PROPOSAL FOR VALIDATION OF AN INVESTIGATIONAL DRUG IN PURASTHA KOLAPERUKKAM (BENIGN PROSTATIC HYPERPLASIA)

CLINICAL PROTOCOL: Summary Information

Clinical Protocol Title:

Validation of *investigational drug* in *Purasthakolaperukkam* [Benign Prostatic Hyperplasia]

Protocol number:

Version number and date:

Phase of clinical investigation:

Phase - 2

Investigational drug(s):

Sponsor:

Study Monitor:

Investigator(s):

Clinical Laboratory (ies), Technical Department(s), and Institution(s) Providing Clinical Study Services:

Introduction:

1.1 Background:

Neer arugal noigal described in Siddha literatures are clinical conditions related to disorders with decreased urine output. *Neer kattu* (Retention of urine), *Neer churukku*or *Neer kricharam* (Oliguria),*Sottu neer* (Drippling of urine), *Neer adaippu* (Anuria) are classified under this category. The above said symptoms except Neer adaippu occurs in Purasthakolaperukkam [Benign prostatic hyperplasia]. Pitha Neer Churukku has been described by the author Yugi in Yugivaidya chintamani. Some of the symptoms in this poem may be compared with the symptoms of Purastha kolaperukkam (Benign Prostatic Hyperplasia - BPH). The symptoms which occur due to obstruction in the prostatic urethra as in BPH are closely related to those described in the following poem:

அழல் நீர்சுருக்கு

"தான்மூத்திர மஞ்சளித்து மிகச்சி வக்குந்
தளர்ந்துமே கைகாலு மசதி யாகும்
பானருக்கிச் சிறுகலா யருவி பாயும்
பாரமாங் குதமண்ட மிலிங்கந் தானும்
கான்வாயு தான்மீறி வயிறு முப்பும்
களகளென்று இரைச்சலாய்க் கசங்கி யேறும்
வேள்காயு வாயுலர்ந்து மிரட்சி யாகும்
விடும்பித்த மூத்திரத்தின் விவரந் தானே"

- யூகி வைத்திய சிந்தாமணி பாடல் - 739[1]

It says that

- yellowish discolouration of the urine,
- reduced stream of the urine,
- bladder distension,
- body tiredness,
- dryness of the mouth are the symptoms of Pitha Neer churukku.

The classical preparation XXX is taken up as new Investigational drug in this clinical study. This preparation is widely used by Siddha physicians for various clinical conditions related to the problems of lower abdomen and genitalia. Some Siddha Physicians have reported with evidence that it acts on *Purasthakola perukkam* and reduces the clinical symptoms appreciably.

The current medical practice produces serious side effects such as Impotence, decreased libido, decreased quantity of semen at ejaculation, gynecomastia, asthenia, hypotension, dizziness, somnolence, fatigue, dyspnea and upper respiratory tract infection. When medication fails surgical intervention is needed but this is costly in practice. Moreover, at present herbal remedies like Saw Palmetto (*Serenoa repens*) produces good results in reducing the complaints of the BPH patients. Literary evidences reveal Siddha formulations are being practiced since ages. In exploring the efficacy of Siddha medication for this particular condition evaluation of a new investigational drug is indispensable.

1.2 Rationale:

The investigational new drug (IND) though a classical preparation, is going to be tested for new indication. So it falls under new chemical entity (NCE). Hence, as per AYUSH guidelines safety study is intended. The approval will be sought from the Institutional Animal Ethical Committee and the Safety studies will be done at Department of Pharmocology, SCRI, Chennai.

Another drug XXX is taken up for another one arm and its efficacy is compared with that of XXX. XXX is a well known Siddha drug and it is in practice since time immemorial. Its indication suits the clinical condition Neer kattu (Retention of urine). Since it is a classical drug which is going to be put into trial, preclinical study is not mandatory. [Ref: ICMR Guidelines& WHO Guidelines]

A sample size of twenty patients from OPD of CCRS Institutes will be randomized and put in two arms as open labeled study. The suitable participants as per inclusion criteria will be enrolled and the trial drugs will be administered orally as mentioned in the classical reference. The duration of the trial period will be three months.

BPH is a common condition that affects aged men. The prevalence of BPH is about 50% of men between 50 to 60 years and more than 90% of men who are older than 80 years old. However, only 25% of men above 50 and 50% of men above 75 are symptomatic.[2]

Benign prostatic hyperplasia (BPH) is a histological diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone. It is the most common benign tumor in men and is not a precancerous condition.

