CENTRAL COUNCIL FOR RESEARCH IN HOMOEOPATHY

DRUG PROVING

PROTOCOL

Generic Drug proving protocol for DP Program with sequential use of potencies in drug proving

Contents

Homoeopathic drug proving: Randomized double blind placebo controlled trial

Regulatory sponsor : Central Council for Research in Homoeopathy, New Delhi
Funding by : Central Council for Research in Homoeopathy, New Delhi

STUDY SUMMARY

Title	Homoeopathic drug proving: Randomized double blind placebo controlled trial
Short Title	Drug Proving
Design	Randomized double blind placebo controlled homoeopathic drug proving
Study Duration	Minimum: 6 months Maximum: One year
Study Center(s)	Identified research centres of the Council. Each drug will be proved at 2 or more centres at different geographical locations.
Objectives	To find out the pathogenetic effects of an IPS on healthy human beings.
Number of Subjects	25 volunteers (per proving centre)
Inclusion Criteria	• Age : 18 – 60 years • Both males and females • Healthy individuals with no apparent disease and normal routine laboratory parameters during screening • Intelligent enough to record carefully the facts, subjective and objective symptoms generated by the drug during proving. • Able to be informed of the nature of the study and willing to give written informed consent
Exclusion criteria	1. Any disease or condition which might compromise the hematopoietic, renal, endocrine, pulmonary, central nervous system, cardiovascular, immunological, dermatological, gastro-intestinal or any other body system 2. Persons with colour blindness. 3. Persons who have undergone surgery in last two months. 4. Planned medical / dental treatment during the proving period including herbal or dietary supplements, procedures, or medications that are likely to interfere with, or substantially alter, responsiveness to the proving substance. 5. Volunteers on regular medication (allopathic, ayurvedic, homoeopathic, naturopathic, unani, etc.) for any acute or chronic disease. 6. Participant must not be on any homoeopathic remedy in the preceding one month and have had no significant change in health status in last one month. 7. Emotionally disturbed, hysterical or anxious persons. 8. Persons having known history of allergies, food hypersensitivity, etc. 9. Women during pregnancy, puerperium and while breast-feeding and women who have undergone hysterectomy. 10. Smokers who smoke more than 10 cigarettes per day 11. Recent history of alcoholism / drug addictions or unlikely to refrain from excessive alcohol consumption / drug intake during the study period 12. Participation in another clinical or proving trial during the last 6 months
Proving cycle	Each cycle consists of proving of IPS in one potency followed by IPS in next higher potency

Study product, dose, route, regimen	The homoeopathic drug will be proved in ascending potencies. For each potency a batch will be prepared for the provers. The provers will be enrolled following a pre-trial medical examination. Subsequent to a run-in period of 1 week the study medication will be prescribed to the prover. Each batch of the drug will have 12 doses; each dose of 4 pills (Size 30). The prover will be asked to take 4 doses in a day (4 hourly) for 3 days from the prescribed batch of the coded drug. After the completion of the batch, one month washout period will be maintained in all provers, before the next batch is initiated.
Duration of administration	3 days per batch (Maximum 12 doses). Number of batches varying depending on the number of potencies in which the drug will be proved.
Intervention arms	IPS and Placebo
Blinding	The study medication will be coded and blinding will be maintained during the study period with the PI at headquarters. The codes will be broken after the study period at the research centre is completed and data will be analyzed.
Study course and data collection	An analysis to extract dependable homeopathic prescribing indications from a drug proving is required to contain the following dimensions: • 1st dimension: All symptoms occurring during the Proving • 2nd dimension: Proving symptoms with relative characterizing assessment • 3rd dimension: Characteristic symptoms (a highly individualized subset)
Data analysis	The proving symptoms will be identified and segregated from the symptoms produced in placebo group. The proving symptoms will form the drug pathogenesis.

1. TITLE
Homoeopathic drug proving: Randomized double blind placebo controlled trial

2. TRIAL REGISTRATION
The trial will be registered on CTRI

3. PROTOCOL VERSION
Version 6 October 2014

4. FUNDING
The study will be conducted by the Central Council for Research in Homoeopathy (CCRH), Department of AYUSH, Ministry of Health and family welfare at its identified research centres. The study will be fully funded by CCRH.

5. ROLES & RESPONSIBILITIES
5.1 Regulatory Committees:
At the level of CCRH headquarters:
The protocol will be placed for approval of:
1. Ethical committee of CCRH
2. Special Committee for Drug Proving of CCRH
3. Scientific Advisory Committee of CCRH

A 'data safety management board' may be constituted by the Director General CCRH for proving of new/non-pharmacopoeial drugs, responsible for supervision of drug proving of new/non-pharmacopoeial drugs.

At each study centre
A Drug proving committee will be formed at each research centre involving faculty from the colleges and scientists at the research centre. The committee shall comprise of 5-6 members responsible for conduct of the study, enrollment & safety of participants, data collection & data integrity, etc.

5.2 Study Team
At CCRH/ Headquarters
Principal Investigator - Director General, Central Council for Research in Homoeopathy, New Delhi
Coordinator & Co-Investigator(s)-Designated officers of CCRH

At Research centre (Centre of CCRH functioning in Homoeopathic Medical College premises)
Site investigator - Designated officer(s) of CCRH responsible for drug proving program
Site co-investigator(s) - Designated officer(s) of homoeopathic college where the proving program is being conducted

5.3 Protocol Preparation Team
1. Dr. RK Manchanda, Director General, CCRH
2. Dr. Anil Khurana, Deputy Director, CCRH
3. Dr. Rajpal, Research Officer (H), CCRH
4. Dr. Renu Mittal, Research Officer (H), CCRH
5. Dr. Divya Taneja, Research Officer (H), CCRH
6. Dr. Vinay Kr. Singh, Senior Research Fellow, CCRH
7. Dr. Shilpa Sharma, Senior Research Fellow, CCRH

All technical persons involved in the study must be technically qualified and registered with the competent authorities in the country.

5.4 Compliance statement

The study will be conducted in accordance with this protocol and will comply with all the requirements regarding the obligations of investigators and all other pertinent requirements

1. Drugs and Cosmetic Act 1940 & Rules 1945 of Government of India[1]
2. Good Clinical Practice[2]
3. Declaration of Helsinki[3]

6. INTRODUCTION & BACKGROUND

6.1 Background

'Drug Proving' is a method, unique to Homoeopathy where the pathogenesis of a drug is evolved through its trials on apparently Healthy Human Volunteers (Provers). Provings are an important part of homoeopathic theory and a mainstay of its practice since the first proving of *Cinchona officinalis* by Dr. Hahnemann in 1790[4]. Based on the pathogenesis, a drug picture is evolved, on the basis of which prescription is made. It provides a necessary tool to find the most appropriate remedy for the patient[5].

Dr. Hahnemann, also called the "Father of Experimental Pharmacology" for developing a new principle for ascertaining the curative power of medicinal substances, laid the foundation of drug proving and detailed the process. He tested 99 drugs on himself, his family and his colleagues, in order to discover the effects of drugs on healthy individuals. In this context he stressed the need of proving drugs on healthy persons, which is the best way to obtain an unadulterated picture of the drug. In his 'Organon of Medicine' (Aphorism 105 –145)[6], Hahnemann gave detailed instructions regarding the method of homoeopathic drug proving in healthy subjects.

Over the years, provings have been conducted by a number of authorities, most of whom have devised their own methodologies. Over the years, the term homoeopathic pathogenetic trials (HPT) is also frequently used for drug proving and these are considered to be clinical trials[7,8]. Drugs and Cosmetics Rules 1945 (Rule 122 DAA inserted in 2005) of the Government of India[1] defines clinical trial as "a systematic study of new drug(s) in human subjects(s) to generate data for discovering and/or verifying the clinical pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects with the objective of determining safety and/or efficacy of the new drug. Proving of drug substances in homoeopathy is done to identify their therapeutic potential and is primarily a study of action of these drugs on healthy human beings. As such these studies fall under the purview of clinical trials, and therefore must confirm to the GCP guidelines[2] issued by the regulatory authorities in the country. HPT trials are similar to Phase I clinical trials with a major difference that the aim of the trial is not to elicit the therapeutic dosage (bio-availability) or pharmacokinetic response, but to elicit the pharmaco-dynamic (biological response) to ultra high diluted, non-toxic doses of the intervention and are observed in terms of symptoms which are temporary and disappear after stoppage of intervention.

Drug Proving was formally initiated by the Homoeopathic Research Committee (formed in 1963). Since inception of the CCRH, the proving program has been continuing and is one of the most important research programs of the Council. The Council has over the years, devised a methodology for drug proving as detailed in the protocol.

The drug proving program of the Council is conducted in coordination with homoeopathic medical colleges and a large number of provers are students of these colleges, apart from provers of non-homoeopathic background. In each program, it is attempted to include volunteers from non-homoeopathy background also, apart from the students. As such the proving team comprises of scientists from the institute/unit of the Council and academicians from the homoeopathic colleges.

6.2 Rationale

The symptoms produced by the healthy provers form the basis of developing a homoeopathic materiamedica which identifies the symptom indications, on which the drug can be prescribed to the patients. As such drug proving is the first step for development of a symptom picture of a homoeopathic medicine. The process needs to be standardized, so that the likelihood of reproducibility increases and the reliability of symptoms so identified increases. The symptomatology so identified will construct an authentic homoeopathic material medica and can be verified clinically based upon the "Laws of Similar". The symptoms identified in drug proving will form the baseline data for subsequent verification and validation studies.

7. STUDY OBJECTIVE

To identify pathogenetic effects of a homoeopathically prepared drug substance (Investigational proving substance or IPS) on healthy human beings

8. STUDY DESIGN

The study will be prospective, parallel arm, randomized, placebo-controlled study.

Study Type:	Interventional
Allocation:	Randomized
Verum/placebo ratio(%):	Unbalanced (70/30)
Masking:	Double blind
Comparator:	Placebo
Endpoint Classification:	Disappearance of symptoms appearing during proving and subsequent symptom free period of 30 days.

9. METHODOLOGY

9.1 Study Settings

The study will be conducted at research centers of the council in coordination with the homoeopathic medical colleges. The identified scientists and faculty of the college will be involved in the study for enrollment of participation, distribution of study drug, recording & reporting of symptoms of the volunteers.

9.2 Eligibility criteria:

9.2.1 Eligibility for study

Ages: 18-60 years
Genders: Both male and female
Health status: Good state of health both somatically & psychologically

9.2.2 Inclusion Criteria:

- Healthy individuals with no apparent disease and normal routine laboratory parameters during screening
- Healthy individuals identified as fit for proving by experts
- Intelligent enough to record carefully the facts, subjective and objective symptoms generated by the IPS during proving.
- Able to be informed of the nature of the study and willing to give written informed consent

9.2.3 Exclusion Criteria:

- Any disease or condition which might compromise the hematopoietic, renal, endocrine, pulmonary, central nervous system, cardiovascular, immunological, dermatological, gastro-intestinal or any other body system
- Persons with colour blindness.
- Persons who have undergone surgery in last two months.

- Planned medical / dental treatment during the proving period including herbal or dietary supplements, procedures, or medications that are likely to interfere with, or substantially alter, responsiveness to the proving substance.
- Volunteers on regular medication (allopathic, ayurvedic, homoeopathic, naturopathic, unani, etc.) for any acute or chronic disease.
- Participant must not be on any homoeopathic remedy in the preceding one month and have had no significant change in health status in last one month.
- Emotionally disturbed, hysterical or anxious persons.
- Persons having known history of allergies, food hypersensitivity, etc.
- Women during pregnancy, puerperium and while breast-feeding and women who have undergone hysterectomy.
- Smokers who smoke more than 10 cigarettes per day
- Recent history of alcoholism / drug addictions or unlikely to refrain from excessive alcohol consumption / drug intake during the study period
- Participation in another clinical or proving trial during the last 6 months

9.3 Sample size:
Each drug will be proved on a minimum of 30 participants, including 30% control. Adding 20% dropout, minimum volunteers needed to enroll in proving becomes 40. Each centre must enroll minimum 15 to a maximum of 25 volunteers in proving. Efforts are to be taken to include atleast 20% volunteers from non-homoeopathic background.

9.4 Proving Process
9.4.1 Screening of volunteers
Applications **(Form A)** from interested volunteers will be invited which may include students, faculty & staff of homoeopathic medical colleges through notices on notice boards of the Institutes/Units/College. The study investigator(s), college teachers may motivate the students and staff of the Homoeopathic Medical College to participate in the Proving Programme. For non – homoeopathic volunteers, members from general local bodies and attendants of the participants visiting the institute/ unit will be motivated.

