Drug Proving
Training Module & Manual

Central Council for Research in Homoeopathy
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"Indeed, a medicine must first of all be essayed in a healthy body, without any foreign admixture; when the odour and taste have been examined, a small dose must be taken, and attention must be paid to every change that occurs, to the pulse, the temperature, respiration and excretions. Then, having examined the symptoms encountered in the healthy person, one may proceed to trials in the body of a sick person." [von Haller, 12]

Preface

Homoeopathic drug proving is an imperative precursor for introduction of any new drug in the homoeopathic materia medica and for enhancing the therapeutic potential of the already existing drugs. The validity and reliability of information gathered from proving is fundamental for the success of homoeopathic practice and clinical research.

The students in Homoeopathic colleges are taught the basics of drug proving in their course curriculum. However, it was identified that the students lack knowledge on practical aspects of drug proving as to how present day proving studies are conducted. The faculty in colleges also frequently face problems in development of proving protocols.

Central Council for Research in Homoeopathy has conducted proving of about 100 drugs. In the initial years, the methodology for proving of the drugs varied widely for different drugs. Over the years, CCRH has been able to develop a standardized methodology for drug proving. Also, Council is in the process of harmonization of its protocol with international guidelines of ECH and LMHI.

CCRH, therefore, decided to develop this training manual and module compiling the experience gained over the years, for the benefit of academicians and practitioners interested in drug proving. This manual compiles the evolution of methodology of drug proving and details the instructions and guidelines given by various authorities. Lastly a model protocol developed by the Council is enclosed. This would facilitate the students to develop a better understanding of the methodology and would be useful for faculty and guides to develop proving studies at their educational institutions.

A training module has also been developed to plan training workshops on this manual. The module takes into consideration that the investigators are likely to be senior faculty from colleges and therefore, gives ample scope for self learning and experience sharing.

This is an endeavour of the Council to extend all possible help in inculcating research aptitude in the students, academicians and practitioners. We hope that the module and manual will be of use for the educational institutions and practitioners groups to develop and conduct drug proving studies. Feedback and response to the manual are most welcome.

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Training Module

About Provings by Dr. Hahnemann:

"I found from the toxicological reports of earlier writers that the effects of large quantities of noxious substances ingested by healthy people...largely coincided with my own findings from experiments with those substances on myself or other healthy people." [Hahnemann, 1810, v.110]

"from this single experiment his mind appears to have been impressed with the conviction that the pathogenetic effects of medicines would give the key to their therapeutic powers." [Dudgeon, xxi]

Introduction

As we all know, Homoeopathic research is a continuous evolving field and to acquaint oneself with the ever developing science continuum learning is vital. Drug proving is one of the fundamental facets of homoeopathy. It is the systematic procedure of testing drugs on healthy subjects in order to elucidate the symptoms reflecting the action of drugs. Homoeopathic Drug provings are one of the source of information of homoeopathic materia medica. The validity and reliability of information gathered from drug proving is therefore fundamental for homoeopathy.

Radical improvement in pathogenetic information is a vital point in the current agenda for homoeopathic practitioners and clinical researchers that deserve a painstaking and dedicated world wide effort, that's why we need sensitive designs and robust methodological procedures for homoeopathic drug proving. But developing designs and methodology is fruitless if its practical implication is nil.

This training module is a part of the CCRH initiative to provide insight of basic phenomenon of drug proving and to familiarize investigator with established systematic methodology for conducting drug proving. The training module has been developed with the vision to build a standard generic knowledge, skills and understanding related to drug proving.

Module is devised for investigator development and group work, which are a vital part of the process. The training module will offer the opportunity to substantially develop existing methodology of drug proving. Further, it has been intended to sensitize trainee with every aspect of drug proving.

The overall developmental objective of this Training Module is to strengthen the competency of the trainee to effectively conduct drug proving intertwining the quality aspects and to draw symptomatic information which is the most important part for developing Homoeopathic materia medica.

Aims & Objectives

Aims

To plan and facilitate training workshops which help making the investigators proficient about the methodology of drug proving and acquaint them with the various facets of conducting drug proving, in an appropriate manner.

Objectives

Primary objectives

1. To skill the investigators about the technique and methodology of the drug proving.
2. To reestablish the understanding for the need to conduct drug proving within the homoeopathic community and to motivate those who are interested in provings.

Secondary objectives

1. To develop information manual which contains all the necessary information related to drug proving.
2. To sensitize the students and the investigators with the methodology of the drug proving.
3. To ensure that expected standards of quality are being addressed.
4. To motivate the investigators for ensuring well conducted provings.
5. To measure the real impact of the development of the new methods.

Anticipated outcomes:

1. Investigators get well versed with the methodology of drug proving.
2. Appreciate the importance of drug proving.
3. It helps the prover for a better understanding of the nature of the qualitative symptoms and unlocks his mind to research procedures.
4. Achieve a greater awareness, understanding and implementation of the drug proving programme ranging from conceptualization to post-evaluation phase.
5. A quick reference tool is made available at any time or as background material.

Training Methodology

Broadly the training sessions are divided into 2 phases.

1. **PHASE I -** Self-reading
   The participants are supposed to go through the manual for better understanding of the session. The duration for self-reading is 10 days.

2. **PHASE II-** Contact session
   The contact session involves training of the investigators. The duration of the contact session will be of 2 days. The sessions would be held comprising of 20-30 trainers. To make the session thought-provoking and intellectual, the sessions will be further divided into

   a. Lecture method
   b. Experience sharing session
   c. Group discussion
   d. Questionnaires
   e. Individual and small group work & presentations
   f. Action plan preparation and presentations

Procedural Technique

Time frame

This training module will be implemented through two day work shop. The module has been designed to provide 10 days of self-study and 12 hrs. of workshop/contact session. This training module has been developed to train the investigators involved in the drug proving programme of the council.

Facilitators/trainers

The trainers shall be one who are proficient in the concerned subject.

Infrastructural requirements

The proposed venues will have adequate infrastructure and facilities for training. The basic requirement for training would be:

1. Facility for seating, presentation, group discussion- the seating will preferably be round table instead of class room seating to encourage participant interaction.
2. LCD projector, computer, audio visual display, display board.

Training venue

1. CCRH Headquarter
2. Institutes of the council

Participants

The participants shall be researchers or the personnel of the council engaged in drug proving programme

Training Manual

Manual for training has also been prepared. The same manual would be used by both the trainers and the participants of the training. The training manual would be sent to the participants registered for training at least 10 days prior to the contact session. The manual comprises of following sections:

1. Historical developments
2. Methodological aspects and their evolution
3. Drug Proving Process
    - During pre- trial Phase
    - During trial Phase
    - Structure of the formats
4. Ethical considerations for drug proving

Each section has one or more sub-sections and chapters. The participants would be expected to go through the Manual before coming to the session.

Contact Session

Contact Session

A sample schedule for coverage of topics during the contact session is given. The trainers will employ a variety of training methods, including demonstrations, power point presentations to the participants, group discussion including experience sharing session etc. at the end of training, a small session for revision of key learning concepts will be held.

During the contact session, the participants will be encouraged to contribute what they know about the topic being discussed. The knowledge that the participants bring into the training situation is as essential to the total learning process as the knowledge that the trainer offers. The success of this approach will be highly dependent on the trainer's capability to encourage their participants to share and the willingness of the participants to take an active part in the training.

Requirements for session: white board, markers pens, training manuals on drug proving, note pads, computer, LCD projector.

Introductory Session

An introductory session of 30 minutes at the beginning of the contact program will be organized that will apprise the participants with the adopted strategies and methodologies that would be followed in each session. An overview of the training and its objectives will be given to the participants in this session.

Revision & Assessment Session

A post training assessment of half hour duration with 30 questions will be made in this session. The feedback from the participants on the training will also be taken.

Topics To Be Covered

S. No.	Area of coverage	Topic	Duration	Suggested methodology
1.	Fundamentals of drug proving	**Introduction** **Aims and Objectives**	30mins	Power point presentation followed by group discussion
		Historical development of the concepts of Drug Proving Origin of concept of drug proving and historical development of the basic concepts of drug proving with special attention on further development in proving process during that era	60mins	
2.	Methodological Aspects and their evolution	• Evolution till date • Pre requisite for drug proving o Drug substance o Potency & dosage o Proving Master o Prover/Volunteer o Ethical issues o Confounding Factors o Randomization/Blinding o Data Recording • Recommendations of HPUS (Homoeopathic Pharmacopoeia of the United States) • Data recording as per CCRH protocol • Methodology adapted by CCRH	90min.	Power point presentation followed by group discussion

3.	Drug proving process	**Pre-trial phase** o Identification of investigators of Drug proving o Literature review, safety and standardization of proving substance o Protocol finalization o Ethical review & approval o Identification of participants **During Trial** o Informed consent o Screening o Pre-trial medical examination o Enrollment o Run in period o Blinding o Intervention o Post - trial medical examination **Structuring the formats of drug recording** • Screening of volunteers **(Form A)** • Prover information sheet **(Form B part I)** • Written voluntary informed consent **(Form B part II)** • Screening of participants **(Form C)** • Pre-trial medical examinations • Post-trial (Terminal) medical examinations **(Form D)** • Provers day book proforma **(Form E)** • Symptom elaboration form **(Form F& G)** • Case off form • Adverse event reporting form	90min	Power point presentation followed incorporating flow charts followed by group discussion & role play

		Analysis & sifting of Drug proving • Decoding & segregation of Verum & placebo symptoms. • Qualitative analysis o Symptom selection criteria o Characterizing features of proving symptoms o Grading of the drug proving as per their value. • Quantitative analyses- Dose-biological response relationship • Analysis & matching of symptoms • Proforma in excel sheet o Quota 1,2,3 o Control o Non- control o Final compilation o Monthly report	60min	Power point presentation of the process. As detailed in the protocol
4.	Ethical & safety issues	• Principles of Biomedical Ethics • Guidelines for drug proving o International guidelines o Guidelines for protocol development • Ethical issues in drug proving • Confidentiality of study participants	30mins	Power point presentation followed incorporating flow charts followed by group discussion

5.	Ideal protocol – checklist	• Protocol • Screening of volunteers • Prover information sheet • Written voluntary informed consent • Screening of participants • Pre-trial medical examinations • Post-trial (Terminal) medical examinations • Provers day book proforma • Symptom elaboration form • Case off form • Adverse event reporting forms	30mins	Power point presentation followed incorporating flow charts by group discussion

Training Manual

"Hahnemann's 'Fragmenta de viribusmedicamentorumpositivis'...gives us, for the first time, an insight into the remarkable, and so far unknown, methods of investigation, which he employed. It supplies reports on the tests of twenty seven medicines the results of years of experiment on himself and his family." [Gumpert, 122]

Historical Developments

Drugs have been used as the standard method of cure for disease since antiquity and were essentially derived from simple herbs and substances to fearsome combinations from every plausible source. Before Hahnemann conceived the idea of drug proving on healthy human being various doctrines of healing were existent. The most interesting among which was the Doctrine of Signatures[1], founded on the belief that each member of the vegetable kingdom carried within itself the likeness of some organ or part of human economy, as a sign that this particular plant was applicable to disturbances of that organ. That was probably the most consistent method among all the very ancient systems of applying drugs.

Among the ancients, experiments undertaken for the purpose of ascertaining the pathogenetic effects of drugs and poisons were found only in the school of the pragmatists like **Heraclides, Mithridates, Attalos Philometer and Nicander of Colophon[2].**

Heraclides of Tarentum demonstrated the symptoms caused by the bites of poisonous serpents. Mithridates, King of Pontus, instituted experiments on himself and on criminals for learning the action of various poisons. Attalos Philometer, King of Pergamos, tested the antidotal powers of Aconite, Hyoscyamus, Veratrum, Hemlock, etc. But it was chiefly, Nicander of Colophon, Greek poet and physician who presented elucidation of the action of various poisons in his two medical poems.

In about 2000 BC, there is a mention of **Shennong or ShenNung**, Emperor of China, venerated as the "Father of Chinese Medicine" who tested herbs upon himself for eliciting therapeutic efficacy. **Erasistratos of Julius**, a Greek royal physician, physiologist and anatomist also gave some account of the action of poisons.

