I J R H

RESEARCH PROTOCOL

Access this article online

Website: www.ijrh.org

DOI: 10.4103/0974-7168.154341

Quick Response Code:

Homoeopathic Drug Proving: Randomised double-blind placebo-controlled trial

Central Council for Research in Homoeopathy

Central Council for Research in Homoeopathy

Address for correspondence: Dr. Raj K. Manchanda, Director General, Central Council for Research in Homoeopathy, New Delhi, India.
E-mail: rk.manchanda@nic.in

Received: 10-03-2015
Accepted: 11-03-2015

ABSTRACT

Background: The methodology of Drug Proving has evolved considerably since the times of Dr. Hahnemann. Standardisation of a proving process and quality of proving studies has been a major consideration for research over the years. Proving guidelines have been developed by various international bodies such as Homoeopathic Pharmacopoeia Committee of United States (HPCUS), European Commission of Homoeopathy (ECH) and *Liga Medicorum Homoeopathica Internationalis* (LMHI). Drug proving has been a major research activity of the Central Council for Research in Homoeopathy (CCRH). CCRH had over the years devised its own methodology for drug proving. A protocol for the drug proving program of the Council has been developed by harmonising the CCRH methodology with that detailed in internationally developed guidelines.

Methodology: This is a generic protocol, which will be applicable for drugs being proved by the Council. These will be multi-centric, prospective, parallel arm, randomised, double-blind, placebo-controlled studies. It is recommended to have at least 30 provers who can complete the total duration of proving. The Investigational Proving Substance (IPS) will be proved in two potencies. Inter- Prover and Intra- Prover placebo control will be maintained. Proving symptoms generated will be analysed on pre-defined criteria, and characteristic symptoms of the IPS will be identified.

Discussion: The protocol aims at combining the possible methods to increase the quality and to minimize bias in the study, at the same time ensuring that the IPS is proved sufficiently to evolve a pathogenesis which can then further be subjected for appropriate clinical response in patients. The protocol is open for discussion and readers are invited to send their comments and reviews on the protocol.

Keywords: Drug proving, Investigational proving substance, Placebo, Potency, Protocol

INTRODUCTION

The concept of proving first appeared in Hahnemann's writings in a 1790 letter.[1] The basic guidelines and principles of drug proving were given in the Organon of Medicine.[2] The method was further improvised over the years and various authorities gave recommendations on the choice of provers, methodology of study, dosage of drug substances under study, inclusion of controls and recording of symptoms.[3]

Drug Proving has been a major research activity of the Central Council for Research in Homoeopathy (CCRH), wherein the focus of research has been to introduce drugs of indigenous systems into Homoeopathy and to re-prove partially proved drugs.[4]

The standardisation of a proving process[5,6] and the quality of proving[7,8] studies have been a major considerations for research over the years. The methodology of drug proving has changed considerably since the times of Dr. Hahnemann. Proving guidelines have been developed by various international bodies[9-11] on the basis of which proving protocols for individual drugs are developed by researchers[12] for individual studies.

Dr. Hahnemann developed the idea of testing of action of drug substances on healthy individuals (Aphorism 106).[2] However, even the healthiest prover will have some variation in day-to-day health. The later experts were of the view that a prover should be in a good state of health, not necessarily absolutely healthy, for that is a rare property.[3] Inclusion of symptoms given by Freidrich Hahnemann who suffered from scoliosis and rickets, in Materia Medica in Hahnemannian proving has been identified as a source of error.[13] To minimise this, background noise[8] some basic criteria for healthy prover needs to be identified.