9.4.2 Written Voluntary Informed Consent
All volunteers will be informed about the objectives, drug proving process, benefits of the trial and anticipated risks through a Provers Information Sheet (**Form B part 1**). A 'Written Informed Consent' (**Form B part II**) will be obtained from each selected volunteers before starting the drug proving process.

9.4.3 Screening of participants
The volunteers will be subjected to a detailed screening comprising of history and general examination (**Form C**). Volunteers identified as healthy will be enrolled as participants.

9.4.4 Pre-Trial Medical Examination
A detailed pre-trial medical examination (PME) of all participants will be taken up through a detailed history, clinical (general & systemic) examination & laboratory investigations to confirm health status of the participants. Volunteers identified as healthy by experts will be enrolled in proving.

PME will comprise of:

Process	To be done by	Form
History & General Examination	Site Investigator	Form D, Part-I
Chest X ray	Identified Radiology Lab/In house laboratory	Form D Part II

Haematological & Bio-chemical examination	Identified Pathology Lab/ In house lab	Form D Part II
Abdominal ultrasonography	Identified Radiology Lab/In house lab	Form D Part II
Psychological examination	Consultant psychiatrist	Form D, Part III
Respiratory, Gastro-intestinal, cardiology, neurology, examination, genito-urinary	Consultant medicine expert	Form D, Part III
Gynaecolocal examination (female participants)	Consultant gynaecologist	Form D, Part III
Dermatology examination	Consultant dermatologist	Form D, Part III
Eye examination	Consultant ophthalmologist	Form D, Part III
ENT examination	Consultant ENT consultant	Form D, Part III
ECG	Identified ECG lab/ In house lab	Form D Part III

Photographic record: One photograph of each selected volunteers in full pose, facing camera for record will be included in the PME. This will be only for record purposes, to assess constitution/physical makeup. Photos will not be disclosed in the research data and or compiled data or in the publication.

Duration: The total PME examination of a volunteer must be completed within two weeks.

9.4.5 Enrollment of provers

The PME of the participants found fit as identified by the site investigator at the research centre will be sent to the PI/CoI/coordinators. This must be sent to CCRH headquarters/ CRI, Noida (DP coordinating centre) within 7 working days of completion of PME. The participants found fit will be enrolled as Provers and a unique identity code (UIC), based on next available number on the randomization list, will be generated for each prover.

9.4.6 Training for participants

A training program for the participants enrolled as provers will be conducted comprising of details of proving process, expectations from provers, maintenance of records, etc. A specific training module will be developed specifically for training of participants.

9.4.7 Coding/randomization

The UIC of the prover will be used for randomization for:

- Inter- individual control: 30% of the provers will be randomized into placebo group
- Intra-individual control: The drug-placebo sequence will be randomized for each prover in the verum group.

Intra-individual control is proposed to be maintained during the proving process to prevent incorrect attribution of symptoms to the IPS[7].

The randomization will be done using computerized random number charts for allocation to intervention. This list will be used as the basis for the preparation and labeling of the study medication. Intervention allocation will be concealed until the proving is completed and the database has been locked. The sealed randomization list will be stored by the principal investigator and co-investigator at CCRH headquarters.

9.4.8 Blinding

The study will be a double blind study, where the site investigators and the participants at the study site will be kept blind about nature of drug substance and the allocation of participants in the verum and placebo groups. The study medication will be sent in coded forms along with a randomization chart. The nature of the proving substance will be known to the PI and the Co-I/coordinator, but the site investigators and the participants will be blind to the nature of the IPS. The coded study medication will be labeled with the UIC and sent to the proving site.

9. 4.9 Interventions

10.3.1 Arms	**Assigned Interventions**
Group I : IPS	The verum group will be advised to take the study medication as per schedule. This group will comprise of about 70% of the enrolled participants. The IPS will be given in multiple batches, out of which 1 batch will be placebo and other batches will be IP.
Group II: Placebo	The control group will be given placebo indistinguishable from the study medication. This group will comprise of about 30% of the enrolled participants. Multiple batches will be given, all of which will comprise of placebo.

Both the drug and the placebo will be same in appearance, odor and taste.

9.4.10 Study Medication

Drugs in compliance with pharmacoepoeial standards from GMP compliant manufacturers would only be procured. The alcohol to be used as placebo will also be purchased from GMP compliant pharmaceutical firm approved by the Council. The IPS will be prepared in the form of globules of size 30 and will be packed in the form of 1 dram glass bottles, labeled with serial number, prover's code and date of packaging. The placebo will be prepared similarly (dispensing alcohol impregnated globules of size 30) and labeled with serial number, prover's code and date of packaging.

The study medication will be labeled with the following information:

- Study medication protocol-code
- Sponsor: CCRH, India
- Dosage: 4 times xxx a day
- Batches XXX/XXX (batches for both IPS/Placebo production)
- Date:
- Date expiry:
- Subject/randomization No.:

Labeling will take place separately for IPS and placebo. The IPS and placebo medication will be packed in two separate lots/bundles.

The preparation of the IPS/placebo as study medication, for dispensing to individual provers will be done separately to avoid mixing of drugs and placebo batches. This would be done at the pharmacy at CCRH headquarters/CRI, Noida under direct supervision of the PI/coordinator.

9.4.11 Potency for proving

In each proving study, the IPS will be proved in at least 2 potencies used in ascending order.

Pharmacopoeial drugs

The IPS can be proved in dilutions/potencies or tinctures, depending on the safety profile of the drug.

New drugs:

The IPS will be proved in potencies above the identified FSD.

9.4.12 Dosage schedule
Each batch will have 12 doses. The provers will be instructed to take 4 pills, 4 times a day at four hourly interval for 3 days.

In case of drugs which the Council proposes to re-prove considering that the previous proving has generated very few symptoms, the following dosage schedule is proposed:

Day	Number of pills*	Number of doses
1	4	4 times
2	8	4 times
3	12	4 times

* the number of pills taken on each day will be increased consecutively in concordance with the Organon of medicine (Aphorism 129), where in it is mentioned that "a few more globules may be taken"[6]

9.4.13 Route & Method of administration of IP/placebo
The IPS/placebo will be sent as study medication to the proving site. The study medication will be prepared in batches for each individual prover. A minimum of 3 batches is proposed for one proving. Each batch will comprise of the drug/placebo in globules of size 30. Study medication used in this drug proving will be administered orally as globules, the content of which is allowed to be absorbed orally.

9.4.14 Run –in period
The time period between completion of PME and receipt of medicine batches by the provers at the research centre will be the run in period. This period will be at least 2 weeks and a maximum of 4 weeks. The investigator will hand over provers day book proforma (**Form E**) to the provers. During this period, the prover will be requested to make note of any change in health status and inform the investigator in case of any change in health. The prover will be requested to fill in the provers day book proforma daily and report to the site investigator once a week. During this period, the site investigator will review the provers day book proforma once a week. The run in period will be useful for:

- Allowing site investigator to check on the willingness and ability of the participant to properly complete the diary (those who do not comply would normally be excluded)
- Some of the baseline health characteristics are established, and this can help later with the interpretation and analysis of proving symptoms.

9.4.15 Initiation of intervention
The investigator will hand over the study medication batch 1 to the respective prover as per their allotted codes. Each prover will be instructed to:

- Take 4 doses in a day (4 hourly) for 3 days. The number of pills to be taken must be explained properly to the prover.
- The study medication is to be taken dry on tongue
- Record the date and time of intake and of number of doses taken in the Form E
- Take detailed notes daily regarding his/her feelings/changes in mind and body after taking the study medication, in the 'Form E'.
- In case is no symptoms appear, the prover is requested to note down the date and time of intake of the respective dose of the drug and mention 'no symptoms' in the form E.
- The prover must follow the instructions in the participant information sheet and those given by the investigator from time to time.
- The prover must inform the site investigator if any symptoms/signs appear or he/she feels there is a change in the health status. If so, Prover must stop the intake of further doses as directed by the site investigator.

9.4.16 Data Recording

The prover will be expected to make a daily record of the date and time of intake of study medication in the prescribed proforma. During the 3 day study medication intake period, the prover will report to the investigator daily. The investigator will interrogate the prover about the change in health status/sign and symptoms if any during this period and will record his/her observations in the symptom elaboration proforma (**Form F & G**).

Each symptom must be completed with respect to order of appearance, time of appearance & disappearance, location, sensation/character, modalities, concomitants, direction/extension of symptoms, etc. Clinical examination findings will also be recorded. Appropriate pathological investigations if required would also be advised and the report will be added. For each symptom, the investigator on detailed interrogation with the prover, will classify and mention their symptoms as follows[9]:

- **NS** - New symptoms, not previously experienced.
- **C-** - Unexpected change representing worsening or aggravation of ongoing or recurring symptoms.
- **C+** - Unexpected change representing an improvement of ongoing or recurring symptoms.
- **RS** - Unexpected recurrence of past symptoms.

The investigator will also record his/her observation about the possible causality of symptoms with the drug intake.

9.4.17 Follow up:

A. If sign(s)/symptoms(s) appear:

- The prover must stop taking the further dose of study medication as soon as he/she feels any change in health status or any sign(s) &/or symptoms(s) develop in accordance with the qualifiers of proving symptoms as described in section 13.2. The investigator will ascertain the qualifiers of the symptom and will advise the prover to stop intake of further doses, once proving symptoms develop.
- The prover notes down the sequence of the appearance of new sign(s) &/or symptoms(s), their progress and the number of doses after which each sign &/or symptom appears with date, time of onset and duration for which it persists. No further dose of the same batch is to be consumed by the prover.
- The prover is expected to report (preferably on a personal visit or telephonically) to the investigator daily (or more frequently) for as long as the symptoms persist.
- Since the symptoms appearing during proving are transient in nature, it is not expected that the symptoms will persist for long. During the course of proving, the prover is referred to medical expert/consultant for examination & for specific laboratory investigation(s), if needed, to rule out any pathological cause for appearance of new symptom(s)/sign(s) in case symptoms persist for more than 3 days or is distressing to the prover. Laboratory tests are also performed to facilitate observation of any correlation between the subjective and objective changes during the course of proving. The opinion of the experts is also taken, on the appearance of new sign(s)/symptom(s), wherever needed.
- Photos of objective findings (e.g. skin eruptions, swellings, etc.) will also to taken and to be kept along with the prover record.

Observation period: During the period that the symptoms persist, the prover will be kept under observation of the investigator. The prover will be instructed to report (preferably on a personal visit or telephonically) to the investigator daily (or more frequently) for as long as the symptoms persist.

Washout period: Subsequent to disappearance of the symptoms, a period of 30 days will be kept as washout period. The prover will report to the investigator once a week (or earlier in case of

development of any symptoms or any change in health status) during which the investigator will interrogate and examine the prover to identify any change in health status. The prover (in form E) and the investigator (in form F&G) will be expected to complete the details of the symptoms as mentioned in section 9.4.16.

In case of appearance of symptoms during this period, the prover will be kept under observation of the investigator. The prover will be instructed to report (preferably on a personal visit or telephonically) to the investigator daily (or more frequently) for as long as the symptoms persist. After symptoms have disappeared, a period of further 30 days symptom free period will be maintained as a wash out period before the start of the next batch of study medication.

B. If no sign(s)/symptoms(s) appear:

Prover may not develop any sign/symptom till the completion of 12 doses. In such as case, the prover notes down as 'No Symptom' with date and time of intake of the respective dose of the drug, verified by the investigator.

Washout period: In such a case, a wash out period of 30 days will be maintained after the last dose of the IP/placebo from the batch has been taken. During this period, the prover will be expected to keep a daily record of his/her health status. The prover will report to the investigator once a week (or earlier in case of development of any symptoms or any change in health status) during which the investigator will interrogate and examine the prover to identify any change in health status. The prover will be expected to record the details of the symptoms as mentioned in 9.4.16 and the investigator is also expected to complete the symptom details as outlined in the same section.

9.4.18 The same procedure is followed till all the batches of the study medication are consumed.

9.4.19 Post –Trial (Terminal) Medical examination (Form D)

After all the batches of the study medication are consumed and a subsequent washout period of 30 days, the provers are examined again as in the PME, and the process is called 'Terminal Medical Examination' (TME). The TME must be completed within two weeks after completion of the washout period.

9.5 Dietary & lifestyle guidelines for Provers

Prover will be instructed to follow his/her normal daily routine and dietary habits till the time he/she is enrolled in proving.

9.6 Steps to maximize adherence & retention

All the provers shall be motivated to adhere to study schedule and for measurement of various investigations from time to time by the investigator. Provers are instructed to return the glass containers with their study medication, and a pill count will take place (or the absence of pills will be confirmed if the subject reports that the full batch was taken).