As medical knowledge progressed, there emanated glimpses of other methods of drug application, but such light was rare and medical practice soon lapsed once more into the gloom of superstition. Two physicians **Theophrastus** von **Hohenheim** commonly known as **Paracelsus** and **Halle** came as a gleam of optimism who attacked the absurd methods of treatment prevalent at that time, saw as clearly as Hahnemann the defects of the ancient system. Paracelsus, a Swiss German Renaissance physician, gained considerable insight into the action of drugs by proving of medicines on the healthy human being and Halle, the Swedish physician, who is apparently a forerunner of Hahnemann in his deliberate experiments to discover the nature of certain remedies. Unfortunately, these attempts were not coordinated and hence made little impression upon the medical world[1].

Later in 16th century, a Zurich doctor, **Conrad Gessner** actually experimented on himself with drugs usually derived from plants.

Another person of note was the Viennese **Anton von Storck** who is remembered for his clinical research of various herbs, and their associated toxicity and medicinal properties. His studies are considered to be the pioneering work of experimental pharmacology and his method can be regarded as forming a blueprint for the clinical trials of modern medicine. Hahnemann may have got the concept of drug proving from him. But Hahnemann acclaimed physician **Albrecht Von Haller** in the footnote to Section 108 of Organon of Medicine for observing before him method of ascertaining the pathogenetic effect of drugs on the healthy human being.

William Alexander, surgeon in Edinburgh, had made a proving on his own body. He nearly lost his life by taking two scruples of Camphor, after which he desisted from drug proving[3]. **Samuel Crumpe**, an Irish physician, published *"An inquiry into the nature and properties of opium."*[3] The Experiments of the toxicologists, and notably those of **Wibmer, Orfila, Majendie** and others, were undertaken chiefly with a view to ascertain the structural alterations produced by the various poisons, and were confined to the lower animals.

The work was not taken up in an orderly way until Hahnemann demanded to know the action of drugs upon the human organism. The fundamental theoretical basis for the proving of drugs on healthy persons was originally enunciated by Hahnemann himself, inspite of the fact that there are still stray instances on record where provings have been done earlier. The major revolution to the then existent theories came in 1790 when while translating the second edition of the book **"A treatise on Materia Medica** by **Dr. William Cullen"** in two volumes consisting of 1170 pages from English into German, Hahnemann came across the statement regarding the action of Cinchona bark in the cure of ague which appeared derogatory to Hahnemann and he was prompted to try this drug on himself[3].

Original Dictum of Hahnemann after taking Cinchona:

"For the sake of experiment I took for several days four quentchen (drachms) of good Cinchona twice a day. My feet, the tips of my fingers, etc. first became cold, and I felt tired and sleepy; then my heart began to beat, my pulse became hard and quick, I got an insufferable feeling of uneasiness, a trembling (but without vigor), a weariness in all my limbs, then a beating in my head, redness of the cheeks, thirst; in short, all the old symptoms with which I was familiar in ague appeared one after the other. Also, those particularly characteristic symptoms which I was not to observe in ague-obtuseness of the senses, a

kind of stiffness in all the limbs, but specially that dull disagreeable feeling which seems to have its seat in the periosteum of all the bones of the body, these all put in an appearance. The paroxysm lasted for two or three hours each time and came again afresh whenever I repeated the dose, not otherwise, I left off, and became well".

After the brain storming experience, Hahnemann then began to search diligently all the records of medicine to find examples where the various medicines had been tested in this way. While searching, Hahnemann found cases of poisoning by various medicinal substances which he corroborated with the experiments he performed and see the disease picture thus formed. Initially he found record of Arnica, that it causes nausea, uneasiness, anxiety, peevishness, headache, oppression of stomach, empty eructation's, cuttings in the bowels, and frequent scanty evacuations, with straining. The symptoms matched with those of the epidemic dysentery in autumn. Arnica when given proves itself specific and cured disease without requiring any other medicine, in doses varying from four to fourteen grains, according to the age of the subject from which he concluded that Arnica is the specific remedy for the dysentery and cures by virtue of its power to cause similar illness[2].

Likewise, he examined parallels for the diseases that presented themselves in the records of the poisonings by medicines and endeavoring to determine the morbid states from these same records. When doubtful of the exact action of the drug, he used to swallow uncomfortably large doses himself to identify its pathogenetic action and observed symptoms that resulted[2].

After going on in this way for a while, he found that symptoms of poisoning were so vague and indefinite that he was never been able to arrive anything better than approximation to a certain choice of the specific drug. On the other hand, while examining the records of medicine he found so little of a positive nature concerning the pure actions of drugs. Now he became convinced that the whole business of testing medicines on the healthy human being had to be done and came to the conclusion that medicine must be tested on the healthy body before they can be properly applied in disease[2].

Hahnemann accordingly after viewing the subject in every possible light and examining carefully every method that had been proposed for ascertaining the action of drugs, recorded the effects of a medicine administered to a healthy person and came at last to the conclusion that the only way to do this is *"to test the medicines singly and alone on the healthy human body"* which foreshadowed his enunciation of one of the first principles of his new method of treatment-Homoeopathy which states *"that to cure diseases we must select medicines capable of causing similar diseases" is "in order to be able to practice successfully, we must ascertain what morbid states the different medicinal substances produce"*[2].

Acting on this thought, he wrote some earnest essays in **Hufeland's journal**, pointing out the glaring inconsistencies and absurdities of the old system, and showing clearly what must be done in order to render the art a certain and successful one, in place of the scientific deformities as it was. Hahnemann's assaults on an ancient medicine had rendered him thoroughly distasteful to his colleagues and met with derision from his colleagues[2].

Hahnemann conducted repeated experiments on himself and the sixty-four volunteers whose names are listed in his Materia Medica Pura. In total he investigated 99 remedies over a period of about half a century, establishing the method which has come to be known as 'Proving'. Several thousand symptoms were recorded in an index covering sixty-six individual medicines. His immediate followers, **Hering, Stapf** and others, carried out their own provings, but continued to turn to Hahnemann for advice. The first generations of Homoeopaths continued this tradition. During the 19th century provings multiplied in Germany, France, England and above all in the United States, under the powerful influence of Hering[4].

Hahnemann set himself to his task and in few years he was able to give to the world the tolerable picture of medicinal substances whose pure pathogenetic action he had ascertained by experiments on himself, his family and friends. He did not however give complete results but styled them in his *Fragmentary observations relative to the positive powers of medicines on the human body* published in 1805. Later in the same year he published his celebrated essay called *Medicine of experience* in which he detailed at length how experiments with medicinal substances are to be conducted in order to ascertain the pathogenetic effects[2].

Hahnemann's directions[5] (§105- §145)

Hahnemann summarized guidelines for proving in §105- to §145 of Organon of medicine.

1. Duty of the true physician is to acquire knowledge of instrument intended for cure i.e. to investigate the pathogenetic power of the medicines by employing it in healthy individuals. The pathogenetic effect of several medicines must be known in order to find the most suitable homoeopathic remedies for most of the natural diseases. (Sec.105-106)
2. In order to ascertain its pathogenetic effect, medicine should not be given to sick individuals as the symptoms of disease will be mixed up with the symptom of the medicine.(Sec.107)
3. The most natural way to ascertain the peculiar effects of medicines is by the administration of the medicines in moderate doses to healthy persons so as to

determine the changes, symptoms and signs are produced at the level of mind and body.(Sec.108)

4. The Primary and Secondary Action of Drugs - Hahnemann observed the following facts regarding the action of drugs in the healthy human beings:
   a. Administration of drugs in excessively largely doses leads to production of certain symptoms during the initial stage which are followed later by symptoms which were of an exactly opposite nature to those that first appeared.
   b. The first set of symptoms constitutes the primary actions of remedies, i.e., Proper action of the medicines on the vital force (Sec. 63) and the following set of symptoms are the reaction of the vital force of the organism, and constitute its secondary action (Sec. 62-67).
   c. Administration of Drugs in moderate doses does seldom or hardly ever produce the least trace of secondary actions. We observe only their primary action i.e. those symptoms where with the medicine deranges the health of the human being and develops in him a morbid state of longer or shorter duration.
   d. Administration of drugs in small doses never produces secondary action.
   e. It differs in case of narcotics (Sec. 113-114) which have been observed to produce secondary action even with moderate doses in the form of increased sensibility and a greater irritability which may be attributed to the fact that in their primary action narcotic medicines take away sometimes the sensibility and sensation, sometimes the irritability of the healthy organism.
   f. Among the symptoms of the primary action of drugs administered in moderate doses, there occur in the case of some medicines not a few which are partially or under certain conditions, directly opposite to other symptoms that have previously or subsequently appeared – which represent the alternating state of the various paroxysms of the primary action and are termed alternating action (Sec. 115).
   g. Referring to the symptoms produced by a medicine, it has been noted that (a) some symptoms are produced more frequently, i.e., in many individuals (b) Others more rarely or in few persons (c) Some only in very few healthy bodies. (Sec. 116)
5. Every medicine differs in its action on the human frame from every other. (Sec. 117-118)
6. In proving, it must be borne in mind that the strong, heroic substances are liable to produce changes in the health even of robust persons even in small doses. (Sec. 121)
7. The medicines of milder power must be given in more considerable quantities. (Sec. 121)
8. In order to observe the action of the very weakest, the subjects of experiment should be one who is delicate, irritable and sensitive persons free from diseases. (Sec. 121)
9. We should take care that the medicines we employ for our proving, are genuine and unadulterated. (Sec. 123)

10. Indigenous plants should be taken in the form of fresh juice mixed with alcohol; exotic vegetable substances in the form of powder, or tincture prepared with alcohol when they were in the fresh state and afterwards mingled with a certain proportion of water; salts and gums should be dissolved in water just before being taken. (Sec. 123)
11. If we can only get the plant dry, and if it be weak, they may be used for the experiment. An infusion of it may be made by cutting the herb into small pieces and pouring boiling water on it, so as to extract its medicinal properties. (Sec. 123)
12. The infusion thus prepared must be taken immediately while still warm as all expressed vegetable juices and all aqueous infusions of herbs pass rapidly into fermentation and decomposition without the addition of spirit by which all their medicinal properties are lost. (Sec. 123)
13. **Dietary restrictions of a prover (Sec. 125)**
    a. The diet of the prover should be strictly regulated. It should be as much as possible destitute of spices. It should be of a purely nutritious and simple character. Green vegetables roots and all salads and herb soups or anything which possess some disturbing medicinal qualities should be avoided.
    b. Young green peas, green french beans, boiled potatoes and in all cases carrots are allowable as the least medicinal vegetables.
    c. It is advised to avoid all medicinal and stimulating beverages.
    d. The subject of experiment must either be not in the habit of taking pure wine, brandy, coffee or tea, or he must have totally abstained for a considerable time previously from the use of these injurious beverages, some of which are stimulating, others medicinal.
14. **Requisites of a prover (Sec. 126)**
    a. He/she must be pre-eminently trustworthy and conscientious and during the whole time of the experiment avoid all over-exertion of mind and body, all sorts of dissipation and disturbing passions.
    b. He should have no urgent business to distract his attention.
    c. The prover must devote himself to careful self-observation.
    d. The prover should be in a good state of health.
    e. He must possess sufficient amount of intelligence to be able to express and describe his sensations in accurate terms.
15. Both male and females are required for experiments. (Sec. 127)
16. **Posology:** The medicinal substances do not exhibit their full amount of powers when given in crude state which they do when taken in high dilutions. (Sec. 128)
17. **Repetition:** (Sec. 129-132)
    a. The best plan of proving the medicines is to give the experimenter, on an empty stomach, daily four to six globules of the substance we wish to test, and continue this for several days, until an effect is produced.

b. It is best to commence the proving with the smallest dose and increase the dose more and more from day to day as not all individuals are affected by the medicines in equally great degree. Sometimes an apparently weak individual may be scarcely affected by moderate doses of a medicine known to be of powerful character while strongly enough acted on by other medicine of a much weaker kind(Sec. 129).

c. If the first dose administered is sufficiently strong than the order of succession of the symptoms and the period at which each appeared can be learnt which is very useful in leading to a knowledge of the genius of the medicine as then the order of the primary actions and that of the alternating actions may be observed in the most unambiguous manner (Sec. 130).

d. A very moderate dose often suffices if the prover is endowed with sufficiently delicate sensitiveness, and is very attentive to his sensations. (Sec. 130)

e. If, however, we do not care about the sequential order of the phenomenon, but merely wish to know the symptoms the drug produces, then the best plan is to give it every day in increasing doses. (Sec. 132)

