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Access this article online

Website: www.ijrh.org

DOI: 10.4103/0974-7168.129680

Quick Response Code:

Proceedings of interactive meet on harmonisation of drug proving programme

ABSTRACT

An interactive meet for harmonisation of drug proving programme of the CCRH was held on 17 September 2013 with an objective to exchange information on standards and methods of proving in the USA, Europe and India and promote international collaboration and harmonisation of drug proving protocol. The Council is in the process of revising its drug proving protocol based on the deliberations of the meet.

Keywords: Drug proving, Homoeopathic pathogenetic trial, Homoeopathy, Protocol, Harmonisation, Drug pathogenesis

BACKGROUND

Drug proving is one of the principle activities of homoeopathic research. It was started in 1963 under the Homoeopathic Research Committee constituted by Government of India. The work was subsequently carried forward by the Central Council for Research in Homoeopathy (CCRH). *Kali muriaticum*[1] was first drug that was re-proved, there after *Abroma augusta folia* and *Cassia sophera* were proved considering their wide use by Indian homoeopaths.[2,3] The focus of the CCRH's drug proving programme is on proving of fragmentarily proved and indigenous drugs. Till now, the CCRH has proved more than 100 drugs. The data has been published in CCRH quarterly bulletins and Indian Journal of Research in Homoeopathy (IJRH),[4] monographs and Councils publications.[5-10] A research protocol was developed in 1987,[11] which was modified in 2007 and was further modified in 2010. Primarily the provings were conducted using double-blind placebo-controlled design. The initial proving were conducted even using mother tinctures and lower triturations but later on only potencies (6-200) are being used.

Drug proving protocols have been a subject of intense debate internationally, the protocols/guidelines have been developed by Liga Medicorum Homoeopathica Internationalis (LMHI),[12] European Committee for Homeopathy (ECH)[13] and Homeopathic Pharmacopoeia Convention of the United States (HPCUS).[14]

Over the years, a need was felt to bring in harmonisation in these proving guidelines, which will be of mutual benefit for the organizations to be in consonance with each other and develop a set of globally acceptable guidelines. This step plays a vital role in regulatory requirements in the countries with regard to new drug discovery in homeopathy. The subsequent drug monographs developed will assure methodological quality and would be more acceptable to the international community. Dr. Robert van Haselen, Editor in chief, Journal of Complementary Therapies in Medicine and member of the Proving and Clinical Evidence Working group of the HPCUS and the Research Working Group of the (ECH) was invited to the Council. An interactive workshop on the harmonisation of drug proving programme of the Council was held on 17th September 2013 at New Delhi. The objective was to exchange information on standards and methods of proving in the USA, Europe and India and promote international collaboration and harmonisation of drug proving protocol. Attended by over 80 participants, the event brought together scientists, administrators and academicians associated with drug proving programmes in the country.

PROCEEDINGS

The interactive meet was inaugurated by Shri Nilanjan Sanyal, IAS, Secretary, Department of AYUSH, Ministry of Health and Family Welfare, Govt. of India. He

stated that harmonisation of global standards is the need of the hour and Council should undertake internationally acceptable researches. The participants of the workshop included Dr. V.K. Gupta, Chairman, Special Committee on Clinical Research, Dr. Niranjan Mohanty, Chairman, Special Committee of Drug Proving, Dr. Raj K. Manchanda, Director General, CCRH, Dr. Anil Khurana, Assistant Director, CCRH, nine scientists engaged in drug proving program, 16 proving associates (faculty from colleges conducting drug proving in collaboration with Council) and 24 other scientists and research administrators of the Council.

Dr. Haselen made a presentation on drug proving in the USA and Europe: Current status, Proving guidelines and methodology. He compared the proving guidelines of the LMHI (version 2, April 2013), ECH (Version 1.1, June 2011) and HPCUS (Version 2, April 2013). Presentation about the development of drug proving programme of CCRH was made, also highlighting the main aspects of the proving protocol. It was compared with the chart of Dr. Haselen and discussion took place on every point.

Major Discussion Points

During proving, symptoms appear in both the control and verum group. As per certain recommendations, those symptoms be also included in the monograph, indicating them as placebo symptoms.[6] It was much debated upon, if the placebo symptom reporting will have any utility to the profession. In CCRH, the symptoms found to be common in all respects in both verum and control are recorded but are not reported in the drug pathogenesis. It was decided to retain the process.

The profile of provers developing symptoms on drug or placebo needed to be understood, so that a general constitution of the drug could also be derived. Since provings are conducted in different geographical terrains and different climates, the drug proving symptoms can be completed in relation to causative factors and environmental changes.

Drug Proving symptoms can be graded as per their value, that is symptoms appearing in more number of provers, peculiar, rare and uncommon symptoms, symptoms reappearing from prior proving, symptoms persisting for long duration.

The safety profiling of the drugs must be conducted prior to undertaking proving. The drug proving protocols need to detail the mechanisms of identification and reporting of adverse events and adverse drug reactions.

It was suggested that proving should be made a part of homoeopathic graduation and post-graduation curriculum for meticulous involvement of students.

Outcome

The comparative statement of the guidelines of the LMHI, ECH and HPCUS as provided by Dr. Haselen was elaborated to incorporate the protocol of the Council. The outcomes of the discussion have been summarised in the last column of the comparative table (Appendix). The Council is in the process of revising its drug proving protocol incorporating these outcomes.

