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Second Edition of LMHI Guidelines for a Homeopathic Drug Proving (HDP)

History of this document:

- The European Committee for Homeopathy, sub-committee Proving, published in November 2004 a draft of “Homeopathic Drug Proving Guidelines”.
- The LMHI International council decided in May 2010 to seek collaboration with ECH for the elaboration of a LMHI Guidelines.
- First draft document elaborated in September 2010 and submitted to all LMHI Vice-presidents.
- Second amended draft presented to and accepted by the I.C. during the 66th LMHI congress.
- The Research W.G. decided in NARA ‘2012’ to discuss the question of placebo control for proving and to prepare a second edition of LMHI Guidelines.

Introduction:

Homeopathic drug proving is essential in the development of the homeopathic art of cure. After clinical verification of the collected symptoms, it provides a necessary tool to find the most appropriate remedy for the patient.

Many theories, methods and protocols have been established. Meanwhile ethical and legal requirements have become more and more important (Declaration of Helsinki (2008), ICH-Guidelines January (1997), revised EU directives on Clinical trials (2012)).

A homeopathic drug proving (HDP) is nowadays considered to be a clinical trial, as such these Guidelines are based on the ICH “Note for Guidance on Good Clinical Practice” (CPMP/ICH/135/95).

Guidelines are not strict rules but will ensure that all relevant items necessary for a Homeopathic proving respecting Good Clinical Practice (GCP) are taken into account. It will help also to obtain comparable results from provings of a same medicine in different places in the world. As example we will propose the most commonly used model of protocol in the world, of course starting from this proposal, all adaptations for another model are possible.

Used wording in this document refers to GCP, if needed, see “Glossary” at the end of this document.



Discussion:

The LMHI Research W.G. intensively exchanges about the usefulness of a placebo control group in a proving (low risk interventional clinical trial).

As result we can conclude that the experience of many researchers is that a placebo control can be useful to reach the best qualitative symptoms, avoiding a lot of mistakes due to “general unspecified trial effects”. It is also useful to insure further reproducibility and to make a link with further clinical trials reducing bias and as such facilitating the registration of the homeopathic medicine. Symptoms, obtained using this design, are more reliable.

In the context of a provings trial, the aim of a placebo control group has no role in proving efficacy. The aim is only to gather qualitative data (see glossary) for bias reduction, therefore a placebo group of 20% of the participants is enough (HPUS guidelines). The cross over design would be the best design avoiding the loss of good provers and loss of sensitivity. The use of different dynamisations in different arms can be recommended.

Since the very begin of the development of homeopathy (Hahnemann) the proving is part of the education of a homeopath. It helps the prover for a better understanding of the nature of the qualitative homeopathic symptoms and opens his mind to research procedures. A control group makes the prover more alert to scrutinize reliable symptoms.

Because of the very long tradition in provings, the absence of contrary effects (very low risk), the use of well-defined qualitative and safe medicines (using dilution above FSD), the qualitative research design and the need for provings for education and registration, the advice of an ethical committee for each performed proving would not be necessary.

Another design comparing the prevalence of each obtained symptom in the general population and in the provers groups (Bayes’ theorem) is also able to select accurately significant, reliable symptoms. As such it is of great importance to select a generally representative population. This design will be further tested in an international multicentric proving design.

Bayes’ theorem is an algorithm for observational and experiential knowledge, like medical diagnostics and homeopathy. The theorem states: a specific variable (symptom) is an indication for a specific outcome (diagnosis or ‘cure’ by a specific medicine) if the symptom occurs more frequently in the target population than in the remainder of the population. The formula expressing this theorem is:

Posterior odds = LR * prior odds

Odds = chance/(1-chance); chance = odds / (1+odds).

LR = Likelihood Ratio = prevalence in target population / prevalence in remainder of the population



Bayes' theorem has important consequences: on the one hand it provides a solid scientific ground for homeopathy, on the other hand it has important consequences for symptoms arising from provings and clinical experience. A specific symptom is indicative for a specific homeopathic medicine **only if** the prevalence of the symptom in the population under study is greater than in a population not responding to the same medicine. This principle is in fact also visible in Hahnemann's aphorism 153 about peculiar symptoms; peculiar symptoms have low prevalence in the general population. In this case we don't need to know the prevalence of the symptom in the general population because it is most probably lower than in the proving group or 'medicine-population' (the population responding well to a specific medicine).

An example: if one in 20 provers has headache during the proving, does that mean that headache is an indication for the medicine under study? Probably not because in the general population more than 5% have headaches. If 15 out of 20 provers had headache this would be meaningful because it is unlikely that 75% of the general population have headaches. It would be helpful, however, to know the prevalence of headache in the general population for sure. This could be retrieved from literature. According to the WHO: *"It has been estimated that 47% of the adult population have headache at least once within last year in general."* <http://www.who.int/mediacentre/factsheets/fs277/en/>

For many homeopathic symptoms data about prevalence in the general population are not available in literature. For these symptoms we could create a panel outside the proving population that can be interviewed about symptoms arising from provings. The size of such a panel should not be underestimated, probably hundreds of participants. On the other hand, with modern internet techniques it is relatively easy to achieve in, say, a population of students, practitioners and dedicated patients.

The purpose of a placebo group may be also to provide a sample of that 'remaining population' that is otherwise subjected to the same experimental conditions as the subjects who receive the homeopathic medicine under investigation in the provings trial. It follows therefore, and given that a placebo group is critically necessary to limit risk of bias, that a provings trial necessarily comprises a placebo-control group.

Still some homeopaths (mostly in Europe) are not recommending a placebo arm. LMHI intend to stimulate more research on this question in the future.



