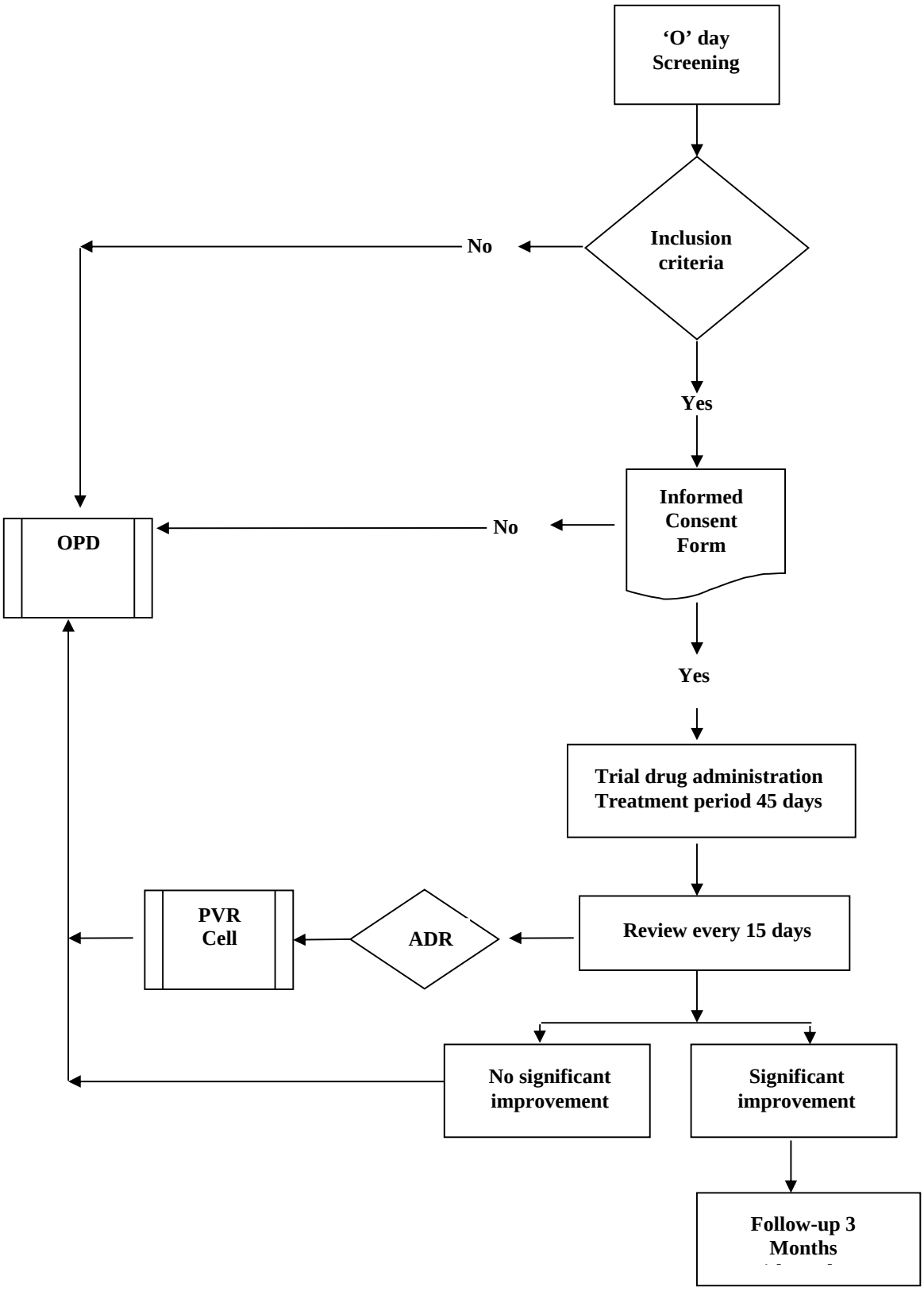
To assess the safety of the trial drug

3. STUDY DESIGN

Open Labelled Phase 2 trial.

Screening will be done as per the Screening Proforma before recruiting the patients. After recruitment, review of patients will be done every week. The Laboratory investigations will be performed on 0^{th}, 15^{th}, 30^{th} and 45^{th} days. USG and X-Ray will be taken on 0^{th} day and 46^{th} day. Duration of drug administration will be 45 days and clinical follow-up will be done at 1^{st}, 2^{nd} and 3^{rd} months after stopping the drug therapy.