18. When we experience any sensation, we should try to find what effect change of position, walking, the open air, the close room, by standing, sitting or lying the symptom is increased, diminished or removed, and whether it returns on again assuming the position in which it was first observed, whether it is altered by eating or drinking, or by any other condition, or by speaking, coughing, sneezing or any other action of the body etc. and to note at what time of the day or night it usually occurs in the most marked manner which will make peculiar and characteristic of each more ambiguous (Sec. 133).
19. All the symptoms a medicine can produce are not observable on one person, so we require testing on many, in order to ascertain all the symptoms (Sec. 134).
20. In order to know the complete pathogenesis of medicine, it should be proved in both sexes and people of various constitutions (Sec. 135).
21. All the phenomenon that arise during the action of this medicine, and must be registered as its symptoms, even though the experimenter has observed the occurrence of similar symptoms a considerable time previously, as arising spontaneously. (Sec. 138)
22. If the physician does not perform the experiments on himself, he should closely superintend the experiments of the person he employs for his purpose, but the best plan is for the medical man to make his experiments on himself; if he does so he gains a great advantage in the accuracy of the symptoms, in acquiring habits and power of observations, and his health, far from his suffering, in the long run will be benefitted by the trials. (Sec. 139)
23. The prover should write down all the sensations, sufferings, accidents and changes of health he experiences at the time of their occurrence, mentioning the time after the ingestion of the drug when each symptom arose and, if it lasts long, the period of its duration. (Sec. 139)

24. The physician should look over the report in the presence of the prover immediately after the experiment is concluded. If the trial lasts several days, physician will check the report every day while everything is still fresh in the memory of the prover so that he can question him about the exact nature of symptom and write down the more precise details about the symptoms prover is experiencing (Sec. 139).
25. If the prover is illiterate and cannot write, he should daily approach physician and should narrate his symptoms. The physician should note down every alteration narrated in the language of the prover. (Sec. 140)
26. In the investigation of the medicinal symptoms all suggestions and leading questions must be carefully avoided. (Sec. 140)
27. The best proving is the one which the healthy, unprejudiced and sensitive physician institutes on himself. (Sec. 141)

Action of the drug on human being as per Dunham[6]

According to Dunham, the drug has a 3 fold action on the human beings. These actions of drug are mentioned below.

1. **Chemical:** It depends on chemical affinity which exists between drugs and the tissues of the body and independent of vitality.
2. **Mechanical** (or Revolutionary): It consists chiefly in violent efforts on the part of the organism to eject from its cavities the offending substance.
3. **Dynamic:** It is contingent upon vitality and resulting from the relations of the peculiar properties of drugs to the susceptibilities of the living, healthy organism.
   - **A. Generic:** Such as are common to all the members of a certain class of drugs and which serve to distinguish between different individuals of the same class. e. g. Vomiting and diarrhea of Arsenic, Cuprum, Veratrum etc.
   - **B. Specific:** Such as results from the dynamic action of the drug and peculiar to it. They serve to distinguish a given drug from all others.
     - **a. Central symptoms:** Appears especially after the drug is taken, is generally the result of *comparatively large doses* and in the case of many drugs, is confined to the **alimentary canal and to the organs immediately connected with it.**
     - **b. Peripheral symptoms:** Appear more tardily, are generally the result of comparatively small doses, taken repeatedly or allowed to act without interruption for a long period and appear in the **bones, skin glands** etc., and in the co-ordinated phenomena of life – often manifestation of a dyscrasia or cachexy.

N.B. Doses which produce central symptoms do not generally produce the peripheral (or at least not until after a long period has elapsed) and vice versa.

e. g. Arsenicum alba

a) In certain doses it develops chemical and revolutionary effects.
b) In smaller doses it develops generic dynamic symptoms.
c) In still smaller doses – it develops specific dynamic symptoms of central variety.
d) In yet smaller doses – it develops specific dynamic symptoms of the peripheral variety. (Those of so-called gradual poisoning)

Piper's Direction[2]

Among those who have written on the subject of physiological experimentation, and who have endeavored to establish fixed rules for its conduct, one of the most explicit and minute is **Dr. G.O. Piper.** Dr. Piper strongly advises that all homoeopathic physicians should institute physiological proving on themselves and he bears out Hahnemann in his assertion that the health is rather improved by them.

Below is the brief resume of his excellent papers on the subject.

1. In order to conduct proving efficiently, dispossess your minds of all preconceived ideas respecting modes of cure, primary actions, secondary actions etc. (Remove bias)
2. Experimenter should not know the substance he is taking. (Blinding)
3. It is absolutely necessary to prove one and the same substance on many different persons in order to obtain a thorough knowledge of its sphere of action. (Sufficient sample size)
4. It is of great importance to ascertain the duration of action of medicine. (Noting the appearance and disappearance of symptom)
5. Self-observation by the prover for a month before commencing to prove medicines during which he should note his daily sensations and carefully register all the abnormalities he observes and if any of these recur during the period of his experiments they should not be noted down as symptoms belonging to the medicine. (Self observation before commencement of proving)
6. The prover should also carefully attend to the various seasons of the year, and not register as an effect of the medicine any symptoms that appear spontaneously at any particular season. (Any change in routine, environment etc.)
7. Drinkers of wine and coffee should begin by leaving off their favorite beverages and smokers by abandoning their customary weed that will increase the susceptibility for the medicine and hence medicinal symptoms will occur with greater precision. (Avoid any stimulant on things with medicinal properties)

8. Those persons are probably the best for undertaking physiological proving who are not in the habit of indulging in the use of any medicinal substance, but who can conduct a proving from beginning to end without having to make any alteration in their diet and regimen.
9. The best time for taking the medicine we wish to prove is just before going to bed at night. The secret operation of the medicine will then go on undisturbed while the prover is asleep, and the first active manifestations of abnormal action will be observed on awaking in the morning. To obtain the full action of the drug, it should be tested in the morning also. (Best time for taking medicine)
10. Posology:
    a. At first the drug should be taken in small doses, and the dose increased or doubled every day.
    b. One single very large dose certainly produces greater effects, but it may prove injurious to the health.
    c. A moderate or even a pretty large dose seems to have scarcely any perceptible action; only a few symptoms are developed during the first few hours.
    d. Large doses are often rejected by the organism very rapidly, and do not penetrate the system and hence commencing proving by taking medicine in dose of one-tenth of what he calls the lowest normal doses.
11. Repetition:
    a. There should be an interval of at least twenty four hours between two doses.
    b. In case of drug, whose action is shorter than 24 hours, a repetition at another period than the twenty four hours must disturb what there is of a typical character in the reaction.
    c. In the case of drugs that act for a longer period than twenty four hours causes no disturbance, but merely an increase of its action.
    d. If after several doses no more symptoms make their appearance, we should then resort to the smallest doses, and after a few days give suddenly a large dose.
    e. When objective symptoms make their appearance the drug taking should be immediately stopped; on the disappearance of the symptoms, if within twenty four hours no new symptom appears, a somewhat larger dose of the drug should be taken, and the daily dose increased until some other objective symptom appears.
    f. In the evening of the same day if the symptom occurs, a pretty large dose should be taken and the effect watched, undisturbed by any fresh dose.
12. If, notwithstanding the observance of these rules, no particular effect should ensue from a decidedly powerful medicinal agent, the following method should be adopted.
    a. No supper (dinner) should be eaten, and whilst the feeling of hunger continues a pretty large dose of the drug should be swallowed.

b. If nevertheless nothing occurs, then the prover may conclude that he is insensible to the action of that particular drug.

13. Abnormal states of the intestinal canal may check the development of many medicinal diseases. A person liable to acidity of the stomach will be insensible to the action of a number of vegetable substances. On the other hand the abnormal or unhealthy condition of an organ – for instance, the lungs – may increase enormously the action of a drug that has a special affinity for it.
14. In such a case it may frequently happen that curative action ensues, if the drug be a specific remedy for the particular affection under which the person labors, and the records of physiological provings are not without occasional instances of this kind.

Idiosyncrasies on the part of the provers are of importance indeed. Hahnemann also considers that the symptoms caused by such idiosyncrasies should be regarded as medicinal symptoms.

Schron Remarks[2]

Schron is of opinion that the proving of medicines is equally important for all the three methods i.e allopathy, antipathy & homoeopathy of treatment, the utility the antipathist and the all opathist could derive from them is small indeed, in comparison with that they offer to the homoeopathist.

The objection often made on our experiments on the healthy are impossible, as there are no absolutely healthy persons, is absurd, as for all purposes relatively healthy individuals are sufficient, and we do not seek to restore patients to a state of absolute but of relative health. The symptoms that occur in each person by virtue of his weak or unhealthy organ will not disturb the purity of the proving, if several persons are engaged in the trial of the remedy; for symptoms produced by this cause will then be easily detected and omitted from the list of the pure effects of the medicine.

1. Both sexes should be employed in provings.
2. With respect to the age of the provers, it is desirable to have those who are able to give a distinct and lucid account of their symptoms. If we employ only grown-ups, then we shall not be able to ascertain the effects of medicines on the thymus gland or on process of the first dentition. In cases of infants we have to content ourselves with purely objective phenomenon.

3. He is opposed to Hahnemann's later idea to prove all medicines in 30th dilutions and refers to the proving from larger doses of the medicines as much more satisfactory nature.
4. With respect to the arrangement of the provings, he was of the opinionthat each proving should be preceded by an introduction, stating in order in which the symptoms appear and giving a sort of general pathological effects of the medicine.

Griesselich's Remarks[2]

The relation of susceptibility shall be there for the prover to be affected by drug to be proved. Susceptibility gets blunted if the prover has taken the drug for certain length of time, for which it is advisable to wait for the same length of time without taking any medicine and begins again with very small dose. It is not advisable to perform such physiological provings in rapid succession; for even a different drug, if it have any action in common with the one that just been proved, will often stir up the organism to reproduce a miniature representation of the symptoms caused by the other drug, if taken too soon after the first one.

He warned against proving medicines in tincture, where it is requisite to obtain an action, to take as many as fifty, hundred, two hundred or more drops; for vehicle of the medicine, the alcohol, will often disturb the pure effects of the drug by its own pathogenetic power in such quantities, and it is an undoubted fact that alcohol has an antidotal relation to many drugs and it is an undoubted fact that alcohol has an antidotal relation to many drugs, therefore it is preferable to take drug in freshly expressed juice of the plant, as a powder, in water or otherwise, or in the form of carefully prepared infusion and decoction.

Dr. Hering's Remarks[2]

Dr. Hering of Philadelphia speaks very approvingly of Hahnemann's recommendation to prove medicines in globules of the 30th dilution and thinks that not only should all medicines be proved in that dilution, but that those medicines which have already been proved in other doses should be re-proved in globules of the 30th dilution/potency. He furnishes us with several substances proved in this manner. Thus, for instance, the following was the way he took to prove the Theridion curassivicum, or poisonous spider of Curacao. From a bottle of rum, in which several of these insects had been put, and which had stood for a year, he took a drop and potentized it up to the 30th dilution. With this dilution he moistened some globules, and gave to the prover only one dose of the drug, consisting of three to six globules. The results, as may readily be imagined, were not very great. **Dr. Hering is**

also an advocate for proving medicines in persons not perfectly healthy. He proposed proving the medicines in the so-called high dilutions, 400, 800, 1000, 2500, etc.

The proving of remedies in globules of the 30th dilution seems to have likewise captivated the fancy of a society of homeopaths in Thuringia, who formed themselves into a body of provers, adopting the following rule: "That, in order to obtain pathogenetic symptoms, only the 30th dilution should be employed for conducting provings on the healthy." No account has ever appeared of the labors of this bold society.

Dr. Drysdale's Remarks[2]

Dr. Drysdale, the father of the British Homoeopathic Association published his classic paper of 1843 on the proper method of testing medicines on healthy humans in British Journal of Homoeopathy, Volume1.[7] He justly lays a stress upon the necessity of not taking too large doses of the medicine to be proved, as thereby we should run the risk of producing its evacuant or chemical and not its specific effects, which are best developed by small doses.

Trinks' Remarks[2]

Trinks, in the introduction to his Materia Medica, has some excellent observations on the proving of medicines. He joins with Rau in denouncing the proving of medicines in the form of high dilutions, and objects to admitting into the Materia Medica symptoms developed in patients while taking a course of some strong medicine.

Dr. Curtis' Remarks[2]

Dr. Curtis of New York, in a lecture delivered before the Hahnemann Society of that city, alleges that we should perform experiments on the healthy to ascertain the effects of deprivation of the substances that enter into the normal composition of the organism. He terms these trials negative trials or provings.

Dudgeon's Remark[2]

- Only those substances should be proved having a decided action. It is pointless to prove substances having no medicinal properties. For example: **Dr. Mure** has wasted his time and our patience in attempting to prove such ridiculous substances as the triturated skine of a dolphin, the diseased potato, guano, the common louse, etc.,

which is surely a work of supererogation, when there are so many powerful medicines as yet altogether unproved, or only very imperfectly proved.