10. When and how to withdraw the provers

It is the responsibility of the site investigator to maintain the prover in the study, provided it is safe to do so. A prover may be discontinued from the study in case of occurrence of serious adverse event(s) or serious inter-current illness or for any of the following reasons, which must be documented in the TME form. The prover who withdraws from the study will be requested to undergo a complete terminal medical examination if possible, or if leaves against advice of site investigator will at least be requested for a final telephonic interview at the same time with regard to the state of prover's health.

Discontinuation of Provers

The prover will be discontinued from proving, and prover will be withdrawn early if

1) Non-compliance to proving protocol
2) Prover withdraws consent
3) Discretion of the investigator(s)

10.1 Data collection and follow up for withdrawn subjects

The data will be collected which includes PME/TME information, prover symptoms, symptom elaboration, clinical and laboratory findings, etc. till the prover is in the study trial. Such data is important to the integrity of the final study analysis since withdrawal could be related to the safety profile of the IPS.

11. STUDY DURATION

The duration of proving for each prover will depend upon the symptoms produced and the subsequent wash out periods, needed, before subsequent doses can be given.

Expected duration for study

11.1 At research centre level:

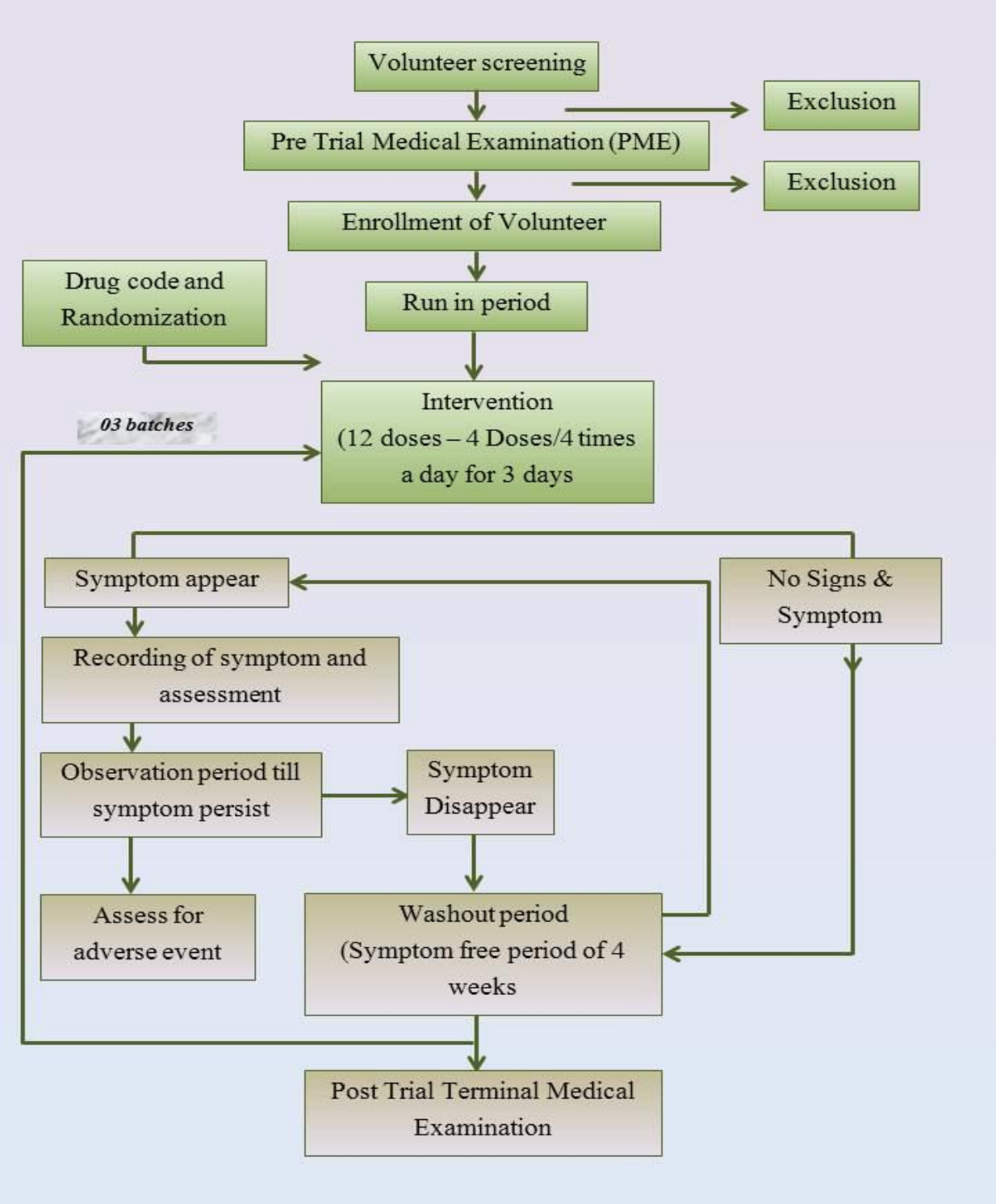
- Prover screening: 1 week
- PME: 2 weeks (for completion of PME at a centre)
- Run in period (till receipt of IP batches): 2 weeks (to a maximum of 4 weeks)
- Administration of first batch: 3 days
- First washout period: 30 days (+ days for which symptoms persisted)
- Administration of second batch: 3 days
- Second washout period: 30 days (+ days for which symptoms persisted)
- Administration of third batch: 3 days
- Third washoutperiod: 30 days (+ days for which symptoms persisted)
- TME: 1 week (to 2 weeks for completion of PME at a centre)

In case where no symptoms appear, a symptom free period of 30 days is maintained. In case(s) where symptoms appear, the observation period for each prover will vary depending on the duration for which the proving symptoms persist, subsequently followed by a 30 day symptom free washout period. (See section 9.4.17 for details)
As such for proving of each IPS an approximate duration of 7 months to 12 months is needed.

11.2 At Headquarters level, the study duration will include:

- Protocol preparation, regulatory approval, pretrial preparations: 2 months
- PME Assessment, randomization and allotment of batches, preparation of batches: 2 weeks (to a maximum of 3 weeks)
- Monitoring and supervision of study at research centre level: 7 months (to approx. 12 months)
- Data compilation & de-coding & analysis: 2 months
- Report preparation: 1 month

11.3 Flow chart for proving cycle and study process



12. PROVER PARTICIPATION TIMELINE

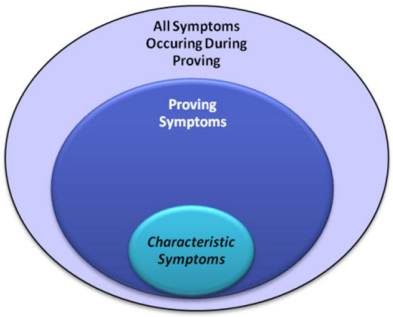
Day/ Month	0 day	Day 1-7	2 weeks	Day 1-3 (batch 1)	no. of days for which symptoms persist	30 days	Day 1-3 *(Batch 2)*	no. of days for which symptom persist	30 days	Day 1-3 *(Batch 3)*	no. of days for which symptom persist	30 days	1 week
Screening (Form A)	√												
Informed consent (Form B1 & B2)	√												
PME (History & General Examination) (Form D)		√											
Photograph		√											
Enrollment of prover			√										
Allocation of subject number at CCRH			√										
Run in period			√										
Intervention				√			√			√			
Face to face interview	√	√		√	√		√	√		√	√		√
Telephonic interaction													
Observation period					√			√			√		
Prover daily diary completion (Form E)			√	√	√	√	√	√	√	√	√	√	
Symptom elaboration proforma (Form F)			√	√	√	√	√	√	√	√	√	√	
Washout period						√			√			√	
TME (Form D)													√
AE/SAE assessment (Form G)				√	√	√	√	√	√	√	√	√	√

13. DATA COLLECTION AND MANAGEMENT

Data compilation and analysis by the proving team is a key factor in the translation of raw Proving data into a meaningful clinical drug picture that can be used by a prescriber. The data analysis process must be carefully designed to avoid excessive inclusion of non-specific, non-characteristic data, yet ensure that the most characteristic and dependable data for homeopathic prescribing is maintained. An analysis process to extract dependable homeopathic prescribing indications from a drug Proving is required to contain the following dimensions (as described in information that follows) [9]:

- 1st dimension: All symptoms occurring during the Proving
- 2nd dimension: Proving symptoms with relative characterizing assessment
- 3rd dimension: Characteristic symptoms (a highly individualized subset)[8]

Figure 1 Dimension of symptoms occurring during proving



Data will be recorded on pre-designed formats& managed on MS Excel spreadsheet at each of the study center. The study site investigators will send periodic updates at end of each stage i.e. PME, completion of each batch of drug and subsequent observation & wash out period and TME. Time line &assessment schedules shall be strictly maintained and recorded in the prescribed formats.

13.1 Language for data recording

The PME will be conducted in English. The prover will be requested to fill in the prover's day book proforma Form E in English/ any other language, as preferred. In case the symptoms have been recorded in other language apart from English, then in that case the investigator should translate the symptoms to English while elaborating them in Symptom elaboration sheet (Form F). The proving symptoms will be compiled in English.

13.2 Definition of proving symptom[9]

Proving Symptoms are any change in normal objective and/or subjective state of mind or body as experienced by the prover, or as observed by proving investigator and/or others occurring during proving period, which are possibly related to the IPS. They are those symptoms or signs that are recorded during the Proving period where causality by the IPS is possible. Symptoms that occur in a severity, duration and frequency consistent with historical tendency (i.e. Unchanged (U) symptoms) of a subject should not be reported as Proving symptoms. Likewise, care should be taken to exclude from this category any symptoms related to a cause that can confidently be determined to be external to the Proving. Proving symptoms will include:

- New symptoms, not previously experienced (NS)
- Unexpected change representing worsening or aggravation of ongoing or recurring symptoms (C-)
- Unexpected change representing an improvement of ongoing or recurring symptoms (C+)
- Unexpected recurrence of past symptoms (RS)
- Abnormal values of laboratory parameters that were in the normal range during the PME

Proving symptoms are therefore all changes in clinical events and laboratory findings reported by volunteers during the trial and recorded in the final report. These are the findings claimed by authors to be compared by practitioners with the symptoms of their patients in order to prescribe the homeopathic medicinal product.

13.3 Data compilation

The original source documents i.e. PME, Prover's Day Book Proforma, Symptoms Elaboration Proforma', TME form, case off form, adverse event reporting forms will be sent by investigators from the centres to the coordinators at CCRH headquarters.

Phases of data compilation:
1: PME & TME compilation
2. Prover wise entry of symptoms produced(or symptoms not produced) with individual batch
3: De-coding & segregation of verum & placebo symptoms
4: Analysis & matching of symptoms and compilation of drug pathogenesis

The data base will be prepared by the coordinator at the headquarters. Un-blinding or breaking of the randomization codes will be done by the study PI at the headquarters after the study has been completed at the study site, followed by first & second phase of data compilation.

13.4 Compilation of Proving symptoms

The sign(s) &/or symptom(s) generated in each prover after the end of each drug batch will be noted along with their prover code, name of the proving center, number of doses after which each of the signs or symptoms appeared and the duration for which they persisted. The sign(s) &/or symptom(s) generated in the drug group will be segregated from those of the control group. In the intervention group sign(s) &/or symptom(s) generated during intake of placebo batch will be segregated from those appearing during IP intake. The sign(s) &/or symptom(s) which are identical (exactly the same in terms of location, sensation, modalities, concomitants) in both drug and placebo will not be included as proving symptoms.

These proving symptoms will be identified. These proving symptoms will be compiled and arranged as per the schema of the Kent's Repertory i.e. Mind, Vertigo, Head, Eye, Ear, …….etc.

To each sign and symptom generated, the following information will be linked:

- Prover code: Number
- Prover gender: M/F
- Proving Center: XX
- Day of symptom appearance (Day 1 being the day of administration of the study medication batch)
- Time of day of symptom occurrence (HH:MM) *(if information available)*
- Characterizing feature(s)
- Duration for which the symptom persisted in terms of hours/days
- Potency of the IPS in the study medication batch

This information would then be the basis where the following types of symptoms are distinguished:
- Characteristic symptoms (if reported)
- Ongoing symptoms that have unexpectedly and markedly improved
- Proving symptoms with one or more characterizing features

14. DATA ANALYSIS

14.1 Qualitative analysis:

14.1.1 Symptom selection criteria:

Drug proving data is in the form of symptoms, where there is no measure of efficacy, but description of individual proving symptoms where qualitative research evaluation will be applied. The evaluation will be done by compilation of the proving symptoms in different categories, representing a certain probability to be associated with the remedy and therefore are the most important ones for further clinical verification.

Example: a symptom will belong to the remedy with great probability if at least one of the following criteria is met[5].

