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 Urolithiasis².

**Kalladaippu (Urolithiasis)**

*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.

> कालदाप्पु युगिनिः सृष्टिविद्या रूपातिरिक्त रूपक विनाशकम्
    कसालाग्राष्टरी योगरूपकम् मयाज्ञातिरिक्त रूपक 
    कालदाप्पु युगिनिः सृष्टिविद्या रूपातिरिक्त रूपक

> अत्राद्वैतम् तत्स्वरूपातिरिक्त रूपकम्
    युगिनिः तत्साधितम् तत्स्वरूपाति

> कालदाप्पु युगिनिः सृष्टिविद्या रूपातिरिक्त रूपक 
    कसालाग्राष्टरी योगरूपकम् मयाज्ञातिरिक्त रूपक 

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    कसालाग्राष्टरी योगरूपकम् मयाज्ञातिरिक्त रूपक 

> अभावताः तत्साधितम् तत्स्वरूपातिरिक्त रूपकम्
    युगिनिः तत्साधितम् तत्स्वरूपाति

> कालदाप्पु युगिनिः सृष्टिविद्या रूपातिरिक्त रूपक

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*. 
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.

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.

In Slethuma Kalladaippu, pain is felt just below the urethra.
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 (தொண்டே கல்லாதைப்பு)

In Thontha Kalladaippu, severe pain is felt at 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 to 40 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 effects such as renal damage, ESWL induced hypertension or renal impairment. Though there are a few recent reports of beneficial effects of medical treatments in enhancing clearance of stones in the distal ureters, 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. Moreover subacute toxicity evaluation of SK did not show much alteration in haematological, biochemical and histological observations. The study confirmed that SK is safe up to 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.

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 0th, 15th, 30th and 45th days. USG and X-Ray will be taken on 0th day and 46th day. Duration of drug administration will be 45 days and clinical follow-up will be done at 1st, 2nd and 3rd months after stopping the drug therapy.
3.1. Flow chart of the study design

- 'O' day Screening
- Inclusion criteria (Yes/No)
- Informed Consent Form (Yes)
- Trial drug administration
  Treatment period 45 days
  Review every 15 days
  - ADR
    - No significant improvement
    - Significant improvement
  - PVR cell
  - OPD
  - Follow-up 3 months
  - Without drug
  - Significance improvement
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
iv. Severe urinary tract infections
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, 15\textsuperscript{th} Day, 30\textsuperscript{th}Day and 45\textsuperscript{th} 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

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<tr>
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<td>0</td>
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<tr>
<td>4-8</td>
<td>2</td>
</tr>
<tr>
<td>9-15</td>
<td>4</td>
</tr>
<tr>
<td>16 &amp; Above</td>
<td>6</td>
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6. Presence of RBCs

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<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>1-15</td>
<td>2</td>
</tr>
<tr>
<td>16-30</td>
<td>4</td>
</tr>
<tr>
<td>31-45</td>
<td>6</td>
</tr>
<tr>
<td>46 &amp; Above</td>
<td>8</td>
</tr>
</tbody>
</table>

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.

REFERENCES

4. Tiselius HG. Epidemiology and medical management of stone disease. BJU Int 2003; 91: 758–767
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:
<table>
<thead>
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<tbody>
<tr>
<td>High school</td>
<td>Higher/Technical Education</td>
<td>Others, specify</td>
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</tr>
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</table>

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)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Vali</th>
<th>Azhal</th>
<th>Iyam</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Lean built</td>
<td>Medium built</td>
<td>Stout/Well built</td>
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<tr>
<td>2.</td>
<td>Low strength</td>
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<td>Good strength</td>
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<tr>
<td>3.</td>
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<td>Excessive sweating</td>
<td>Oily Body</td>
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<td>4</td>
<td>Dry and dark skin</td>
<td>Pinkish or yellowish skin</td>
<td>Fair, soft &amp; smooth skin</td>
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<tr>
<td>5.</td>
<td>Scanty and brown hair</td>
<td>Early graying and baldness</td>
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</tr>
<tr>
<td>6</td>
<td>Fickle minded</td>
<td>Short tempered</td>
<td>Steady and patient</td>
</tr>
<tr>
<td>7</td>
<td>Irregular appetite and thirst</td>
<td>Excessive appetite and thirst</td>
<td>Normal appetite and thirst</td>
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<tr>
<td>8</td>
<td>Constipate tendency</td>
<td>Frequent and large stools</td>
<td>Normal steady bowel</td>
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<tr>
<td>9</td>
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<td>Average sleep</td>
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Udaliyal: Vali Azhal Iyam Thontham