- Each medicine should be proved on persons of various *age, temperament, and sex,* and we can't hope to obtain anything like a perfect knowledge of any substance unless the number of provers has been considerable.
- Genuineness and purity of the medicinal agent we employ should be prime requisite, and patient endurance and prolonged attention on the part of the prover are indispensable to the success of the trials.
- The records of cases of poisoning do not in general throw a very satisfactory light on the pathogenetic action of the drug, for in such cases it has generally been swallowed in such large doses as to cause more of its general or irritant actions than of its specific characteristic effects.
- The prover must possess the **proper balance in function** and be in a normal, healthy state, so that we can estimate and weight the amount of the disturbance caused when we deliberately upset the balance of health.
- Patient endurance and prolonged attention on the part of the prover are indispensable to the success of the trials.
- Another essential quality of the prover is his **sensitivity**. Sensitive provers are valuable asset for the proving as they bring out the symptoms found rarely or in few persons, some only in very few healthy bodies.
- The Susceptible prover makes the best prover as they develop the peculiar, rare and characteristic symptoms of the drug yet those who are less susceptible cannot be rejected.

The method of testing medicines on the healthy human being was widely prevalent all across the world evident by endeavor of professionals present at that time.

Professor **Jorg of Leipzic** founded a society for the purpose of proving medicines. He made confession about the wretched state of Materia Medica and proposed instituting experiments on the healthy to endeavor to ascertain action of medicine but on the contrary he was against the method of experimentation of Hahnemann and called their therapeutic rule a delusion. Jorg sought to obtain from his proving indications for the employment of medicines agreeably to the principle Contraria Contrariis, and finding, for example, that nitre was a powerful irritant, he said that it was decidedly a wrong medicine to use in pneumonia, though the experience of his own school was entirely in favor of its utility in that disease[2].

An attempt was made in 1828 by **Dr. Von Wedekind** to induce his brethren to prove medicines, in order to lay a sure foundation for the Materia Medica; but his eloquence was

of little avail to overcome the apathy of his brethren on that subject and with the exception of a miserable attempt on the part of a few to swallow some doses of Hepar sulphuris and Colchicum, nothing resulted from Wedekind's recommendation. So also **Professor Martin** of Jena attempted in 1844 by foundation of a society for the purpose of making physiological experiments with medicines, but this too came to naught[2].

A bolder and more sustained effort was made a few years ago by **the Society of Vienna Physician**s to prove remedies on different individuals but the committee who had the drawing up of the report of the results of the trials cut down the symptoms of each prover and recorded symptoms common to most of the experimenters. The experiments are mentioned in the British Journal of Homeopathy, Vol. vi. Pg. 265.

Among allopathic writers who have spoken favorably of physiological experimentation **Jonathan Pereira** was one who said in his work on Materia Medica, that the homoeopaths are perfectly right in summing that the study of the effects of medicines on the healthy body as it is the only way by which the pure pathogenetic action of drugs can be ascertained as when we administer our medicines to patients the symptoms of the disease present become mixed up with those that the drug and the latter can seldom be distinguished with any degree of clearness or certainty[2].

In the medical section of the **French Scientific Congress**, held at Strasburg in 1842, **Professor Forget**, President, the following resolution was passed

"The medical section is unanimously of opinion that experiments with medicines on healthy individuals are, in the present state of medical science, of urgent necessity for physiology and therapeutics." The urgency of the necessity was not, however, so great as to induce the respective members to institute such experiments on their own precious persons[2].

In like manner **Dr. Forbes**, in his onslaught upon homoeopathy, indicates as one of the desiderata of medicine, *"to reconsider and study afresh the physiological and curative effects of all our therapeutic agents, with a view to obtain more positive results than we now possess."*

And so with many other clear-headed allopathists, from Haller down to Forbes, indicated the way, but not trod it themselves. Knowing well what work there was to be done, they have still continued enthralled in the trammels of a degrading and antiquated routine without making an effort for their release.

Whereas, in Austria, from 1842 onwards the Homoeopathic society of Vienna undertook numerous reproving and established new pathogeneses of medicines including Argentum nitricum, Kalium bichromicum and Coccus cacti.

Fortier-Bernoville has described the proving scene in America in the last century[4]:

"In America, the method become very refined and, thanks to the dedication to the groups of interested and highly motivated students, proving on the healthy continued on a large scale. In the Homoeopathic colleges, young people voluntarily intoxicated themselves and remained for days or sometimes several weeks in their rooms, or took to their beds. They noted all the symptoms they experienced. On comparing the symptoms reported it was possible to rank them according to their frequency. This was the zenith of proving."

The fruits of the great research effort by Hahnemann were published by **Timothy Allen** in 1874, in his twelve-volume encyclopedia which contained numerous reprovings as well as new pathogenesis. The names of the provers are indicated, along with the doses used in each case. The number of volunteers is sometimes very large, the greatest being to 226 for Arsenic. The doses employed varied from sub toxic material doses up to the 30C. In 1906 in the United States, concentrations from the mother tincture to the 3X were used in the proving of Belladonna carried out by **Bellows**. During the same period, also in the USA, Kent and his school were using the 30C in their reprovings[4].

The technique of proving was gradually improved largely by the introduction of new methods of experimentation supplemented by instrumentation and laboratory investigations. The single-and double-blind techniques which have subsequently become the norm in pharmacological experimentation were discovered and developed by Homoeopathic researchers which is evident from the fact that even before the death of Hahnemann, certain workers were performing pathogenetic experiments in which the nature of the substance under study was unknown to the volunteer also witnessed in the monograph on Aconite, published by **Gerstel**:

These studies were performed in the first three or four months of 1943. The volunteers (most of whom were doctors) were all unaware of the name of the medicine being studied. The doses were particularly high, going up to definitely toxic levels. The doses were increased gradually from 20 to 40, 80 and 100 drops of the tincture; two of the provers even finally took 200 and 400 drops (of Aconite tincture).

The report on these provings, contained in a hefty 665-page volume, shows that certain subjects did not receive placebo at all, other only in the first few days while others received placebo only in the final days of proving according to the method now known as cross over system. Cross over method compares the response of same subjects to two different substances (intra subject comparison). This method makes it easy to distinguish placebo-resistant subjects.

In the United States this technique was perfected by the use of placebo in proving. In a reproving of Belladonna carried out two in Boston in 1906, one by the American Homoeopathic Ophthalmological and Otorhinolaryngological Society, three under the direction of Professor Howard P. Bellows, the general instructions for the conduct of the proving specify the use of the double-blind technique[4].

Modern provings are conducted in the same spirit. **F. Lamasson**, former president of the International Homeopathic Medical League has on many occasions stressed the need to improve our proving methods to keep pace with progress in instrumental and laboratory techniques but without ever forgetting the subjective, psychic and sensory symptoms[3].

Lamasson has discussed the experimental conditions which can be applied in modern provings. He insists on the necessity of single or double blind technique, on varied subjects, using a range of dilutions and at different times of the year[3].

It is only in such conditions that one can take account of the full action of a given medicine, in winter, autumn, or summer, in dry weather or wet weather. All the modalities provoking or relieving symptoms should be carefully noted in the course of the proving. It is essential that attention be directed to all the variable concomitants to the appearance and disappearance of symptoms[4].

Such was the history of the drug proving. As evident from above, numerous experiments were undertaken, copious work was done which came with the arousal of abundant theories. But one theory that existed and is still existent is the theory of drug proving on healthy human being idea of which was originally enunciated by Sir Albert Von Haller but was placed in front of the medical fraternity by Hahnemann proudly known as the “Father of Homoeopathy”. We are on way to develop a better method of drug proving, taking its merit and removing its flaws….path is long and improvement has no limit.

References:

1. Close Stuart. The Genius of Homoeopathy.
2. Dudgeon R. E. Lectures on the theory and practice of Homoeopathy.
3. Nagpaul VM. Drug proving and Central Council for Research in Homoeopathy. The British Homoeopathic Journal, 1987; 76:76-80.
4. Demarque D. the development of proving methods since Hahnemann. The British Homoeopathic Journal, 1987; 76: 71-75.
5. Hahnemann S. Organon of Medicine.5th& 6th edition. India: B. Jain publisher; 2010.
6. Dunham C. Homoeopathy, the Science of Therapeutics. India: B. Jain publisher.
7. Stephenson J. British Homoeopathic journal [internet], 1961; Volume 50[2]:129–131. Available from: www.sciencedirect.com. DOI-10.1016/S0007-0785(61)80030-6.

Methodological Aspects And Their Evolution

Research is the search for knowledge or a useful investigation without any prejudices and with an open mind. Research methodology is the mantra of achieving accuracy and exactness when it comes to facts and knowledge about something.

The uniqueness in science of homoeopathy is that the knowledge and complete information about the therapeutic use of a drug is gathered by proving the drug on apparently healthy volunteers, apart from the toxicological, accidental and clinical findings. These proving or the symptoms generated during proving are of utmost importance as these are the pillars for homoeopathic practice.

Without accurate proving all prescribing indications are bound to be vague at best, and pure fiction at worst. There is no other way to predict the effect of any given substance as a remedy with any degree of accuracy, and the use of signatures, toxicology or fancy ideas cannot approximate the precise knowledge gained by a thorough proving[1].Thus for achieving accuracy and exactness in Drug Proving Research, the research methodology adapted should be of high quality.

Since inception, homoeopathy has presented itself as a medicine of experimentation. It accomplished this well before experimental pharmacology even began to be structured. This explains why the methods developed from the 18th century through the 19th century in homoeopathy were the most pertinent for that period and the findings obtained by these methods were confirmed by over century by reproving and validated by practical experience[2].

But it was also quite evident that the methodology of drug proving followed during that time was not of high quality and needed reform. Even with the best of scientific intentions Hahnemann has inadvertently introduced bias which results in unexpected outcomes. Hahnemann could not have anticipated some of the systematic errors that might result in unacceptable results and in unreliability and overestimation of medicine effects in general.

The main flaws among which is absence of control group which is a cardinal sin that increases the likelihood of non-medicinal symptoms and false positive results. The well-known friends and lecture audiences were used as volunteers (‘believers’). These volunteers informed that they were recording all complaints, symptoms and changes observed during action of the medicine even if the person had noted similar symptoms in himself a considerable time before, absence of masking in volunteers or in trial supervisors, sudden

prohibition of coffee, tea, spices and alcoholic drinks (or medicinal drugs), vague definition of healthy volunteers, inclusion of non-healthy volunteers, no random assignment of subjects. Taken together these flaws are sufficient to provoke serious doubts concerning the validity of the specific pathogenetic symptoms reported in Hahnemann's writings[3].

Recent developments in proving suggest that even Hahnemann can be subjected to appropriate updating[4]. The revival of proving has been witnessed in 25 years with a synchronous effort to formulate more explicit rules for the conduct of proving. Without overturning the detailed rules established by Hahnemann, the technique of proving was steadily improved, largely by the introduction of methods supplemented by instrumentation and laboratory investigations.

In 2007, a systematic review[5] was published in six languages (English, German, Spanish, French, Portuguese and Dutch) in which author have critically analyzed every aspect of drug proving conducted from 1945 to 1995. The analysis revealed many flaws in the conduct of drug proving in terms of study design, quality of reporting, ethical aspects, selection criteria of participants, medicines and rationale, study design, pathogenetic effects of the medicines, safety issues, and methodological quality of the trial. The article highlighted that most of the HDP's were of low methodological quality.

Many of the provings conducted in the 20th century lacked the refinements of earlier provings. We have very less number of in-depth proving and the Materia Medica is mainly composed of partial provings or toxological reports. Numerous remedies in **Boericke and Synthetic repertory** have partial/incomplete proving that brings out the incomplete picture of the remedy and hence partly suits the similimum.

It was found that there was great heterogeneity among studies regarding methods and outcomes description. The quality of reports was in general poor, and much important information for methodological analysis and reproducibility of HPTs was omitted from many reports. Complete description of the source of medicines was not given in many publications. Reports did not state the age and gender of volunteers. Little information on volunteers' characteristics was reported. Some studies of apparently good design did not describe adequately their methods and outcomes. The Quasi experimental designs, without control groups were the most common type of study, particularly before–after studies, followed by trials using placebo parallel group. The studies included very small sample size. Duration of the study was very small. Use of placebo control by volunteers was highly variable, a placebo run-in phase preceded 16% of trials, and pre observation period without placebo was reported in 14% of trials, 3% had two run-in phases with and

without placebo. Placebo was described as indistinguishable from verum in 21% of reports. Inclusion criteria were not mentioned in 78% of reports. Most studies were of flawed design, mainly absence of proper randomization, blinding, placebo control and criteria for analysis of outcomes. The sequence generation was not described and it was difficult, from reading the reports, to clearly separate concealment of allocation from masking procedure. Post-trial verification of blinding was not reported in any publication.