- Occurrence of the symptom in two or more volunteers
- Objective, measurable signs corroborating with the symptoms
- Distinct intensity of the symptom
- Occurrence of the symptom several times shortly after administration of the drug
- Recurrence of the symptom several times over the course of a number of days
- Recurrence of the symptom using different potencies
- Striking, singular, uncommon symptoms
- Striking, seldom or paradox modalities and/or concomitants of the symptom

However, all symptoms including those appearing in lesser number of provers, less distinct or common symptoms will all be included in the proving data. Symptoms, which are not thought to belong to the drug picture, would also be stated, but under separate headings, marked in a specific manner so they are not lost for clinical verification. Such symptoms may be compared with the clinical verification symptoms at a later stage if required.

14.1.2 Characterizing features of proving symptoms:

All provers are to be included in the analyses. The symptoms obtained under verum or placebo must be listed separately. The proving symptoms are identified and their characterizing feature[9] will be detailed:

- **A.** New symptoms with marked severity, duration or frequency
- **B.** Ongoing or recurring symptoms present during the proving that have been unexpectedly and markedly improved
- **C.** Ongoing or recurring symptoms that have been unexpectedly and markedly worsened
- **D.** Symptoms that recur from the past but have not occurred in the 12 months preceding the proving
- **E.** Symptoms that display alteration with another symptom in a single volunteer in such a way that the alteration is strongly individualizing
- **F.** Symptoms associated with modalities or concomitant symptoms occurring in other parts of the same prover
- **G.** Symptoms that involve multiple body parts or organs in a similar manner or multiple symptoms within the same subject with a similar associated modality, forming an easily recognizable pattern of reaction
- **H.** Similar symptoms occurring in multiple provers. Such symptoms may be related by similar sensation, modality, or body system and can be recognized through a qualitative analysis similar to red – line symptom reporting in homoeopathic literature.
- **I.** Any objective finding/including abnormal laboratory values associated with subjective symptoms.

14.1.3 Grading of the Drug Proving Symptoms as per their value:

Symptoms will be graded as follows:

Grade I symptoms:

- Symptoms appearing in more than 2 provers, at two different study sites (Symptom in 1 or more prover at one site and similar symptom in 1 or more provers at the second site. i.e. if two provers separated by distance and time with no contact with each other what so ever give the same symptom).
- Peculiar, rare, queer, strange, characteristic symptoms
- Symptoms reappearing from prior provings.

Grade II symptoms
All proving symptoms other than those in grade I

14.2 Quantitative analysis - Dose- biological response relationship

The principal analyses will employ the 'intention-to-treat' approach and will include all randomized participants in their randomly assigned groups. Comparison of the baseline characteristics among the two groups will use standard parametric & nonparametric statistical techniques.

The overall incidence of proving symptoms in each trial will be calculated by dividing the number of volunteers who had at least one reported proving symptom (pathogenetic effect) by the total number of volunteers taking the IPS (not on placebo)[7].

The incidence of proving symptoms per volunteer is defined as the total number of findings claimed in the trial divided by the total number of subjects using the IPS (not placebo)[7].

One proving symptom will be counted as a piece of information which could be included in a homeopathic repertory as an independent subheading. For instance, boring headache ameliorated by pressure is counted as one claim [7].

15. ASSESSMENT OF SAFETY

Safety for the volunteers is an important prerequisite in planning of clinical trials. According to the Basic Principles mentioned in the World Medical Association (WMA) Declaration of Helsinki[3], "Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available."

In drug proving, there is no conventional pharmacodynamic action of the drug, because it is administered in high dilutions, which according to experience provokes transient "proving symptoms", but does not cause toxicological effects. Additionally the administration of the IP usually will last only for a short time, which again minimizes the probability of adverse events. All volunteers will be informed about the objectives, potential risks, inconveniences and benefits of the trial and will sign an informed consent form before the beginning of the trial.All changes on the physical and mental levels will be observed.

For identification of adverse events and their management, the HPCUS guidelines[9] are being adapted.

15.1 Adverse events

Adverse events (AE) are all unwanted & clinically significant illnesses, diseases, injuries or accidents occurring or worsening in severity during the study period, no matter whether they are causally related to the study intervention or not. The intensity of AE and the causal relationship

with the study interventions have to be assessed and documented. An adverse event, causality of which can be definitely linked to the IPS will be identified as an adverse drug reaction.

To classify as an adverse event, the unexpected symptoms and signs must have at least one of the following characteristics:

- have duration longer than expected
- have clinical severity greater than expected
- have clinical severity that falls within the definition of Serious Adverse Effect
- require therapeutic intervention,
- results in removal from the Proving

All AE that do not meet any of the criteria for serious will be regarded as non-serious events. At the end of the study, any new clinically significant finding/abnormality that meet the definition of an AE will also be recorded and documented as an AE.

15.2 Serious adverse event:

A serious adverse event (SAE) is an adverse event occurring during any phase of the study and at any dose of the IPS or placebo, which fulfils one or more of the following criteria:

- Results in death
- Is immediately life threatening
- Requires in subject hospitalization
- Results in persistent or significant disability or incapacity.
- Medical event that may jeopardize the participant, and may require intervention to prevent one of the serious outcomes noted above.

15.3 Causation likelihood

At each contact with the participant, the investigator will seek information on AE by specific questioning and as appropriate, by examination.
In case of an adverse event, causation likelihood should be determined and would be labeled as:

- 'Possibly related' meaning there is evidence to suggest a 'Reasonable possibility' of a causal relationship between the drug and the adverse event.
- 'Unrelated' meaning there is no evidence to suggest a causal relationship between the IP and the adverse event.

Causation likelihood will be determined prior to un-blinding by the investigator on the basis of

- Temporal relation to IPS administration
- Strength of association
- Consistency over repeated dosing within one subject or across the study population
- Observed increase of symptoms with repetition of dose or increase in attenuation
- Coherence with known facts on the biology of disease

An adverse event must be informed to the CCRH headquarters within 2 working days by telephone/email/fax. A SAE must be informed to the CCRH headquarter within the next 24 hours. The information will be recorded in the Form H. Once AE/SAE is reported to the CCRH headquarters, the principal investigator will identify the participant allocation by un-blinding to re-assess the causality, based upon known biological properties of the substance.

If the causality of the AE/SAE is linked to the IPS, the same would be communicated to the chairperson of the ethical committee and to the site investigator and immediately, along with the follow up course of action.

15.4 Un-blinding procedure

Un-blinding of a single participant status will be done by the PI at the headquarters, at his discretion in the event of development of AE/SAE in the prover. The participant allocation will

be informed to the investigator at the study site in case therapeutic intervention required. The code will be accessible only to the concerned investigator and the prover/prover's care giver. The details of any data access including specific personnel who obtained or viewed this information, information that was obtained, date in which it was obtained, and reason for un-blinding will be recorded.

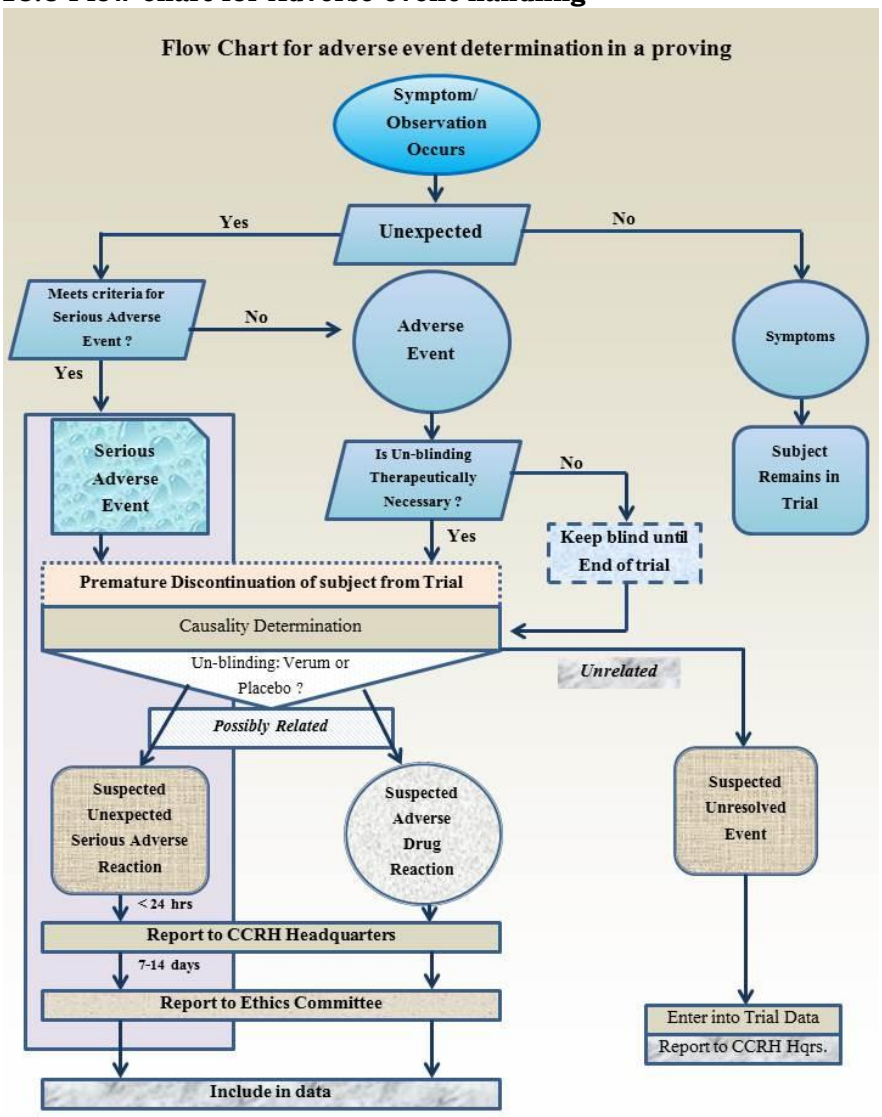
Depending on the incidence/severity of AE(s) and its causal relation to the IPS, the PI may opt to un-blind the allocation to entire participants. However, only the allocation for the specific participants will be communicated to the investigator at the study centre.

15.5 Follow-up of provers after AE (including SAE)

The prover will be withdrawn from the proving in case of development of an AE. Appropriate therapeutic intervention will be given in case of development of an AE. Based on the totality of the presenting symptoms a suitable homoeopathic drug may be chosen on symptom similarity basis and prescribed to the prover. The participant will be provided free treatment for as long as the symptom(s) exist(s).

All unresolved AEs will be followed by the investigator until the events are resolved, stabilized, or the participant is lost to follow up, or the AE is otherwise explained. At the last scheduled visit, the investigator will instruct each participant to report any subsequent events(s) that the participant, believes might reasonably be related to participation in this study.

15.6 Flow chart for Adverse event handling



16. RECORD KEEPING

16.1 At Study Center

The center will keep track of all participants screened, enrolled and will maintain a filing system to keep all study records study protocol, related documentation, source documents, laboratory investigation reports, assessment sheets medicine distribution records, etc. The investigator is responsible for the completeness and accuracy of the study materials. Participant files are to be stored in numerical order and stored in a secure and accessible place and manner. No unauthorized access to the study documents shall be permitted. The records would be accessible only to the study investigator or the members of data review board at the institute/unit. The records will be handed over by the study investigator to the monitoring or inspection team as deputed by Director General CCRH. Third person access would be permitted only after prior written permission of Director General CCRH. The photocopy of the original records of participant will be entered and kept on file at the study centers and the originals will be sent to the CCRH headquarters at the end of each phase. Participant files will be maintained in storage for a period of 5 years after publication of results.

16. 2 At Headquarters

The study PI will review the original source documents & the data received from the investigators. The PI/Co-I will inform the investigators about the discrepancies in the records. All study related data, reports, meeting minutes, review and assessment records, monitoring records and documents would be kept at one place in the custody of Co-I. The proving data will be entered in the computer and maintained in MS excel formats.

17. MONITORING

This study will be monitored periodically by the Director General, CCRH or officers designated by him. The site investigators at the Institute/Unit will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. Participation as an investigator in this study implies acceptance of potential inspection by CCRH & government regulatory authorities

17. 1 Monitoring process

1. Off site monitoring: through original source documents, reports and records sent by the site to CCRH headquarters post/email. Investigators at the study site may be requested to present the study related documents/data at CCRH headquarters.
2. On site monitoring: Site visit, as per decision of DG, CCRH will be made by competent designated officer(s) of the Council &/or independent experts identified.

17.2 Specific considerations

Non achievement of sample size at a particular site/center –

i. In case of non achievement of sample size in the study period, there will be an option for extension of the study for further period
ii. If a particular site/center fails to achieve the sample size or is not complying to the protocol, the study will be discontinued and there will be an option for inclusion of one more center

18. PREMATURE TERMINATION OF STUDY

The Council is entitled to terminate the trial prematurely at any time. This decision will be made on the recommendation of the Advisory Committees of the Council. In case the trial is terminated prematurely, a complete final examination would be made with each individual participant as far as possible.