3.1. Flow chart of the study design



4. SUBJECT SELECTION

A total of 30 patients reporting to the OPD will be recruited to the study as per the inclusion criteria. Only those patients who are willing to sign the Informed Consent Form will be recruited to the study.

4.1.Subject inclusion criteria

1. Age group: 18 to 65 years
2. Presence of any three of the following signs and symptoms:
    a. Intermittent dull / colicky pain in back radiating from loin to groin, which aggravates on movements
    b. Burning micturition
    c. Haematuria
    d. Frequent micturition
3. Evidence of calculus in any of the following modern diagnostic procedures:
   X-Ray - KUB region
   Ultrasonogram - KUB region
4. Patients with renal stones of size 3 to 10 mm.

4.2 Subject exclusion criteria

i. Stag horn calculi

ii. Severe Hydronephrosis / Pyelonephrosis

iii. Cystitis

iii. Severe urinary tract infections

iv. Any other complications related to calculus

vi. Pregnant and lactating women

vii. Patients undergoing treatment for chronic illnesses – Diabetes mellitus, Cardiovascular diseases, Tuberculosis, Hypertension etc.

5. STUDY DRUG - SK

5.1. Study drug compliance

The recruited subjects will be asked to fill up the Drug Compliance Form as per schedule to ensure observance of the drug dosage regimen.

5.1.1. Withdrawal due to non-compliance

During the course of the trial treatment, if the patient could not follow the necessary instructions or if any serious condition develops which requires urgent treatment, such subject may be withdrawn from the trial and managed by the principal investigator accordingly. Missing the drug regimen for three consecutive days will be treated as non-compliance and the patient may be

withdrawn from the study. In the event of the study discontinuation all data will be deleted unless the patient explicitly wishes and affirms further analysis of his/her data.

The withdrawn subjects will be replaced by new subjects as per inclusion criteria.

5.2. Study drug supplies

Formulation and packaging

The trial drug will be prepared and supplied by the Pharmacy, Siddha Central Research Institute, Chennai.

Preparation of SK:

Take 20 g of chooranam and add 32 parts (approx. 640 ml) of water. Boil the mixture till 1/8th of total volume (80 ml) is obtained. Filter the decoction using muslin cloth and use it within 3 hours.

5.3.Drug administration

a) Potable water should be used for the preparation of decoction.
b) The decoction should be taken orally, preferably in empty stomach.
c) The prepared decoction should be used within 3 hours.

5.4.Study drug storage and accountability

Trial drug should be stored in room temperature and dry place. A stock register should be maintained by the Principal Investigator / Co-Investigator.

5.5.Concomitant medication

If required, use of oral analgesic/anti-inflammatory drugs will be permitted during the treatment. But persistent usage will not be allowed and the subject shall be discontinued from the study as per withdrawal criteria.

6. Research Study Procedures

6.1. Screening procedures

During the first visit the patients will be screened as per the Screening Proforma (Form-A). Routine blood and urine investigations will be done. Radiological and Sonological investigations will be made immediately. Based on the inclusion criteria patients will be recruited for the study. A detailed history of patients will be recorded in CRF-I. The investigations will be recorded in Form (B).

6.2. Study drug procedures

Drug administration will be initiated at the earliest after recruitment. The trial drug will be dispensed as 20 g packs. During the treatment period clinical assessment will be done as per CRF-II. Blood and urine examination will be done during each visit (i.e. on 0th, 15th, 30th and 45th days). X-Ray and USG will be done before recruitment and on 46th day to detect calculi.

6.3. Follow-up procedures

After stopping the trial drug, follow-up will be done for 3 months to assess the recurrence of renal stones, if any. Blood and urine examination will be done during each visit (i.e. after 1st, 2nd and 3rd months). At the end of 3rd month, USG / X-Ray will also be done to check recurrence of calculi.

7. Assessment of Safety and Effectiveness

This open labelled study is aimed at evaluating the efficacy of Siddha coded formulation SK on Clinical recoveries and recovery in diagnostic parameters (Biochemical, Radiological and Sonological).

a) Clinical: A complete history of the patient's illness will be recorded in Case Record Form I. The Assessment criteria specifically for Urinary Calculi will be carried out at 0 Day, 15th Day, 30thDay and 45th Day and recorded in Case Record Form II.
b) Biochemical / Lab investigations: At least 25% reduction in the presence of pus cells, epithelial cells, RBCs and Calcium oxalate crystals will be considered as significant.
c) Radiological / Sonological: Absence of calculus or at least 25% reduction in the number and size of calculi will be considered significant.