BPH causes obstruction of urethra leading to obstructive urinary symptoms-hesitancy, thin urinary stream, intermittent stream and straining to pass urine. Obstruction induced changes in bladder function and age-related changes in both bladder and nervous system function lead to irritative voiding symptoms-urgency, frequency and urge incontinence. There are two components of obstruction-Dynamic and Static. Dynamic obstruction is due to the increase in the tone of smooth muscles of the prostate. The tone of the smooth muscles is mediated by alpha-1 adrenergic receptors and its effects are blocked by alpha-1 adrenergic receptor blockers. The static component of obstruction is due to the mass effect of enlarged prostate which can be counteracted by drugs which causes shrinkage of prostate.[2]

The specific approach used to treat BPH depends upon number of factors like age, prostrate size, weight, prostate-specific antigen level and severity of the symptoms. 5α-reductase inhibitors decrease the production of dihydrotestosterone within the prostate, which results in decreased prostate volume, increased peak urinary flow rate, improvement of symptoms, decreased risk of acute urinary retention and need for surgical intervention. α_1 -adrenergic receptor (α_1 -AR) antagonists decrease LUTS and increase urinary flow rates in men with symptomatic BPH, but do not reduce the long-term risk of urinary retention or need for surgical intervention. Clinical efficacy of either 5α-reductase inhibitor or α_1 -AR antagonist has been further improved by using combination therapy; however, long-term outcomes are still awaited. Many more potential new therapies are under development that may improve the treatment of BPH. This article gives a brief account of rationale and efficacy of different treatment options presently available in the management of BPH.

The existing conventional drug treatment has potential side effects like impotence, decreased libido, decreased semen quantity at ejaculation, gynecomastia, asthenia,hypotension, dizziness, somnolence, fatigue, dyspnea and upper respiratory tract infection.

2. Clinical Study Objectives:

2.1 Primary Objective:

To validate the efficacy of the XXX in *Purasthakola perukkam* [Benign prostatic hyperplasia] by measuring the International Prostate Symptom Score.

1.2.Secondary Objectives:

a) Evaluation of the safety of the investigational drug XXX.
b) Standardization of process of the XXX.
c) To assess the effect in the level of PSA, if any.
d) Exploring Siddha clinical parameters of the clinical condition *Purasthakola perukkam* [BPH].