19. ETHICAL CONSIDERATIONS

The study protocol is in compliance with the international and national ethical guidelines for bio-medical research.

Specific ethical considerations:

- Safety & standardization analysis of the IPS is a pre-requisite for conducting drug provings.
- The IPS are proposed to be proved taking into consideration the safety of the drugs.
- Voluntary written informed consent shall be taken from all participants prior to their participation in the study
- Only participants found to be healthy, sound body and mind will be enrolled in the study.
- Participant confidentiality and safety would be the prime concern at all stages.
- Participant will be informed about the risks and benefits of all the proposed interventions and available support to help participants to complete the full course of trial.
- Adverse events and unblinding procedures have been identified
- The trial would be registered with clinical trial registry of India, prior to its initiation.
- The study protocol has been approved by the ethical committee of the Council.
- Appropriate participant education shall be conducted for participants in both the groups.

19.1 Confidentiality:

All information collected in this study will be kept strictly confidential, except as may be required by law of the land. The privacy and confidentiality of the participants will be honored.
The names of the provers may be included in the proving report, however, the allocation will not be revealed, nor the symptoms produced will be linked to the prover's names.

19.2 Prover incentive

Monetary compensation as determined by the Council's Standing Finance Committee will be given to the provers for participation in the study, which is limited to cover incidental expenses of the prover's travel for reporting to the investigators.

The prover is provided a 'certificate of participation' after completion of proving program, for provers who have completed the trial or who were withdrawn from the study due to appearance of AE/SAE.

20. TRAINING

Training shall be imparted to the investigator at CCRH headquarters before initiation of study. The investigator will train the provers and other staff at each of their center. Trainings if needed will also be done during the course of the study. This training shall involve quality trainings and ethics trainings.

21. PROTOCOL AMENDMENTS

The investigator has to meet the study requirements as specified in the protocol. Protocol amendments are possible only in exceptional cases (e.g. where the health or wellbeing of the participant is affected) and only after authorization by the Council. If there is any modifications in the protocol addendum of the same shall be circulated to the investigator after due approval by the Scientific advisory committee. Circulating protocols shall be numbered and a list of their distribution shall be retained. The investigator shall up-date the protocol by adding the amendment.

In the case of administrative or technical amendments which do not affect the health of participant, an administrative change is possible after agreement of all those concerned. These are also to be justified in writing and all those concerned are to be informed.

22. PUBLICATION OF STUDY RESULTS:

- All data derived from the study will be the property of the Council.
- The principle deliverables will be a proving clinical study report (plus related technical reports as appropriate) and derived publications in journals

- The original papers on the outcomes emerging from the study will be published by the Council. The names of the scientists who have participated and contributed significantly in the protocol development, collection of data at site & data analysis will be considered for authorship of manuscript. Investigators at the Institute/ Unit shall not publish the paper on the research data of Institute/ Unit without prior written specific permission of PI.
- Authorship credit shall be based on:
  - Substantial contributions to conception and design of protocol, or acquisition of data, or analysis and interpretation of data;
  - Drafting the article or revising it critically for important intellectual content; and
  - Final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- Institute participating in the study will be listed. The research team requires preparing the scientific technical reports based on their interim and final report. Scientists will be encouraged to present the findings at scientific conference and meetings with the prior approval of the Director General, CCRH.
- The report will be shared with the homoeopathic colleges involved in the study.

23. ACKNOWLEDGEMENT

Involvement of authorities of the Homoeopathic Medical College, members of DP committee at the centres/colleges and participants of the proving study will be duly acknowledged for associating in the proving programme.

24. OPERATIONAL DEFINITIONS

24.1 Healthy volunteer

A person with no clinically significant disease or abnormal laboratory findings and has had no significant change in health status in the last one month. The volunteer will be subjected to a general and systemic examination and identified laboratory tests, on the basis of which he/she would be certified as 'healthy, fit for proving' by the medical specialists.

24.2 Investigational Proving Substance (IPS)

Drugs with potential to develop pathogenetic effects will be investigational proving substances under the study. Only single drug will be used for proving at a time in a prover.

1. These could be drugs already existing in the Indian/international homoeopathic pharmacopoeias/ formularies.
   a. These are those drug substances whose basic standardization and safety parameters are known.
   b. These could include drugs proved and used in homoeopathy or drugs fragmentarily proved, but used in homoeopathy; drugs not proved, but being used in other systems of medicine.

   These drugs will be proved in potentized form in different potencies. In case where specific safety data about the drug substance is available for lower dilutions and potencies, the drug can also be used for proving in lower dilutions.
2. New products, with no reported use in homoeopathic system of medicine in any literature will be considered as new drugs. In such a case standardization and safety studies shall be completed before undertaking human proving. The first safe dilution (FSD) would be identified in this case and proving would be conducted only in potencies/dilutions higher than the identified FSD.

In either case, safety and standardization parameters will be recorded and compiled, before initiation of drug proving. The detailed literature review compiling the summary of findings from previous proving & clinical trials known and potential risk and benefits to human subjects will be prepared before initiation of the proving. The drug monograph will reflect the details of the IP including Latin name, chemical name, common names, source, origin, habitat, collection, pharmacognosy, physico-chemical parameters, pharmacological aspects, etc. A certificate of authenticity of this nature will be procured from the manufacturing firm.

24.3 Placebo
Dispensing ethyl alcohol (used as a vehicle to prepare homoeopathic medicines) soaked pills will be used as placebo. The placebo will also be dispensed in sugar globules of standard size 30. The placebo is indistinguishable from IPS in terms of taste, appearance & smell.

24.4 Adverse events (AE)
Adverse events are all unwanted & clinically significant illnesses, diseases, injuries or accidents occurring or worsening in severity during the study period, no matter whether they are causally related to the study intervention or not. Within the context of drug proving an adverse event is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of proving. It may be a new illness, worsening of a concomitant illness, an injury, or any concomitant impairment of a subject's health (including symptoms and observed clinical effects) that is unexpected and clinically significant.

24.5 Reasonable Possibility
Within the context of provings, the causality of adverse events by the IPS is a reasonable possibility when the presence of facts or evidence or arguments suggests a causal relationship.

24.6 Serious Adverse Reaction
Within the context of provings, an adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death
- a life threatening adverse event
- 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 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 patient or 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 an 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.

24.7 Suspected Adverse Reaction & Adverse drug reaction (ADR)
Within the context of Provings is defined as any adverse event for which there is a reasonable possibility that the IPS caused the adverse event. An adverse event, causality of which can be definitely linked to the IPS will be identified as an adverse drug reaction.

24.8 Suspected Unexpected Serious Adverse Reaction
An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. The event is considered a suspected serious adverse reaction if there is cause to suspect a relation to the investigational Proving Substance administration and the event, and the severity would make the event a Serious Adverse Event.

24.9 Symptom – Any change in the normal objective as well as subjective state of mind or body, as experienced by the subject, or as observed by the practitioner and/or others. (Adapted from Swayne et al)[9]

- **Characteristic Symptom** – Symptom produced in a Proving subject which has a high probability of being related to the test substance, and may include strong, peculiar, or highly individualistic symptoms as well as those symptoms which are strongly aggravated or ameliorated during the Proving. Additional parameters are listed in Section 14.2.
- **Concomitant Symptom** – Symptom associated with other symptoms in different parts of the body, or the mind, that appears at the same time or during the same disease process, e.g. a headache that occurs during diarrhea, or anxiety that occurs with stomach pain, etc.
- **Existing Symptom** – Symptom reported by subject or noted by the supervisor that was previously experienced or is experienced by the subject in an ongoing manner prior to test substance administration within the recent past and could be expected to occur during the Proving period. Note: such symptoms are often referred to as "Old" symptoms in the homeopathic Proving literature.
- **New Symptom** – Symptom reported by subject or noted by the supervisor that was not previously experienced by the subject prior to test substance administration.
- **Past Symptom** – Symptom reported by the subject to have occurred prior to the test substance administration that was resolved and would not be expected to recur during the Proving time period.
- **Peculiar Symptom** – also referred to as a Strange, Rare or Peculiar Symptom. This is a symptom which is highly individual because it is uncommon, surprising (e.g. paradoxical), or unusual in itself (e.g. a small child craving hot curry), idiosyncratic, or strikingly uncharacteristic of the complaint (e.g. a painless wound).
- **Proving Symptom** – Symptom or sign occurring during the proving period which is possibly related to the IPS. These are any change in normal objective and/or subjective state of mind or body as experienced by the prover, or as observed by proving investigator and/or others. These also included symptoms or signs occurring during proving period, which are possibly related to the IPS. Symptoms that occur in a severity, duration and frequency consistent with historical tendency, or can confidently be attributed to a cause external to the proving should NOT be reported as proving symptom; where as if the severity, duration or frequency is different from the historical tendency, the symptom will be reported as proving symptom.
- **Unexpected** – Symptom or sign occurring during the Proving period that is not consistent with investigational product information. For the purposes of provings, unexpected symptoms include any symptoms or signs that have duration longer than the proving period, have clinical severity greater than described in the Informed Consent, have clinical severity that falls within the definition of Serious Adverse Effect, require therapeutic intervention, or result in removal from the Proving.

25. REFERENCES:

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Annexure 1

Form A

CENTRAL COUNCIL FOR RESEARCH IN HOMOEOPATHY

Homoeopathic drug proving: Randomized double blind placebo controlled trial

APPLICATION FOR PARTICIPATION IN DRUG PROVING PROGRAM

Annexure 2

Form-B - 1

CENTRAL COUNCIL FOR RESEARCH IN HOMOEOPATHY

Homoeopathic drug proving: Randomized double blind placebo controlled trial

PARTICIPATION INFORMATION SHEET

Introduction

I am _____, working under Central Council for Research in Homoeopathy. We are doing research study 'Homoeopathic drug proving: Randomized double blind placebo controlled trial'. I am going to give you information and invite you to be part of this research. There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, these would be clarified.

Drug proving by CCRH

Drug proving is a research program of the Central Council for Research in Homoeopathy (CCRH). CCRH has been conducting drug proving since its inception in 1978 and more than 95 drugs have been proved so far. Over the years, the drug proving program of the CCRH has evolved into a highly scientific program, monitored and regulated by experts and regulatory authorities. The protocol of the study has been developed in conformation with international and national guidelines for research, ethics and drug proving.

Aims & Objectives

Homoeopathy is based on the premise that the drug is capable of curing what it can cause. The presentation of any disease is in the form of sign/symptoms. It is presumed that when a healthy person takes a drug, there is a transient effect that the drug has on the person manifested as symptoms. These symptoms are deduced to form the drug pathogenesis i.e. the symptoms on which the drug can be prescribed to sick persons. This is basic guiding principle of homoeopathic drug proving. The objective of this study is to identify pathogenetic effects of a homoeopathically prepared drug substance on healthy human beings

Drug Proving Methodology

Drug proving is conducted on healthy human volunteers (provers). The volunteers are enrolled after a detailed medical examination (termed as **Pre-trial Medical Examination (P.M.E.)**). This examination will include a detailed screening and haematological and biochemical investigations, ECG, chest X-ray and ultrasonography.

Once enrolled in the study, you will be assigned a code number. Drug substance will be coded at CCRH headquarters and will be received at the proving centre. You will be provided with the study medication, as received from CCRH headquarters. The study medication is received in 3 batches. One batch consists of 12 doses. You are requested to:

- From the first batch, take 4 doses in a day (4 hourly) for 3 days. One dose comprises of 4 pills.
- The study medication is to be taken dry on tongue
- Record the date and time of intake and of number of doses taken in the Form E
- Take detailed notes daily regarding your feelings/changes in mind and body after taking the study medication, in the 'Form E'.
- Report to the site investigator daily, to detail the feelings/changes in mind and body after taking the study medication

- In case is no symptoms appear, you are requested to note down the date and time of intake of the respective dose of the drug and mention 'no symptoms' in the form E.
- Once the 12 doses of the first batch is consumed fully, there would be an observation period of one month after which the second batch will be initiated. Third batch will be initiated similarly after completion of the second batch.
- The prover must follow the instructions in the participant information sheet and those given by the investigator from time to time regarding intake of further doses.
- You must stop the intake of further doses as directed by the site investigator.

At the end of30 day observation period after consuming the last batch of study medication a post trial (TME) will be conducted. This would be similar to the PME and involves the same set of investigations.

Recording of symptoms

In the initial one week (to 2 weeks) prior to intake of a drug, there would be a run in period. During this time, you will be required to note down any feelings/changes in mind and body/changes in health status during this period.