In order to arrive to a standardized Homeopathic Drug Proving Protocol, 2 aspects must be considered, the content of the protocol and the case report form:

A/ Content of the Protocol

General information:

- a) Protocol title and identification (number and date);
- b) Name and address of sponsor and monitor (if other than sponsor);
- c) Name and title of the person(s) authorized to sign the protocol and the protocol amendments for the sponsor (i.e. principal investigator);
- d) Name, title, address and telephone number(s) of sponsor's medical expert for the trial (if applicable);
- e) Name(s) and title of the investigator(s) (proving doctors), who is (are) responsible for conducting the trial (proving) and the address(es) and telephone number(s) of the trial site(s) (if different groups are taking part in the proving);
- f) Names and addresses of other institutions involved in the trial (i.e. pharmacies).

Background and medicine information:

- a) Name and description of the investigational product (proving medicine), exact information is mandatory to guarantee reproducibility as well for the manufacturing process as for re-provings (see checklist for proving medicine Appendix 1);
- b) Summary of findings from previous provings on the medicine if available (specific literature references and check if statement);
- c) Summary of the known and potential risks and benefits, if any, to human subjects;
- d) Description of and justification for the route of administration, dosage, dosage regimen and treatment (administration of proving medicine) period(s) (as soon as proving symptoms occur, the intake of the remedy will be stopped);
- e) A statement that the trial (proving) will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s);
- f) Description of the population under study:
 1. Recruitment of volunteers (it is recommended to state how volunteers had been recruited aimed at verifying if different methods of recruitment could lead to different results);
 2. Ethnic origin of volunteers (to be documented in their individual case taking forms);
 3. Location of the proving;
 4. Language (example: the case taking, filling of diaries and reporting symptoms will be done in Portuguese but accompanied with an English translation; at least the proving symptoms will be documented in their original wording by the director of the proving).
- g) References to literature and data that are relevant to the trial (proving) and that provide background information for the trial (proving). As a HDP protocol may be judged e.g. by members of ethical committees not familiar with Homeopathy, a general information about Homeopathy would be included.



Trial (Proving) objectives and purpose:

This protocol is designed to conduct HDP for the purpose of creating or amending a symptom list and drug picture of Homeopathic medicines. This is more an aspect of quality than of quantity. A proving is not the proof of the medicine efficacy but it is aimed at testing its qualities. The symptoms will be collated and communicated so that they can be clinically verified (law of similar).

Trial (Proving) design:

- a) Description of the primary endpoints and of secondary endpoints, if any, to be measured during the trial (Proving). The purpose of a HDP is not to show the efficacy, but to obtain complete individual symptoms of a drug. It is a systematic observation and recording of reversible symptoms which occurs after the defined administration of a homeopathically potentized and diluted drug to healthy persons (volunteers). The 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 taking of the case history.
- b) Description of the type/design of trial (Proving) to be conducted (e.g. double blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages (scheme of personal contact to proving doctor, time schedule, inclusion and exclusion criteria, preliminary observation period, administration scheme, observation period, post observation period, processing of data, final report). A three arm design can be considered, two different remedies and a placebo arm. It may allow a better comparison of obtained symptoms and as such a better conclusion on the specificity of the symptoms but cost/benefit balance is not established.
- c) A description of the measures taken to minimize/avoid bias, including randomization and blinding. In HDP the proving medicine is not applied to create predefined effects and prove efficacy, but to describe the individual response of every volunteer to the application of the medicine. Therefore volunteers and investigators should not know the proving medicine. They are not only blind to the question if medicine or placebo is given, but also to the questions what the medicine is and what the level of potency is taken. For proving, even if no blanks (placebos) are used, to reduce symptoms of anticipation the name of the proving medicine would remain secret for volunteers and investigators. The use of placebo is not to measure a placebo effect, but to try to raise the critical alertness of the volunteers and to find out how far the quality of “proving symptoms” under placebo differs from real “proving symptoms”. Whereas the meaning of “placebo” is different in conventional trials and HDPs, it is proposed to use a better wording such as “blanks”.
- d) A description of the dosage regimen in the investigational product(s). Also include a description of the dosage form, safety, storage, packaging and labelling of the investigational product(s). Packaging has to be done in a way that contamination among proving substance and blanks is prevented. Aluminium foil has proved to prevent contamination during storage (G.I.R.I.); manufacturing and packaging of both products would not be done in the same area. If possible, contacts between provers would be avoided also.



- e) Expected duration of subject (volunteer) participation, and a description of the sequence and duration of all periods, including follow-up, if any. This comprise education of volunteers (sense and objectives of proving, use of the diary), extensive case history and homeopathic interview (in- and exclusion criteria), preliminary observation period (at least one week filling out already the diaries, regular contact with the proving doctor, failure in keeping the diary properly may lead to exclusion), contact with volunteer, period of observation and post observation period (daily telephone contact and personal contacts during observation, fewer in post observation period).
- f) A description of the “stopping rules” or “discontinuation criteria” for individual subjects (volunteers), parts of trial (proving) and entire trial (proving).
- g) Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any. (Who produced and provided them? Who is responsible for controlling all the steps, including randomization?).
- h) Maintenance of trial treatment, randomization codes and procedures for breaking codes. (example: randomization and coding by an independent defined institution, the sealed codes will be kept by “name of principal investigator” or of person who keeps them and is responsible for decision to open in case of adverse events –time, reason and person who opened it has to be marked on the envelope–, at the end of the proving after final inclusion and exclusion of symptoms, the code will be broken).
- i) The identification of any data to be recorded directly on the Case Report Forms (CRF) and to be considered to be source data. For HDP only a personal case report form of each volunteer is needed.