2. Study Design:

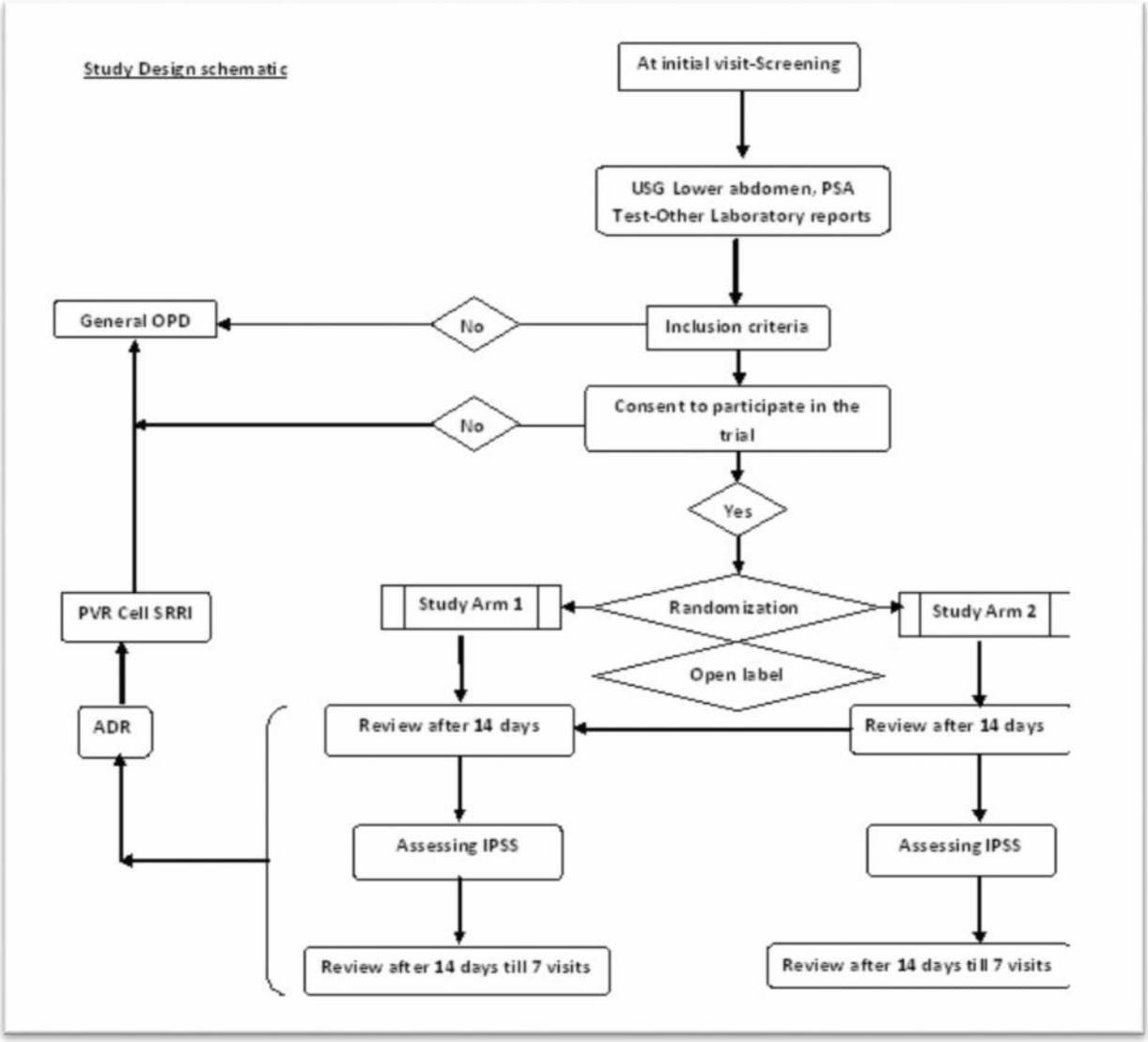
Open clinical study

[Randomized, comparative open labeled clinical study]

Since the trial is in two arms, to avoid the bias in the study participants, randomization is opted. The efficacy will be compared with the known Siddha drug XXX. The indication tried with that of XXX is a novel idea, Henceforth the baseline study will be of open labeled.

The expected total duration of subject participation will be six months. Data summarization, Statistical analyzing and monograph preparation will need additional three months. The drug therapy will be of 12 weeks. The follow up will be done without drug on 45th day and 90thday.

3.1 Study design schematic:



3.2 Allocation to treatment:

This clinical study involves two arms. The sample size of subjects is 20. 10 subject each in a single arm. They will be randomized by appropriate method.

3.3 Breaking the blind:

Blinding is not opted as both the trial drugs are classical preparations. The making of placebo is little bit difficult. The study comes under Phase II category. There is lack in published data. Hence a open clinical study is designed.

4. Subject selection:

The proposed clinical evaluation of the investigational new drugs will be done in the OPD's of peripheral Institutes of CCRS. The estimated total number of individuals to be enrolled in this clinical study will be twenty. The subjects to be enrolled will be provided with patient information sheet and informed consent form.

4.1 Subject inclusion criteria:

- Male patients between 40 and 75 years of age.
- Patient diagnosed with BPH and with clinical signs and symptoms of BPH for ≥ 3 months.
- Confirmed diagnosis: a) Ultra sonogram study
  b) **P**rostatic **S**pecific **A**ntigen Score 4 ng to 8 ng /mL
  [Normal range-PSA Score 0.8 to 4 ng /mL]
- Patient having a post-void residual urine volume of ≤ 350 cc.
- Participants who adhere to protocol requirements with written informed consent.

4.2 Subject exclusion criteria:

- PSA score beyond acceptable range and patients with a history of prostate cancer or a serum PSA >8 ng/mL [will be excluded by reviewing the past medical history and the current medication]
- History of urinary urethral obstruction due to stricture, valves, sclerosis or tumor at initiation
- Clinical evidence of prostate cancer at initiation
- Clinical evidence of any of the bladder or urinary tract conditions, which may affect lower urinary tract symptom at initiation
- Patient having a post void residual urine volume ≥ 350 cc.
- Patients who have participated in any drug study during the past 3 months
- Any condition which are likely to hinder the compliance with the protocol.