In spite of the enrolment of healthy provers, it may be difficult to measure health and day-to-day fluctuation results in variations, which can be identified as symptoms. The Hawthorne effect, known to be a significant non-specific effects of participation[14] in trials, which are likely to increase in drug proving due to the kind of close scrutiny inherent in the process.[8] A proving of *Pulsatilla* reported the response to the process of trial rather than to the agent being proved, wherein the results failed to give statistically significant evidence for effect of *Pulsatilla*.[15] Pre-observation period or having a run-in period is considered to be a method to prevent incorrect attribution of symptoms to the medicines. However, it has been reported that only a small number of trials used a pre-observation run-in period with or without placebo; in general, they did not present the symptoms collected during this period or how they differed from the reported pathogenetic effects.[7]

As per Dr. Hahnemann, all the sufferings, accidents and changes of health of the experimenter during the action of medicine are solely derived from the medicine (Aphorism 138).[2] Consequently, the prover is expected to record any subjective symptoms or deviations from normal conditions of life. However, later authorities suggested that evaluation and selection of symptoms on pre-defined criteria may be made[5,16] to identify symptoms that will belong to the medicine with greater probability. The study investigator is expected to identify potential etiological factors of the symptoms appearing during proving determined by either temporal or presumed causative relatedness to onset of a symptom.[11] The segregation of symptoms, which can be attributed to the drug being investigated during proving from symptoms arising in a natural course of day-to-day variations in health, is an important consideration, wherein errors in reporting may occur.

Another fundamental question facing contemporary proving studies is to what extent adoption of a randomised control method will increase accuracy and decrease errors due to human observation.[17] Hahnemann did not use blinding in the proving studies. However, over the years, blinding of provers was introduced and blinding technique was a routine procedure. As Randomized Control Techniques (RCT) developed, homoeopathic clinical researchers adopted blinding procedures.[17] In drug provings, the placebos are not given to measure a placebo effect, but to raise the critical alertness of the volunteers and eventually to find out how far the quality of "Proving symptoms" under placebo differs from real proving symptoms.[9] There are, therefore, variations in the proving studies conducted on the inclusion of a control group on placebo and on the percentage of controls, which is identified as a design flaw, to an extent that the results of such studies are unreliable and potentially harmful to patients treated, in good faith, by homoeopaths.[7] The methodological quality of the study, therefore, depends highly on the use of placebo-controlled design. There are however, no uniform guidelines on the percentage of participants on placebo.

The Council over the years devised the methodology for Drug Proving and the first drug proving protocol of CCRH was published in 1987.[18] The protocol gave broad guidelines on the aims and objectives of proving, personnel involved, inclusion, exclusion of provers, determination of dosage, nature of trials, number of participants, recording, ethical and legal considerations, etc., Subsequently, for about 20 years proving studies were conducted on this protocol.

A workshop on drug proving was conducted by the Council in 2010, to compile the experience of

researchers from India on drug proving and to develop a protocol with their consensus. This protocol had major changes from the previous protocols. In the initial drug proving studies, the provers were given 56 doses, which were completed in all provers. In the 2010 revised protocol (unpublished), the dosage of proving substance was reduced to 12 doses. Also, this protocol recommended that the proving drug from the same batch be stopped immediately on appearance of symptoms, and after a symptom-free wash-out period of 30 days, the next batch of medicines will be started. The potency that resulted in the symptoms in a prover will not be repeated in that prover.

In 2013, a second workshop was held at CCRH to develop the drug proving protocol in harmonisation with the international guidelines being developed for drug proving.[9-11] During this workshop the protocol of the Council was compared with the international guidelines.[19] Based on the outcome of this meet, a protocol for the drug proving program of the Council has been developed by combining the CCRH methodology with that detailed in internationally developed guidelines. This is a generic protocol, which will be applicable for the drugs being proved by the Council.

The objective of the proving study is to identify pathogenetic effects of a homoeopathically prepared drug substance (Investigational Proving Substance IPS) on healthy human beings. These will be prospective, parallel arm, randomised, double-blind, placebo-controlled studies, conducted in accordance with this protocol. The protocol has been approved by the ethical committee of the CCRH (vide letter no. 1-3/2014-15/CCRH/Tech/18th EC/197 dated 4th July 2014), 4th meeting of special committee on drug proving and 56th meeting of the Scientific Advisory committee.

The drug proving studies 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 under the Drugs and Cosmetic Act 1940 and Rules 1945 of Government of India[20] and Good Clinical Practice.[21]

MATERIALS AND METHODS

Investigational Proving Substance

Drugs with the potential to develop pathogenetic effects will be Investigational Proving Substance (IPS) under the study. Only single drug will be used for proving at a time in a prover.