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How to cite this article: Manchanda RK, Khurana A, Taneja D. Proceedings of interactive meet on harmonisation of drug proving programme. Indian J Res Homoeopathy 2014;8:46-66.

Source of Support: Nil, **Conflict of Interest:** None declared.

पृष्ठभूमि: संयुक्त राज्य अमेरिका, यूरोप और भारत में औषध प्रमाणन के स्तर और तरीकों पर जानकारी के आदान प्रदान के उद्देश्य से दिनाँक 17 सितम्बर 2013 को परिषद् के औषध प्रमाणन कार्यक्रम में सामंजस्य स्थापित करने हेतु परिषद् मुख्यालय के आयुष सभागार में एक बैठक का आयोजन किया गया। बैठक में विचारों के आधार पर औषध प्रमाणन प्रोटोकॉल में संशोधन किये जा रहे है।

APPENDIX

Comparison of drug proving guidelines of LMHI, ECH, HPCUS, with protocol of CCRH

Title	LMHI*	ECH*	HPCUS*	CCRH**	Discussion and outcomes
Version	**Version 2, April 2013**	**Version 1.1, June 2011**	**Version 2, 14 April 2013**	**August 2010**	**2014 onwards**
Purpose	It will help to obtain comparable results from provings of a same medicine in different places in the world	Re-establish the understanding for the need to conduct drug provings within the homoeopathic community and to attract those who are interested in provings. And to lay down a framework outlining the minimum criteria which have to be covered in a protocol for a good homoeopathic proving	Establish transparency for monograph sponsors and review committee for requirements for a proving to establish a new substance into the homoeopathic pharmacopoeia of the U.S. through the monograph process	Drug proving is a building block of homoeopathic material medica. Primary action of a drug substance should be known before it can be taken as a homoeopathic drug. A well proved drug will help in construction of an authentic materia medica, which in turn, will facilitate the selection of similimum	Introduction will be modified to incorporate the well defined purpose for conducting the proving and its subsequent use in clinical verification
Structure of document	Two parts primarily: (Part A) content of the protocol: (Part B) Series of case report and other forms (examples) used in provings	Exceptions to ICH E6 guidance Samples of documents to be used in conduct of a proving	Requirements Recommended practice	Two parts primarily: (Part A) Protocol: (Part B) Case report and forms for recording proving data	The protocol will retain its present format, i.e., Part A will be protocol and Part B will be the formats to be issued for the study
Good Clinical practice	Refers to the ICH E6 guidelines on good clinical practice	Refer to the ICH E6 guidelines on good clinical practices as the central guidance and augment the ICH guidelines in areas where homoeopathy differs from conventional medicines and pharmaceutical development	Refer to the ICH E6 guidelines on good clinical practice	No reference to ICH E6 guidelines	The protocol will be in compliance with the Good Clinical Practices (GCP) guidelines as issued by the Government of India. Compliance statement will be added

Important definitions

*Comparison of protocol of LMHI, ECH and HPUS provided by Dr. Robbert van Haselen

** Comparison of CCRH protocol 2010 added by Dr. Anil Khurana, Dr. Divya Taneja and Dr. Shilpa Sharma

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Meet on harmonization of drug proving

Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Adverse event	Any untoward medical occurrence in a volunteer administered a proving medicine and which does not necessarily have a causal relationship with the action of the medicine. An AE can therefore be any un-favourable and unattended sign, symptom or disease temporally associated with the administration of a proving medicine, whether or not related to it		Any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a proving and which is unexpected and clinically significant	Nil	Definition of adverse event will be added as per HPCUS guidelines
Unexpected	Nil	Nil	Symptoms or sign occurring during the proving period that is not consistent with investigational product information. For the purposes of proving, unexpected symptoms include any symptoms or signs that have duration longer than the proving period, have clinical severity greater than described in the informed Consent, have clinical severity that falls within the definition of Serious Adverse Event, require therapeutic intervention, or result in removal from the Proving	Nil	Definition of adverse event will be added as per HPCUS guidelines
Adverse drug reaction	In homeopathic drug proving a conventional ADR will not occur, because there are no toxicologic effects. Of the proving substances, since they usually are administered in high dilutions. An additional term “Adverse Proving Symptoms” is added to differentiate	In homeopathic drug proving a conventional ADR will not occur, because there are no toxicologic effects. Of the proving substances, since they usually are administered in high dilutions. An additional term “Adverse Proving Symptoms” is added to differentiate	An adverse event or suspected adverse reaction is considered ‘unexpected’ if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.	Nil	Appropriate definitions of serious adverse event, adverse drug reaction, serious adverse drug reaction will be added