Selection and Withdrawal of subjects (volunteers):

- a) Subject (volunteer) **inclusion criteria**. The volunteer must be healthy in the sense that he 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. A medical history and physical examination should confirm this. The person must be trustworthy, able and ready to express and describe his experiences during the proving. There should be no plans for important life changes like moving, change of job, marriage, etc. The usual habits and conduct of life should be continued. The person should not plan to begin medical treatments like dentistry, surgery or psychotherapy during the drug proving. Age over 18 years.
- b) Subject (volunteer) **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 three months (or being mentioned in the diary). Surgical treatment within past two months. Pregnancy, breast feeding. Under age of 18.
- c) Subject (volunteer) **withdrawal criteria** (i.e. terminating proving) and procedure specifying:
 - 1. When and how to withdraw subjects (volunteers) from proving. Stopping of intake of proving medicine as soon as symptoms occur does not mean withdrawal from the proving; only in case of a serious adverse event will a volunteer be withdrawn.



2. The type and timing of the data to be collected for withdrawn subjects (volunteers). If a volunteer has to be withdrawn because of a serious adverse event, the data is kept together with those of all other volunteers in the CRF of the volunteer, marked as “withdrawal”.
3. Whether and how subjects (volunteers) are to be replaced. Usually there is no replacement of withdrawn volunteers in a proving.
4. The follow-up for subjects (volunteers) withdrawn from the trial (proving). See assessment of safety.

Treatment of subjects, administration of proving medicine to volunteers:

- a) The description of the administration of proving medicine include the name(s) of all the products, the dose(s), the dosing schedule(s), the route(s)/mode(s) of administration, and the treatment period, including the follow-up period(s) for subjects (volunteers) for each investigational product proving / trial (proving) administration group / arm of the trial (proving). Example: the proving medicine will be administered orally as opened capsules, the content of which is applied sublingually. One dose about every two hours, maximum 6 times for one day, with minimum 15 minutes before or after eating. The exact time of drug intake has to be stated in the diaries. As soon as proving symptoms occur, the intake of the remedy will be stopped.
- b) Medication(s)/ treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial (proving). Example: in case of serious adverse events, the investigator (proving doctor) decides, if an antidote is given (see assessment of safety); no concomitant medication.
- c) Procedures for monitoring subject (volunteer) compliance. To ensure the proper intake, the volunteer will report to his proving doctor at the end of each day of intake.

Assessment of results:

- a) A proving is not a drug efficacy trial.
- b) Assessment of efficacy in HDPs means observing of proving symptoms (qualitative research). A volunteer must note down distinctly the sensations, sufferings, accidents and changes of health s/he experiences at the time of their occurrence, mentioning the time after the ingestion of the drug, when each symptom arose. 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 the volunteer, shown during the taking of the case history. However, the ultimate proof of whether a symptom really belongs to a remedy cannot be obtained while conducting the HDP, but only in a second step afterwards, by clinical verification. The clinical verification occurs when the proving symptoms has led to the choice of the remedy, following the similarity rules, and has cured these symptoms in the patient. Some criteria to estimate the probability of a symptom belonging to the proving medicine exist (see statistics).



Assessment of safety:

Even for the participation of healthy volunteers, basic principles mentioned in the World Medical Association Declaration of Helsinki (2008) are of application. The design of all studies should be publicly available.

- a) Specification of safety parameters (if needed).
- b) All changes on the physical, psychic and mental levels are observed. Safety for the volunteers is an important prerequisite in planning clinical trial (proving). In HDP, the proving medicine is administered in safe dilutions, which excludes toxicity risks. In HDP there is no conventional pharmacodynamic action of the medicine to be considered, we are only looking at “reactions” to these homeopathic dilutions so called “proving symptoms”. Additionally, the administration of the proving medicine usually will last only for a short time, which again minimized the probability of adverse events. All volunteers will be informed about the objectives, potential risks, inconveniences and benefits of the trial and will sign an informed consent form before beginning of the HDP.
- c) Procedures for eliciting reports of and for recording adverse events and intercurrent illnesses:
 1. Adverse events.
 2. Adverse drug reaction, as stated before, the term “adverse drug reaction” is not appropriate for HDPs.
 3. Adverse proving symptoms:
 - Adverse events and adverse proving symptoms, as well as intercurrent illnesses will be recorded on the Adverse Event Form, attached to the Case Report Form (CRF) of each volunteer.
 - The beginning will be stated and described in the diary of the volunteer.
 - An adverse proving symptom might require the withdrawal of the volunteer from the HDP.
 - The envelope containing the trial codes will be kept within easy reach by the proving doctor or his designated assistant, only to be opened in case of a severe adverse event or a severe adverse proving symptom. If this occurs, the drug intake will be stopped immediately, the code will be broken and, in case of verum, either an antidote will be given, or the doctor in charge will take care of the volunteer personally and organize adequate treatment.
 - The sponsor and principal investigator will be informed within 24 hours by email or fax.
- d) The type and duration of follow-up of subjects (volunteers) after adverse events. It is recommended to prepare a scheme for follow-ups after adverse events. Example: Any volunteer experienced an adverse event will be followed up free of charge as long as the symptom(s) exist(s), which caused the withdrawal from the proving or it is determined that the symptom(s) were not caused by the proving medicine.