- These could be drugs already existing in the Indian/ International Homoeopathic Pharmacopoeias/ formularies
  a. These are those drug substances whose basic standardisation 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 potentised 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.

- New products, with no reported use in homoeopathic system of medicine in any literature will be considered as new drugs. In such a case, standardisation 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 standardisation parameters will be recorded and compiled, before initiation of drug proving. The detailed literature review compiling the summary of findings from previous proving and clinical trials known and potential risk and benefits to human subjects will be conducted. A certificate of authenticity of this nature will be procured from the manufacturing firm.

The IPS will be proved in at least two potencies used in ascending order. The IPS will be dispensed in sugar globules of standard size 30.

Comparator (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 will be indistinguishable from IPS in terms of taste, appearance and smell.

Study Sites

Drug Proving will be conducted at identified research centres of the Council [Text Box 1] in coordination

with homoeopathic medical colleges involving scientists from the Council and faculty of the college.

Text box 1: Drug proving centres of CCRH

- Central Research Institute for Homoeopathy, Noida
- Central Research Institute for Homoeopathy, Kottayam
- Regional Research Institute for Homoeopathy RRI (H), Gudivada
- Homoeopathic Drug Research Institute, Lucknow
- Dr. Anjali Chatterjee Regional Research Institute for Homoeopathy, Kolkata
- Regional Research Institute for Homoeopathy, Navi Mumbai
- Drug Proving Unit (H), Bhubaneswar
- Other centres may be included after approval of the competent authority

CCRH: Central Council for Research in Homoeopathy; RRI (H): Regional Research Institute for Homoeopathy

Study Process

The flow chart for the proving cycle and the study process is given as Figure 1

Recruitment Process and Inclusion/Exclusion Criteria

Applications from interested volunteers will be invited from students, faculty and staff of homoeopathic medical colleges through notice boards of the Institutes/Units/College. A Provers Information Sheet, detailing the objectives, drug proving process, benefits of the trial and anticipated risks has been prepared. A 'Written Informed Consent' will be obtained from interested volunteers