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
			The event is considered a suspected serious adverse reaction if there is cause to suspect a relation to the investigational proving substance administration and the event, and the severity would make the event a Serious Adverse Event.		
Proving symptoms	Proving symptoms are defined as those changes of the mental, emotional or physical state of the volunteer, which are likely to be caused by the administration of the proving medicine and are out of the ordinary patterns of reaction of administration of the proving medicine and are out of the ordinary patterns of reaction of the volunteer, shown during the taking of the case history. Proving symptoms are generally temporary symptoms, lasting for several hours or days	Differentiated into "Proving Symptoms" and "Adverse Proving Symptoms" based upon both the likely causality by the IMP and "disturbance of normal daily routine"	Any change in the normal objective as well as subjective state of mind or body, as experienced by the subject, or as observed by the practitioner and/or others. (Adapted from Swayne *et al*.) (25) Symptoms or sign occurring during the Proving period which is possibly related to the IPS. Symptoms that occur In a severity, duration and frequency consistent with historical tendency, or can confidently be attributed to a cause external to the Proving should NOT be reported as a Proving symptom	Not mentioned	Definition of proving symptom will be added
Healthy volunteer	The volunteer has to be healthy in the sense of being free from important physical or psychic symptoms and does not consider himself to need medical treatment	The volunteer has to be healthy in the sense of being free from important physical or psychic symptoms and does not consider himself to need medical treatment		The volunteer must not be suffering from any acute or chronic disease. Experts examine the volunteer and certify that the volunteer is healthy	Appropriate definition identifying health status of the volunteer will be added
Independent ethics committee	Required in glossary; not required in the body of document	Required. Requires inclusion of homeopathic professionals when reviewing proving	Requirement: must have ethics board review and approval for proving No requirement for inclusion of homeopathic professionals	Ethics committee has not been defined. As a part of the procedural mechanism in the organisation, the protocol is has approved cleared by the ethical committee of the council	Ethical clearance as per the regulatory requirements in the country will be obtained
Serious adverse events	Since Homeopathic Drug Provings are done with only non-toxic dilutions of a proving substance, it is very unlikely to have serious adverse drug reactions	Since Homeopathic Drug Provings are done with only non-toxic dilutions of a proving substance, it is very unlikely to have serious adverse drug reactions	See SADR	Not included	See ADR

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Serious adverse drug reaction	Since Homeopathic Drug Provings are done with only non-toxic dilutions of a proving substance, it is very unlikely to have serious adverse drug reactions	Since Homeopathic Drug Provings are done with only non-toxic dilutions of a proving substance, it is very unlikely to have serious adverse drug reactions	Within the context of proving, and adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life threatening adverse event, inpatient hospitalisation or prolongation of existing hospitalisation, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalisation may be considered serious when, based upon appropriate medical judgment, they may jeopardise the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency of drug abuse	Not mentioned	See ADR
Sponsor	An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or funding a HDP. The principal investigator in a HDP automatically takes the role of the sponsor. The sponsor does not necessarily give money for the proving, but is always responsible for the proving	This is to say that the principal investigator in a Homeopathic Drug Proving automatically also takes the role of the sponsor	Sponsors may also be Principal investigators, but this role is not assumed. PI is kept as a separate role/ responsibility	CCRH funds the project	

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Therapeutic intervention			Medical or other treatment deemed medically necessary by the Supervisor for a subject during the course of a Proving other than the IPS or treatment that was ongoing prior to Proving initiation	During the course of proving, the prover is referred for specific investigations to rule out any pathological cause for appearance of new symptoms (s)/sign (s)	Therapeutic intervention, as per need, will be elaborated
Personal qualifications					
Principal investigator	5 years homeopathic experience, must have done proving of medicines on self at least 3 times, must have 2 years experience in conducting proving.	5 years homeopathic experience, must have done proving of medicines on self at least 3 times, must have 2 years experience in conducting proving	Required: 5 years homeopathic experience, experience or publication demonstrating human clinical research expertise Recommended: prior proving experience	Scientists of the organisation are coordinators for the study, specific but qualifications are not being identified in the protocol	The protocol for CCRH will have the involvement of regular scientists of the organisation. If other organisations intend to use this protocol, they would need to identify the qualification requirements
Sub-investigators	5 years homeopathic experience, must have done proving of medicines on self at least 3 times	In Homeopathic Drug Provings usually the investigators (proving doctors) have no sub investigators	Sub investigators would be synonymous with Proving Supervisors, Requirement: 200 h of homeopathic training, 1 year homeopathic clinical experience Recommended: training in record keeping and Quality assurance for clinical trials	Scientists of the organisation are proving masters/proving coordinators for the study, specific but qualifications are not being identified in the protocol. Faculty from homoeopathic colleges, where proving is conducted are also involved as proving associates	The same procedure will be followed
Ethics training			Required for PI within 3 years, Recommended for supervisors.	Nil	The training requirements of the scientists of the organisation is a part of procedure in the organisation.
IMP					
Efficacy testing	Not applicable to provings	Not required for provings	Not applicable to Provings		
Safety data		Not required as homeopathic remedies are generally safe	Required if available	Drug substances are administered in potency only, which does not cause toxicological effects. As an organisational procedure drugs where drug standardisation have already been performed	Identification of first safe dose is a good proposition. How to assess, shall be worked out where proving is proposed to be conducted in the form of mother tincture or low dilutions/ potencies