Statistics:

- a) In HDP there is no measurement of efficacy, but description of individual proving symptoms. Only qualitative research evaluation can be applied. The value of proving symptoms does not ultimately depend on number of volunteers who had a particular symptom. Symptoms obtained in a small number of volunteers, are equally valuable. The evaluation will not be done by conventional statistical analyses, but by compilation of the proving symptoms in different categories, representing a certain probability to be associated with the remedy and therefore are the most important ones for further clinical verification.
- Example: a symptom will belong to the remedy with great probability if at least one of the following criteria is met.
1. Occurrence of the symptom in two or more volunteers;
 2. Objective, measurable signs and symptoms;
 3. Distinct intensity of the symptom;
 4. Occurrence of the symptom several times shortly after administration of the drug;
 5. Recurrence of the symptom several times over the course of a number of days;
 6. Recurrence of the symptom using different potencies;
 7. Striking, singular, uncommon symptoms;
 8. Striking, seldom or paradox modalities and/or concomitants of the symptom;
9. Mutual pathophysiology in serious symptoms (i.e. inflammation in different joints).
“There will be a ranking of intensity, given by the volunteers and a classification, as to whether it was an old, new or altered symptom that was experienced. Symptoms, which are not thought to belong to the drug picture, should also be stated, but in separate chapter, so they are not lost, but marked in a specific manner. In the final report, symptoms will be compiled according to the format of Clarke’s *Materia Medica* and/or *Kent Repertory*, English editions. (In the *Dictionary of Practical Materia Medica*, published between 1900-1902 by J.H. Clarke's, each remedy is described as to source, description, clinical application, characteristics, relations, and the symptoms themselves.) (In *Kent's Repertory*, first published in 1897, 1,423 pages, 642 remedies, the symptoms from provings and materia medica’s are classified in chapters from *Mind to Generalities*, to each symptom are the remedies linked.)”
- b) The number of subjects (volunteers) planned to be enrolled. In multiarmed trials (proving), the number of enrolled subjects (volunteers) projected for each arm of the trial should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial (proving) and clinical justification. Example: there will be 12/15 male and female volunteers in each proving, three of them receiving blanks (or placebo). The blank is given to keep volunteer unsure, whether they got an active medicine (verum) or blank. This number (12/15) has been sufficient to give good proving symptoms in former provings.
- c) In HDPs adverse events are very seldom. Unlikely, if 3 or more volunteers are developing serious adverse proving symptoms, the proving will be stopped.
- d) The selection of subjects (volunteers) to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects). All volunteers who reported symptoms should be included in analyses of symptoms. The symptoms obtained under verum or blanks (placebo) must be listed in different groups.



Direct Access to Source Data/Documents:

The sponsor should ensure that it is specified in the protocol or other written agreement that investigator(s)/institution(s) will permit trial (proving) related monitoring, audits, IRB/IEC review and regulatory inspection(s), providing direct access to source data/documents. This access to source data and original wording of a symptom is also crucial for further research in homeopathy such as confirmation of the proving symptoms and clinical verification. Ideally a repertory should provide the information, stating from which volunteers a symptom has been assessed.

Quality Control and Quality Assurance:

The Case Report Form (CRF) is one of the most important documents for quality control in clinical trials (HDPs). It is the reference document for Audit and Monitoring. The entries therefore have to be complete and correctly represent the data obtained. In case of corrections, the original item must be kept legible (only cross out, not erase) and the correction must be signed with date and initials. This is useful to trace back the changes and allows eventual further inquiry. The investigator confirms the correctness of the data in the CRF by this signature.

Ethics:

Description of ethical considerations relating to the trial (proving) must be considered. See a.o. above "Assessment of Safety".

Data Handling and Record Keeping:

Also notes eventually added by the investigators, proving doctor(s) or other responsible persons will be kept within the CRF of each volunteer. The HDP is considered to have been completed on the day of the delivery of the final report to the sponsor. After the completion of the HDP, the sponsor will provide secure space for the records to be kept as long as required by legal regulations. In HDP, keeping the obtained data is not only necessary for legal purpose but also for confirmation and/or clinical verification and use of the proven medicine. Often the therapeutic reaction to a homeopathic remedy, applied according the law of similar, is the more reliable, when the wording of the volunteer in the proving corresponds with the words of a patient.

Funding and Insurance:

In HDP which are done within the homeopathic community, a fee is not usually paid to volunteers. The proving medicine and blanks are commonly offered by a competent pharmacist or pharmaceutical company. For a homeopathic proving medicine the notion of first safe dilution is applicable to avoid any risk for volunteers. It is only expected that reversible proving symptoms will be experienced by the volunteers after administration of the proving medicine. Nevertheless, this risk will be covered by insurance for the volunteers and proving doctor(s), provided by the sponsor (person responsible for the proving).



Publication Policy:

This is part of an agreement with the sponsor.

Supplements:

The protocol and the clinical trial (proving)/study report are closely related. Further relevant information can be found in the ICH Guidelines E3 for structure and Content of Clinical Study Reports.

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B/ Case Report Form (CRF) for Homeopathic Drug Proving (HDP)

General information:

A case report form is a record of the data and other information on each subject (volunteers) in a trial (proving) as defined by the protocol. The data may be recorded on any medium, including magnetic and optical carriers, provided that there is assurance of accurate input and representation, and allows verification. As stated in the Informed Consent Form, all information has to be kept confidential with respect to the identity of the donor of the information.

In order to present the results of a clinical trial (proving) adequately, it is essential that a fully comprehensive collection of information on the subject (volunteer), the administration of the proving medicine being investigated and the outcome of the protocol procedures is available. This is done, using a Case Report Form (CRF) which should be established to facilitate observation of the subject (volunteer), and which also takes the protocol for the trial into account.