DEFINITION OF GRADES

The clinical and laboratory parameters will be assessed based on the grading as mentioned below:

1. **Pain at rest / on movement**

Severe (6)	: Patient cries with excruciating pain
Moderate (4)	: Frequently complains of pain with painful look
Mild (2)	: Complained by patient after interrogation
Nil (0)	: No pain

2. **Tenderness**

To be examined by digital pressure and where impracticable by passive movement
Grade 1: The patient says the renal angle is tender
Grade 2: The patient winces
Grade 3: The patient winces and withdraws the affected part
Grade 4: The patient does not allow the affected area to be touched

3. **Presence of Pus cells**

Upto 5	: 0
6 – 20	: 2
21-40	: 4
41-60	: 6
61 & Above	: 8

4. **Presence of Calcium oxalate crystals**

Upto 5	: 0
6 – 20	: 2

21-40 : 4
41-60 : 6
61 & Above : 8

5. Presence of Epithelial cells

Upto 3 : 0
4-8 : 2
9-15 : 4
16 & Above : 6

6. Presence of RBCs

Nil : 0
1-15 : 2
16-30 : 4
31-45 : 6
46 & Above : 8

By calculating the above scores in percentage, the over-all assessment will be done.

a. Good response - 75% and above - improvement with complete removal of stones and relief from clinical symptoms.
b. Fair response – 50 to 74% - improvement with 50% reduction in size / No. of stones.
c. Poor response –< 50% - improvement with 25% reduction in size / No. of stones.
d. No response – 0 % - improvement (No relief in the presenting clinical symptoms)

8. Adverse Event Reporting

8.1 Adverse event definitions

Adverse event means any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related.

Adverse reaction means any adverse event caused by a drug.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction"

Life-threatening, suspected adverse reaction. A suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.

Serious, suspected adverse reaction.A suspected adverse reaction is considered "serious" if, in the view of the Investigator (i.e., the study site principal investigator) or Sponsor, it results in any of the following outcomes: death, a life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

- Important drug-related medical events that may not result in death, be life-threatening, or require hospitalization may be considered "serious" when, based upon appropriate medical judgment, they may jeopardize the research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2. Reporting adverse events to the IEC

The Sponsor-Investigator will report, to the IEC, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s)*; 2) *serious*; and 3) *unexpected*.

Applicable adverse events will be reported to the IEC and Pharmaco-Vigilance Cell as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Follow-up information to a reported adverse event will be submitted to the IEC as soon as the relevant information is available.

9. Statistical Methods/Data Analysis:

9.1 Study endpoints

9.1.1 Primary endpoints

a) Absence or reduction in size / No. of stones
b) Reduction in presence of Pus cells, Epithelial cells, RBCs and Calcium oxalate crystals in urine.

9.2 Effectiveness analysis

Clinical symptoms and laboratory parameters will be analyzed using appropriate statistical method with the guidance of a Biostatistician.

10.Ethics

10.1.Approval of Institutional Ethical Committee.

The Sponsor-Investigator will obtain, from the IEC, prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

10.2.Ethical and scientific conduct of the clinical research study

The clinical research study will be conducted in accordance with the current IEC-approved clinical protocol and ICH GCP Guidelines.

10.3.Subject informed consent

The Sponsor-Investigator will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation and their rights as research subjects. The Sponsor-Investigator, or a sub-investigator(s) designated by the Sponsor-Investigator, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The Sponsor-Investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

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CLINICAL EVALUATION OF *SK*
IN THE MANAGEMENT OF*KALLADAIPPU* (UROLITHIASIS)"

FORM (A) – SCREENING PROFORMA

1. Code No:
2. Level of study: OPD
3. Subject No:
4. Name & Address of the patient:

5. Gender: Male / Female
6. Age:

CRITERIA FOR INCLUSION:

i. Age between 18 and 65 years	Yes	No
ii. Intermittent pain in low back, radiating from loin to groin	Yes	No
v. Radiology / Sonology: Presence of stone in KUB	Yes	No
iv. Renal stones of size 3 to 10 mm	Yes	No
v. Haematuria	Yes	No
vi. Reduced / Frequent micturition	Yes	No
vii.Burning micturition	Yes	No