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Monitoring	Not financially feasible	Not financially feasible		The proving studies are multi-centric and monitoring is done at each study centre. A proving committee comprising of homoeopathic experts, scientists of the Council and faculty members of colleges is formed at each study centre to scrutinise and monitor the study	Monitoring is a part of organisational procedure. This would be elaborated in the protocol
Identification criteria	Sufficient information to reproduce the compound in future provings or use.	Full Latin name, common names (if necessary), zoological name	Required: Full Latin name, common names, synonyms, sufficient information to identify the unique compound	Different drugs are proved on a common protocol. Broad outline for pre-requisite information related to the drug substance, i.e., pharmacopeial standards, standardisation studies (for new drug substances) is mentioned in the protocol	Different drugs are proved on a common protocol. Broad outline for pre-requisite information related to the drug substance will be included in the protocol. These will be included in the drug monograph
Plants	Full Latin name, locality of sample, habitat, time of harvest, parts used	Full Latin name, locality of sample, habitat, time of harvest, parts used	Full Latin name, locality of sample, habitat, time of harvest, parts used	Not mentioned in protocol. But is included in the drug monograph	-as above-
Mineral	Composition, pureness, analysis method	Composition, pureness, analysis method	Composition, pureness, analysis method	Not mentioned in protocol. But is included in the drug monograph	-as above-
Animal	Habitat, parts used.	Habitat, parts used.	Habitat, parts used.	No details are mentioned	-as above-
Nosodes	Exact origin and source material	Exact origin and source material	Exact origin and source material	No details are mentioned	-as above-
Manufacturing			Must comply with GMP and HPUS standards	Drugs are procured only from GMP certified pharmacies	Drug are procured only from GMP certified pharmacies.
Attenuation/ preparation	Must be described; variety of examples given	Must be described; variety of examples given	Required: attenuation selection to ensure safety, less than 12c not to be used if safe human dose is unknown Recommended: Attenuation>30c	Drugs are proved in 6C, 30C and 200C potencies only. Drugs prepared as per the specifications and standards laid down in the homoeopathic pharmacopoeia of India are used for proving	The same procedure will be continued
Vehicle/ administration	Oral dose recommended	Oral dose recommended	Recommended: lactose vehicle with oral administration Required: Rationale if alternate vehicle or route used	Drugs/placebo is given orally in pure sucrose globules. Dosage schedule is mentioned in the protocol	The same procedure will be continued

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Placebo preparation		2 types allowed; substance vehicle only or vehicle sprayed with 83% non-succussed alcohol	Required: Indistinguishable from verum, if used	Placebo consists of pure sucrose globules impregnated with unsuccussed dispensing alcohol. The administration scheme is identical in the placebo control group to that of the intervention group	The same procedure will be followed
Manufacturer identity	Required	Required	Required	Drugs are procured from GMP certified Pharmacies	The same procedure will be continued. Manufacturer identity will be disclosed at the time of publication of study data
Toxicology			Required: Summary of known effects, literature review and reference list for toxicology reports	As per the protocol, justification of the new substance being proved including the background literature, pharmacological, toxicological literature available about the substance is required	Drug standardisation studies are completed before undertaking drug proving studies
Prior Clinical Info			Recommended: Provide summary of literature	The protocol is a generic protocol and is used for proving of a number of drugs and is not for a specific drug. As such prior clinical info is not included in the protocol	The literature review will be included in the drug monograph
Prior Proving Info			Recommended: Provide all available prior proving information	The protocol is a generic protocol and is used for proving of a number of drugs and is not for a specific drug. As such prior proving info is not included in the protocol	The literature review will be included in the drug monograph
Design/methods					
Insurance requirement	Required	Required	Requirement: Must be sufficient to permit ethics board approval	In case of any adverse event the participant will be referred to concerned consultant. The Council will bear the expenses required for the treatment	The same procedure will be followed
Patient information sheet	Required as part of informed consent; example provided	Required as part of informed consent; example provided	Required as part of informed consent	Required as a part of informed consent	Patient information sheet will be retained as a part of informed consent

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Meet on harmonization of drug proving

Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
(Risks)		The substance administered to each volunteer will be a homeopathic preparation or a blank (Placebo see also 6.4.3), which has been potentised, i.e., to a C12 or C30 potency with a dilution of 1×10 24 resp. 1×10-60. The toxicity of these preparations is considered to be extremely low, however it is expected that reversible Proving symptoms will be experienced by the Volunteers after administration of the Proving substance. Proving symptoms are defined as those changes of the mental, emotional or physical state of the Volunteer, which are likely to be caused by the administration of the remedy and are out of the ordinary patterns of reaction of the volunteer, shown during the talking of the case history. Proving symptoms are generally temporary symptoms, lasting for several hours or days		No serious risks are anticipated out of this Drug Proving as the drug is proved in potentised form, which is non-toxic	The patient information sheet will be detailed
(Benefits)c	Former symptoms may be ameliorated or healed by taking the substance	The Proving symptoms obtained are used for therapeutic purpose or treatment after the Proving according to the law of similar and thereby are beneficial for a great number of patients	To be completed through the Ethics Board requirements	It is well evident that a prover improves his health and resistance of the body. Provers learn and develop the skill of astute observation, and gain homoeopathic knowledge through direct involvement in the proving process. Provers may be cured of certain ailments where the remedy being proved corresponds closely to the prover's pre-proving state.	The patient information sheet will be detailed
Recruitment process	Method of Recruitment should be noted	Method of Recruitment should be noted to help differentiate results of different strategies in the future.	No specific requirement	Method of recruitment defined in the protocol	