Physical examination

1. Height:          cms
2. Weight:           kg
3. Pulse:           / min
4. Blood pressure:     mm/Hg
5. Body temperature:    °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:**

<table>
<thead>
<tr>
<th>Description</th>
<th>Normal</th>
<th>Abnormal</th>
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<td>MOOLAI</td>
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<td>CHUKKILAM / SURONITHAM</td>
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**ENVAGAI THERVUGAL:**

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<td></td>
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</tr>
<tr>
<td>VIZHI:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALAM:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOOTHIRAM:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
   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:

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>Treatment Period</th>
<th>Follow-up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 Day 7 Day 14 Day 21 Day 28 Day 35 Day 45 Day</td>
<td>1 M 2M 3M</td>
</tr>
<tr>
<td>a. Subjective parameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent dull / colicky low backache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning micturition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent micturition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Objective parameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalluria / Turbid urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>NA NA NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>Sugar</td>
<td>NA NA NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>pH</td>
<td>NA NA NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>Pus cells</td>
<td>NA NA NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>RBCs</td>
<td>NA NA NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>Epithelial cells</td>
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<td>NA NA</td>
</tr>
<tr>
<td>Calcium</td>
<td>NA NA NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>Oxalate</td>
<td>NA NA NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>Uric acid</td>
<td>NA NA NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>Potassium</td>
<td>NA NA NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
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<td>DC</td>
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</tr>
<tr>
<td>ESR</td>
<td>NA NA NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>Hb%</td>
<td>NA NA NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>----------------------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Urea</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>S. Creatinine</td>
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<td>NA</td>
</tr>
<tr>
<td>S. Uric acid</td>
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<td>NA</td>
</tr>
<tr>
<td>S. Calcium</td>
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<td>NA</td>
</tr>
<tr>
<td><strong>Renal Function</strong></td>
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<td>NA</td>
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<tr>
<td><strong>Tests</strong></td>
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<td></td>
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<td><strong>Liver Function</strong></td>
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<td>NA</td>
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<tr>
<td><strong>Tests</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>X-Ray - KUB</strong></td>
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<td>NA</td>
</tr>
<tr>
<td><strong>USG - KUB</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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
6. Presence of RBCs

<table>
<thead>
<tr>
<th>Range</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>Nil</td>
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<tr>
<td>1-16</td>
<td>2</td>
</tr>
<tr>
<td>16-31</td>
<td>4</td>
</tr>
<tr>
<td>31-46</td>
<td>6</td>
</tr>
<tr>
<td>46 &amp; Above</td>
<td>8</td>
</tr>
</tbody>
</table>

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.
Name of the patient:

Date:

Assistant Director(S)-i/c

Signature of Research Official

Name of Research Official:
அம்பாபாதா விளக்கம்

அம்பாபாதா விளக்கம் மாற்றும் வழிகாட்டி

1. மாற்று வழிகாட்டி விளக்கத்தின் வரிசையில் ஒரு மண்டல வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

2. மாற்று வழிகாட்டியானது விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

3. மாற்று வழிகாட்டியானது விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

4. மாற்று வழிகாட்டியானது விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

5. மாற்று வழிகாட்டியானது விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

6. மாற்று வழிகாட்டியானது விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

7. மாற்று வழிகாட்டியானது விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

8. மாற்று வழிகாட்டியானது விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

9. மாற்று வழிகாட்டியானது விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

10. மாற்று வழிகாட்டியானது விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

முன்னோர்க்குறிப்பிட்டு

1. அம்பாபாதா விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

2. அம்பாபாதா விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

3. அம்பாபாதா விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

4. அம்பாபாதா விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

5. அம்பாபாதா விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

6. அம்பாபாதா விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

7. அம்பாபாதா விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

8. அம்பாபாதா விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

9. அம்பாபாதா விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

10. அம்பாபாதா விளக்கத்தின் வரிசையில் குறுக்கு மாற்று வழிகாட்டியானது மற்றும் மண்டல வழிகாட்டியானது.