Drysdale has very well illustrated the character of Hahnemann's records or proving, and demonstrated the necessity that exists for re-provings, such as those undertaken by the Austrian Proving Society, when he compares the Hahnemannian schema to the symptoms of any disease discovered from their natural connections, and arranged in a completely artificial manner, according to their anatomical schema[6].

Watzke also stressed on the necessity for making a revision of the Materia Medica is not so much in the matter that has been communicated by Hahnemann as the form in which he has arranged the results of his observations and toil. The materials Hahnemann collected are unfortunately not arranged in their natural and physiological connection, but are arranged in strained artificial schema, wherein the practitioner, unless he had himself assisted at the proving or unless he possessed Hahnemann's own wisdom, is too frequently at a loss to perceive the exact meaning and value of the fragmentary and unconnected symptoms before him[6].

From the above, it is not possible to answer the main question posed in HDPs: Do homoeopathic medicines in high dilution, cause changes in healthy volunteers? If they do, how can we discriminate the effects due to the substance tested from incidental effects?

This highlights the need for methodological improvements to ensure that the HDPs are rigorous and their result can be trusted which lead to the emergence of modern methodology of finding the pathogenetic effect of the substance in healthy volunteers which Hahnemann best named it as "*Prüfungen*"[7].

Pre-requisites for Drug Proving

1. **Drug substance:**
   The prime requisite is genuineness and purity of the medicinal agent.Thedrug substance to be used in proving should be pure free from any adulterationor mixtureof any other drug substance and must possess all the properties in active state. In **Section 122**, Hahnemann stated that the purity, genuineness and energy of the drug

substance should be thoroughly assured on which depends the exactitude of the whole medical art.

Council has its own drug standardization cell responsible for the evaluation of the homoeopathic drugs in respect of their pharmacognostical, physico-chemical and pharmacological profiles which sets bench mark standard for every drug which is included in HPI. The medicinal substance used in drug proving is procured from GMP certified pharmaceutical company ensuring the genuineness of the medicinal substance.

2. Potency and Dosage:

Posology in drug proving has been well documented by Hahnemann in Sec. 129 of Organon of medicine. He states that it is best to commence proving with the smallest dose and increase the dose until an effect is produced as every individual has different sensitivity. According to **Hahnemann**, the single dose of 30C is preferable because it allows primary and secondary action to develop in pure sequence. **Kent** insisted that the remedy is administered until symptoms begin and then stopped. On the other hand **P. P. Wells**, a contemporary of Hering states that when drug has been introduced to the life force, it should be left alone and should not be disturbed by any other medicinal agent until sufficient time has been elapsed for the original dose to exhaust its action so that its true character may be fully revealed. If any symptoms occur, no further dose should be taken. Well remarked that a single dose or a single collective dose should be given in order to observe the natural order of appearance and duration of symptom. This clarity is obscured if the remedy is given injudiciously as it will lead secondary reaction. By then the vital force is opposing the medicine.Hence it is obvious that repeating doses continuously is of lesser value[6].

According to Drysdale[10], the simplest form of administration should be adopted i.e. to begin with small dose and increase it gradually till distinct symptoms appear, most useful doses are the one which are just sufficient to produce distinct symptoms chiefly primary symptoms. He suggested that it is desirable to repeat the proving on a large number of individuals in order to avoid the admission of accidental symptoms and obtain a complete view of the action of a medicine as all individuals are not susceptible of all the effects of a medicine.

As per the guidelines proposed by ECCH[9], 2-3 potencies should be used to explore the subtle aspects of the remedy and dosage method may be determined prior to beginning of proving. The committee advocates the administration of **One to six doses** (up to three times a day) and stopping of medication as soon as clear symptoms

develop. As per the guidelines of **ECH**[7], Homoeopathic preparation should be given in C12 or C30 potency as the toxicity of these preparations are considered to be extremely low. The description of the dosage regimen of the investigational product(s) including the description of the dosage form, storage, packaging and labeling of the investigational product(s) should be given prior to initiation of proving. According to guidelines of **HPUS**[12], attenuations greater than 30C and lower than 12C should not be used. HPUS recommends dosing frequency of test medication greater than three times daily with non-repetition of doses and has warned against the continuation of medicine to stop test medication in subjects with no discernible response after 1 week.

CCRH introduced plentiful changes in the protocol in terms of administration of medicine, repetition of medicine etc. Initially, there was no definite dosage regimen and determination of the dosage depended on the nature of the drug e.g. some drugs like *Abroma augusta folia* was proved in 200,30, 6, mother tincture whereas *Kali muriaticum* was proved in 1000C, 200C, 30C, 12x, 6x to 1x. The basic concept followed was if the first dose of medicine produces no effect, enough time should be allowed to be sure that the prover is not sensitive to it, the next best thing to do is to create sensitiveness to it, which may be attempted safely by administering the drug thrice daily for a period of seven days unless the symptoms arise. The drugs were given in order of descending potency followed by in order of ascending potency however some drugs were given in ascending potency and then descending potencywith no definite washout period.Control group comprising of 1/3rd of the total prover remained on placebo throughout the proving. All the provers received placebo during the initial period of proving to rule out any symptoms arising from personal idiosyncrasies. Few proving were conducted as cross over trials in which the control group was given drug and the verum group was put on placebo in the second phase of the trial. In 2007, CCRH protocol underwent further revision wherein **56 dose** regimen was proposed and the drug was given in descending potency starting from 200 followed by 30 and 6 respectively. For each potency the drug was administered in 4-6 globules, four times a day for fortnight with awashout period of 14 days and rest period of 7 days. The protocol was again improvised in the year 2010 which 12 dose regime was followed in which 4-6 globules of the coded drug were given four times a day daily for 3 days with a rest period and wash out period of 30 days. Another revision in the protocol has been done in 2014 in which four potencies (6, 12, 30 and 200) will be taken up for proving and the doses will be 12 for each potency but as per §129 the number of globules will be increased from 4 globules on 1st day to 8 globules on 2nd day and 12 globules on 3rd day.

3. **Proving Master or Investigator:**

According to **J. T. Kent**, Master prover will be the one responsible for the overall conduct of proving like procurement of medicine, allocation of the subject for proving. He/she is supposed to monitor the drug proving programme and should have knowledge about every aspect of drug proving and should be a good observer as he has to assess the prover at every stage of proving.

As per European committee for Homeopathy[8] (ECH) Guidelines for Homeopathic Drug Proving (HDP):

- **Investigator in HDP** (In homeopathic literature also referred to as: Observer; Supervisor; Proving doctor): A person responsible for the direct contact with the volunteer(s). He reviews the diaries (journals) together with each volunteer in order to clarify and if necessary amend the symptoms.
- **Principal Investigator** (In homeopathic literature also referred to as: Master Prover; Coordinator; Director of Proving): Is responsible for the conduct and organization of the Homeopathic Drug Proving following GCP Guidelines, e.g. contact with Independent Ethical Commission and the report of severe adverse events, storing of study documents.

As per guidelines of **European Council for Classical Homeopathy[9] (ECCH)**, the involvement of supervisor is mandatory as it help in determining the initial symptoms as careful observation and sound judgment are vital to observe the development of the initial symptoms before taking further doses as they may confuse the symptom picture and even pose a safety hazard. The Council is carrying out Drug Proving Research Programme at seven centers across India. A proving Master /Site Investigator is appointed at each center who will be in direct contact with the provers and will observe and review the day-to-day changes in form of symptom(s)/sign(s) noticed in them. Apart from the Proving Master, one person from the faculty of the Homoeopathic Medical College is appointed as the Proving Associate who will work in close association with the Proving Master.

4. **Prover/Volunteer:**

In section 126, **Hahnemann** has identified the requisite quality of the prover i.e. the provershould be healthy, trustworthy, intelligent and should keep himself away from all distraction, must devote himself to careful self-observation. Whereas, **Dudgeon[6]** was of the opinion that the prover should be healthy, sensitive and susceptible to drug substance as it will help in bringing out the peculiar characteristic symptoms with endurance and attentiveness as another essential attributes of the prover. According to

Drysdale[10], in order to extract maximum effect of the medicine, it should be tested on individuals of all ages, of both sexes, of all temperaments which go in agreement with views of Hahnemann (Sec. 135). Further, he advocates that before commencement of the experimentsa pre observationperiod of a week or ten days should be kept in which each prover should observe himself accurately. **Dr. Nagpaul**[11] in his article published in British Journal of Homoeopathy advised to include minimum of 20-30 subjects at one center including 25-30% of controls. The subject should be of age group between 18-45 years, should be well acquainted with homoeopathic methodology.

As per the guidelines of ECCH[9], ideal proving group should be a balanced combination of participants in terms of gender, age and knowledge of homoeopathy. Participant should be competent persons over 18 years of age. Participants must be at least 2 months clear of any previous homoeopathic remedy with no significant changes occurring in the past 3 weeks with no history of any kind of drug intake (medical or 'pleasure', birth control pills, HRT etc.), should have no mental and chronic physical pathology.

As per the guidelines defined by ECH[8],volunteer should be healthy in the sense of being free from important physical or psychic symptoms and does not consider need for medical treatment. Before the start of the conduct of the study the ethnic origin volunteers should be documented as there is a great influence of location of a proving in the proving symptoms. In multicenter trials, we should specify the number of enrolled subjects projected for each trial site, reason for choice of sample size. In the selection criteria, the one who have taken contraceptive pills in the past three months will not be included in the study. The safety parameters need not be defined as in HDP we don't focus on single parameters like blood pressure, pain or metabolic changes etc. All changes on the physical, psychic and mental levels should be observed.

On the other hand, **Homeopathic Pharmacopoeia Convention of the United States (HPCUS)**[12] recommended minimum sample size of 20 subjects comprising of individuals between 18 years to 75 years of age, including male and female. However, the subjects with any 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 proving substance, subjects under current homoeopathic treatment within the past 30 days should be excluded from the study.

At the time of inception of **Drug Proving Research Programme** in **CCRH**, there were no standard criteria in terms of number and age of the prover. Every monograph dictates a different story. The number of provers included in the proving varied from 15 to 30 prover comprising of both sexes. Age group of the volunteers was also not consistent; it differed in every proving. In 2007, the drug proving protocol of CCRH was revised in which certain modifications were made like identification of sample size consisting of 15-20 apparently healthy subjects (provers) including both sexes between the age group of 18-50 years at one center in which 30% are controls. It is customary to provide certain period for self-observation to the prover in which he will deeply observe his ordinary habits so that he can minutely observe any deviation from health after taking medicinal substance. In 2014, further modifications have been considered.

5. **Surrounding and environment of the prover:**

The prover must be surrounded by normal surroundings, so that the drug can express its action under conditions and circumstances normal to the prover, that any deviation from normal in the prover's condition cannot be attributed to different circumstances and conditions of his life, but directly to the action of the drug.[7] There should be no change in the atmosphere of the prover otherwise it will be difficult to judge genuineness of the symptom whether it is because of the medicinal substance or change of the atmosphere. That may be possible reason why ECH[8] in their guidelines have debarred those volunteers having plans for migration from their place. According to **Drysdale**, we must enquire about the change of symptom with respect to different circumstances. ECH[8] and ECCH[9] has recommended that it is imperative to document the location of the volunteers before the start of the conduct of the study as there is a great influence of location of a proving in the proving symptoms. **Hering** was also of the opinion that volunteers living in some distant place report strikingly different symptoms from the symptoms of the volunteers living at same place.

CCRH is enrolling the volunteers from the homoeopathic medical colleges near the centers where the Drug Proving Research Programme is undergoing. The volunteers are given instructions to note down any deviation in their routine in relation to diet, environment, sleep pattern, untoward incidence etc. as this may lead to appearance of symptom(s)/sign(s) not because of the drug substance administered for proving.

6. **Ethical issues:**

Kent preferred to err on the side of caution. We should be aware that in a proving our first duty is to protect the prover. Repeating the remedy indiscriminately may not be

safe for the prover. In the scorpion proving some people just continued to take remedy, regardless of instructions and developed persistent and unpleasant symptoms. It is the duty of the investigator to closely observe and check every prover if he has developed any symptom as it has been observed that prover sometimes continue taking medicinal substance even after appearance of symptom as they develop and are grafted into the constitution.