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Subject population selection			Required: Widest range of subjects possible	Both male and female volunteers, above the age of 18 years	Age limit will be revised to 18-60 years
Demographics of subjects	Ethnicity should be documented.	Ethnicity should be documented.	Required: Documentation of ethnicity Recommended: Limit ages 18–75, inclusion of both male and female subjects	Drug proving is conducted at multiple centres. Age, gender, religion and socio-economic condition are documented	Each drug will be proved at 2 different geographical locations
Location of proving	Should be included	Should be included	Required to be noted.	Included in the protocol	Included in the protocol
Language	Different languages permitted, original language descriptions must be preserved, translation permissible as long as method determined and documented prior to proving	Different languages permitted, original language descriptions must be preserved, translation permissible as long as method determined and documented prior to proving		Not mentioned in protocol, but during proving generally data is recorded in English. As a procedure all languages are permitted while recording the symptoms by the prover, which are then translated to English by the proving master	The procedure will be added and detailed in the protocol
Objectives	Must be described	Must be described		Described	The protocol will retain the objectives, methodology, etc.,
Trial method description	Required: Crossover design recommended; Multiple arms with different potencies recommended	Required	Required: Describe and justify design, denote single or multi-center, must be prospective Recommended: double-blind, placebo control	Methodology clearly defined. Provings are conducted as double-blind, randomised, placebo-controlled parallel studies	
Control use	Unclear whether recommending or not	Not recommended	Recommended to use placebo control Required: if blinding not possible, designed to minimise bias in proving, minimum of 20% of subjects if used	Recommended	Percentage of placebo control is generally kept as 30%. This will be added in the protocol
Randomisation	Recommended if use control	Not recommended	Recommended to use Required: Compliance with GCP to ensure unbiased allocation of subjects.	Recommended	Randomisation procedure will be added
Blinding					
Prover blinding to substance	Recommended	Required	Recommended if permissible by Ethics board.	Recommended. Double blinding is followed in all proving.	The protocol will retain the same.
Prover blinding to verum allocation	Recommended if use control	Not required; suggested as not applicable.	Required; for PI, supervisors, subjects, co-ordinator.	Recommended. Double blinding is followed in all proving.	The protocol will retain the same.
PI Blinding to substance		Required	Recommended if permissible by Ethics Board.	Not mentioned	The level of blinding will be added
Packaging	Aluminium foil wrapping recommended	Aluminium foil wrapped single dosing required		Proving substance is prepared as 'Quotas', i.e., separate lots for each prover	Detailed packaging procedures and requirements will be added in the protocol

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Meet on harmonization of drug proving

Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Subject education	Recommended	Required	Recommended to include: How to record symptoms, reporting adverse events, interim contact process.	Explained in prover information sheet.	Separate prover education sheet manual will be prepared
Stopping rules	Recommended	Required	Required	Mentioned and recommended	The protocol will retain the same
Data recording		Only subjective data from subjects allowed	Both Subjective and Objective Data included	Both subjective and objective data is being considered while data recording	The protocol will retain the same
Initial interview	Can be by questionnaire or in person; direct interview recommended. Four different interview/ questionnaire scenarios are presented with pros and cons for each approach	Can be by questionnaire or in person; direct interview recommended. Four different interview/ questionnaire scenarios are presented with pros and cons for each approach	Required: Face to face interview to include age, gender, past medical history, Medications, allergies, current conditions, prior symptoms that required treatment, clinically important symptoms occurring in the past 3 months, Recommended: Full homeopathic history and physical with the development of the homeopathic picture	Direct interview being conducted by the investigator (Proving master) on a standard questionnaire. Full homoeopathic history and examination is conducted at this stage	The protocol will retain the same procedure
Initial interview form	Example provided to be completed by the physician. Form gives past medical history, check list for review of symptoms, and homeopathic general symptoms. Free text area also provided	Example provided to be completed by the physician. Form gives past medical history, check list for review of symptoms, and homeopathic general symptoms. Free text area also provided	Per the sponsor	Standardised case record form is a part of the protocol. Form details presenting complaints, history of complaints, past history, family history, physical built, physical general, mental generals, general physical examination and examination of nervous system, eyes, ears, nose, throat, psychological, respiratory, cardiac, gastro-intestinal, genitalia, urinary, skin, pathology	The protocol will retain the same procedure
Case taking method	Should be stated in protocol along with reasons for choosing method			Method of case taking not detailed, but case taking proforma are included in the protocol as annexure	The protocol will retain the same procedure
Proving evaluations		Recommended daily for 15-20 min	Recommended: at least weekly by telephone or face to face	Recommended: at least weekly face to face	Daily assessment during the period of drug intake and till symptoms persist is recommended

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
IMP administration					
IMP route of admin	Oral given as example; route not otherwise limited	Oral	Recommendation: oral route, Requirement: alternate route must be accompanied by justification.	Oral	Only oral route will be recommended
IMP Frequency	Example of every 2 h up to 6 times per day given, not otherwise limited	One dose every 2 h, up to 6 doses in one day; stop if subject believes a symptom may be occurring	Required: Dosing timeline established and approved by Ethics board before trial. Recommended: Not more than 3×daily.	Each quota of the drug has 12 doses. Each dose consists of 4 pills (Size 20). Four doses in a day (4 hourly) for 3 days	The same procedure will be retained
IMP Non-repetition/ discontinuance criteria	When a symptom first occurs (not defined further)	Subject believes a symptom is occurring	Required: Define criteria prior to proving, must include development of symptoms by prover as defined in protocol Recommended: to include stopping administration if no symptoms develop within 7 days	Clearly defined. The prover is asked to stop taking the drug as soon as he/she feels any change or any sign (s) &/or symptoms (s) develop. No further dose of the particular quota is to be consumed by the prover	The protocol will retain the same procedure
Selection criteria					
Inclusion criteria	The volunteer must be healthy in the sense that the does not show severe psychic or physical symptoms and does not consider himself to be in need of medical treatment. Also the proving doctor does not see a necessity for treatment	Required	Required: To be defined and approved by Ethics board before enrolment period	All male and female participants above the age of 18 years, with experts certifying that the participant is healthy, after detailed examination	Will be elaborated
Exclusion criteria	As examples, current medical treatment or homeopathic drugs in the past four weeks or in the preliminary observation period or during the proving. Contraceptives in the past 3 months (or being mentioned in the diary). Surgical treatment within past 2 months. Pregnancy, breast feeding. Underage of 18.	Required	Required: To exclude those at health risk, to remove confounding factors to the proving, to ensure ability to report/record symptoms accurately, mentally incompetent subjects, Recommended: exclusion of<18, >75 years, pregnant subjects, subjects with serious emotional disorders, subjects who plan medical/ dental treatment during test period, under current homeopathic treatment (30 days), lifestyle habits likely to alter results	Specific exclusion criteria given. Volunteers suffering from any acute or chronic disease, volunteers under any kind of treatment	Will be elaborated.