In establishing a CRF, the following items should be considered. Omissions of one or more of these items should be explained:

- a) Date, place and identification of the trial (proving);
- b) Identification of the subject (volunteer);
- c) Age, sex, height, weight, and ethnic group of the subject (volunteer);
- d) Particular characteristics of the subject (volunteer), e.g. smoking, special diet, pregnancy, previous treatment;
- e) Diagnosis, indication for which the medical treatment is administered in accordance with the protocol. Since a HDP is not a medical treatment, the indication is “the administration of the proving medicine is aimed at observing proving symptoms that could be caused in reaction to the intake of it in healthy volunteers”.
- f) Adherence to the inclusion/exclusion criteria;
- g) Duration of disease, time of last exacerbation (if applicable). In HDP make sure that the volunteer is healthy in the sense of the definition given in the protocol;
- h) Dose, dosage schedule and administration of the medicinal product, notes on compliance;
- i) Duration of treatment, administration of proving medicine;
- j) Duration of observational period;
- k) Concomitant use of medicinal products and non-medicinal interventions/therapy;
- l) Dietary regimens;
- m) Recording of the effect parameters (incl. date, time, recorder’s signature);
- n) Recorded adverse events. Type, duration, intensity, etc; consequences and measures taken (adverse event report form);
- o) Reason for withdrawal (if applicable) and/or breaking of the code (adverse event report form);
- p) Following forms (6) must be filled in, checked for signature and attached to the CRF of each volunteer:



CRF – Informed Consent Form

Study: Homeopathic drug proving of “*medicine name*”

Name and first name of Participant:

I hereby confirm that I have been informed in detail about the purpose and conduct of the homeopathic drug proving. The possible risks and benefits have been thoroughly explained and all my questions or concerns have been answered. I have fully understood the purpose, goal and procedure of the homeopathic drug proving. My participation is absolutely voluntary at all stages of the study and refusal to participate or my withdrawal at any stage will not in any way subsequently disadvantage me. All personal information, given by me orally or in written form, will be treated as strictly confidential in accordance with legal requirements. Furthermore, I have been informed that all participants are insured in case any severe adverse events associated with the intake of the proving substance should occur.

If I have any questions or if any adverse events during the study, I have been provided with a 24-hour contact phone number where I can reach my proving doctor or one of his/her colleagues.

.....
Date

.....
Participant signature

.....
Date

.....
Investigator signature



Participant Information Sheet

(This text is an example, has to be adjusted according to each particular proving protocol)

Study: Homeopathic drug proving of “*medicine name*”

Purpose:

The aim of this homeopathic drug proving is to constitute a homeopathic remedy picture at hand of the symptoms associated with the application of the proving substance. The objective of the homeopathic drug proving is to find out the entire realm of action of the proving substances, with respect to both the subjective and objective symptoms.

Outline of the proving: *In this section, a summarised description of the trial will be given. There will be detailed information about the trial by the principal investigator of the homeopathic drug proving. After this there will be a personal examination and evaluation by the proving doctor and, when you meet the inclusion criteria and have signed the Informed Consent Form, the proving begins.*

There will be “x” male and female volunteers taking part in each proving, “x” of them receiving blanks. All participants will be trained in keeping a diary during the proving, to note down daily entries during all phases of the homeopathic drug proving. The homeopathic drug proving will have a maximum duration of “x” weeks in total.

1) Preliminary observation period.

During this phase, all symptoms will be noted, which may occur without taking a proving substance or remedy.

2) Administration of proving substance / Period of observation.

The homeopathic preparation will be administered on the first day of this phase, following a set schedule. You are likely to experience reversible symptoms caused by the proving substance. All symptoms that occur due to the substance are noted down in the diaries. During this phase, each participant will be in daily contact with the proving doctor, to report his/her wellbeing and symptoms. Normally the symptoms associated with the intake of a homeopathic proving substance are not severe and will have ceased after a few days. In case of strong symptoms or adverse events, immediate appropriate care will be organised. Of course, there is an insurance covering every participant to compensate for any ongoing adverse events caused by the drug. There are also potential benefits arising out of a homeopathic drug proving, because former symptoms may be ameliorated or healed by taking the substance.

3) Post observation period. The diaries are still filled in, to see, if further symptoms occur.

Withdrawal from the homeopathic drug proving: Every participant has the right to withdraw from the proving at any stage for whatever reason without affecting their future medical care.

Confidentiality: The personal statements are kept **strictly confidential**, the participants will be known only by a special code in the records.

24-Hour– Emergency – Number: In case of emergency there will be a telephone number where a doctor can be reached at any time.



CRF – Homeopathic Interview Form (HIF)

General considerations for the homeopathic interview and for the structure of diaries (journals):

It has to be decided whether the homeopathic interview is taken personally by the proving doctor or if the volunteer fills in a questionnaire. The use of a questionnaire is less time consuming for the proving doctor, therefore this method will be used if a proving doctor is in charge of many volunteers. It should be clearly stated that it is a great disadvantage for the quality of the proving, if the proving doctor cannot provide a minimum of fifteen to twenty five minutes per day for each one of the volunteers during the observation period of the proving. The way of taking the case (direct interview or questionnaire) may considerably influence the symptoms noted for each volunteer.

There are results in clinical trials, where the efficacy of a drug has “changed” when the effect of the same drug has been stated either in the volunteer’s own words, or by filling in a questionnaire. It has been shown in trials, performed with Flurazepam by Kohnen and Lienert (Placebo-Effekte-Ein Phänomen der Untersuchungsmethode? In: Das Placeboproblem S.49-60. Gustav Fischer, Stuttgart 1986), that more placebo effects are reported, when questionnaires are answered, than with verbal description of effects (63% verum and 17% placebo effects with free description = 46% efficacy; versus 83% verum and 58% placebo with questionnaire answering = 25% efficacy, related to five quality items of sleep). This could mean, for the homeopathic interview, that several of the symptoms mentioned in filling in a questionnaire may not be very reliable and that symptoms mentioned in the diaries after the administration of the proving medicine may be given only because they are interrogated in a questionnaire.

The consequence of this would be to analyse the symptoms given by the volunteers very thoroughly, whether given by free description or by filling in a questionnaire. This is only possible when there is close contact between proving doctor and volunteer and requires a lot of experience from the proving doctor.