Another point **Kent** emphasizes is that one should never stop a proving and restart again. One might stop for a week thinking nothing is happening and then take a few more doses. When the remedy is repeated an intermingling of effects occurs, with the possible danger of grafting symptoms onto the constitutions. The remedy may be repeated only if one is sure that the effects of the first proving has been finished[10].

The guidelines **ECH[8]** involves calculation of risk before the conduct of proving, public availability of the designs of the study specification of safety parameters, informing the volunteers about the objectives, potential risks, inconveniences and benefits of the trial and signing consent form before the beginning of the Homeopathic Drug Proving, reporting of adverse events, adverse drug reaction and adverse proving symptom, insurance coverage to all the volunteers in case proving symptoms adversely affect the well-being of a volunteer.

According to **HPUS guidelines[12]**, inclusion of subject must be accompanied by approval from suitable rationale and Ethics or Institutional Review Board, requirement of insurance coverage for volunteers subjected to approval from Ethical or Institutional Review Board. The ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and the applicable regulatory requirements. Informed Consent Financial Disclosure certification must be completed by the Principal Investigator and Clinical Coordinator/ Subject Supervisors.

The ethical issues covered by the Council's protocol include obtaining consent in writing from the subject. The nature and purpose of the drug proving must be explained to the subject or prover. For toxic symptoms, we should rely solely on the reports of accidental provings recorded in toxicological literature. The investigator or the investigating team should discontinue proving if in his/her or their judgment, the proving, if continued, would be harmful to the subject. In the revised protocol of CCRH, certain modifications were made for ensuring the Safety of the volunteers like formation of Ethical Committee of the Council, administration of drug substance in non toxicological doses. Taking care of the safety of the volunteer, it has also

been recommended to prescribe an antidote basing on the totality of presenting distressing symptoms from which the prover is suffering for more than three days. The investigator will get the opinion of the respective expert/consultant and get the necessary investigations done to rule out any pathological condition. The Council is also considering the recommendations of CDSCO in relation to the compensation to be given to the subjects being enrolled in any clinical trial.

7. **Addressing the confounding factors:**

The confounding factors depend on the qualities of the Proving Master and the prover. If the proving master is not vigilant enough or the prover is not careful in noting down the mental and bodily changes occurring or is over coloring the facts, this will lead to inappropriate and false data regarding the drug. Thus it is very important to make the volunteers aware of the significance of Drug Proving and motivate them to be honest and work towards the betterment of this pathy.

8. **Randomization/Blinding:**

Drysdale[10] was the one who introduced the concept of double blind method in drug proving. Later all the proving conducted followed the same methodology. **HPUS**[12] also recommends to adopt **randomized, double blind, placebo controlled design** in the proving trial. The protocol developed by CCRH was primarily based on the Hahnemann's concept of drug proving on healthy human volunteers with modifications proposed by Drysdale[10]. After the selection of the prover, the project officers were asked to send the names of the selected prover along with the Pre-Medical Examination records for each one of them to the Central Drug Proving Cell, New Delhi for randomization and allotment of code number. Each prover was given a unique code number. To reduce the bias the blinding regarding the name of the drug being prescribed for proving and volunteers in control or verum group is being done.

9. **Data recording :**

As per the recommendation of Drysdale[10], while recording data the following should be kept in mind.

a. **Classification of symptoms** into primary and secondary.
b. **Note down the course of symptoms** rather than just noting symptom following administration of drug.
c. In describing symptoms, **character of the sensation** must be observed with great minuteness and accuracy.
d. It is imperative to know the **etiological relations of the action of the medicine** as it indicates the characteristic action of the medicine.

As per the guidelines of ECCH[9] for HDP

a. Daily contact has to be maintained between participant and supervisor as long as symptoms continue to appear.
b. At the end of each day, symptoms reported by participant should be reviewed, investigated, clarified and recorded in detail by supervisor.
c. Supervisor should always seek to elicit any feelings and modalities that have been overlooked.
d. Organizing **proving meetings** to be conducted 4-6 weeks after starting the proving when most of the symptoms have subsided. Additional proving meetings can be arranged 2-3 months after taking the remedy in which the extraction work should be started under the guidance of the proving coordinator and assistance is given to those that have difficulties or a large volume of material to extract.
e. The duration of supervision, particularly for those who clearly respond, should last a minimum of three months. They should also have a six month follow – up.

Recommendations of HPUS[12]

a. **Timeline**
   - ✓ Prover's interview in person, or via telephone and/or voice or video should be conducted at least weekly with duration of prover reporting to be at least 6 weeks.
   - ✓ In person evaluation by the supervisor or principal investigator should be conducted at the final evaluation or exit point of the proving for each subject.
   - ✓ Final follow up of subjects can be extended up to least 3 months.

b. Use of **Electronic formats** for data collection.
c. **Pre-defined classification criteria** for all reported symptoms.
   - ✓ (N) denotes new symptom,
   - ✓ (U) denotes existing, unchanged symptom (within expected range of frequency, duration and severity),
   - ✓ (C+) denotes changed existing, unexpectedly better / improved (qualify according to frequency, duration, or severity),
   - ✓ (C-) denotes changed existing, unexpectedly worse (qualify according to frequency, duration, or severity).
   - ✓ (R) denotes past, unexpected recurrence.

d. **Causality determination** prior to un-blinding.
e. All serious adverse events must be recorded and reported to Ethics or Institutional Review board within the specified time period, have given the

Data recording as per CCRH Protocol

a. Predesigned documents called **medical record books (Pre-Medical Examination booklet, Prover's Day Book Performa, Symptom Elaboration Performa, Performa for noting changes in mental and physical aspects of volunteer and Post- Medical Examination booklet)** are used for recording and collected drug information.
b. The provers are asked to report to the Proving Master every day and hand over the recorded symptomatic data.
c. The intensity of each symptom and sequence of their appearance and their repetition are noted. The numbers of the provers who brought the identical symptoms are noted.
d. Clinical serological and biochemical investigations are done whenever the symptoms indicated their necessity and data are recorded on the explanatory sheet just below the recorded symptom.
e. Those signs and symptoms which are distinctly experienced by the provers who are administered the drug are reported in schematic arrangement borrowed from Kent's General Repertory of Homoeopathic Materia Medica.
f. The data is collected and compiled at Central Drug Proving Cell and then placed before the Working Group for approval. This was the practice till 2010. Since 2010, this data is placed for approval before the Special Committee on Drug Proving and Scientific Advisory Committee of the Council.

Wrap up about methodology adapted by CCRH

Drug proving programme was officially instigated by the Homoeopathic Research Committee formed in 1963 as one of the most imperative research programs of the Council. CCRH has developed a variety of study protocols for HDP but has now incorporated modern standards in the last few years. The present revised protocol (2014) is the product of harmonization of guidelines given by ECH, ECCH, HPUS, and LMHI along with the directions given by stalwarts. Now, under inclusion criteria the age group of the volunteer has been raised to 60 years, certain aspects are added in exclusion criteria like the prover having any disease or condition compromising the vital systems of the body or have undergone surgery in last two months, planned medical/dental treatment during the proving, women who have undergone hysterectomy etc.

In order to make the proving more resourceful, the protocol incorporates the concept of intra individual control besides inter individual control. Intra individual control is proposed to prevent incorrect attribution of symptoms to the IPS. **12 doses regimen** is adopted in which 4 pills, 4 times a day at four hourly intervals for 3 days with a wash out period of 30

days after disappearance of symptom. In case of re-proving of drugs considering that the previous proving has generated very few symptoms, **the new dosage schedule** proposed is 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". Run –in period will be least 2 weeks and a maximum of 4 weeks.

New classification for each symptom has been added in which (NS) stands for New symptom i.e. symptom which is never before experienced, (OS) stands for Old symptom i.e. symptom occurred more than one year ago, (RS) stands for Recent symptoms i.e. symptoms experienced within the last year, (AS) stands for Altered symptom i.e. a normal symptom changed during proving. (e. g. headache used to be left side, now on the right side).

Subsequent to disappearance of the symptoms, a period of 30 days will be kept as washout period. New definition to the proving symptom has been added in which New symptoms, not previously experienced will be demarcated by (N), Unexpected change representing worsening or aggravation of ongoing or recurring symptoms by (C-), Unexpected change representing an improvement of ongoing or recurring symptoms by (C+), Unexpected recurrence of past symptoms by (R), the Change in pathological parameters identified during laboratory testing from that of the baseline (PME). The concept of adverse events, serious adverse event, and causation likelihood are now added.

A modern analysis of Hahnemann's guidelines found many flaws all likely to lead to an over-estimation of pathogenetic effects. Radical improvement in pathogenetic information is a vital point in the current agenda for homoeopathic practitioners and clinical researchers that deserve a painstaking and dedicated world wide effort. We need sensitive designs and robust methodological procedures for homoeopathic drug proving. It is imperative to develop a protocol with emerging requirements for reporting HDPs so that we may build a pure homoeopathic Materia Medica, with valid and reliable information gathered from well conducted proving so that we can get better results in our clinical practice and research. With the perspective of building the experimental pillar of homoeopathy which can meet the increasing need to investigate and develop valid methodology incorporating modern strategies, CCRH has tried to make some contribution to the homoeopathic fraternity by bringing forth such drug proving protocol which may contribute in building the true Materia Medica and erase the errors in the methodologies earlier adopted. This chapter has given the entire information on the evolution of methodological aspects of Drug Proving from the time of Dr. Hahnemann till date and how CCRH has adopted various concepts and guidelines and framed it's methodology for proving and re-proving the drugs. The generic drug proving protocol of CCRH, for which this Training Manual is drafted, gives the methodology to be followed for carrying out the Drug proving research programme.

References:

1. Stephenson J. British Homoeopathic journal [internet], 1961; Volume 50[2]:129–131. Available from: www.sciencedirect.com. DOI-10.1016/S0007-0785(61)80030-6.
2. Belon P. provings concept and methodology. British homeopathic journal. 1995; 84:213-214
3. Dantas F. How can we get more reliable information from homoeopathic pathogenetic trials? A critique of provings. British Homoeopathic Journal. 1996; 85: 230-236
4. Homeopathic pathogenetic trials and provings: the need for harmonized guidelines, Homeopathy (2014) 103, 1-2
5. Dantas F., Fisher P. et al. A systematic review of the quality of homoeopathic pathogenetic trials published from 1945 to 1995. Homeopathy (2007)96, 4-16.
6. Dudgeon R. E. Lectures on the Theory & Practice of Homeopathy.
7. Hahnemann S. Organon of Medicine, 6th edn. New Delhi: B Jain Publishers, 1992.
8. European committee for homeopathy version 1.1, June 2011
9. ECCH guidelines for homoeopathic proving, 2009
10. Drysdale J. J. Proving of medicines on healthy human body. British Homeopathic Journal.1843;1: 135-151
11. Nagpaul V.M. Proving, Planning and Protocol. British Homeopathic Journal, Volume 76, April 1987, pp. 76-80
12. Homoeopathic Pharmacopoeia Convention of the United States, April 14, 2013

Drug Proving Process

Process in the Pre-Trial Phase

I. Identification of investigators of drug proving

The study investigators must be trained physicians with sufficient experience to be able to look after the well-being of the study volunteer(s). They must have relevant knowledge and experience to understand the process of drug proving, be able to interview the volunteers and be able to judge symptoms if they can be considered complete.

II. Literature review & safety and standardization of proving substance

Generally, only single drug should be used for proving at a time in a prover. A complete literature review of the drug substance to be proved must be undertaken. The substance must be identified by its scientific name and common name. The safety and standardization parameters should be recorded and compiled. The detailed literature review compiling the summary of findings from previous proving & clinical trials known and potential risk and benefits to human subjects should be prepared. The details such as scientific name, chemical name, common names, source, origin, habitat, collection, pharmacognosy, physico-chemical parameters, pharmacological aspects, method of preparation of mother tincture, method of preparation of potencies, source of procurement of raw material/ tincture/potencies etc. must be prepared and included in the study protocol. A certificate of authenticity of this nature should be procured from the manufacturing firm. The detailed toxicology information must be included in the protocol. Based on the literature review the potency of proving must be decided upon.

For the drugs already existing in the Indian/international homoeopathic pharmacopoeias/ formularies:

These are those drug substances whose basic standardization and safety parameters are known. 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 can 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.

For new products, with no reported use in homoeopathic system of medicine in any literature:

These should be considered as new drugs. In such a case standardization and safety studies should be completed before undertaking human proving. The first safe dilution (FSD) should be identified in this case and proving should be conducted only in potencies/ dilutions higher than the identified FSD.