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Withdrawal criteria must be pre-defined	Recommended	Required	Required	Not clearly detailed	Will be included in the protocol
Subject handling					
Name of IMP must be given to subject	Recommended	Required	Only if required by the Ethics Board.	Not mentioned	The level and process of unblinding will be detailed in the protocol. Will be included
Dosage of IMP must be given to subject	Recommended	Required	Only if required by the Ethics Board	Not mentioned	
Compliance monitoring	Daily report by each subject during proving	Daily report by each subject during proving		Provers are instructed to record the details of drug intake and any change daily in the proforma provide to them. Record the date and time of intake and of number of doses taken Take detailed notes daily regarding feelings/ changes in mind and body after taking the drug, in the 'Prover's Day Book Proforma'. Proving master interrogates the prover to verify the signs and symptoms every day or at the earliest	Will be further elaborated so as to enhance quality of recording and reporting of symptoms
Code breaking/ Un-blinding	Should be done during the trial in the event of an adverse event of an adverse event	Should be done during the trial in the event of an adverse event of an adverse event	Required: Only done if required by Ethics board, a serious adverse event occurs, or after all data is locked into final unalterable database, done in such a way that minimises disclosure of information to personnel and subjects in the proving	Not mentioned	Will be included and elaborated
Therapeutic intervention			Required: Must be recorded, PI will determine if subject remains in trial, must be handled as an adverse event	The investigator or the investigating team should discontinue the proving if in his/her or their judgement, the proving, if continued, may be harmful to the prover	The need for therapeutic intervention and handling of adverse events will be included in the protocol
Proving duration	Must be defined; 21 days recommended	Must be defined; 21 days recommended	Required: defined run in period, test period duration, subject reporting and evaluation frequency Recommended: subject interview at least weekly, duration of reporting at least 6 weeks, in person evaluation at beginning and end of trial.	Not defined	Will be defined

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Run in observation period	7 days recommended (without placebo use)	7 days recommended (without placebo use)	Required, but not defined in terms of length	Not mentioned. Run in period is followed but is not included in the protocol	Specific duration of run in period will be added
Follow up period			Recommended to extend 3 months for final follow up	One month wash out period is maintained after each quota of drug is completed. After completion of proving, a terminal medical examination is conducted	The details of follow up period, observation period and washout period will be added
Sample size	Recommended to be noted	Should be noted	Required: at least 10 subjects must receive verum Recommended: at least 20 subjects in total.	Studies are multi-centric with 15 provers at each centre, and minimum 30 provers for each drug	The protocol will retain the same procedure
Selection of subjects for inclusion in analysis		All should be listed; placebo response should be listed separately	Requirement: All included unless process for exclusion listed in protocol prior to proving initiation	All included in analysis	The procedure will be detailed in the protocol
Data collection/ record keeping					
Record-keeping	Recommended in any format that can be locked to point of entry	Records kept in original hand writing; notes may be added by supervisor; once complete	Recommendation: Electronic format recommended, handwritten format is acceptable	At the centres records are kept in the hard form but at the compilation stage the data is maintained electronically	Will be further elaborated in the protocol
Record storage	Sponsor will provide for storage according to legal requirements.	Sponsor will provide for storage according to legal requirements.		Data processing cell maintains the record	Will be further elaborated in the protocol
Confidentiality	Recommended	Required; not detailed	Required: PI responsible to ensure PHI is protected	Recommended and maintained	
Case report form		(Example provided)		Specific format followed and included in the protocol	
Compliance report		Required	Required	Not mentioned in the protocol. As an organisational procedure, monthly reports are obtained from all research centres	Compliance report and monitoring procedures will be elaborated
Dosage report		Required	Required	Time and date of intake of drug is noted by each individual prover in the prover's diary and the symptom elaboration form, which are standardised formats	The protocol will retain the same procedure
Concomitant treatment		Required	Required	A participant is not included in the trial if he/she is on any other medication	The protocol will retain the same
Effect report		Required (but no detailed)	Required	Evaluated on the basis of Prover day book	The protocol will retain the same