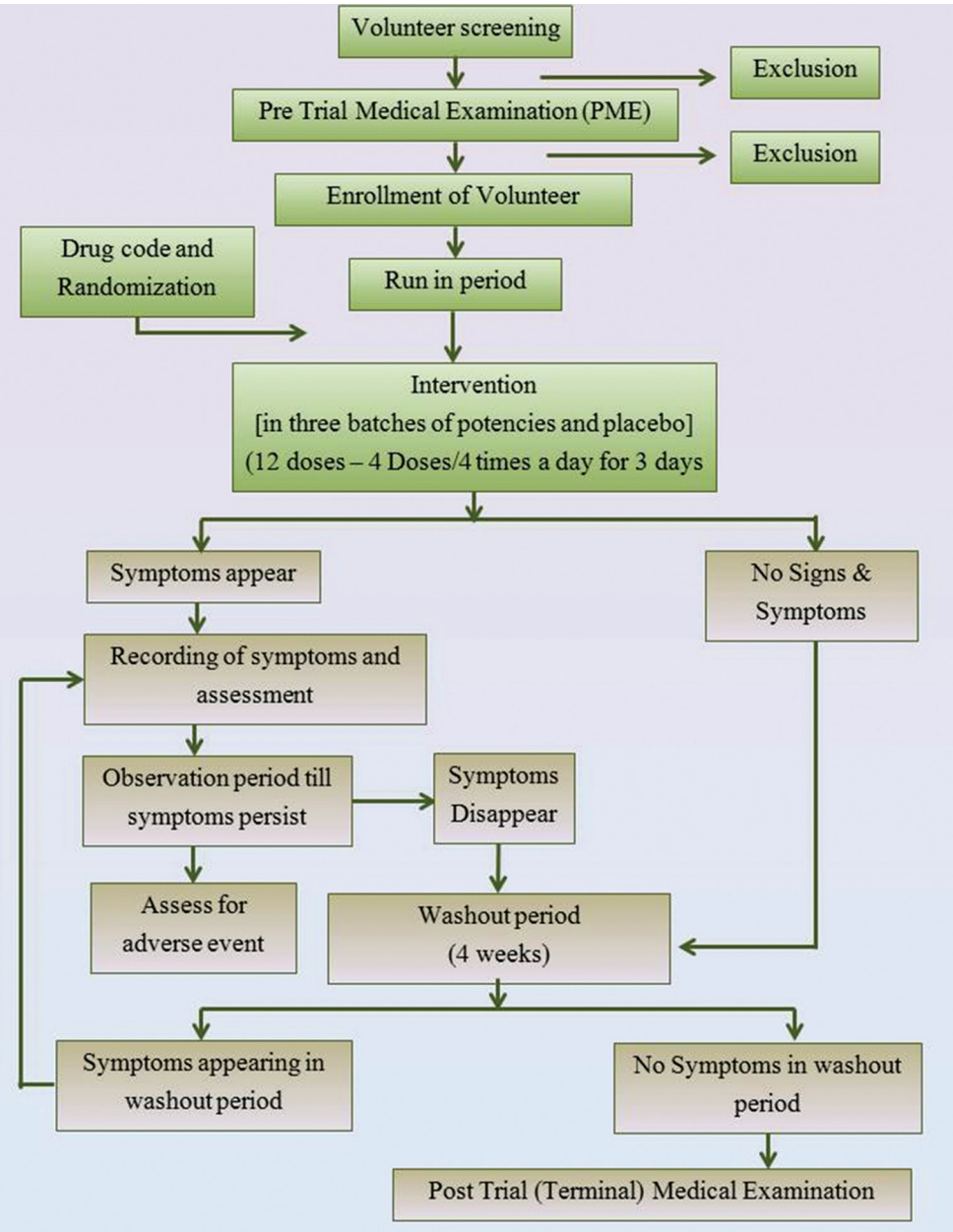

Figure 1: Proving cycle

before starting the drug proving process. The volunteers, who give written informed consent, will undergo preliminary screening for general health assessment and examination. Healthy Individuals of either sex, aged between 18-60 years with no apparent disease will undergo a detailed Pre-trial Medical Examination (PME). PME comprises detailed history, clinical (general and systemic) examination, and laboratory investigations to confirm health status of the participants. Details of inclusion and exclusion criteria are given in Table 2. The participants found fit will be enrolled as prover.

Randomisation and Blinding

A Unique Identity Code (UIC) will be generated for each prover. Randomisation will be done using computerised random number charts for allocation to intervention. The randomised allocation will be made according to the UIC as follows:

- Inter-individual control: 30% of the provers will be randomised into placebo group
- Intra-individual control: The drug-placebo sequence will be randomised for each prover in the verum group. It is proposed to be maintained during the proving process to prevent incorrect attribution of symptoms to the IPS.[7]

The nature of the proving substance and the allocation will be known to the study coordinator at the coordinating centre/CCRH headquarters. The study medication will be sent by the study coordinator in coded forms along with a randomisation chart to the proving centre. Intervention allocation will be concealed until the proving is completed and the database has been locked. The sealed randomisation list will be stored by the principal investigator at CCRH headquarters.

Text box 2: Inclusion and exclusion criteria for drug proving

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

Exclusion criteria

- Any disease or condition that might compromise the haematopoietic, 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 six months

IPS: Investigational proving substance

Intervention

Group I: IPS: The verum group will be advised to take the study medication as per schedule. This group will comprise about 70% of the enrolled participants. The IPS will be given in multiple batches (usually three), out of which one batch will be placebo and other batches will be IPS.

Group II: Placebo: The control group will be given placebo indistinguishable from the study medication. This group will comprise about 30% of the enrolled participants. Multiple batches (usually three) will be given, all of which will comprise placebo.

Study Medication

Drugs in compliance with pharmacopoeial standards from Good Manufacturing Practices (GMP)[22] compliant manufacturers would only be procured. The IPS will be packed in the form of 1 dram glass bottle, labelled with serial number, prover's code and date of packaging. The placebo will be prepared similarly and labelled with serial number, prover's code and date of packaging. The preparation of the IPS/placebo for dispensing to individual provers will be done separately under direct supervision of the Principal Investigator/Coordinator.