5. Study drug(s):

Arm 1: xxx

(In reference text book the dosage is mentioned as 488 mg, but in this clinical study the dosage is fixed as 100 mg)

[This is given along with milk and administered two times a day after food.]

Arm 2: xxx

[To 20 gram of powder 150 ml of water is added and boiled. It is then filtered and made into decoction. It is administered two times a day before food]

Both the trial drugs will be administered orally. The total drug therapy will be of three months duration.

5.1 Study drug compliance/adherence

Research subject compliance with the assigned study drug will be recorded in the form during the periodical visits of the study participants.

5.1.1 Withdrawal of subjects due to non-compliance / adherence

During the course of the trial study period if any serious condition develops which requires urgent treatment such subject may be withdrawn from the trial and managed by the principal investigator accordingly.

5.2 Study drug supplies:

Drugs will be procured from SCRI, Chennai. In case, if there is any difficulty, direction may be given to purchase the trial drugs from any GMP certified firms.

5.2.1 Formulation and packaging:

Each drug will be packaged in the packing paper or polythene cover according to the said dosage. It will be given for 15 days. The review of the participants will be advised accordingly.

5.2.2 Mode of dispensing:

The study drugs will be kept in the co investigator's room and dispensed from there**.**

5.2.3 Drug administration:

Each study drug will be administered as investigator directed procedure. Specific instructions like do's and don'ts, foods which have to be avoided or added and drug compliance will be given to participant during each review.

5.4 Study drug storage and accountability:

Appropriate storage of the study drugs to ensure their stability will be observed by the investigators. Accountability of the study drugs are also done with documentation. Disposition or other destruction of the study drugs upon completion of the study will be done according to the instructions of the investigators.

5.5 Concomitant Medications:

If any infectious illness occurs to the study participants during the trial period, the concomitant medications will be advised by the investigators.

5.5.2 Rescue Medication:

If any problems occur, rescue medication will be governed by the investigators accordingly.

6. Research Study Procedures:

This study is a randomized, comparative, open-labeled comparing the safety and efficacy of XXX and XXX for 12 weeks in 20 patients with *Purasthakola perukkam* [benign prostatic hyperplasia]. The primary outcome measures will be validating the efficacy of interventional drug with comparator drug by change in Total International Prostate Symptom Score from baseline to end of treatment. The secondary outcomes will be evaluation of the safety of the investigational drug, Process Standardization and exploring Siddha clinical parameters of the clinical condition *Purasthakola perukkam* [BPH].

6.1. Screening procedures:

The eligible participants will be enrolled according to the inclusion criteria. The full details of the history and physical examination of the patient will be recorded as per the Proforma (Form 1 & 2) Clinical Assessment will be done on 0, 15, 30,45,60,75 and 90^{th} days (Form 3). Laboratory investigations will be recorded as per the proforma (Form 4) before treatment (0 day), after treatment (at the end of 3^{rd} 6^{th} and 9^{th} month).

6.2 Study drug procedures:

The study arm 1 will receive 100mg of drug with milk q.s after food at morning and night.

The study arm 2 will receive 60 ml of decoction before food at morning and night.

6.3 Follow-up procedures:

Follow ups in both arms will be carried out after 45^{th} and 90^{th} day after completion of 3 months treatment period.

6.4. Schedule of activities (Study table):

Type of study	Randomized, comparative, open labeled clinical study									
Phase	2									
Sample size	20 [without including drop outs, lama]									
Randomization	By appropriate method									
Study arms	Arm 1 => 10 subjects					Arm 2 => 10 subjects				
Intervention	xxx – 100 mg bid with milk after food					xxx- 60 ml bid before food				
Study period	6 months [3 months drug therapy + 3 months follow up]									
Visits		At initial visit (0)	I visit (15^{th} day)	II visit (30^{th} day)	III visit (45^{th} day)	IV visit (60^{th} day)	V visit (75^{th} day)	VI visit (90^{th} day)	Follow up 6^{th} month	Follow up 9^{th} month
Arm 1	1 0 subjects	Screening	Measuring IPSS and other Clinical data	Measuring IPSS and other Clinical data	Measuring IPSS and other Clinical data	Measuring IPSS and other Clinical data	Measuring IPSS and other Clinical data	Measuring IPSS and other Clinical data	Reporting ADR if any	Reporting ADR if any
Laboratory investigations		USG,PSA test and other investigations						USG,PSA test and other investigations		
Arm2	10 subjets	Screening	Measuring IPSS and other Clinical data	Measuring IPSS and other Clinical data	Measuring IPSS and other Clinical data	Measuring IPSS and other Clinical data	Measuring IPSS and other Clinical data	Measuring IPSS and other Clinical data	Reporting ADR if any	Reporting ADR if any
Data compilation	Data compiled for preparing monograph. Research article will be communicated after compiling the data.									