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Adverse event report		Required	Required	Not included	Details of adverse events identification, handling, reporting, etc., will be included
Withdrawal reasons		Required	Required	Not mentioned in the protocol. As an organisational procedure, monthly reports are obtained from all research centre, where reasons for withdrawal are to be mentioned	Withdrawal procedures will be detailed
Subject diary					
Deletions of info	Must be crossed out, no erasure, date and initials	Must be crossed out, no erasure, date and initials	Requirement: changes locked to person who does the input	No clear instructions issued in the protocol, but during the training the instructions are issued to the proving master not to delete any information from the records	Deletions of information will not be permitted. The participants/ investigators will be instructed to highlight the changes and detail the same with due justifications
Data labelling	Form provides recommended date and source	Form provides recommended date and source	Required as to source and date	Included in the provers day book proforma	Data handling procedures will be detailed in the protocol
Data locking	Recommended		Required: data entry locked to only that source, must remain intact as originally input	As data is entered in hard copy, once entered cannot be altered	
Procedure for accounting for spurious, lost or misplaced data		Not required	Required: subject withdrawal of more than 10% must be accompanied by explanation, any missing data must be accounted, continuity of subject data must be guaranteed	Explanations are sought from the proving masters on the basis of the submitted monthly reports in case of dropouts along with their reasons	
Information for subject reporting	Can be by questionnaire or in person; direct interview recommended. Four different interview/ questionnaire scenarios are presented with pros and cons for each approach	Can be by questionnaire or in person; direct interview recommended. Four different interview/ questionnaire scenarios are presented with pros and cons for each approach	Requirement: Must be described before proving	Done by face to face interview and simultaneous recording in standardised formats	The protocol will retain the same
Symptoms in subjects own words	Recommended	Required	Required	Required	The protocol will retain the same

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Symptom qualities	Location (chart provided), Side of body, Time, kind of sensation, events related to symptom initiation, modalities related to amel./aggr	Location (chart provided), Side of body, Time, kind of sensation, events related to symptom initiation, modalities related to amel./aggr	Requirement: all symptoms will include body location, time of occurrence, duration, frequency or period city, severity on a scale, relation to other symptoms, modalities related to amel/aggr, identifiable potential etiologic factors	Symptoms detailed as time of intake of medicine, symptom observed, time of appearance and disappearance of symptom, location, sensation/ character, modalities, concomitants, extension/ direction, causation, clinic-pathological findings if any	The protocol will retain the same procedure
Determination of symptom type			Requirement: Supervisor will investigate any symptoms that resemble historical complaints to clarify relatedness and any relative change in symptom severity, frequency, duration	Proving master interrogates the prover and elaborates the symptoms	The protocol will retain the same procedure
Symptom classification	Recommended	Recommended	Required using a pre-determined scale	Recommended	Recommended using a pre-determined scale
Symptom classification scale	Rated by subject: NS, OS, AS, CS, ES, RS, FS, (new, old, altered, cured, previous existing, recent, family member)	Rated by subject: NS, OS, AS, CS, ES, RS, FS, (new, old, altered, cured, previous existing, recent, family member)	Recommended: scale recommended to be used including new, existing unchanged, existing improved, existing worsened, recurrence of past or historical symptom	Rated by subject: New symptom, recent symptom, old symptom, alteration un present or old symptom, an unusual symptom	Will be elaborated further
Symptom severity	Recommended; 1-5 scale for severity provided	Recommended; 1-5 scale for severity provided	Required: scale will be pre-defined by PI	Recommended. VAS scale is used to assess symptom severity	Will be elaborated
Frequency of data entry by subject	Recommended at least once daily		Requirement: Daily during at least time period of dosing and at least 2 weeks after last dose, final entry should occur at the final face to face contact with supervisor Recommended: Daily during run-in period, until last symptoms are noted, not recommended longer than 6 weeks after last dose of IMP	Recommended at least once daily, during the period of drug intake	Will be elaborated
Record frequency and timing of doses taken	Recommended			Included. The timing of intake of drug is recorded in the provers's day book proforma	The protocol will retain the same

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Meet on harmonization of drug proving

Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Input from investigator/ supervisor	Space present on form	Space present on form.	Requirement: must be predefined in protocol, supervisor must review every diary entry to ensure clarity of data	Separate standard form is included for the proving master to include the symptom details after interrogation and add his/her observations	The protocol will retain the same
Clarification of subjective data		Recommended on form.	Requirement: Occur during or after proving period only as a result of direct interrogation or examination of subject, used to qualify raw symptom data and ensure completeness and clarity of symptom information, must be completed prior to sealing of data	Recommended. Proving master is required to elaborate the symptoms of the provers which are then recorded in the symptom elaboration sheet	The protocol will retain the same
Observational data			Requirement: observational data should be recorded, Recommendation: supervisor should investigate and record any observed symptoms not noted in the diary by the subject	The observational data is recorded while elaboration of the symptoms in the 'symptom elaboration proforma' by the proving master	The methodology for recording of observational data will be included in the protocol
Biomarker testing			Recommended: Biomarker testing and recording is recommended for physical examination, radiographic, laboratory or other testing	Conducted at pre-trial and terminal medical examination stage. Appropriate laboratory tests are advised as per need to facilitate observation of correlation between and subjective and objective symptoms	The protocol will retain the same
Sealing of data			Requirement: once subject diary and supervisor input is completed and trial period is finished, no further changes to data can occur	Requirement: once participant daily proforma and proving master elaboration proforma is completed and trial period is finished, no further changes to data can occur, only clarifications are sought in case of incomplete information	The protocol will retain the same
Confidentiality	Recommended		Requirement: PI will ensure adequate protection of all PHI	Requirement. The provers confidentiality is maintained and prover identity is not disclosed at any stage	The protocol will retain the same