If only questionnaires are filled in, it will be very difficult to judge the symptoms later and the quality of a proving will be much lower when there is no personal contact between proving doctor and volunteer during case taking and/or observation period. This point has to be stressed, because the design of a drug proving protocol depends to a great extent on this question, and a proving doctor can only see a limited number of volunteers per day, since most provings are done by doctors during their day-to-day practice.



Four suggestions for performing the case taking (homeopathic interview):

- 1. The proving doctor takes the case personally with each of his volunteers and s/he fills in the Homeopathic Interview Form (HIF) of the volunteer at the case taking. Afterwards he has a second interview with the volunteer when any points can be answered, which may have been forgotten during the first interview. The advantage is that the spontaneous report is not lost and no item will be forgotten. The disadvantage is that it takes up a great deal of time.*
- 2. The proving doctor takes the case personally with each of his volunteers and the volunteer fills in the HIF after having had the interview with the proving doctor. The advantages are the same than in the first suggestion and additionally less time consuming for the proving doctor. Volunteers may be able to write down symptoms, which they were not able to express verbally. The disadvantage is that it takes up a great deal of time for the volunteer and eventually problems of compliance, because the volunteer has answered most of the questions already during the personal interview.*
- 3. The volunteer fills in the HIF before the interview and gives it to the proving doctor in advance, so that the proving doctor can read it beforehand. The advantage is that the proving doctor will already know the most important items and can complete any lacking information. No item will be forgotten. The disadvantage is the spontaneous report is lost. This way also takes a great deal of time, but volunteer and proving doctor have only to meet once for the completion of the interview.*
- 4. The volunteer fills in the HIF and sends it to the proving doctor. No personal interview is done. The advantage is that it is least time consuming. No item will be forgotten. The disadvantage is that the spontaneous report is lost. The individuality of the volunteer is not fully experienced by the proving doctor.*

The method of case taking to be used should be stated in the protocol, together with the reasons for choosing that method.



Homeopathic Interview (Case Taking) Form (HIF)

Notes:

** it is assumed that every proving doctor will do the case taking personally with the volunteers for whom he/she is responsible for and the he/she uses this form as a reminder. Accordingly this form is not meant to be handed out to a volunteer. It has been designed to give the proving doctor a guideline to ensure that no important information will be forgotten.
* Also, in case the proving doctor does not use this form, after the proving, ALL NOTES taken during the original case taking must be kept in the Case Report Form of each volunteer!*

Given name(s)

Surname

Address Zipcode

City Birthdate/Place

Telephone (private) (work)

Occupation Retired

Education Employed by/as

Married Separated Divorced Single Widowed

Live with: Spouse Parents Relatives Friends Alone

How is your general state of health? Excellent Good Fair Poor

Bodyweight kg - Height m - Blood pressure/..... mmhg (if known)

Health problems, which you have now or have had in the past.

Chief complaint:

Others:

1)

2)

3)

4)

When did your main health problem begin?

What was your general life situation at that time? Were there important changes on a personal level or in your external circumstances? Do you think, there could be a correlation with the onset of the complaint(s) and your circumstances at that time?

.....
.....
.....



Previous illnesses

	when		when		when
Mumps	Polio	Whooping cough
Measles	Diphtheria	Other
German Measles	Chickenpox		

Have you had **vaccinations**: DT Pertussis Polio MMR
 Hib BCG Influenza Tick fever Hepat.A/B Other

Did you (or your parents) ever notice adverse reactions or illnesses after a vaccination?

Have you had or do you still have any other **illnesses or complaints** e.g.:

Allergies	Eczema	Alcohol abuse	Asthma	Herpes	Anorexia	Bulimia
Gout	Goiter	Depression	Heartburn	High Blood Pressure		Pneumonia
Psychosis	Gonorrhoea	Drug abuse	Urticaria	Chronic infections		
Major teeth problems						

Hospitalizations/Surgery

Illness	Date	Hospital/Town
.....
.....
.....
.....
.....

Medications

Please list all prescription medication, you are presently taking

Other likes Birth Control Pills, Hormones, Thyroid replacement, Vitamins, etc.

Family history

Please list the years of birth of your family members and the major illnesses or complaints. If they are deceased, please state the cause of death and the year, they died.

	Year of Birth	Died	Cause of death/major illness(es)
Mother
Father
Brother(s)

Sister(s)

Maternal grandmother
Maternal grandfather
Paternal grandmother
Other(s)



Has anyone in your family had one of the following illnesses:

Cancer	Heart	Varicosis	Stomach	Depression	HBD
Diabetes	Allergies	Gallbladder	Seizures	Suicide	Stroke
Gout	Hay fever	Kidneys	Asthma	Venereal disease	
Tuberculosis	Rheumatism				

Mental symptoms

Which experience in your life (pleasant or unpleasant) has affected you most deeply, i.e. are you still mourning for a relative, the death of whom you did not overcome, has there a mortification you are still suffering from, etc. ?

.....
.....

How do you cope with your worries?

.....
.....

What would be enough for you to make you weep?

.....
.....

How do you respond to consolation?

.....
.....

How do you tolerate having to wait?

.....
.....

Please describe any fears/dreams that you had in childhood or you have now, as well specific as general fears (dogs, thunderstorms, heights, confined spaces, future, being alone, etc.)

.....
.....

Under which circumstances/when do you become or have you been jealous?

.....

How satisfied are you with your professional life and/or choice of occupation?

.....

Which kind of troubles may you get after anger, grief, lovesickness, mortification, shock, bad news or how do you react to them?

.....

What is your attitude towards death, when are you very sad?

.....

What about conscientiousness, accuracy, in daily life?

.....