Safety and Effectiveness Assessments:

7.1 Safety assessment:

Blood and Urine examination will be done to evaluate the safety of the study drug. Laboratory investigations will be recorded as per the proforma (Form 4) before treatment (0 day), after treatment (at the end of 3rd 6th and 9th month).

7.2 Effectiveness assessment:

The IPSS, ultra sonogram study and test for PSA range will be done according to the proforma.

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"

Reasonable possibility. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

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 occurred in a more severe form and 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, but life-threatening, or requiring 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.

Unexpected, suspected adverse reaction. A suspected adverse reaction is considered "unexpected" if it is not listed in the general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified

8.2 Recording / Reporting requirements

8.2.1 Eliciting adverse event information:

Participants will be routinely observed and questioned about adverse events during their visits.

8.2.2 Recording requirements:

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s).

Adverse events or abnormal test findings felt to be associated with the study drug(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

8.2.2.1 Abnormal test findings:

An abnormal test finding will be classified as an *adverse event* if one or more of the following criteria are met:

The test finding is accompanied by clinical symptoms

The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy

Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study

The test finding is considered an adverse event by the Sponsor-Investigator of the IND application

8.2.2.2 Causality and severity assessment:

The Sponsor-Investigator of the IND applicationwill promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s); and 3) if the adverse event meets the criteria for a *serious adverse event*.

If the Sponsor-Investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s)", the adverse event will be classified as *associated with the use of the study drug(s)* for reporting purposes. If the Sponsor-Investigator's final determination of causality is "unknown but not related to the study drug(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

9. Statistical methods/Data Analysis:

Clinical symptoms and Laboratory parameters will be analyzed using appropriate statistical method.

9.1 Study endpoints:

9.1.1 Primary endpoints:

a) Measuring International Prostate Symptom Score

b) Prostate Specific Antigen test

SYMPTOM SCORE - IPSS SCORE *

INTERNATIONAL PROSTATE SYMPTOM SCORE SHEET

Dr Name: ..... Address: .....

Patient Name: ..... Address: .....

Date: .....

Age Group: 40-49 ☐ 50-59 ☐ 60-69 ☐ 70+ ☐

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. INCOMPLETE EMPTYING Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. FREQUENCY Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. INTERMITTENCY Over the past month, how often have you found you stopped and started several times when you urinated?	0	1	2	3	4	5	
4. URGENCY Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. WEAK STREAM Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. STRAINING Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
7. NOCTURIA Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	None 0	1 time 1	2 times 2	3 times 3	4 times 4	5 or more times 5	

Which of the above do you regard as most troublesome (1-7) _____

TOTAL PROSTATE SYMPTOM SCORE _____

	Delighted	Pleased	Mostly satisfied	Mixed - satisfied and dissat-isfied	Mostly dissat-isfied	Unhappy	Terrible
QUALITY OF LIFE DUE TO URINARY SYMPTOMS If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? (tick one).	0	1	2	3	4	5	6

*International Prostate Symptom Score

IPSSymptom Score= sum of questions A1 to A7

- Mild Score : 0-7
- Moderate Score: 8-19
- Severe Score: 20-35

The Assessment will be made before and after treatment by calculating the International Prostate Symptom Score. Based on this the clinical condition may be divided into mild, moderate and severe. The response will be categorized as mentioned above.

9.1.2 Secondary endpoints:

Measuring Siddha clinical parameters like Envagai thervu, Neerkkuri and Neikkuri

11. Data Handling and Record-Keeping:

11.1 Data recording / Case Report Forms:

A Case Report Form (CRF, see Appendix 1) will be completed for each subject enrolled in the clinical study. The Sponsor-Investigator will review, approve and sign/date each completed CRF; the Sponsor-Investigator's signature serving as attestation of the Sponsor-Investigator's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the *Source Data* recorded on the *Source Documents*.