CRITERIA FOR EXCLUSION:

i.Stag horn calculi	Yes	No
ii. Severe Hydronephrosis / Pyelonephrosis	Yes	No
iii. Cystitis	Yes	No
vi. Severe urinary tract infections	Yes	No
vii. Any other complications of calculus	Yes	No
vi. Pregnant and lactating women	Yes	No
vii. Patients undergoing treatment for chronic illness – Diabetes mellitus, Cardiovascular diseases, Tuberculosis, Hypertension etc.	Yes	No

Whether the patient is suitable for enrollment **Yes** **No**

If enrolled, patient's S.No:

Date: Signature of the Research Official

"CLINICAL EVALUATION OF *SK*

IN THE MANAGEMENT OF *KALLADAIPPU* (UROLITHIASIS)"

CASE RECORD FORM I – HISTORY PROFORMA

1.Code No:

2. Level of study: OPD

3.Subject No:

4. Name & Address of the Patient:

5. Age:

6. Gender: Male / Female

7. Educational Status:

Illiterate Semiliterate Primary school Middle school

High school Higher/Technical Education Others, specify

8. Occupation: 9. Income per capita per month: Rs.

10. Religion: 11. Marital status:

CHIEF COMPLAINTS WITH DURATION:

1. Intermittent dull or colicky low back pain:	Absent	Present	Duration _____
2. Pain increased with movement / jerks:	Absent	Present	Duration _____
3.Haematuria:	Absent	Present	Duration _____
4.Increased frequency of Micturition:	Absent	Present	Duration _____
5. Incontinence of Micturition:	Absent	Present	Duration _____
6. Crystalluria:	Absent	Present	Duration _____
7. Irregular urine flow:	Absent	Present	Duration _____
8. Burning micturition:	Absent	Present	Duration _____

History of present illness:

1. Onset of disease:	Acute	Insidious
2. Duration of disease		
3. Urinary Tract infection	Yes	No
4. Underwent any Surgery	Yes	No

If yes, specify_____

History of past illness (If any):
Family history:

1. Hypertension Yes No
2. Diabetes mellitus Yes No
3. Urolithiasis Yes No
4. Cancer Yes No
5. Tuberculosis Yes No
6. Gout Yes No
7. Others (Specify) Yes No

Personal history:

1. Diet: Vegetarian / Non-vegetarian
2. Sleep: Good Disturbed Insomnia
3. Addiction: Smoking / Alcohol / Tobacco chewing / Milk / Coffee / Tea / Aerated drinks

Udaliyal (Body constitution)

S.No	Vali		Azhal		Iyam	
1.	Lean built		Medium built		Stout/Well built	
2.	Low strength		Medium strength		Good strength	
3.	Dry Body		Excessive sweating		Oily Body	
4	Dry and dark skin		Pinkish or yellowish skin		Fair, soft & smooth skin	
5.	Scanty and brown hair		Early graying and baldness		Black and thick hair	
6	Fickle minded		Short tempered		Steady and patient	
7	Irregular appetite and thirst		Excessive appetite and thirst		Normal appetite and thirst	
8	Constipate tendency		Frequent and large stools		Normal steady bowel	
9	Disturbed Sleep		Average sleep		Sound deep sleep	

Udaliyal:Vali Azhal Iyam Thontham

Physical examination

1. Height: cms
2. Weight: kg
3. Pulse: / min
4. Blood pressure: mm/Hg
5. Body temperature: º F
6.Respiration: / min
7. Deformities Present Absent
   If so, specify_____
8. Lymphadenopathy Present Absent
9.Pallor Present Absent
10. Cyanosis Present Absent
11. Jaundice Present Absent
12. Clubbing Present Absent
13. Koilonychia Present Absent
14 JVP Normal Elevated
15. Pedal Oedema Present Absent
16 Muscle wasting Present Absent

KOSANGAL (Systemic Examination)

1.Manomaya Kosam **(Cardio-Vascular System)** Normal Abnormal
If abnormal, details_____

2.Vignanamaya Kosam (**Central Nervous System - Higher Intellectual Functions)**

Mental status	Normal	Abnormal
Memory	Normal	Abnormal
Dressing and behaviour	Normal	Abnormal