Head symptoms

Headache Vertigo Migraines Dizziness Seizures/faint
Other

Eye symptoms

Infections Styes Skin eruptions Poor eyesight Other

Ear symptoms

Chronic infections - left/right Ringing – left/right Hearing loss Inflammation meatus
Other

Nose symptoms

Epistaxis Herpes Sinus infections Other

Face symptoms

Flushes of heat Swellings of glands Blushing easily Other

Mouth/teeth symptoms

Cracked lips Herpes Aphtae Gum infections Other

Inner throat/neck symptoms

Pain Chronic infections of tonsils Hoarseness Swelling of glands Other

Appetite

Do you have strong desire for particular foods or drinks?
Do you have an aversion against particular foods or drinks?
Do you generally prefer warm or cold food and/or drinks?
Do you have loss of appetite related to specific circumstances?
What about your consumption of alcohol tobacco coffee black tea
(please give daily quantities)

Stomach symptoms

Gas Ulcers Heartburn Pain Indigestion after meals
Belching Nausea Other

Abdomen

Pain Hernia Cramps Bloating Other

Stool/anus

Hemorrhoids Rectal itching Straining at stools Blood in stools Diarrhoea
Constipation Other

Urogenital system

Painful urination Frequent urination Involuntary urination
Inflammation of bladder/kidneys Other

Male sexual organs

Prostate Warts/Condylomata Pain testicles Erection problems



Female sexual organs

Leucorrhoea Itching Orgasms Other

Menses

When was your first menstruation? Are the intervals regular?

How long do the periods usually last?

Is the menstrual flow excessive/strong/weak? Pains during menses?

Any other concomitant symptoms around the menses?

Number of pregnancies Complications during pregnancies?

Number of birth Abortions Miscarriages Menopause since

Respiratory system

Asthma Chronic cough Pneumonia Other

Chest/Heart

Congestion Palpitations Pain Herpes Other

Back

Pain in scapular Dorsal Lumbar Injuries Other

Upper/lower limbs

Joint pain Muscle pain Pain in bones Numbness Coldness

Ulcers or sores Cramps (localisation) Nail changes Other

Skin

Itching Eczema Infections Urticaria Moles Warts

Herpes Other

General symptoms

How do you react to cold/hot.dry weather?

How do you feel at the seaside or in the mountains?

Do you feel better or worse in the sun wind heat cold?

Do you perspire easily? Do you feel cold easily?

Do you consider yourself to be a warm-blooded person or cold-blooded person?

If there is anything which has not yet been covered and which is important for you to tell, please note down on back page.



CRF – Homeopathic Drug Proving (HDP) Diary

General information for filling in the diary (journal):

The quality of the symptoms gained during the proving is the essential outcome and goal of this HDP. Therefore the symptoms recorded in this diary should be as specific as possible. Please note the following items, if applicable, supplemented by a statement about the intensity and duration of the symptom. All symptoms should be recorded without compromise **in your own words**.

- 1) **Location and time of occurrence.** State the side of the body, if applicable, and if it extends to other parts of the body. State time of occurrence after intake of proving medicine. State also, if it changes from one side to another.
- 2) **The kind of pain or sensation** (e.g. burning, stitching, splitting etc.). State, if there are other experiences together with the symptom (e.g. feeling cold during headache).
- 3) **How did the symptom begin?** Was it due to a special cause or after a certain event (e.g. bladder inflammation after sitting on a cold rock; headaches after drinking coffee).
- 4) **What makes the symptom better or worse?** (cold air, heat, being inside or outside, moving, lying down, etc.)

Please state the symptoms as completely as possible, following the “Head to Foot scheme”, outlined in the leaflet.

Pay attention also to your surroundings. How do you react to your family members or other people around you? Do you or someone else recognise alterations in your moods and habits? How is your general wellbeing, how do you cope with your work, your worries?

Are there changes in the way you react during the time of the HDP versus the time before? Please make notes **every day**, best is to take notes a few times a day (say 3-4 times), even if you think, there are no symptoms to report, but this should usually not take you more than several minutes a day.

Note also slight or inconspicuous symptoms.

Please write legibly in your diary.

There are a total of 42 pages in this diary, two pages corresponding to each day of the HDP. If you need additional space, please use the back sides of the pages or contact us. The proving consists of three phases:

- 1) Day 1 – 7 = Preliminary observation period.
- 2) Day 8 – 14 = Homeopathic Drug Proving observation period.
- 3) Day 15 – 21 = Post observation period.



When you experience symptoms, please note at the end of each symptom the **category** and **intensity** as follows:

NS = new symptom never before experienced.

OS = old symptom, a symptom you had earlier and which now appears again.

AS = altered symptom, a normal symptom changed during the proving (e.g. usual headache experienced on left temple now appears at the right temple).

CS = cured symptom, old symptoms that are no longer present.

ES = previous existing symptom

RS = recent symptom

FS = symptom in family members

Please mark the **intensity** of each symptom beside the category, rating as follows:

Intensity of symptoms

1 Very low/slight	2 vague	3 clear	4 strong	5 bothersome
-----------------------------	-------------------	-------------------	--------------------	------------------------

It is helpful to mark these abbreviations by a circle

(e.g.: “new, clear symptom” = (**NS3**))

Please fill in the remedy code from page 1 on, although the remedy is taken on day 8. This is to ensure proper assignment of the symptoms.



Participant Information Sheet for the day of administration of proving medicine

1) Please remember to note the medicine code on the corresponding page of the day of intake in your diary.

2) The substance should be taken approximately every two hours for maximum 6 times only for this one day. One dose consists of the content of one capsule. The capsule is to be opened and the medicine taken under the tongue. Remember also to take no food for 15 minutes before and after taking the proving medicine.