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Raw data exclusion			Requirement: permitted, but process must be established prior to trial Recommended: not to exclude data	Not mentioned	Data management procedure will be elaborated
Safety					
Ethics board approval	Not necessary	Required; homeopathic member required to be on the board	Requirement: must have approval of protocol prior to proving initiation	Required; institutional ethical committees consist of both homoeopathic and non-homoeopathic experts. Approval of protocol must prior to proving initiation	The protocol will retain the same
Assessment of safety	Recommended (if needed)	Required	Required	Required	The protocol will retain the same
Safety parameters		There is no need for defined safety parameters, because in HDP we don't focus on single parameters as blood pressure, pain or metabolic changes, etc., All changes on the physical, psychic and mental levels are observed		Not defined. Complete physical and pathological examination conducted at pre-trial and terminal medical examination stage	Complete physical and pathological examination conducted at pre-trial and terminal medical examination stage
Informed consent	Recommended	Required; example provided	Requirement: Required for all subjects, complies with U.S. Federal regulations, contains eight basic elements, is understandable by all subjects	Requirement for all participants	The protocol will retain the same
Adverse event reporting	Form provided	Form provided	Requirement: All shall be reported and managed according to regulations and ethics board requirements	Not included	Adverse event handling and reporting will be included in the protocol
Causation determination	Suggested for adverse events that require treatment or are ongoing		Requirement: a process for determination of likelihood of IPS causation of AE shall be in place prior to proving Recommendation: standard format for causation determination and scale provided.	The causation determination is a part of proving masters recording and assessment in the 'symptom elaboration proforma' by the proving master	Process for determination of causality will be included in the protocol further
Report of causation			Requirement: must be reported for all AES using ICH descriptors 1. Possibly related 2. Unrelated	The causation determination is a part of proving masters recording and assessment in the 'symptom elaboration proforma' by the proving master. Timeline for reporting is included in the protocol	Reporting procedures will be further elaborated in the trial

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Meet on harmonization of drug proving

Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Adverse drug reaction management	Statement that ADRs are non-applicable to proving	Statement that ADRs are non-applicable to proving	Requirement: all AES with possibly related causation must be reported and managed as ADRs per ICH guidelines including provision of report of causation assessment, report of AE timeline and outcome, report to cognizant authority and IRB per regulations, report to the manufacturer	Not mentioned	Adverse event handling and reporting will be included in the protocol
Serious adverse events			Requirement: must be recorded, must be reported to ethics board per their protocol, to manufacturer within 24 h, to any regulatory authority as required, a predetermined protocol for SAE management should be part of the protocol	Requirement	Adverse event handling and reporting will be included in the protocol
Emergency contact information provided to all subjects	Recommended	Required	Required	Provided in prover information sheet	The protocol will retain the same
Emergency protocols			Requirement: fail safe procedure for un-blinding is required	Not mentioned	Will be added
Therapeutic intervention evaluation			Requirement: PI must investigate whether therapeutic intervention in any AE could potentially effect quality of proving, and determine if subject should be discontinued	PI investigates and consults the experts for their opinion. Participant will be referred to concerned consultant for necessary treatment	The protocol will retain the same
Subject withdrawal criteria			Requirement: voluntary withdrawal must be permitted at any time, may occur at the direction of the PI at any time during the trial as long as the criteria and timing are recorded, Reasons for withdraw must be reported	Not mentioned clearly	Will be included
Locking of data for withdrawn subjects			Requirement: data must be locked with no further data entry permitted	As data recording is done by in hard copies, so once the entries are made, data cannot be altered	Will be included
Rules for stopping the proving	If 3 or more provers develop serious adverse proving symptoms			Not mentioned	Will be included

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Title	LMHI	ECH	HPCUS	CCRH	Discussion and outcomes
Adverse Event handling flow chart			Provided	Not mentioned	Will be added
Data analysis					
Symptoms analysis	Recommended to not be done using standard statistical methods	Symptoms, which are not though to belong to the drug picture, should also be stated, but in a separate chapter, so they are not lost, but marked in a specific manner	Required: Specific methodology given	Not mentioned	Specific methodology will be included
Characterising feature analysis	Recommended and list of features provided		Recommended and template provided	Not mentioned	HPCUS recommendation will be followed.
Characteristic symptom determination			Requirement: shall be evaluated and reported using criteria provided.	Not mentioned	HPCUS recommendation will be followed
Report of analysis			Must include: quality and number of proving symptoms, quality and number of similar proving symptoms in one or multiple provers	Done while compilation and also mentioned in the monograph	Data analysis procedure will be detailed
Use of control results		Should be reported but not include in analysis	Requirement: should not be included in analysis of remedy picture produced, any use of control result must be established prior to proving initiation Recommendation: may include in the report of symptoms experienced by subjects provided they are clearly labelled as control recipients	Should be reported, record is maintained but is not included in drug pathogenesis	The protocol will retain the same procedure
Monograph report	Follows ICH guidance with specified exceptions	Follows ICH guidance with specified exceptions	Requirement: follows ICH guidance, with specified exceptions	Not mentioned. All proving data is published	Publication policy of the Council will be followed
Financial disclosure			Requirement: must be provided by PI and supervisors if not employed by PI, must include honoraria, fees paid by sponsor, proprietary interested in tested product, significant equity interest in the sponsor or manufacturer	Not applicable	

HPCUS: Homeopathic Pharmacopoeia Convention of the United States, LMHI: Liga Medicorum Homeopathia Internationalis, ECH: European Committee for Homeopathy, CCRH: Central Council for Research in Homoeopathy, HDP: Homeopathic Drug Proving, ADR: Adverse drug reaction, ICH: International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, IMP: Investigational medicinal product, NS: New symptom, OS: Old symptom, AS: Altered symptom, CS: Cured symptom, ES: Previous existing symptom, RS: Recent symptom, FS: Symptom in family member, PI: Principal investigator, IPS: Investigational proving substance, AES: Adverse event(s).