3.Pranamaya Kosam(**Respiratory System**) **Normal** **Abnormal**
If abnormal, details _____

4. Annamaya Kosam(**Digestive System**) **Normal** **Abnormal**
If abnormal, details _____

5.Anandhamaya Kosam(**Uro-Genital System and Reproductive System**)
Normal **Abnormal**
If abnormal, details----------

PORIGAL / PULANGAL

1. MEI (Skin) Normal Abnormal
   If abnormal, details _____
2. VAAI (Mouth) Normal Abnormal
   If abnormal, details _____
3. KAN (Eye) Normal Abnormal
   If abnormal, details _____
4. MOOKKU (Nose) Normal Abnormal
   If abnormal, details _____
5. SEVI (Ear) Normal Abnormal
   If abnormal, details _____

UDAL KATTUGAL:

SAARAM	Normal	Abnormal
SENNEER	Normal	Abnormal
OON	Normal	Abnormal
KOZHUPPU	Normal	Abnormal
ENBU	Normal	Abnormal
MOOLAI	Normal	Abnormal
CHUKKILAM / SURONITHAM	Normal	Abnormal

ENVAGAI THERVUGAL:

NAADI:
SPARISM:
NAA:
NIRAM:
MOZHI:
VIZHI:
MALAM:
MOOTHIRAM:
Neerkkuri:

Neikkuri:

Date: **Signature of Research Official**

"CLINICAL EVALUATION OF *SK*

IN THE MANAGEMENT OF *KALLADAIPPU* (UROLITHIASIS)"

CASE RECORD FORM II –CLINICAL ASSESSMENT

1. Code No:
2. Subject No.
3. Name_____
4. Gender: Male /Female Age:

Date of assessment: 0 Day: 7th Day: 14th Day: 21st Day:
28th Day: 35th Day: 45th Day:

Clinical Parameter	Treatment Period							Follow-up Period		
	0 Day	7 Day	14 Day	21 Day	28 Day	35 Day	45 Day	1 M	2M	3M
a. Subjective parameter										
Intermittent dull / colicky low backache										
Burning micturition										
Frequent micturition										
b. Objective parameter										
Haematuria										
Crystalluria / Turbid urine										
Urine examination										
Albumin		NA	NA		NA	NA		NA	NA	
Sugar		NA	NA		NA	NA		NA	NA	
pH		NA	NA		NA	NA		NA	NA	
Pus cells		NA	NA		NA	NA		NA	NA	
RBCs		NA	NA		NA	NA		NA	NA	
Epithelial cells		NA	NA		NA	NA		NA	NA	
Calcium		NA	NA		NA	NA		NA	NA	
Oxalate		NA	NA		NA	NA		NA	NA	
Uric acid		NA	NA		NA	NA		NA	NA	
Potassium		NA	NA		NA	NA		NA	NA	
Blood										
TC		NA	NA		NA	NA		NA	NA	
DC		NA	NA		NA	NA		NA	NA	
ESR		NA	NA		NA	NA		NA	NA	
Hb%		NA	NA		NA	NA		NA	NA	

Urea		NA	NA		NA	NA		NA	NA	
S. Creatinine		NA	NA		NA	NA		NA	NA	
S. Uric acid		NA	NA		NA	NA		NA	NA	
S. Calcium		NA	NA		NA	NA		NA	NA	
Renal Function Tests		NA	NA	NA	NA	NA		NA	NA	
Liver Function Tests		NA	NA	NA	NA	NA		NA	NA	
X-Ray - KUB		NA	NA	NA	NA	NA		NA	NA	
USG - KUB		NA	NA	NA	NA	NA		NA	NA	

NA – NOT APPLICABLE

DEFINITION OF GRADES

1. **Pain at rest / on movement**

Severe (6) : Patient cries with excruciating pain
Moderate (4) : Frequently complains of pain with painful look
Mild (2) : Complained by patient after asking
Nil (0) : No pain

2. **Tenderness**

To be examined by digital pressure and where impracticable by passive movement
Grade 1: The patient says the renal angle is tender
Grade 2: The patient winces
Grade 3: The patient winces and withdraws the affected part
Grade 4: The patient does not allows the affected area to be touched