Dosage

Each batch will have 12 doses. The provers will be instructed to take four pills, four times a day at four-hourly intervals for three days.

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 two weeks and a maximum of four weeks. The investigator will give a specially designed prover's day book proforma to the provers. The prover will be requested to make note of any change in health status in this proforma daily and report to the site investigator once a week or earlier in case of change in health status. It will help the investigator to know the willingness, ability of the participant to properly complete the diary and the baseline health characteristics of the prover.

Initiation of Intervention

On completion of the run-in period, 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 the dosage as per schedule. Prover will be instructed to follow his/her normal daily routine and dietary habits till the time he/she is enrolled in proving. Other detailed instructions related to intake of medicines and observation and recording of change in their health status will also be given.

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 three-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 a symptom elaboration proforma.

Follow-up

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. The prover will be requested to stop taking the further dose of study medication as soon as he/she feels any change in health status or any sign (s) and/or symptoms (s) develop in accordance with the qualifiers of proving symptoms. 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) and/or symptoms (s), their progress and the number of doses after which each sign and/or symptom appears with date, time of onset and duration for which it persists. Since the symptoms appearing during proving are transient in nature, it is not expected that the symptoms will persist for long. In case symptoms persist for more than three days or is distressing to the prover, during the course of proving, the prover is referred to a medical expert/consultant for examination and for specific laboratory investigation (s), if needed, to rule out any pathological cause for appearance of new symptom (s)/sign (s).

No further dose of the same batch is to be consumed by the prover. Subsequent to disappearance of the symptoms, a period of 30 days will be kept as wash-out period. After this wash-out period, the dosage from the next batch is initiated. The same procedure is followed till all the batches of the study medication are consumed.

Post-Trial (Terminal) Medical Examination

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

Withdrawal of Provers

A prover may be discontinued from the study in case of occurrence of serious adverse event (s) or serious inter-current illness or non-compliance to proving protocol or the prover withdraws consent or at discretion of the investigator. The prover who withdraws from the study will be requested to undergo a complete post-trial medical examination if possible, or if leaves against advice of site investigator, will at least be requested for a final telephonic interview with regard to the state of prover's health.

Adverse Event Handling

The definition of adverse event and process for handling of adverse events has been adapted from HPCUS.[11]

STUDY DURATION

The duration of proving for each prover will depend upon use of batches, symptoms produced and subsequent wash-out periods.

SYMPTOM CLASSIFICATION

The study investigator on detailed interrogation with the prover must complete each symptom with respect to the order of appearance, time of appearance and disappearance, location, sensation/character, modalities, concomitants, direction/extension of symptoms, etc., Clinical examination findings and pathological investigations will also be recorded. For each symptom, the investigator will classify[11] and mention the symptoms as follows:

- 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.

Proving Symptom[11]

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. These are symptoms or signs that are recorded during the proving period where causality by the IPS is possible. Symptoms that occur in 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. Abnormal values of laboratory parameters that were in the normal range during the PME will also be included in the proving symptoms.

Compilation of Proving Symptoms

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

The proving symptoms identified 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 Centre: 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)
- Characterising 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 be the basis to distinguish symptoms as:

- Characteristic symptoms (if reported)
- Ongoing symptoms that have unexpectedly and markedly improved
- Proving symptoms with one or more characterising features

DATA ANALYSIS

Qualitative Analysis

The evaluation will be done by compilation of the proving symptoms in different categories, representing a certain probability to be associated with the IPS intake. A symptom will belong to the IPS with great probability if at least one of the following criteria[9] is met:

- 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. The characterising features for proving symptoms of the IPS are given in Text box 3. The symptoms will be further be graded in Grade – I and II, wherein first grade symptoms refer to symptoms linked more strongly to the IPS than all others identified as second grade [Text box 4].

Quantitative Analysis[7]

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). 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). 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.