III. Protocol finalization

Based on the literature review the protocol for drug proving must be prepared. The protocol must be in conformity with the ICH-GCP guidelines and must follow the provisions of declaration of Helsinki and ethical regulations for biomedical research on human participants.

The protocol must detail the literature review, study design, study process, details of intervention, participant safety and handling of adverse evenets, data collection & data analysis, etc. The protocol can be developed as per the international SPIRIT 2013 guidelines (Standard Protocol Items: Recommendations for Interventional Trials).

IV. Ethical review and ethical approval

The study protocol must be reviewed by the Institutional Ethics Committee/Independent Ethics Committee of the institute where the study is proposed to be undertaken. The regulatory and legal requirements must be fulfilled for constitution & proceedings of the ethics committee. The study trial must be registered into a trial registry (Clinical Trial Registry of India or other internationally accepted registries.

V. Orientation of potential participants

In a drug proving study it is preferable to include persons from both homeopathy and non-homeopathy backgrounds as study participants/provers. For this appropriate orientation programs / sensitization meets may conducted to invite interested volunteers. The volunteers must be sensitized to the process of drug proving and must be capable of making an independent decision for participation in proving studies.

Process during the Period of Trial

I. Informed consent

Objective:

- To give detailed trial related information to the potential participants
- To obtain 'Voluntary' 'Informed' 'Written' consent participation for the study

Process:

- The investigator needs to identify the knowledge about drug proving that the volunteer possess. The investigator needs to detail the total process of drug specifically taking into consideration the participation of the volunteer. The volunteer is informed about his/her rights, and responsibilities. The doubts and the questions raised by the volunteer is answered to the satisfaction of the persons.
- Upon being informed of the drug proving trial, the volunteer agrees to participate in the trial. The volunteer signs the copy of the consent form. The investigator signs the consent form. The copy of the participant information sheet and the signed consent form is provided to the volunteer. A copy of both the documents is retained by the investigator and filed.

Points to be taken care of:

- Voluntary informed written consent is a regulatory requirement
- The process must not be rushed through and the queries of the volunteer must be answered through. The trial process is explained to the volunteer in the language that he/she understands.
- The volunteer can refuse to consent for participation. This must not affect the relation between CCRH and its centre and the investigator and the volunteer at any stage.
- Since this would be the first formal interview between the volunteer and the investigator, it gives an opportunity for the investigator to assess if the participant is intelligent enough to understand the process of drug proving, is able to comprehend his/her rights and if the volunteer will be able to complete the responsibilities of the provers.

II. Screening of volunteers

Objective:

- To identify potential participants who are apparently healthy and segregate form those who have specific medical condition as per the inclusion/exclusion criteria of the protocol.

Process:

- The process involves 22 yes/no questions identifying any condition that the participant could be suffering from.
- The investigator will next conduct a basic minimum physical examination to identify any aberrations.
- Based on above the investigator will conduct as assessment of the participant for a detailed pre-trial medical examination.

Points to be taken care of:

Although primarily based on yes/no questions, the process will require the investigator to exercise his/her clinical acumen to ensure that the participant is not suffering from any overt medical condition or has any complaints warranting further investigations.

III. Pre-trial medical examination:

Objective:

- To identify healthy volunteers 'fit' for drug proving
- To develop a baseline of pre-trial information, so that any deviations in the health occurring during drug proving can be assessed

Process:

The PME will detail:

1. Constitution of the individual
2. Identify any clinical /laboratory abnormality in the prover on the basis of which the investigator will be able to adjudge the suitability of the participant for inclusion as a prover in the trial.
3. To identify any overt medical condition or abnormality which will make the participant unfit for proving.

PME will be conducted in 3 steps:

Step 1: General history & life space, investigations and assessment of constitution of the prover. This will require the acumen of the physician to clearly delineate the individuality of the prover. This is an important aspect which will be useful in developing the constitutional profile for the drugs being proved.

Points to be taken care of:

- Complete the format, use extra sheets, include every minutest detail.
- It is expected that the prover will not be having any presenting complaints or may have some minor acute complaints/symptoms.
- It is important to record in either case to ensure that the prover is healthy and he /she is not suffering from any acute condition at the time of PME. In case of the same, the prover can be requested to come again after 1 week of resolution of the acute episode.
- The life space investigation should taken into account. The details of social, personal & economic circumstances of the prover must be detailed.
- The past medical history and family history will be useful in identifying the tendencies of the prover.

The next step will be undertaken only if the investigator is of the opinion that the prover is suitable for proving.

Step 2: Investigations

- The participants will be subjected to a number of routine haematological, biochemical, examinations and routine examination for stool & urine, X-ray Chest and USG whole abdomen will be conducted.
- Copies of the reports will be annexed to the PME proforma and will also be made available to all the consultants conducting the subsequent examination.

Points to be taken care of:

- All investigations will be conducted in the identified laboratories.
- Copies of reports may also be provided to the provers if they request for the same

Step 3: Examination by consultants

Detailed systematic examination of the prover will be done. This will involve history taking and complete physical examination of the prover, by the respective consultants as detailed below:

Psychological examination	Consultant psychiatrist
Respiratory, Gastro-intestinal, cardiology, neurology, genito-urinary examination	Consultant medicine expert
Gynaecological examination (female participants)	Consultant gynaecologist
Dermatological examination	Consultant dermatologist
Eye examination	Consultant ophthalmologist
ENT examination	Consultant ENT
ECG	Identified ECG lab

Points to be taken care of:

The consultants are not trained in homoeopathy and may not be conversant with all the requirements of drug proving. The investigator must be in contact with the consultants to discuss the details of the clinical/laboratory investigation of a prover and specific queries must be answered before-hand. The investigator and the consultants are a team of health care providers on whom the combined responsibility for prover safety and trial integrity rests. As such the final decision of recommendation of the prover to be fit/unfit for proving will be made by the investigator.

Based on the detailed PME, the investigator will draw a case summary to identify if the participant can be enrolled as a prover in the study.

IV. Enrollment of prover:

Objective:

- To enroll volunteers identified fit for proving as provers

Process:

A Unique identity code (UIC) will be generated for each prover enrolled and will be communicated to the site investigator. The UIC will be used for randomization of the prover into drug and placebo groups. The trial drug will bear the same UIC for prover. All correspondence regarding the prover between the site investigator and the PI/Co-I/ study coordinator will be in reference with this UIC.

V. Run in period:

Objective:

- To allow 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)
- To establish some of the baseline health characteristics, and this can help later with the interpretation and analysis of proving symptoms.

Process:

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 1 week and at most 2 weeks. The investigator will hand over provers day book proforma 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 prover is to be told to write down the details of his/her daily routine and any changes mentally/physically associated with the day to day routine. The minutest detail, even if it appears irrelevant to the prover must be penned down. This will inculcate the sense of self examination and introspection in the prover that is very much required, before an actual intervention is initiated.

Points to be taken care of:

- The prover will be expected to develop a sense of introspection and observe his/her mind and life situations carefully and record them correctly and minutely.
- The investigator is to assist the prover in understanding what is expected of him/her and ensure that the prover is able to complete the day book proforma properly.

VI. Blinding

Objective:

- To reduce bias in the study
- To segregate changes in the population occurring due to environmental factors from those occurring in the volunteers due to intervention of trial medication

Process:

The study will be a double blind study, where the site investigators and the participants at the study site will be kept blind about the nature of the drug substance and the allocation of participants in the drug and placebo groups. The coded study medication will be labelled with the UIC and sent to the proving site.

The blinding will be maintained throughout the period of proving. Unblinding will be done by the principal investigator at the time of data analysis.

Unblinding will also be done in case of appearance of an adverse event/serious adverse event warranting intervention. Unblinding of a single participant status will be done by the PI at the CCRH, at his discretion in the event of development of AE/SAE in the prover. The participant allocation will be informed to the PI at the centre in case of therapeutic intervention required. The code will be accessible only to the PI and the prover/prover's care giver. The details 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 proving substance, 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.

Points to be taken care of:

The fact that the prover could be on placebo should not deteer the participant or the investigator to detail /report/note the symptoms /changes in health status of the prover.

VII. Intervention:

Objective:

- To provide the intervention of the prover and make note of any change in his/her health status

Process:

The investigator will hand over the study medication 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. Each dose will comprise of 4 pills. 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 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 proforma.
- The prover must follow the instructions in the participant information sheet and those given by the investigator.
- 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.

The intervention period will be followed by an observation period and wash out period as detailed in the study protocol.

VIII. Post (Terminal) Medical Examination (TME)

Objective:

- To identify the health status of the prover after proving study is completed
- To compare any deviation in the health status from that of baseline (established during PME)

Process:

- The process of post trial medical examination will be 'exactly' the same as the PME.
- The process will be equally detailed and all steps will be fulfilled.

Points to be taken care of:

- The investigator along with the consultants will compare the findings of the PME with that of the TME and will also be required to detail their opinion on the possible causality of any deviations identified.

Data Collection Formats

Sl. No.	Formats	To be filled in by	To be retained by
1.	Application Form (Form A)	Volunteer interested in enrollment as a prover	Site investigator
2.	Prover Information Sheet (Form B1)	Site investigator	Site investigator & Volunteer
3.	Written Informed Consent Form (Form B2)	Volunteer & Site investigator	Site investigator & Volunteer
4.	Screening Form (Form C)	Site investigator	PI & copy by the site investigator
5.	Pre-trial Medical Examination Forms (Forms D, parts I-III)	Site investigator & consultants associated with the study	PI & copy by the site investigator
6.	Prover's Day Book Proforma (Form E)	Prover during the run in period, intervention period and observation period	PI & copy by the site investigator
7.	Symptoms elaboration proforma (Forms F)	Site investigator	PI & copy by the site investigator

Ethical Considerations For Drug Proving

Four principles of Biomedical Ethics:

1: The Principle of Autonomy:

Autonomy, meaning self determination can be defined as the right of free and voluntary decision-making by an individual. The principle is based on respect for persons. This includes right to privacy and confidentiality and obligations to protect vulnerable groups. Health care professionals should respect the autonomous decisions of competent adults. This principle is the basis for "informed consent" in the physician - patient transaction in health care and researcher – participant transaction in research

Autonomy of vulnerable populations

According to The Belmont Report (1979), vulnerable populations are those groups that might "bear unequal burdens in research" because of their "ready availability in settings where research is conducted", such as prisons, hospitals, institutions and camps. Specific vulnerable groups are women and children, students, employees, refuges, poor, elderly and addicts. Individuals of such groups may have the potential to be exploited by researchers. This could be more so if they are dependent on institutions/ NGOs for their daily needs, treatment etc. Hence, there is a call for extra protection for these groups.

2 : The Principle of Beneficence

The principle of beneficence holds that clinicians and researchers should aim to do good i.e., to promote the interests of their patients. Any research done should be beneficial to the participants of the research or the communities they represent. It also calls for assessing the benefits of conducting a specific research in relation to the risks involved in it. This is also referred to as risk-benefit ratio.

3 : The Principle of Non-maleficence

The third principle, non-maleficence requires that clinicians and researchers should do no harm. In other words, the principle means not to inflict needless harm or injury by one's acts of commission or omission. For example, the carelessness of a health care professional

that could result in unreasonable risk of harm on the patient is maleficent and amounts to negligence. Moral convictions and the law of the land require that a proper standard of care that minimizes the risk of harm be provided. The legal criteria for determining negligence are as follows:

1. the professional must have a duty to the affected party
2. the professional must breach that duty
3. the affected party must experience a harm; and
4. the harm must be caused by the breach of duty.

4 : The Principle of Justice

In health care, justice is defined as fairness or "giving to each that which is his due". When we consider research, there should be fair distribution of burdens and benefits of the research. In other words, the principle of Justice demands that the fruit of research be equitably distributed amongst the beneficiaries and the participants in research. This concept of equitable distribution has gained global importance in view of the growing international collaboration between developed and developing countries. Selection of subjects, equitable study design and access to post trial benefits are the hallmarks of this principle.