12. Ethics:

12.1 Institutional Review Board (IRB) approval

12.2 Ethical and scientific conduct of the clinical research study

The clinical research study will be conducted in accordance with the current IRB-approved clinical protocol; ICH GCP Guidelines adopted by the FDA; and relevant policies, requirements, and regulations of the CCRS, ICMR.

12.3 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 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.

The Sponsor-Investigator shall make certain appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the Sponsor-Investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

14. References:

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2. Smith's General Urology, 17th Edition, Page no.348-374
3. Quality control standards for certain Siddha formulations Published by CCRAS, 1991, Page 34
4. Neelima Dhingra & Deepak Bhagwat, Indian Journal of Pharmacology, Benign prostatic hyperplasia:An overview of existing treatment, Year 2011, Volume 43, Issue 1, Page 6-12
5. American Urological Association Guideline, Management of Benign Prostatic Hyperplasia, Revised 2010,
6. Roger S. Kirby, The Clinical Assessment of Benign Prostatic Hyperplasia, CANCER Supplement, July 1,1992, Volume 70, No. 1,284-290
7. Timothy J. Wilt, MD, MPH; Areef Ishani, MD; Gerold Stark, MD; Roderick MacDonald, MS;

   Joseph Lau, MD; Cynthia Mulrow, MD, MS, Saw Palmetto Extracts for Treatment of Benign Prostatic Hyperplasia A Systematic Review, JAMA, November 11, 1998—Vol 280, No. 18, 1604-09

PROTOCOL FOR VALIDATION OF XXX IN

PURASTHA KOLAPERUKKAM (BENIGN PROSTATIC HYPERPLASIA)

FORM-1 SCREENING PROFORMA

1. Centre
2. Code No _____ Level of study OPD
3. Subject No_____ Name of the patient_____
4. Address:

5. Gender Male
6. Age _____Yrs
7. Group A / B

CRITERIA FOR INCLUSION:

8. Male patients between 40 and 75 years of age Yes No
9. Clinical signs and symptoms of BPH for ≥ 6 months. Yes No
10. Ultra sonogram study for BPH Yes No
11. PSA Score 4 ng to 8 ng /mL Yes No
12. Post-void residual urine volume ≤ 350cc Yes No
13. Adhere to protocol requirements with written informed consent Yes No

CRITERIA FOR EXCLUSION:

14. History of prostate cancer or a serum PSA >8 ng /mL Yes No
15. History of urinary urethral obstruction Yes No
16. Clinical evidence of prostate cancer Yes No
17. Clinical evidence of any of the bladder or Urinary tract conditions Yes No
18. Post void residual urine volume ≥ 350 mL by ultrasound Yes No
19. Patients who have participated in a drug study in the past 3 months Yes No
20. Any condition which are likely to hinder the compliance with the protocol Yes No

VALIDATION OF XXX IN

PURASTHA KOLAPERUKKAM (BENIGN PROSTATIC HYPERPLASIA)

FORM II – HISTORY PROFORMA

1. Centre Siddha Regional Research Institute, Puducherry

2 .Code No ---------- Level of study OPD

3. Subject No--------- Name of the patient----------

4. Address:

5. Gender Male

6. Age ----------Yrs

7. Educational Status

Illiterate Read &Write Primary school Middle school

High school College Others Specify----------

8. Occupation:

9. Income per capita per month in rupees ----------

CHIEF COMPLAINTS WITH DURATION

I. Obstructive symptoms:

1. Hesitancy Present Absent Duration-----

2. Decreased force and caliber of stream Present Absent Duration-------

3. Sensation of incomplete bladder emptying Present Absent Duration-

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4. Double voiding (urinating a second time

within 2 hours of the previous void) Present Absent Duration-------

5. Straining to urination Present Absent Duration--

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6. Post void dribbling Present Absent Duration-------

II.Irritative symptoms:

7. Urgency Present Absent Duration--

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8. Frequency Present Absent Duration------

-

9. Nocturia Present Absent Duration-

HISTORY OF PRESENT ILLNESS:

1. Onset of illness Acute Insidious
2. Duration of illness
3. Mode of treatment taken Siddha Ayurvedic Homeopathy
   Unani Modern medicine
   Result obtained

FAMILY HISTORY:

1. Cardiovascular diseases Yes No
2. Tuberculosis Yes No
3. Others Yes No

If yes specify----------

PERSONAL HISTORY:

1. Diet Veg. Non-veg.
2. Emotional stress Yes No
3. Addiction Yes No

If yes, specify----------

4. Bowel habit Regular Constipation
5. Sleep Good Disturbed Insomnia
6. Presence of anxiety Yes No

PHYSICAL EXAMINATION

1. Height (cm) ----------
2. Weight (kg) ----------
3. Pulse (per min.) ----------
4. Blood Pressure Systolic/Diastolic (mm Hg) ----------
5. Body temperature (F^o) ----------
6. Respiration (per minute) ----------
7. Anaemia Absent Present
8. Pigmentation Absent Present
9. Deformities Absent Present
10. Lymphadenopathy Absent present

SYSTEMIC EXAMINATION

1. CVS Normal Abnormal
   If abnormal, details----------
2. CNS Normal Abnormal
   If abnormal, details----------
3. Respiratory system Normal Abnormal
   If abnormal, details----------
4. Digestive system Normal Abnormal
   If abnormal, details----------
5. Urogenital system Normal Abnormal
   If abnormal, details----------
6. Eye visual acuity Normal Abnormal
   If abnormal, details----------
7. Ear Audibility Normal Abnormal
   If abnormal, details----------

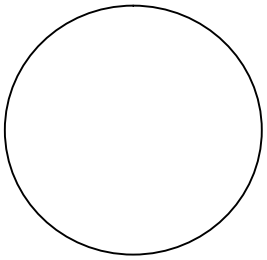
ENVAGAITHERVU:

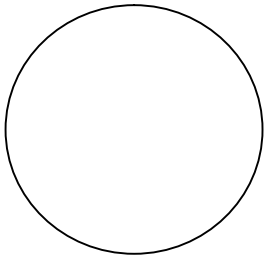
1. Naadi
2. Sparisam
3. Naa
4. Niram
5. Mozhi
6. Vizhi
7. Malam
8. Moothiram
   a)Neerkkuri
   b)Neikkuri

Nei kuri examination:

Before Treatment

After Treatment





Description:

Udaliyal:

S.No	Vatham		Pitham		Kabam	
1.	Lean built		Medium built		Stout / Well built	
2.	Less strength	`	Medium strength		Good strength	
3.	Dry body		Excessive sweating		Oily body	
4.	Dry & Dark skin		Pinkish or yellowish skin		Fair, Soft & smooth skin	
5.	Scanty and brown hair		Early graying & baldness		Black & thick hair	
6.	Fickle minded		Short tempered		Steady & patient	
7.	Irregular appetite & thirst		Excessive appetite & thirst		Normal appetite & thirst	
8.	Constipating tendency		Frequent & large stools		Normal steady bowel	
9.	Disturbed sleep		Average sleep		Sound deep sleep	

Vali ☐

Azhal ☐

Iyyam ☐

Thontham ☐

Udaliyal: _____

Date: **Signature of Research Official**

PROTOCOL FOR VALIDATION OF XXX IN PURASTHA KOLAPERUKKAM (BENIGN PROSTATIC HYPERPLASIA)

FORM III – CLINICAL ASSESSMENT FORM

Date	Day	Weight	BP	Clinical Data	IPSS	Sign of Research official
	0					
	I- Visit 15th day					
	II-Visit 30th day					
	III- Visit 45th day					
	IV- Visit 60th day					
	V – Visit 75th day					
	VI- Visit 90th day					

VALIDATION OF XXX IN

PURASTHA KOLAPERUKKAM (BENIGN PROSTATIC HYPERPLASIA)

FORM IV – LABORATORY INVESTIGATIONS

1. Center

2 .Code No.

3. Subject No._____ Name_____

4. Gender Male ☐ Female ☐

5. Age_____yrs.

6. Date of Assessment _____

LABORATORY INVESTIGATIONs *:*

1. Ultra Sonogram

2. Blood

i. Prostatic Specific Antigen (PSA)

ii. TC

iii.DC. P L E M B

iv. ESR

v. Blood sugar F & PP

vi. Hb%

vii. Sr. Cholesterol

viii. Serum Urea

ix. Serum Uric acid

x. Serum Creatinine

xi. Alkaline phospatase.