3. **Presence of pus cells**

Upto 5 : 0
6 – 20 : 2
21-40 : 4
41-60 : 6
61 & Above : 8

4. **Presence of Calcium oxalate crystals**

Upto 5 : 0
6 – 20 : 2
21-40 : 4
41-60 : 6
61 & Above : 8

5. **Presence of Epithelial cells**

Upto 3 : 0
4-9 : 2
9-16 : 4

16 & Above : 6

6. Presence of RBCs

Nil : 0
1-16 : 2
16-31 : 4
31-46 : 6
46 & Above : 8

Assessment of Symptoms

Response:

a) Good ☐
b) Fair ☐
c) Poor ☐
d) No response ☐
e) LAMA ☐
f) Death ☐

Date: **Signature of Research Official**

**"CLINICAL EVALUATION OF *SK*
IN THE MANAGEMENT OF*KALLADAIPPU* (UROLITHIASIS)"**

Form (B) – Laboratory Investigations

1. Code No:
2. Subject No._____ Name_____
3. Gender Male Female
4. Age ____yrs.
5. Date of assessment _____

URINE

i. Colour
ii. pH
iii. Specific gravity
iv. Sugar
v. Albumin
vi. Pus cells
vii. R.B.Cs
viii. Casts / Deposit
ix. Bile pigments / Bile salts
x. Urine for culture and sensitivity

HAEMATOLOGICAL INVESTIGATIONS

i. T.C
ii. D.C
iii. Hb%
iv. E.S.R

BIOCHEMISTRY

i. Blood Urea
ii. Serum Creatinine
iii. Serum Uric acid
iv. Serum Calcium
v. Urine Calcium
vi. Urine Oxalate
vii. Urine Uric acid
viii. Urine Potassium

Renal Function Tests

Liver Function Tests

RADIOLOGY / SONOLOGY

i. Plain X-Ray – Abdomen (KUB)

ii. Ultrasonogram - KUB

Date: **Signature of Research Official**

“CLINICAL EVALUATION OF SK
IN THE MANAGEMENT OF *KALLADAIPPU* (UROLITHIASIS)”

INFORMATION TO PATIENTS

- **Purpose of research and benefits**
  - More than one third of the world’s population suffers from urolithiasis.
  - The clinical study in which your participation is proposed aims to confirm the safety and efficacy of oral administration of a classical Siddha formulation –*SK*, a safe and effective drug in practical use for the management of *Kalladaippu* /Urolithiasis.
  - It is expected that you would be benefited by using this medication, not only in terms of improvement of symptoms but also because of lesser chances of developing side effects and to avoid unnecessary surgical procedures.
  - The knowledge gained from the study would be of benefit to thousands of patients who, like you, suffer from urolithiasis.
  - About 30 consenting patients with urolithiasis will be included in the study.

- **Study Procedures**
  - You will be expected to use the medicine as advised by the physician and to attend the clinic as specified.
  - Care has been taken to design the study so as to minimize any possibilities of harm, with appropriate screening tests and examinations by the doctor.
  - Any adverse reactions e.g. local skin reactions like rash, itching or dryness, nausea, pain in abdomen, headache etc., should be informed to the investigator. You should not take any other medications throughout the study unless the investigator says so.
  - This includes over the counter medications such as cold remedies and pain killers. If you do, you should inform the doctor in your next visit.

- **Confidentiality**
  - Your medical records will be maintained with confidentiality and will be revealed only to other doctors/investigator of this study and if required, to the drug regulatory authority.
  - The results of the study may be published in a scientific journal but you will not be identified by name.

- **Your participation in the study and your rights**
  - Your participation in the study is voluntary and you may withdraw from the study anytime without having to give suitable reasons for the same.
  - If at anytime you feel worse or suffer any other illness then please tell your concerned physician.
  - If the treatment appears to be unsuitable for you it will be stopped.

- We will tell you if any new information becomes known during the study which may affect your willingness to continue in the study.

For further questions or problems you may contact:

CLINICAL EVALUATION OF SK

IN THE MANAGEMENT OF *KALLADAIPPU* (UROLITHIASIS)

FORM (C) - PATIENT CONSENT FORM

I ----------S/o-D/o----------

aged---------years residing at----------

---------- agree and exercising my free power of choice, hereby give my consent to be included as a subject in the "Clinical study on *SK* in the management of *Kalladaippu* (Urolithiasis)" which is to be conducted at ----------.