After the intake of drug, you have to note down the any feelings/changes in mind and body/changes in health status. The noting should be as detailed as possible, including details of location, sensation, modalities, extension, concomitants, causation, is any identified, change inroutine, circumstances, etc. in the Form E provided to you. This form is called the Prover's Day Book Proforma. In case if no symptoms appear, you will write 'no symptom' in the Form. During the 30 day observation period you would again be required to note down any feelings/changes in mind and body/changes in health status. The same pattern of recording of symptoms will be maintained till all batches of drug are exhausted.

General information for filling in the provers Day Book Performa:

The symptoms generated during the proving are the essential outcomes and goal of this study. The symptoms must be recorded in your own language **avoiding technical and medical terms**. Pay careful attention to your feelings, sensations and write freely, detailing about the symptoms as much as possible. Attempt to complete the symptoms by taking following aspects into consideration:

1) Location, extension and time of appearance & disappearance- The site and extension, if any, to other parts of the body. The time of appearance and disappearance to be cited clearly.
2) Sensation- State any burning, stitching, splitting etc. sensation experienced together with the symptom (e.g. feeling cold during headache). Try to explain the sensation as clearly s you can.
3) Relation with any event e.g. the symptom appeared after exposure to cold, exertion, any change in diet, etc.
4) Any specific condition which makes the symptom better or worse. (cold air, heat, being inside or outside, moving, lying down etc.)
5) Any other associated symptom.

Also,

- Pay attention also to your surroundings.
- Change in your reaction to your daily routine.
- How do you react to your family members or other people around you?
- Any change in your moods and habits?
- Any change in your mental and physical state.

Intensity of symptoms

Record the intensity of each symptom by rating it on a scale of 0 to 10 as follows:

0 10

Where,

0 is no complaint, 1 is very low/slight and 10 is extremely bothersome. Indicate increasing intensity with increase in number

Please remember

Your proving day book proforma is the most important record of this study. We seek your full cooperation in filling up this form. Please make notes **every day,** best is to take notes a few times a day (say 3-4 times). This will usually not take you more than few minutes at a time. Even if you think, there are no symptoms to report, make a record that there is no change and no symptoms. **Note also slight or inconspicuous symptoms.**
Please write legibly in your proforma.

Please remember

Your proving day book proforma is the most important record of this study. We seek your full cooperation in filling up this form. Please make notes **every day,** best is to take notes a few times a day (say 3-4 times). This will usually not take you more than few minutes at a time. Even if you think, there are no symptoms to report, make a record that there is no change and no symptoms. **Note also slight or inconspicuous symptoms.**
Please write legibly in your book.

Reporting to the investigator

You would be required to report to the site investigator daily during the run-in period. During the period of study medication intake, you will be required to report to the site investigator daily or twice a day. If needed you may report to the investigator more frequently, to discuss any change/symptoms. For as long as the symptom persistyou would be required to report to the site investigator daily or twice a day. Once the symptoms abate/disappear you would be required to report to the investigator once a week for the next 30 days which would be the observation period.

The site investigator will undertake a detailed interrogation to identify the nature of symptom appearing. You are requested to co-operate with the site investigator to complete the symptom as much as possible and for determination of nature of symptom and causation likelihood.

Investigational proving substance

The homoeopathic drugs used in drug proving are all pharmacopeial preparations. The drugs are procured from the GMP certified manufacturers. The drugs are proved in ultra-low doses in potentised form. The safety and standardization parameters of the drug are recorded and compiled, before initiation of drug proving and includes detailed literature review compiling the summary of findings from previous proving & clinical trials known and potential risk and benefits to human subjects. The drugs are being used in safe doses. The drug will be given in the form of oral sucrose pills. During the period of study, you may also be given placebo, which will be dispensing ethyl alcohol (used as a vehicle to prepare homoeopathic medicines) soaked pills. The IPS and placebo will be indistinguishable in terms of taste, appearance & smell. Neither you, nor the site investigator will know, when you are being given the IPS nor when you are being given the placebo. This however, should not deter you from detailing your symptoms in the Form E and to the site investigator.

Benefits of drug proving

Homoeopathic drug proving is the founding stone for the science of homoeopathy. By participating in this program, you are assisting in developing the science of homoeopathy. You will learn to be a better observer of your complaints/sensation/feelings. You will also learn to appreciate complaints/sensation/feelings of other persons. If you are a student of homoeopathy this would be a learning experience to develop an understanding of the materia medica. As per homoeopathic literature, it has been understood that drug proving improves the health of a person.

Risks from Drug Proving

There could be a transient change in your health status during the period of drug proving. However, this change should not be bothersome or affect your daily routine. In case if it does you are requested to report to the site investigator immediately. Your site investigator is fully capable of handling the complaints which may arise during drug proving.

Adverse events

Safety for the volunteers is an important prerequisite. In drug proving, there is no conventional pharmacodynamic action of the drug, because it is administered in high dilutions, which according to experience provokes transient "proving symptoms", but does not cause toxicological effects. Additionally the administration of the IPS usually will last only for a short time, which again minimizes the probability of adverse events. For identification of adverse events and their management, the HPUS guidelines are being adapted.

Adverse events are all unwanted & clinically significant illnesses, diseases, injuries or accidents occurring or worsening in severity during the study period, no matter whether they are causally related to the study intervention or not. A serious adverse event is an adverse event occurring during any phase of the study and at any dose of the IPS or placebo, which may results in death or disability.

In case of identification of an AE/SAE its intensity and causal relationship with the study will be assessed. An adverse event, causality of which can be definitely linked to the IPS will be identified as an adverse drug reaction.

Follow-up of provers after AE (including SAE)

The participant will be provided free treatment for as long as the symptom(s) exist(s). All unresolved AEs will be followed by the investigator until the events are resolved, stabilized, or the participant is lost to follow up, or the AE is otherwise explained. At the last scheduled visit, the investigator will instruct each participant to report any subsequent events(s) that the participant, believes might reasonably be related to participation in this study.

Advise for the provers

- You are requested not to make any change in your routine habits like sleep, exercise, bathing, meals etc.
- Avoid taking any other medicine/ drug, be it allopathic, homoeopathic, ayurvedic, herbal or naturopathic during the period of your participation in drug proving. In case if any such situation arises you are requested to contact your site investigator immediately.

Allowance

Monetary incentive as determined by the Council's Standing Finance Committee is given to the provers for participation in the study. The incentive is limited to cover incidental expenses of the prover's travel expenses for reporting to the investigators. The prover is provided a 'certificate of participation' after completion of proving program.

Confidentiality

All information collected in this study will be kept strictly confidential, except as may be required by law of the land. The privacy and confidentiality of the participants will be honored.
The names of the provers may be included in the proving report, however, the allocation will not be revealed, nor the symptoms produced will be linked to the prover's names in the proving report and publications.

Withdrawal of participants

A prover may be withdraw from the study at any stage or may be discontinued from the study. You would be requested complete TME at the time of withdrawal. The withdrawal will not affect your relation to CCRH at any stage. The data collected till your withdrawal would however, be included in the study report.

Whom to contact

If, at any time during the course of the study, you have any doubts, questions or concerns related to the study, you may contact the site investigator.

Name, address and telephone no. of Investigator-

In case of any further clarifications, you may write to:
Director General, Central Council of Research in Homoeopathy, 61-65, Institutional area, Janakpuri, New Delhi 110058
Fax: 91-11-28521060 Email- dgccrh@gmail.com

Annexure 3

Form-B – 2

CENTRAL COUNCIL FOR RESEARCH IN HOMOEOPATHY

Homoeopathic drug proving: Randomized double blind placebo controlled trial

INFORMED WRITTEN CONSENT FORM

I, _____, agree to participate in the Homoeopathic drug proving: Randomized double blind placebo controlled trial being undertaken at _____ Institute/Unit.

I understand that it will involve receiving oral study medication and regular reporting over a period of six months. I have fully understood the methodology of the study. I understand that during the period of my participation in proving, I would be taking the study medication as advised by the site investigator. I understand that I have to fill in the study related formats as advised which are to be handed over to the investigator at the time of reporting. I understand that my photograph and other records would be the property of the Council and would be used for data analysis. I am assured that my confidentiality would be maintained at all stages.

I have been informed of the risks of participation. I am aware of the monetary compensation for the participation in the study. I have been provided with the name of a researcher who can be easily contacted using the number and address I am being given.

I have understood the information in the information sheet and have been given an opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this study and follow the instructions given to me by the investigator.

I understand that I have the right to withdraw from the research at any time without in any way affecting my relation with CCRH and its Instt./Unit.

Signature of Participant _____ **Date ____/_____/_____**
Day/month/year

Name of Participant_____ Tel.no._____ email_____

I have accurately read the participation information sheet and the consent form to the potential participant, and the individual has had the opportunity to ask questions. All questions have been answered to his/her satisfaction. I confirm that the individual has given consent freely. A copy of this participation information sheet and Informed Consent Form has been provided to participant

Name of Investigator_____

Signature of Investigator _____ Date: _____/_____/_____
Day/month/year

Annexure 4

Form-C

CENTRAL COUNCIL FOR RESEARCH IN HOMOEOPATHY

Homoeopathic drug proving: Randomized double blind placebo controlled trial

PART – 1 SCREENING

Date _____

Name of Participant _____

Age_____ Sex: Male ☐ Female ☐

Address_____

Tel. no._____ E mail_____

Step 1 Ask the volunteer:

a) Do you have or have you ever had any of the following?

	No	Yes	If Yes, give details
Heart complaint, high blood pressure or high cholesterol			
Epilepsy or any neurological disorder			
Stroke or vascular disorder			
Asthma or any other lung complaint			
Diabetes, bowel, kidney or bladder disorder			
Alcohol or drug dependence			
Professional advice to reduce alcohol consumption			
Migraine, persistent headache or chronic fatigue			
Disorder of the reproductive system (eg prostate, ovary) or sexually transmitted disease			
Cancer or leukaemia or Haemophilia or blood disorder			
Liver disorder, hepatitis or test indicating past or present hepatitis infection			
Any allergies			
Any disorder of the eyes, ears, nose or throat			
Cyst, mole or skin lesion requiring medical advice or treatment or any other skin disorders			
Strained back, sciatica, whiplash, spondylitis or any other back, neck or spinal problem			
Disorder of the joints or muscles, arthritis, gout or repetitive strain injury			
Treatment or counselling for depression or any nervous, anxiety, stress or mental health condition			
Any other operation, disability, illness or injury, medical investigation or test (eg. Genetic test, mammogram, ultrasound, ECG) not already mentioned			
Have undergone hysterectomy (removal of uterus)			

b) Other than already stated, have you in the last 5 years:

	No	Yes	If Yes, give details
Taken any prescribed medication on a regular or ongoing basis?			

Used (by mouth, inhalation or injection) any drug not prescribed by a doctor, other than medicines purchased at a chemist?			
Do you NOW have any other disability, illness, injury or symptoms not already mentioned?			
Do you contemplate seeking any advice, test, investigation or treatment?			

If 'No' to all move to step 2

Step 2 Conduct a general physical examination of the participant and record the findings

GENERAL PHYSICAL EXAMINATION:	**Yes**	**No**
Pallor		
Jaundice		
Cyanosis		
Clubbing		
Oedema (general/ partial)		
Enlarged Lymph nodes		

If 'No' to all move to step 3

Step 3: Record the following:

Blood pressure	
Pulse rate	
Temperature	
Respiratory rate	
Weight (without shoes)	
Height (without shoes in cms.)	

If the readings are within normal limit for the age and gender of the participant, assess the following for inclusion of participant in the trial

Step 4: Assessment for inclusion in drug proving:

	Parameters	**Yes**	**No**
1	Participant is in the age of 18-60 years		
2	From general examination and history undertaken, the participant appears to be a healthy individual with no apparent disease		
3	From general behavior and conversation participant appears intelligent enough to record carefully the facts, subjective & objective symptoms generated by the IPS during proving		
4	Participant has been informed of the nature of the study and has given his/her written informed consent		
5	From general examination and history undertaken, participant appears to have some disease or condition which might compromise the hematopoietic, renal, endocrine, pulmonary, central nervous system, cardiovascular, immunological, dermatological, gastro-intestinal or any other body system		
6	Participant has colour blindness.		
7	Participant has undergone surgery in last two months.		
8	Participant has a planned medical / dental treatment during the next six months including herbal or dietary supplements, procedures, or		

	medications that are likely to interfere with responsiveness to the proving substance.		
9	Participant is on regular medication (allopathic, ayurvedic, homoeopathic, naturopathic, unani, etc.) for any acute or chronic disease.		
10	Participant is on any homoeopathic remedy in the preceding one month		
11	Participant has had significant change in health status in last one month.		
12	Participant is emotionally disturbed, hysterical or anxious persons.		
13	Persons has a history of allergies, food hypersensitivity, etc.		
14	Participant is a pregnant woman		
15	Participant is a women, presently under peurperium		
16	Participant is a nursing mother		
17	Participant smokes more than 10 cigarettes per day		
18	Participant has a recent history of alcoholism / drug addictions		
19	Participant is unlikely to refrain from excessive alcohol consumption / drug intake during the study period		
20	Person has participated in another clinical or proving trial during the last 6 months		

If YES to 1-4 and 'No' to all other parameters, proceed for detailed history taking and general examination of the participant as per Form D, Part – I.