3. Urine

i. Albumin

ii. Sugar

iii. Deposits.

iv. Culture

VALIDATION OF XXX IN

PURASTHA KOLAPERUKKAM (BENIGN PROSTATIC HYPERPLASIA)

FORM V - PATIENT CONSENT FORM

I ----------S/o-H/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 trial of Siddha drug for the treatment of Benign Prostatic Hyperplasia which is to be conducted at----------.

I understand that I may be treated with Herbal /Metal/ Herbo-mineral preparations of Siddha system of medicines for the disease. I am suffering from ----------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.

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:

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

PATIENT INFORMATION SHEET

Research Officials:

Site of investigation:

Contact No:

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

What is the study about?

Research is going on to find a suitable Siddha product for the treatment of Purasthakola perukkam (Benign Prostatic Hyperplasia). You are invited to participate in such a study in which you will receive Siddha trial drug.

The aim of the present study is to clinically validate the efficay of xxx and xxx in the management of Benign Prostatic Hyperplasia patients.

Totally 20 patients from this hospital will be taking part in this study.

The Prostate Gland

The prostate is a walnut-sized gland that forms part of the male reproductive system. The gland is made of two lobes, or regions, enclosed by an outer layer of tissue. As the diagrams show, the prostate is located in front of the rectum and just below the bladder, where urine is stored. The prostate also surrounds the urethra, the canal through which urine passes out of the body.

Benign Prostatic Hyperplasia: A common part of aging

It is common for the prostate gland to become enlarged as a man ages. Doctors call this condition benign prostatic hyperplasia (BPH), or benign prostatic hypertrophy.

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 three months for

completion. After this period, you are expected to visit the hospital every fortnight. The interval between the first and second visit will be around 14 days.

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

One week later, at your second visit, if you are fit, you would be put on trial treatment for 90 days. You may receive trial drug for 90 days. You should follow life style modifications (Diet, Exercise) as given along with information Sheet.

What happens at the end of the study?

The trial treatment will be stopped at the end of 90 days. You will be asked to report for further follow up at the General OPD of SRRI.

Are there any risks?

The trial drug may cause mild gastric irritation or watery stools in some cases, if not taken along with adjuvant. In case of such symptoms, you should immediately take butter milk and report to the doctor.

What are the alternatives?

Your doctor will be pleased to explain to you the available alternative treatment for your complaint.

When can you leave the study?

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

What is the cost of the study?

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

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

What happens now if you decide to take part?

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

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

What about the confidentiality?

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

Any other additional information regarding this trial?

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

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

*Translate in to regional Language

DRUG COMPLIANCE REPORT FORM– 1st Visit

[To be filled by study participant]

1. Code No.
2. Subject No._____ Name_____
3. Trial commenced on:
4. Drug: _____

Instructions:

a) Write the date and put "tick"mark after taking the appropriate dose.

b) Put "X" mark if you do not take the medicine.

c) Write if any adverse events found during intake of medicine.

d) Please return the unused medicine along with the drug compliance report duly filled.

S.No	Date	Dose 1 (after breakfast)	Please enter the time	Dose 2 (after dinner)	Please enter the time
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					
11.					
12.					
13.					
14.					
15.					

Next visit may be on..... (Date and time is to be filled by the Investigator)

Signature of the patient **Signature of the research official**

Assessment form – Visit I

INTERNATIONAL PROSTATE SYMPTOM SCORE SHEET

Dr Name: ..... Address: .....

Patient Name: ..... Address: .....

Date: .....

Age Group: 40-49 ☐ 50-59 ☐ 60-69 ☐ 70+ ☐

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. INCOMPLETE EMPTYING Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. FREQUENCY Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. INTERMITTENCY Over the past month, how often have you found you stopped and started several times when you urinated?	0	1	2	3	4	5	
4. URGENCY Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. WEAK STREAM Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. STRAINING Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
7. NOCTURIA Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	None 0	1 time 1	2 times 2	3 times 3	4 times 4	5 or more times 5	

Which of the above do you regard as most troublesome (1-7) _____

TOTAL PROSTATE SYMPTOM SCORE _____

	Delighted	Pleased	Mostly satisfied	Mixed - satisfied and dissat-isfied	Mostly dissat-isfied	Unhappy	Terrible
QUALITY OF LIFE DUE TO URINARY SYMPTOMS If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? (tick one).	0	1	2	3	4	5	6

Date: **Signature of the Research Official**