List of resources

Details of regulatory requirements for research studies can be accessed at:

- Ethical committee: http://icmr.nic.in/bioethics.htm
- Clinical trial registry of India: www.ctri.nic.in/
- The Drugs & Cosmetics Act & Rules. Ministry of Health and Family Welfare (Department of Health). New Delhi IN: Department of Health, Ministry of Health and Family Welfare 2005. Available from: http://cdsco.nic.in/html/copy%20of%201.%20d&cact121.pdf
- CDSCO. GCP guidelines of India.
- Declaration of Helsinki: www.wma.net/en/30publications/10policies/b3/

International guidelines for drug proving:

- European Committee of Homeopathy. ECH Homeopathic Drug Provings

Guidelines Version 1.1 June 2011 [cited 2014 Feb 26]. Available at: http://www.homeopathyeurope.org/publications/guidelines/homeopathic-provings/ECH_Proving_Guidelines_v1.pdf

- Ross A., WassenhovenMv. Second Edition of LMHI Guidelines for a Homeopathic Drug Proving (HDP). April 2013. [cited 2014 Feb 26]. Available at: http://liga.iwmh.net/index.php?menuid=95&reporeid=310
- Homeopathic Pharmacopoeia of the United States. HPCUS Proving guidelines April 14, 2013. [cited 2014 Feb 26]. Available at: http://www.hpus.com/Draft-HPCUS-Proving-Guidelines.pdf

Guidelines for development of protocols and for reporting

- EQUATOR Network: http://www.equator-network.org/
- Standard protocol items for clinical trials www.spirit-statement.org/publications-downloads/
- Formal guidelines
  - Case studies (CARE) http://www.care-statement.org/
  - Randomized controlled trials (CONSORT) http://www.consort-statement.org/consort-statement/overview0/
  - Supplement for reporting homoeopathy trials (RedHot): http://cdn.elsevier com/promis_misc/yhompredhot.pdf
  - Observational studies (STROBE) http://www.strobe-statement.org/Checkliste.html.
  - Systematic reviews and meta-analysis (PRISMA) http://www.prisma-statement. org/statement.htm

Addressing Ethical Issues in Drug Proving

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

Specific ethical considerations which must be considered while conducting the drug proving study:

- Safety & standardization analysis of the proving substance is a pre-requisite for conducting drug provings.

- The drug must be proved in potencies identified as safe (i.e. in dilutions above FSD).
- Voluntary written informed consent should be taken from all participants prior to their participation in the study
- Only participants found to be healthy, sound body and mind should be enrolled in the study.
- Participant confidentiality and safety should be the prime concern at all stages.
- Participant shall 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 must be identified in the protocol and be based on internationally accepted guidelines
- There must be necessary clearance of the respective ethical committees at the study centers where the study is being proposed to undertaken prior to initiation of the trial
- Appropriate participant education should be conducted for all participants.

Confidentiality of study participants

All information collected in drug proving study must be kept strictly confidential, except as may be required by law of the land. The privacy and confidentiality of the participants should be honored at all stages. The allocation to drug and placebo in case of double blind placebo controlled studies may not be revealed, nor the symptoms produced be linked to the prover's names. Appropriate coding and randomization procedures should be followed while allocation of intervention. The provers should not be identified by name. At the time of data analysis, to each sign and symptom generated, the following information may 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)

- 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

At the time of publication of the study data, the prover codes linking codes to participants should not be published. The proving report may give a list of prover's at the end without linking the provers to the symptoms generated.

Model Protocol

Homoeopathic Drug Proving: Randomized Double Blind Placebo Controlled Trial

Introduction

The concept of provings 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, recording of symptoms [3].

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

The standardization of a proving process [5,6] and quality of proving [7,8] studies has been a major consideration for research over the years. The methodology of drug proving has changed considerably since the times of Dr. Hahanemann. Proving guidelines have been developed by various international bodies [9,10,11] 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 materiamedica in Hahnemannian proving has been identified as a source of error [13]. To minimize this, background noise[8] some basic criteria for healthy prover needs to be identified.

In spite of enrollment of healthy provers, it may be difficult to measure health and day to day fluctuations results in variations, which can be identified as symptoms. The Hawthorne effects, which are known to be a significant non-specific effect of participation [14] in trials is 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, where in 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 which 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, where in errors in reporting may occur.

Another fundamental question facing contemporary proving studies is to what extent adoption of a randomized 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 by 1900, the blinding techniques 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 homeopaths [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 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 will be stopped immediately on appearance of symptoms and after a symptom free wash out period of 30 days, next batch of medicines will be started. The potency which 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 harmonization with the international guidelines being developed for drug proving [9,10,11]. 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 or IPS) on healthy human beings. These will be prospective, parallel arm, randomized, 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 & Rules 1945 of Government of India [20] and Good Clinical Practice[21].

Materials And Methods

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 conducted. A certificate of authenticity of this nature will be procured from the manufacturing firm.

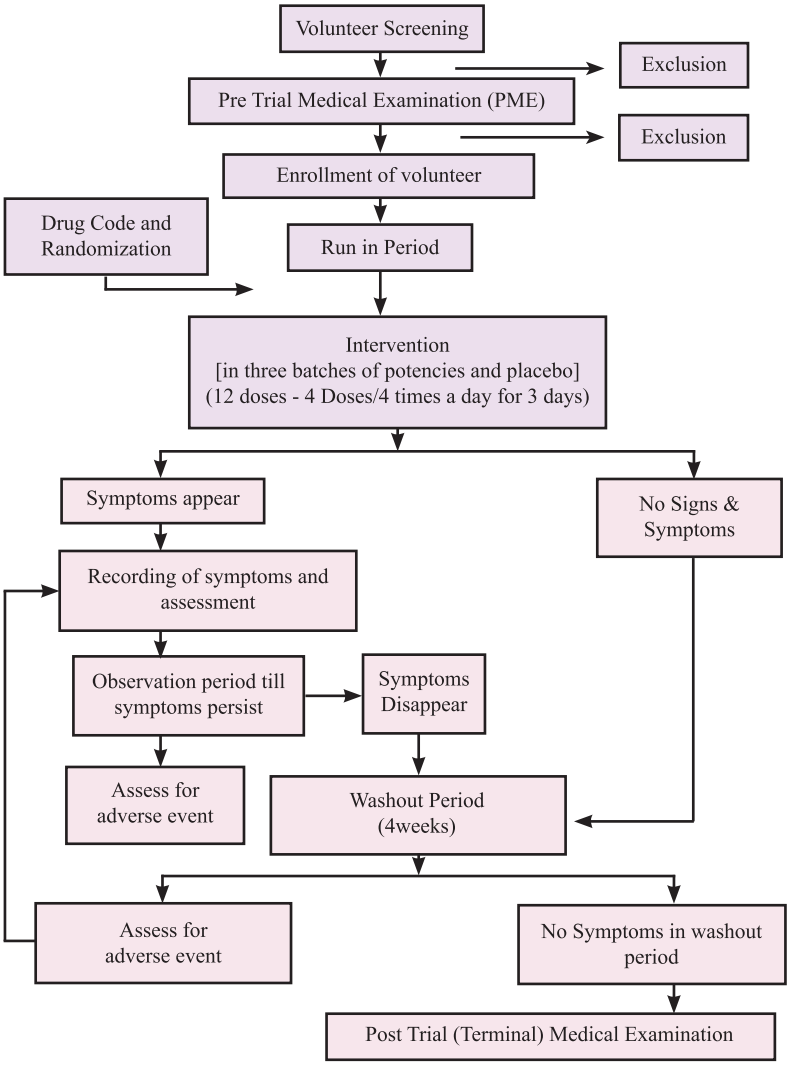
The IPS will be proved in at least 2 potencies used in ascending order. The IPS will be dispensed in sugar globules of standard size 30.

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 & smell.

Study process

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



Flow Chart – 1 Proving cycle

Recruitment process and inclusion/exclusion criteria

Applications from interested volunteers will be invited from students, faculty & staff of homoeopathic medical colleges through notice boards of the Institutes/Units/College. A Provers Information Sheet, detaining 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 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 of detailed history, clinical (general & systemic) examination & laboratory investigations to confirm health status of the participants. Details of inclusion & exclusion criteria are given in Text Box- 1. The participants found fit will be enrolled as prover.

Text Box- 1 Inclusion & 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 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

Randomization & Blinding

A unique identity code (UIC) will be generated for each prover. Randomization will be done using computerized random number charts for allocation to intervention. The randomized allocation will be made according to the UIC as follows:

- 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. 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 randomization chart to the proving Centre. 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 at CCRH headquarters.

Intervention

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 (usually 3), 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 (usually 3) will be given, all of which will comprise of placebo.

Study Medication

Drugs in compliance with pharmacoepoeial 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 bottles, labeled with serial number, prover's code and date of packaging. The placebo will be prepared similarly and labeled 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 4 pills, 4 times a day at four hourly intervals for 3 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 2 weeks and a maximum of 4 weeks. The investigator will give a specially designed provers 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 to 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 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 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) &/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) &/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. 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 3 days or is distressing to the prover, 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).

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 washout 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 washout 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 washout 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 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 order of appearance, time of appearance & disappearance, location, sensation/character, modalities, concomitants, direction/extension of symptoms, etc. Clinical examination findings & 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) &/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 intervention 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 IPS 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.
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 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)
- 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 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 characterizing 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 characterizing features for proving symptoms of the IPS are given in TextBox– 2. The symptoms will be further be graded in Grade – I & II, where in first grade symptoms refer to symptoms linked more strongly to the IPS than all others identified as second grade (Text Box – 3).

Text Box – 2 Characterizing 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 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.

Text Box – 3 Grading of symptoms

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

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.

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 enroll 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) &/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. The use of placebo, in these studies, is therefore expected to minimize 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 organized 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 minimize 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.

References:

1. Belon P. Provings. Concept and methodology. British Homoeopathic Journal. 1995; 84(4): 213-217
2. Hahnemann S. Organon of Medicine, 5th& 6th Edition. Translated by Dudgeon RE, Boericke W. New Delhi. B Jain. Reprint 2010.
3. Dudgeon RE. On the Proving of Medicines from Lectures on the Theory and Practice of Homeopathy 1853. New Delhi. Jain Pub Re-print 1982
4. CCRH. Activities & Achievements. Act & Achievements).
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. British Homoeopathic Journal. 1997; 86(4): 229-234
6. Walach H. The pillar of homoeopathy. Homoeopathic drug provings in a scientific framework. British Homoeopathic Journal. 1997; 86 (4): 219-224
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(1): 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 [cited 2015 February 26]; 9(32):94-103. Available from: http://www.feg.unesp.br/~ojs/index.php/ijhdr/article/view /373/444)
9. European Committee of Homeopathy. ECH Homeopathic Drug Provings Guidelines Version 1.1 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 66]
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 1 homeopathic drug proving trial. Trials. 2010; 11:80
13. Khurana A. Drug proving- sources of errors. CCRH Quarterly Bulletin. 1994; 16 (3&4):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. Controlled Clinical Trials. 2000;21(2):103-114
15. Clover AM, Jenkins S, Campbell AC, Jenkins MD. Report on Proving of Pulsatilla 3X. British Homoeopathic Journal. 1980; 69 (3) : 134-149).
16. Riley DS. Extracting symptoms from homoeopathic drug proving. British Homoeopathic Journal. 1997; 86 (4): 225-228
17. Kaptchuk TJ. When Does unbiased become biased? The dilemma of Homeopathic Provings and Modern Research Methods. British Homoeopathic Journal. 1996; 85(4): 237-247
18. Nagpaul VM. Provings-planning and protocol. British Homoeopathic Journal. 1987;76 (2):76-80.
19. Manchanda RK, Khurana A, Taneja D. Proceedings of interactive meet on harmonisation of drug proving programme. Indian Journal of Research in Homoeopathy 2014;8(1):46-66
20. Government of India. The Drugs & Cosmetics Act & Rules. Ministry of Health and Family Welfare (Department of Health). New Delhi Available from: http://cdsco.nic.in/html/copy%20of%201.%2 0d&cact121.pdf [Last accessed on 2015 Feb 16]
21. Good Clinical Practices for Clinical Research in India. Available at: 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 at: http://www.cdsco.nic.in/html/GMP/ScheduleM(GMP).pdf [Last accessed on 2015 Feb 16]

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Abbreviations

AE / SAE Adverse Event / Serious Adverse Event

CCRH - Central Council for Research in Homoeopathy

ECH - European committee for Homeopathy

ECCH - European Council for Classical Homeopathy

FSD - First safe dose

HDP - Homoeopathic Drug Proving

HPUS - Homeopathic Pharmacopoeia of the United States

HPCUS - Homeopathic Pharmacopoeia Convention of the United States

LMHI - Liga Medicorum Homoeopathica Internationalis

PME - Pre-trial Medical Examination

SPIRIT - Standard Protocol Items: Recommendations for Interventional Trials

TME - Post-trial (Terminal) Medical Examination

UIC - Unique Identity code