Text box 3: Characterising features of proving symptoms[9,11]

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 individualising

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 recognisable 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 recognised 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

Text box 4: Grading of symptoms

Grade I symptoms

- Symptoms appearing in more than two provers, at two different study sites (symptom in one or more provers at one site and similar symptom in one or more provers at the second site i.e., if two provers separated by distance and time with no contact with each other whatsoever 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

DISCUSSION

A thorough proving of a drug substance is completed when a drug is proved in different environments, on persons of different characteristics, on different age groups, both genders. Also, it must be studied in different potencies, to come up with a detailed pathogenesis of the drug. To include provers from different environments, a drug will be proved at multiple centres, which are at different geographical locations. Most of these centres are conducting drug proving studies in collaboration with homoeopathic medical colleges and students of Homoeopathy frequently enrol as provers in these studies. However, to include persons from different backgrounds, it is desirable to include at least 20% of provers from non-homoeopathic background.

Some authorities prefer to conduct proving on single potencies (usually 12C[12] or 30C[9] or use different potencies in different arms.[10] However, at CCRH, the methodology has been devised to test the IPS in different potencies on the same prover. In the various studies conducted, it has been observed that whereas some provers produce symptoms in one potency, they may not show symptoms on other potencies. This has been independent of the potencies used and the sequence in which they have been applied in the proving batches.

The percentage of participants in control group has been varied from 50%[6] to 25-30%,[18] to 20%[11] Others do not recommend inclusion of a control group necessarily into proving.[9] In this protocol, a control of 30% is maintained, i.e. 1/3rd of the participants will be on placebo, as were being followed in the CCRH studies previously. Also, all participants would be given placebo at least in one batch as an intra-individual control.[7] The symptoms generated during placebo period or by provers in placebo are also recorded. However, these symptoms will be segregated from the symptoms appearing in the verum group, while on the IPS. The sign (s) and/or symptom (s) that are identical (exactly the same in terms of location,

sensation, modalities, concomitants) in both drug and placebo will not be included as proving symptoms. The use of placebo, in these studies, is therefore expected to minimise bias[11] and raise the critical alertness of the volunteers and eventually to find out how far the quality of 'Proving symptoms' under placebo differs from real proving symptom.[9]

Some guidelines permit proving on a small sample, and it is suggested that sufficient sample size must be selected to ensure that a minimum of 10 subjects receive verum.[11] Although proving on small verum groups can add on to the development of drug pathogenesis, when pooled together, the clinical utility of data of individual studies with a small sample is doubtful. As such for organised proving, efforts need to be made to have a larger number of provers. In provings conducted by CCRH, 30 provers are recommended who complete the total duration of proving.

The protocol aims at combining the possible methods first to increase the quality and to minimise bias in the study, at the same time ensuring that the investigational substance is proved sufficiently to evolve a pathogenesis which can then be verified clinically. The protocol is open for discussion and readers are invited to send their comments and reviews on the protocol.

CONTRIBUTIONS

Study concept & design: Raj K. Manchanda[1], Anil Khurana[2]
Protocol drafting: Anil Khurana, Renu Mittal[3], Divya Taneja[4]
Review of protocol & Scientific Advisor: Robert van Haselen[5]
Drafting of manuscript: Renu Mittal[3], Divya Taneja[4]
Review of manuscript: Anil Khurana[2]

CONTRIBUTOR'S INFORMATION

[1]Director General , CCRH
[2]Deputy Director (Homoeopathy), CCRH
[3]Research officer (Homoeopathy), CCRH
[4]Research officer (Homoeopathy), CCRH
[5]Member Homeopathic Pharmacopoeia of the United States (HPUS), Member Proving Working Group HPUS, Lead Clinical Data Working Group HPUS

ACKNOWLEDGEMENT

We acknowledge the contribution of Dr. Rajpal, Research Officer (H), Dr. Vinay Kr. Singh, Senior Research Fellow (H), Dr. Shilpa Sharma, Senior Research Fellow (H) in development of protocol of drug proving.