I am suffering from urinary stone (Kalladaippu). I have been informed to my satisfaction by the attending physician about the purpose of clinical trial, the nature of drug treatment and follow up including the laboratory investigations to monitor and safeguard my body function. I understand that I will be treated with a polyherbal preparation of Siddha system of medicine for the disease. The consent, which I am giving to participate, is out of my own interest with my knowledge and full consciousness and after studying the patient information sheet given to me by the investigator and after full clarification of all my doubts.

I also state that the consent is not given out of any undue influence or any other measures.

Signature / Thumb impression of the patient.

Date: Name of the patient:

Assistant Director(S)-i/c Signature of Research Official

Name of Research Official:

ஆய்வின் விவரம்

ஆய்வின் நோக்கம் மற்றும் பயன்கள்

- உலகின் மக்கள் தொகையில் மூன்றில் ஒரு பங்கு மக்கள் கல்லடைப்பு நோயால் பாதிக்கப்பட்டுள்ளனர்.

- நீங்கள் பங்கு கொள்ள இருக்கும் இந்த மருத்துவ ஆய்வின் மூலமாக ளுழு என்ற பாரம்பரிய சித்த மருந்தின் பயன்கள் மற்றும் பக்கவிளைவுகள் குறித்து நிரூபணம் செய்ய திட்டமிடப்பட்டுள்ளது.

- இந்த ஆய்வின் முடிவுகள் உங்களைப் போன்று கல்லடைப்பு நோயினால் பாதிக்கப்பட்டுள்ள ஆயிரக்கணக்கானோர் பயன்பெற உதவும்.

- இந்த ஆய்வில் சுமார் 30 கல்லடைப்பு நோயால் பாதிக்கப்பட்டவர்கள் பங்குபெற உள்ளனர். ஆய்வில் பங்கு கொள்ள நீங்கள் செலவு எதுவும் செய்ய வேண்டியதில்லை. மருத்துவ ஆலோசனை, மருத்துவ ஆய்வுக்கூடப் பரிசோதனைகள் மற்றும் மருந்து உங்களுக்கு இலவசமாக வழங்கப்படும்.

ஆய்வில் உங்களுடைய பங்கு ?

- ஆய்வு பற்றிய விவரங்களை உங்கள் மருத்துவர் உங்களுக்கு விளக்குவார். ஆய்வில் பங்கேற்க நீங்கள் விரும்பினால், அதில் கூறப்பட்டுள்ள விதிமுறைகளை தவறாமல் கடைபபிடி ்க்கவும்.

- ஆய்வில் உங்களைச் சேர்த்துக்கொள்ள தேவையான மருத்துவ மற்றும் ஆய்வுக்கூட பரிசோதனைகள் இலவசமாக மேற்கொள்ளப்படும். ஆய்வில் கலந்து கொள்ளும் உங்களுக்கு ஆய்வுக்கு முன்பும், பின்பும் தேவையான ஆய்வுக்கூட பரிசோதனைகள் இலவசமாக மேற்கொள்ளப்படும்.

- இந்த ஆய்வு எந்த விதமான தீங்கும் நேராத வகையில் மேற்கொள்ளத் திட்டமிடப்பட்டுள்ளது. எனினும் மருந்து உட்கொள்ளும் காலத்தில் உடல் அரிப்பு, தோல் வறண்டு போதல், குமட்டல், வாந்தி, வயிற்று வலி, தலைவலி மற்றும் அசாதாரண குறிகுணங்கள் ஏற்பட்டால் உடனே ஆய்வு மருத்துவரிடம் தெரிவிக்கவும்.

- ஆய்வுக் காலத்தில் வேறு உடல் தொந்திரவுக்களுக்காக மருந்துகள் உட்கொள்ள நேர்ந்தாலும் உடனே ஆய்வு மருத்துவரிடம் தெரிவிக்கவும்.

நம்பகத்தன்மை

- ஆய்வில் பங்குகொள்ளும் உங்களின் மருத்துவ ஆவணங்கள் வேறு எவர்க்கும் (ஆய்வில் சம்பந்தப்பட்ட மருத்துவர் அல்லது ஆய்வாளர்கள் தவிர) வெளியிடப்படமாட்டாது.

- ஆய்வின் முடிவுகள் தகுந்த ஆராய்ச்சி இதழ்களில் வெளியிடப்படும் எனினும் உங்கள் பெயர் மற்றும் அடையாளங்கள் குறிப்பிடப்படாது என்று உறுதியளிக்கப்படுகிறது.