Name of Investigator_____
Signature of Investigator _____ Date: _____/_____/_____
Day/month/year

Annexure – 5

Form D

CENTRAL COUNCIL FOR RESEARCH IN HOMOEOPATHY

Homoeopathic drug proving: Randomized double blind placebo controlled trial

PRE-TRIAL MEDICAL REPORT PROFORMA

Research Institute/ Unit……..

Date…….. Regn. No. ……..

Proving code (to be provided by CCRH, Hqrs.)……..

1. PERSONAL DATA

Name of participant ……

DOB …… Age…….years Sex - Male/ Female Religion…. ….. Nationality……

Name of Mother/Father/Husband/Guardian……..

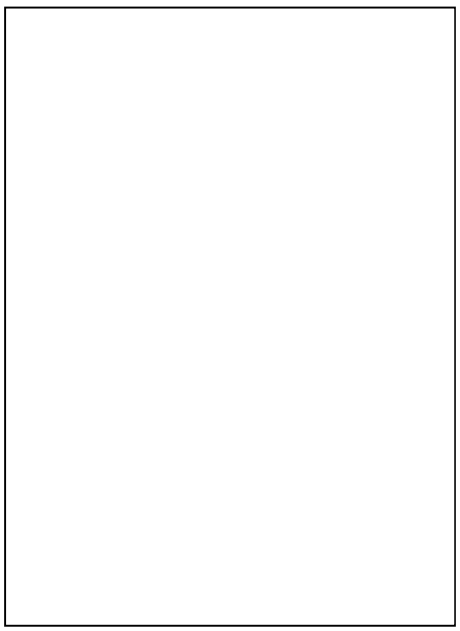
Address……

……

Telephone (Res.)…….. (Mobile)…… Email……..

Occupation ……

2. Space for photograph of Prover (Full photograph facing in front)



Part-I

(To be filled by site investigator)

1. HEALTH - STATUS OF THE VOLUNTEER

1.1 Presenting complaints, if any

1.2 History of presenting complaints:

1.3 Tendencies if any with details

1.4 recurring complaints if any, with details

2. **LIFE SPACE INVESTIGATIONS (should take form of a biographical account)** Record, if any factor, out of these has relation with present complaints or effect on mind and disposition of the patient**: -**

2.1 Occupational history

2.2 Marital history /sexual functions/orientation

2.3 Present social history

2.4 Alcohol, drug and smoking history (Details of smoking and drinking habits; any recent change or adverse effect on physical health or social activity, e.g. occupation, family relationships and financial situation. Use of other drugs, e.g. heroin, LSD, cocaine, amphetamines, barbiturates, cannabis, tranquillizers.)

a) Do you drink alcohol?

No ☐

Yes ☐

Number of standard drinks:

Per day ☐ Per week ☐

Or

b) If no, have you ever drunk alcohol?

No ☐

Yes ☐

Number of standard drinks:

Per day ☐ Per week ☐

Or

/ / ☐ / / ☐

Note: one standard drink = 1 glass of beer/wine/nip of spirit

c) Have you smoked tobacco or any other substance or used any nicotine-containing product in the last 12 months?

No ☐

Yes ☐

What type? eg cigarettes, gum, patch

☐

☐ / /

☐

Daily quantity Date ceased

d) Have you in any time in the last 12 months used an addictive drug such as narcotics or opiods or used any recreational drug?

No ☐

Yes ☐

What type? eg drug name & mode of intake

☐

☐ / /

Daily quantity Date ceased

2.5 Dietary habits

3. PAST MEDICAL HISTORY (Illnesses, operations and accidents in chronological order; treatment received – when and by whom. The patient's reactions to them).

Disability, illness, injury, condition or test	Test results	When did it start?	When did it cease?	Type of treatment	How long off work?	Have you completely recovered?

4. FAMILY HISTORY: Have any of your parents, brothers or sisters or any other first relative (living or dead) suffered from any of the following?

- Cancer
- Heart disease
- Stroke
- Diabetes
- Kidney disease
- Rheumatoid Arthritis/any other rheumatological conditions
- Huntington's disease
- Motor neurone disease
- Muscular dystrophy
- Familial polyposis
- Multiple sclerosis
- Any other hereditary disorder
- Any skin complaints
- Any respiratory complaints
- Any psychiatric/mental disorders

No ☐ Yes ☐ Please provide details below

Relationship	Medical condition	Age condition began	Age at death (if applicable)

5. MENSTRUAL HISTORY (if applicable):

Menarche: L.M.P.:

Regular/ irregular Cycle/ Duration	**Character of Flow (Quantity, Consistency & clots, color, odor, acridity)**	**Any complaints (Before, during and after)**	**Abnormal discharges per vagina**

6. OBSTETRIC HISTORY (if applicable)**:**

G (gravida) P (para) A (abortion) S (still birth) L (Living)

a) Have you had any complications of pregnancy or childbirth?

No ☐ Yes ☐

b) Are you currently pregnant?

No ☐ Yes ☐ Due date ☐ / /

7. PHYSICAL GENERALS:

Appetite	
Taste	
Thirst	
Desire / Cravings	
Aversion/ Repugnance	
Food Aggravation/ Intolerance	
Food Amelioration	
Stool	
Urine	
Sweat	
Discharges	
Urethral discharge	
Sleep	

8. MENTAL GENERALS

8.1PSYCHIC FEATURES* with causative or modifying factors, Aberration of mind, morbid affections of the moral & intellectual.
(*Especially change in mind & disposition during disease is to be highlighted.
Also mention: Are intellectual functions, power of thought, memory or desire or ability for mental or bodily exercise weakend?)

A. EMOTIONS

B. INTELLECT & MEMORY

C. WILL including desire/aversion in general(/ special senses ,strong with a drive

D. DISPOSITION & BEHAVIOR AS OBSERVED BY THE PHYSICIAN

E. ANY OTHER, SPECIFY

9. GENERAL PHYSICAL EXAMINATION

Pallor	Present/absent
Jaundice	Present/absent
Cyanosis	Present/absent
Clubbing	Present/absent
Oedema (general/ partial)	Present/absent
Enlarged Lymph nodes	Present/absent
Tongue (colour/coating, etc)	
Nails (colour of nail bed/specific features, etc)	
Oral health (health of gums & teeth)	
Blood pressure	mmHg

Pulse rate	Per minute
Temperature	Degree F
Respiratory rate	Per minute

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of History & General Examination, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the investigator	
Date of examination	
Signature of investigator	
Stamp of investigator	

If the volunteer is Suitable for proving, refer for laboratory investigations as per Form D – Part – II-A.

Part-II-A
To be filled by Pathologist

LABORATORY EXAMINATION

Investigation	Value	Reference range	Date of investigation
BLOOD			
Hb			
TLC			
DLC			
ESR			
Platelet count			
Peripheral smear			
BLOOD SUGAR			
Fasting			
LIPID PROFILE			
Triglyceride			
LDL			
VLDL			
HDL			
Cholesterol			
LIVER FUNCTION TEST			
Bilirubin (Direct)			
Bilirubin (Indirect)			
T. Bilirubin			
SGOT			
SGPT			
Alk. Phosphatase			
Albumin			
Globulin			
A/G ratio			
KIDNEY FUNCTION TEST			
S. creatinine			
S. urea			
Total protein			
URIC ACID			
THYROID PROFILE			
T3			
T4			
TSH			

URINE EXAMINATION

	Investigation	Value	Reference range	Date of investigation
Routine examination				
Microscopic examinations				

STOOL EXAMINATION

	Investigation	Value	Reference range	Date of investigation
Routine examination				
Microscopic examinations				

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of Laboratory Examination, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the pathologist	
Date of pathological examination	
Signature of pathologist	
Stamp of pathologist	
Signature of investigator	

Note for site investigator:If the volunteer is Suitable for proving, refer for radiological investigations as per Form D – Part – II-B.

Part-II-B
To be filled by Radiologist

X-Ray chest-
Date of X-Ray:

Findings:

ULTRASOUND WHOLE ABDOMEN
Date of ultrasound:

Findings:

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of Radiological Examination, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the radiologist	
Date of reporting	
Signature of the radiologist	
Stamp of the radiologist	
Signature of Investigator	

Note for site investigator: If the volunteer is Suitable for proving, refer for detailed examination by Consultants per Form D – Part – III.

Part-III

PSYCHOLOGICAL EXAMINATION

To be filled by Psychiatrist

1. Is there any abnormality related to appearance, memory, thoughts, speech, attention, concentration, orientation, intelligence etc.?

   No ☐

   Yes ☐

   If yes, please give details

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

2. Is there any sign of past or present psychiatric/psychological disease or abnormality?

   No ☐

   Yes ☐

Abnormal findings	**Associated symptoms, if any**	**When did possibly it start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

3. Is there anything to suggest that the participant is emotionally unstable?

   No ☐

   Yes ☐

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of psychiatry examination, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the psychiatrist	
Date of examination	
Signature of the psychiatrist	
Stamp	

To be filled by consultant medicine

RESPIRATORY SYSTEM

1. What is the rate and character of respiration.

Respiration Rate ____ per minute

Character ____

2 Is there any abnormality of the respiratory system to percussion or auscultation?

No ☐

Yes ☐

If yes, please give details

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

3. Characteristic of breath sounds

Bronchial ☐

Vesicular ☐

4. Is there any signs of past or present respiratory disease?

No ☐

Yes ☐

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of examination of respiratory system, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the consultant	
Date of examination	
Signature of the consultant	
Stamp	

CIRCULATORY SYSTEM

1. What is the rate and character of the pulse?

   Pulse rate ☐ per minute

   Character ☐

2. What is the position of the apex beat of the heart?

   In the ☐ interspace ☐ cm from the mid-sternal line

3. Is there any evidence of cardiac enlargement?

   No ☐

   Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

4. Is there any abnormality in the heart sounds or rhythm?

   No ☐

   Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

5. Is there any murmur present?

   No ☐

   Yes ☐ If yes, Describe fully including site, timing, intensity and transmission. Also indicate any effect of posture or respiration on the murmur

6. What is the blood pressure (auscultatory method)?

The diastolic level is to be taken at the cessation of all sound. If the first systolic reading is above 135 or below 100, or the diastolic above 85 or below 60, two further readings at 5 to 10 minute intervals are required. The recumbent position should be used where possible.

Systolic	Diastolic
mm Hg	mm Hg
Systolic	Diastolic
mm Hg	mm Hg
Systolic	Diastolic
mm Hg	mm Hg

7. Is there any abnormality of the peripheral arterial or venous circulation?

No ☐

Yes ☐

If yes, please detail

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

8. Do you consider the heart and the vascular system to be abnormal?

No ☐

Yes ☐

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

9. Please detail the findings of the ECG

Date of ECG: Time of ECG:

Findings:

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of examination of circulatory system, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the consultant	
Date of examination	
Signature of the consultant	
Stamp	

DIGESTIVE AND LYMPHATIC SYSTEM

1. Is there any abnormality of tongue, mouth or throat?

No ☐

Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

2. Is there any abnormality or evidence of disease of any abdominal organ, including liver or spleen on palpation and percussion of abdomen?