25
அம்பாளியை  ஏற்றத்தில் பயிரிக்கப்படும் தரவு நிறைவு

1. ஆட்சியில் பிளாஸ்டிகாக்சு ஏற்றத்தில் கம்பிக்கும் பயிரிக்கலாம். வானிலை நிலை விளக்கமிட்டுள்ளது. ஆட்சியில் பயிரிக்கும் பிளாஸ்டிகாக்சு ஏற்றத்தில் தடங்கி நிறைவு செய்யப்பட்டுள்ளது.

2. நிலை விளக்கம் ஏற்றத்தில் பெரும்பாக ஏற்றத்தில் செய்யப்படும் ஆட்சியில் பயிரிக்கப்படும் தடங்கி நிறைவு செய்யப்பட்டது.

3. முன்னாள் ஆட்சியில் பயிரிக்கப்படும் குறுக்கு பொருள் குறுக்குகள் இறக்கி ஏற்றத்தில் செய்யப்படும் தடங்கி நிறைவு செய்யப்பட்டது.

முன்னாள் பயிரிக்கப்படும் தடங்கிகளைச் சாய்த்து பயிரிக்கப்படும் ஐன்மறைகள்.
FORM (C)- வைராம்பாலிப்பில் வுருவத்துப் படிவம்

----------------------------------------------- அதிமிக நாள் ( க : ஐ நூற்றாண்டு )----------------------------------------------- ( எணிக்கை நிலை )

----------------------------------------------- பின்பகுதியில் ஆண்டுக்காரன் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக அனுமதிக்கப்பட்டிருந்தோம் இறைவன் மற்றும் ஆண்டுக்காரன் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக உரிமை பெற்றோரத் தலைமுறை.

ஆண்டுக்காரன் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக உரிமை பெற்றோரத் தலைமுறை எனும் "தலைமுறை" என்றும் ஆண்டுக்காரன் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக உரிமை பெற்றோரத் தலைமுறை எனும் "தலைமுறை" என்றும் ஆண்டுக்காரன் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக உரிமை பெற்றோரத் தலைமுறை என்றும் ஆண்டுக்காரன் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக உரிமை பெற்றோரத் தலைமுறை என்றும் ஆண்டுக்காரன் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக உரிமை பெற்றோரத் தலைமுறை என்றும் ஆண்டுக்காரன் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக உரிமை பெற்றோரத் தலைமுறை என்றும் ஆண்டுக்காரன் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக உரிமை பெற்றோரத் தலைமுறை என்றும் ஆண்டுக்காரன் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக உரிமை பெற்றோரத் தலைமுறை என்றும் ஆண்டுக்காரன் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக உரிமை பெற்றோரத் தலைமுறை.

இது ஆண்டுக்காரன்களும் மக்கள்துறைத் தலைவர்களும் யுவானார்களும் பார்வைச்செய்ய வுருவத்துப் படிவத்தாக உரிமை பெற்றோரத் தலைமுறை எனக்கொள்ள வேண்டும்.

இயுவாம்

நம்பிக்கை:

இயுவாம் பார்வைச்செய்ய வுருவத்துப்

இயுவாம் பார்வைச்செய்ய வுருவத்து

2-ஆம் திம்மண்டம் (திகுறை) - பார்வைச்செய்ய வுருவத்து
CLINICAL EVALUATION OF SK
IN THE MANAGEMENT OF KALLADAIPPU (UROLITHIASIS)

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

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. (மருத்துவத்தில் கதவைப் பயன்படுத்தவும்)

2. Please come for the next visit on __________

<table>
<thead>
<tr>
<th>Day</th>
<th>வருமான் போட்டி</th>
<th>காலம் - Morning</th>
<th>Neuk; Time</th>
<th>காலம் - Evening</th>
<th>Neuk; Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td>2.50 am</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td></td>
<td>2.50 pm</td>
<td>Please ✔ after taking the medicine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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