ஆய்வில் உங்கள் பங்கேற்பு மற்றும் உரிமை

- ஆய்வில் சேர்த்துக்கொள்ள உங்களின் விருப்பத்தை பெற்றபின் தான் சேர்த்துக் கொள்ள முடியும். மேலும், நீங்கள் எந்த நேரத்திலும் இந்த ஆய்விலிருந்து விலகிக்கொள்ளலாம்.

- மேலும் இந்த மருந்து உங்களுக்கு பயனளிக்கவில்லை என்றாலும் ஆய்விலிருந்து விலகிக் கொள்ளலாம்.

- இந்த ஆய்வின் போது இது தொடர்பாக ஏதேனும் புதிய தகவல்கள் இருந்தால் உங்களுக்குத் தெரிவிக்கப்படும்.

மேலும் தகவல் மற்றும் சந்தேகங்களுக்கு உங்கள் ஆய்வாளரை அணுகுங்கள்:

FORM (C)- **நோயாளியின் ஒப்புதல் படிவம்**

----------ஆகிய நான் (த ∴ க பெயர்)---------- (வசிக்கும் இடம்) ---------- வயது) ----------என் சுய நினைவுடன் புதுச்சேரியில் உள்ள சித்த மருத்துவ மண்டல ஆராய்ச்சி நிலையத்தால் நடத்தப்படும் சித்த மருத்துவ ஆராய்ச்சி மூலம் சிகிச்சைபெற எழுதிக் கொடுக்கும் ஒப்புதல் படிவம்.

நான் கல்லடைப்பு நோயால் பாதிக்கப்பட்டுள்ளதால், ---------- நடத்தப்படும் ளுமு குடிநீர்" என்கிற ஆய்வின் மூலம் சிகிச்சை பெற என் சுயநினைவுடன் முழு ஒப்புதலையும் தெரிவித்துக் கொள்கிறேன். இந்த ஆராய்ச்சியின் நோக்கம், மருத்துவம் செய்யும் முறை, தொடர் கண்காணிப்பு மற்றும் என் உடல் நலம் குறித்த மருத்துவப் பரிசோதனைகளைப் பற்றிய விரிவான விளக்கம் எனக்கு மருத்துவம் செய்யும் மருத்துவ அலுவலரின் மூலம் தெளிவுபடுத்தப்பட்டுள்ளது. இந்த ஆய்வில் பயன்படுத்தப்படும் சித்த மருந்தில் மூலிகைப் பொருட்கள் அடங்கியுள்ளது குறித்து மருத்துவர் கூறக்கேட்டு முழுமையாக தெரிந்து கொண்டேன்.

இந்த ஆராய்ச்சியில் பங்குகொள்ளும் என் ஒப்புதல் என் சொந்த விருப்பத்தினால் சுய நினைவுடன் கொடுக்கப்பட்டது. யாருடைய நிரப்பந்தமும் காரணமில்லை என்பதைத் தெரிவித்து க்கொள்கிறேன்.

இப்படிக்கு

பெயர்:
முகவரி:

தேதி: நோயாளியின் கையொப்பம்

நோயாளியின் பெயர்:

உதவி இயக்குனர் (சித்தா)- பொறுப்பு ஆராய்ச்சி மருத்துவர்

CLINICAL EVALUATION OF SK

IN THE MANAGEMENT OF *KALLADAIPPU* (UROLITHIASIS)

FORM (D) - DRUG COMPLIANCE FORM – 1st & 2ndvisit

1. Center: _____
2. S.No. of the patient: _____
3. Name of the patient: _____
4. Sex: Male ☐ Female ☐

Instructions:

1. Please take ____ ml of the medicine twice a day before food.
   (மி.லி மருந்தை காலை - மாலை, உணவுக்கு முன் சாப்பிடவும்)
2. Please come for the next visit on _____

   (நீங்கள் மருத்துவமனைக்கு வரவேண்டிய அடுத்த தேதி :)----------

Day	தேதி Date	காலை - Morning		மாலை - Evening	
		மருந்து உட்கொண்ட பின் ✓குறிக்கவும் Please ✓ after taking the medicine	Neuk; Time	மருந்து உட்கொண்ட பின் ✓குறிக்கவும் Please ✓ after taking the medicine	நேரம் Time
1.					
2.					
3.					
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15.					

Date: _____ **Signature / Thumb impression of patient:**
(Nehahsh; ifnahg;gk;)