No ☐

Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

3. Is there any abnormality of the lymph nodes in the neck, axillae or inguinal regions?

No ☐

Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

4. Is a hernia present?

No ☐

Yes ☐

Abnormal findings	**Associated symptoms, if any**	**When did possibly it start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of examination of digestive & lymphatic system, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the consultant	
Date of examination	
Signature of the consultant	
Stamp	

NERVOUS SYSTEM

1. Is there any defect of vision or abnormality of the eyes?

   No ☐

   Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

2. Is there any defect in hearing or speech?

   No ☐

   Yes ☐

   In case of present or past ear discharge or deafness, state result of auriscopic examination

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

3. Is there any evidence of mental disorder?

   No ☐

   Yes ☐

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

4. Is there any evidence of any disorder of the central or peripheral nervous system?

No ☐

Yes ☐

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of examination of nervous system, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the consultant	
Date of examination	
Signature of the consultant	
Stamp	

MUSCULOSKELETAL SYSTEM

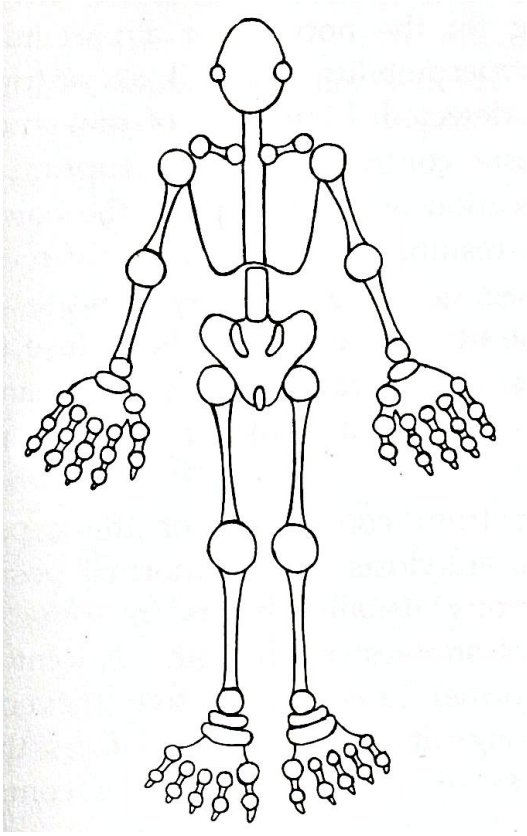
1. Is there any abnormality in the form or function of the joints, muscles or connective tissue?

No ☐

Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

2. Please detail any swellings, redness, skin changes, Wasting of regional muscles, deformity, crepitus, movement in joints



3. Is there any abnormality in the form or function of the back or neck including the cervical and lumbar spine?

No ☐

Yes ☐

Abnormal findings	**Associated symptoms, if any**	**When did possibly it start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of examination of musculoskeletal system, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the consultant	
Date of examination	
Signature of the consultant	
Stamp	

GENITO-URINARY SYSTEM

1. Is there any evidence of abnormality of the genito-urinary system?

No ☐

Yes ☐

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of examination of genitor-urinary system, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the consultant	
Date of examination	
Signature of the consultant	
Stamp	

To be filled by consultant gynaecologist

Gynaecology examination (Females only)

1. Is the examinee pregnant?

No ☐

Yes ☐ Expected date of confinement ☐ / /

2. Is there any abnormality in menstrual cycle?

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

3. Is there any evidence of discharge or other symptoms of possible gynaecological conditions?

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

4. Please detail per vaginal examination/per speculum examination findings (in case PV/PS are conducted)

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of examination of gynaecological system, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the consultant	
Date of examination	
Signature of the consultant	
Stamp	

To be filled by consultant dermatologist

Dermatology examination

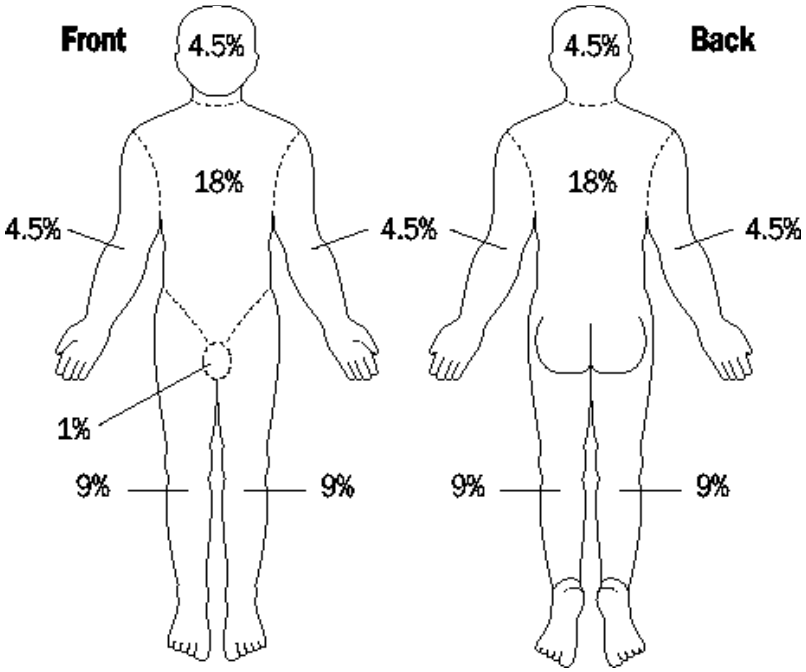
1. Is there any evidence of any disorder of the skin?

No ☐

Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

2. Mark the skin lesions in the diagram & record the type of lesion



3. Photographic record enclosed

No ☐

Yes ☐

If photographs enclosed, number of photographs_____

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of examination of dermatological system, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the consultant	
Date of examination	
Signature of the consultant	
Stamp	

To be filled by consultant ophthalmologist

EYE

1. Is there any abnormality in the form or function the Eye?

No ☐

Yes ☐

Abnormal findings	**Associated symptoms, if any**	**When did it possibly start?**	**Possible illness, disability or condition**	**Further tests required/ recommended**

2. Please detail the examination findings:

a. Vision
(Give vision both with spectacles & without spectacles if the participant uses spectacles)

b. Ophthalmoscopy:

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of examination of eye, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the consultant	
Date of examination	
Signature of the consultant	
Stamp	

To be filled by ENT consultant

ENT

1. Is there any abnormality in the form or function any disorder of the Ear?

   No ☐

   Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

2. Is there any defect in hearing or speech?

   No ☐

   Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

3. Please detail the findings of:

   a. Auriscopic examination

   b. Hearing tests

   c. Tuning fork test

4. Is there any abnormality in the form or function any disorder of the Nose ?

   No ☐

   Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

5. Is there any abnormality in the form or function any disorder of the Throat?

No ☐

Yes ☐

Abnormal findings	Associated symptoms, if any	When did it possibly start?	Possible illness, disability or condition	Further tests required/ recommended

Observations- any of the factors which make the participant unfit for proving as per protocol	1
	2
	3
	4
	5
Based upon the findings of ENT examination, whether the volunteer is suitable or not for enrollment in proving (chose the relevant option)	Suitable for proving Not suitable for proving
Name of the consultant	
Date of examination	
Signature of the consultant	
Stamp	

CASE SUMMARY

To be filled by site investigator after completion of Form D, Part-II by the respective consultants

Constitution of prover

Specific observations

Clinical abnormality, if any

Pathological abnormality, if any

Radiological abnormality, if any

Participant recommended for proving: Yes

No

Signature of Site investigator
Name: _____
Date: _____
Stamp:_____

Annexure -6

Form-E Part 1

PROVER'S DAY BOOK PROFORMA

INSTITUTE/ UNIT ……..

CENTRAL COUNCIL FOR RESEARCH IN HOMOEOPATHY, NEW DELHI

RUN-IN PERIOD

Name of the Prover……..

Date	Symptoms(s)/ any change in bodily functions/change in mental state in order of their appearance*	Time of		Intensity of symptoms	Any change(s) in lifestyle, circumstances, environment, etc.
		Appearance	Disappearance		

PROVER'S SIGNATURE

***** Prover must write in own language. Avoid all medical terms. Elaborate the symptom as vividly as possible

ᵠ Intensity of the symptom: Mark your symptom on a sale of 1 to 10, where 1 is very low/slight and 10 is extremely bothersome

Form E Part 2

DRUG INTAKE PERIOD

Name of the Prover……..Proving Code No. CCRH/……Batch No……

Day	Dose	Date	Time of intake of the drug	Symptoms(s)/ any change in bodily functions/change in mental state in order of their appearance*	Time of		Intensity of symptoms	Any change(s) in lifestyle, circumstances, environment, etc.
					Appearance	Disappearance		
Day 1	1							
	2							
	3							
	4							
Day 2	1							
	2							
	3							
	4							
Day 3	1							
	2							
	3							
	4							

PROVER'S SIGNATURE

***** Prover must write in own language. Avoid all medical terms. Elaborate the symptom as vividly as possible

ᵠ Intensity of the symptom: Mark your symptom on a sale of 1 to 10, where 1 is very low/slight and 10 is extremely bothersome

Form-E Part - 3

OBSERVATION PERIOD

Name of the Prover……..Proving Code No. CCRH/……Batch No……..

Date	Symptoms(s)/ any change in bodily functions/change in mental state in order of their appearance*	Time of		Intensity of symptoms	Any change(s) in lifestyle, circumstances, environment, etc.
		Appearance	Disappearance		

PROVER'S SIGNATURE

***** Prover must write in own language. Avoid all medical terms. Elaborate the symptom as vividly as possible

ᵠ Intensity of the symptom: Mark your symptom on a sale of 1 to 10, where 1 is very low/slight and 10 is extremely bothersome

Annexure 7

Form F

SYMPTOM ELABORATION PROFORMA

(to be filled by SITE INVESTIGATOR)

INSTITUTE/ UNIT ……

CENTRAL COUNCIL FOR RESEARCH IN HOMOEOPATHY, NEW DELHI

General instructions:

- Write legibly.
- Do not use any abbreviations.
- Write complete sentences.
- Record verbatim conversation with the prover.
- In table – 1 record the detailed conversation held with the prover "verbatim". From the symptoms detailed in table – 1 and further clarifications made with the prover, complete each individual symptom in table 2
- Query for all details related to circumstances, environmental factors, climatic conditions.
- Attempt to complete the symptoms in all possible aspects
- Avoid all medical and technical terms. Explain each term used as vividly as possible.
- Identify intensity of symptoms on a VAS scale on a scale of 0-100mm. Attach sheets with VAS scale separately
- Under the heading of classification of symptoms ($): Classify the symptoms as follows after complete questioning with the prover & taking into consideration the previous recordings made with the prover during the PME & run-in phase:
    - New symptoms, not previously experienced (NS)
    - Unexpected change representing worsening or aggravation of ongoing or recurring symptoms (C-)
    - Unexpected change representing an improvement of ongoing or recurring symptoms (C+)
    - Unexpected recurrence of past symptoms (RS)

Name of the Prover……Proving Code No. CCRH/……Batch No……

Face to face reporting by the prover:

Date	Time	Date	Time	Date	Time

Telephonic reporting by the prover

Date	Time	Date	Time	Date	Time

Table - 1

Date	Time of administration of the drug	Verbatim record of symptoms(s)/ any change in bodily functions/change in mental state experienced by the prover in order of their appearance as detailed by the prover

Symptom segregation, completion & development of chronology of complaints

Table - 2

Date	Time of administration of the drug	Symptoms(s)/ any change in bodily functions/change in mental state experienced by the prover in order of their appearance	Time of		Change in daily circumstances, routine, habits of the	Change in environmental conditions, climatic conditions, if any	Change in physical &/or mental generals	Cause-effect relation	Classification of symptom $	Investigations advised	Remarks
			Appearance	Disappearance							
		Onset: Location: Sensation: Aggravations: Ameliorations: Concomitants: Extension:									
		Onset: Location: Sensation: Aggravations: Ameliorations: Concomitants: Extension:									
		Onset:									

		Location: Sensation: Aggravations: Ameliorations: Concomitants: Extension:									
		Onset: Location: Sensation: Aggravations: Ameliorations: Concomitants: Extension:									
		Onset: Location: Sensation: Aggravations: Ameliorations: Concomitants: Extension:									
		Onset: Location:									

		Sensation: Aggravations: Ameliorations: Concomitants: Extension:									
		Onset: Location: Sensation: Aggravations: Ameliorations: Concomitants: Extension:									

Specific observations by the investigator, if any

Laboratory investigations conducted, if any (Annex reports):

Investigation	Value	Reference range	Date of investigation	Date and Value in the past	Is there any change in pathological parameters form that of the baseline

SIGNATURE OF SITE INVESTIGATOR

Annexure – 8

Form G

CENTRAL COUNCIL FOR RESEARCH IN HOMOEOPATHY

Homoeopathic drug proving: Randomized double blind placebo controlled trial

Adverse event reporting proforma

1. Prover name:
2. Proving Code No. CCRH

3. Batch no. ……
4. Date and **Time of intake of the last dose of IPS**

3. Date of reaction:

4. Description of the reaction (Full description of reaction(s) including body site, severity, signs and symptoms, examination findings, possible diagnosis)

5. Laboratory investigations, if any (Annex reports):

Investigation	Value	Reference range	Date of investigation	Date and Value in the past	Is there any change in pathological parameters form that of the baseline

6. Seriousness if the reaction:
Death (dd/mm/yyy)___
Life threatening
Required Hospitalization
Disability
Required intervention to prevent permanent impairment / damage
Other (specify)

7. Outcome & date of outcome
Fatal
Continuing
Recovering
Recovered

Unknown
Other (specify)___

8. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat
reaction)

9. Causality Assessment

10. Date & time of this report (dd/mm/yyyy)

Signature of Site investigator
Name: _____
Date: _____
Stamp:_____