REFERENCES

1. Belon P. Provings. Concept and methodology. Br Homoeopath J 1995;84:213-7.
2. Hahnemann S. Organ on of Medicine. 5th and 6th Reprint edition. Translated by Dudgeon RE, Boericke W. New Delhi: B Jain. 2010. p. 140-161.
3. Dudgeon RE. On the Proving of Medicines from Lectures on the Theory and Practice of Homeopathy 1853 Reprint edition. New Delhi: Jain Publising Co. 1982. p. 176-211.
4. CCRH: Activities and Achievements. New Delhi: CCRH; 2014. p. 48.
5. Weiland F. Good Homoeopathic Provings the need for GHP guidelines a brief survey of recent developments in methodology of homoeopathic drug proving in Europe. Br Homoeopath J 1997;86:229-34.
6. Walach H. The pillar of homoeopathy Homoeopathic drug provings in a scientific framework. Br Homoeopath J 1997;86:219-24.
7. Dantas F, Fisher P, Walach H, Wieland F, Rastogi DP, Teixeira H, *et al.* A systematic review of the quality of homeopathic pathogenetic trials published from 1945 to 1995. Homeopathy 2007;96:4-16.
8. Rogers, J. Hahnemann and the methodology of pathogenetic trials in healthy volunteers: A reappraisal. International Journals of High Dilution Research [online]. 2010;9:94-103. Available from: http://www.feg.unesp.br/~ojs/index.php/ijhdr/article/view/373/444) [Last accessed on 2015 February 26].
9. European Committee of Homeopathy. ECH Homeopathic Drug Provings Guidelines Version Available from: http://www.homeopathyeurope.org/publications/guidelines/homeopathic-provings/ECH_Proving_Guidelines_v1.pdf [Last accessed on 2015 Feb 16].
10. Ross A, Wassenhoven MV. Second Edition of LMHI Guidelines for a Homeopathic Drug Proving (HDP). Available from: http://liga.iwmh.net/index.php?menuid=95 and reporeid=310 [Last accessed on 2015 Feb 16]
11. Homeopathic Pharmacopoeia of the United States. HPCUS Proving guidelines. Available from: http://www.hpus.com/Draft-HPCUSProving-Guidelines.pdf [Last accessed on 2015 Feb 16].
12. Teut M, Hirschberg U, Luedtke R, Schnegg C, Dahler J, Albrecht H, *et al.* Protocol for a phase homeopathic drug proving trial. Trials 2010;11:80.
13. Khurana A. Drug proving- sources of errors. CCRH Qtly Bull 1994;16:19-20.
14. De Amici D, Kiersy C, Ramajli F, Brustia L, Politi P. Impact of the Hawthorne effect in a longitudinal Clinical study: The case of anesthesia. Control Clin Trials 2000;21:103-14.
15. Clover AM, Jenkins S, Campbell AC, Jenkins MD. Report on Proving of Pulsatilla 3X. Br Homoeopath J 1980; 69:134-49.
16. Riley DS. Extracting symptoms from homoeopathic drug proving. Br Homoeopathic J 1997;86:225-8.
17. Kaptchuk TJ. When does unbiased become biased? The dilemma of homeopathic provings and modern research methods. Br Homoeopath J 1996;85:237-47.
18. Nagpaul VM. Provings-planning and protocol. Br Homoeopath J 1987;76:76-80.
19. Manchanda RK, Khurana A, Taneja D. Proceedings of interactive meet on harmonisation of drug proving programme. Indian J Res Homoeopathy 2014;8:46-66.
20. Government of India. The Drugs and Cosmetics Act and Rules. New Delhi, Ministry of Health and Family Welfare (Department of Health). Available from: http://cdsco.nic.in/html/copy%20of%201.%2 0d and cact121.pdf [Last accessed on 2015 Feb 16]
21. Good Clinical Practices for Clinical Research in India. Available from: http://cdsco.nic.in/html/GCP. htm [Last accessed on 2015 Feb 16].
22. Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products. [Schedule M]. Available from: http://www.cdsco.nic.in/html/GMP/ScheduleM (GMP).pdf [Last accessed on 2015 Feb 16].

How to cite this article: Central Council for Research in Homoeopathy. Homoeopathic Drug Proving: Randomised double-blind placebo-controlled trial. Indian J Res Homoeopathy 2015;9:3-11.
Source of Support: Nil, **Conflict of Interest:** None declared.