3) State in your diary the times you take each dose of the proving medicine.

4) If you feel, a symptom may be occurring please stop taking another dose and call us.

5) In case you do not need all doses, please return the unused proving medicine to us within the closed capsules at your next visit.

6) Telephone number, which connects you directly to the proving doctor or his assistant:

.....



Preliminary Observation Period

Date

Remedy Code

SYMPTOMS

Head to foot scheme

**For comments
(proving MD)**

- Mind (mental, emotional)
-
- Generals (e.g. "I feel" – cold/warm – energetic/exhausted)
-
- Head**
-
- Eyes**
-
- Ears**
-
- Nose**
-
- Teeth**
-
- Mouth**
-
- Throat**
-
- Stomach**
-
- Abdomen**
-
- Stool/Rectum**
-
- Urinary organs**
- **Kidneys**
-
- **Bladder**
-
- **Prostate**
-
- **Urethra**
-
- **Urine**
-
- Male/Female (sexual organs)**
-
- Respiration/Cough**
-
- Chest**
-
- Heart**
-
- Neck/Back**
-
- Extremities**
-
- Skin**
-
- Sleep/Dreams**
-
- Fever**
-





Day of Intake of Proving Medicine

Date Remedy Code
Intake: hour (dose 1) hour (2) hour (3) hour (4) hour (5) hour (6)

SYMPTOMS

Head to foot scheme

**For comments
(proving MD)**

- Mind (mental, emotional)
- Generals (e.g. "I feel" – cold/warm – energetic/exhausted)
- Head
- Eyes
- Ears
- Nose
- Teeth
- Mouth
- Throat
- Stomach
- Abdomen
- Stool/Rectum
- Urinary organs
- Kidneys
- Bladder
- Prostate
- Urethra
- Urine
- Male/Female (sexual organs)
- Respiration/Cough
- Chest
- Heart
- Neck/Back
- Extremities
- Skin
- Sleep/Dreams
- Fever



Observation Period

page 9 to 14

Date

Remedy Code

SYMPTOMS

Head to foot scheme

**For comments
(proving MD)**

- Mind (mental, emotional)
-
- Generals (e.g. "I feel" – cold/warm – energetic/exhausted)
-
- Head**
-
- Eyes**
-
- Ears**
-
- Nose**
-
- Teeth**
-
- Mouth**
-
- Throat**
-
- Stomach**
-
- Abdomen**
-
- Stool/Rectum**
-
- Urinary organs**
- **Kidneys**
-
- **Bladder**
-
- **Prostate**
-
- **Urethra**
-
- **Urine**
-
- Male/Female (sexual organs)**
-
- Respiration/Cough**
-
- Chest**
-
- Heart**
-
- Neck/Back**
-
- Extremities**
-
- Skin**
-
- Sleep/Dreams**
-
- Fever**
-





Post Observation Period

page 15 to 21

Date

Remedy Code

SYMPTOMS

Head to foot scheme

**For comments
(proving MD)**

- Mind (mental, emotional)
-
- Generals (e.g. "I feel" – cold/warm – energetic/exhausted)
-
- Head**
-
- Eyes**
-
- Ears**
-
- Nose**
-
- Teeth**
-
- Mouth**
-
- Throat**
-
- Stomach**
-
- Abdomen**
-
- Stool/Rectum**
-
- Urinary organs**
- **Kidneys**
-
- **Bladder**
-
- **Prostate**
-
- **Urethra**
-
- **Urine**
-
- Male/Female (sexual organs)**
-
- Respiration/Cough**
-
- Chest**
-
- Heart**
-
- Neck/Back**
-
- Extremities**
-
- Skin**
-
- Sleep/Dreams**
-
- Fever**
-



CRF – Adverse Event Report Form

Study: Homeopathic drug proving of “name of medicine”

Volunteer code: Remedy code: Date of birth: Sex: M/F
Randomization Enveloppe opened by: Date: Verum/Blank

Description of the event occurred on: duration: hrs/days

Details (example – intercurrent disease/ accident/ Adverse proving symptom)
all to be described in detail :

Intensity:

Diagnostic and therapeutic measures taken:

Hospitalization yes/no

Course and outcome of the event:

Completely recovered Not yet recovered Unknown

Other

Name and Tel number of MD being in charge of further medical care:

.....

Principal investigator of the homeopathic drug proving informed about this adverse event by:

.....

Date Daytimehrs

Sponsor informed about this adverse event by the principal investigator of the proving:

Date Daytimehrs

Other information:

.....

.....

This Adverse Event Report Form has been filled by:

Investigator's name(s) and signature(s)



Appendix 1

Checklist for Proving Medicine

Identity of the medicine

A.1 Exact specification of the original material (original provings are sometimes done with different basic material i.e. Apis, Petroleum, Carcinosinum, etc. The determination/specification in the pharmacopoeia or monographies is often incomplete. If the homeopathic proving medicine is already officially registered in the country, a reference to this dossier is needed. Specify full latin name, i.e. Pulsatilla pratensis nigricans, Bryonia alba, and synonyms in plants, or specify exact composition of other material. If necessary, common names in country of origin. Animals: zoological identification. Identification process done by: “name of person who identified the plant or substance”, if necessary photography. Specification of First Safe Dilution (see glossary).

A.2 Origin of proving medicine: Range and habitat. Description of the geographic area and physical habitat, in which the source material occurs and specific information, where it is collected and how.

Plants : * locality of sampling, habitat, i.e. Arnica montana: above or under 600m. * time of harvesting, i.e. during, before flowering, date. * parts used, i.e. leaves, roots, flowers, etc.

Minerals/ chemical substances: * composition. * pureness. * mode of analysis / source.

Animals/Insects: * habitat. * parts used.

Nosodes/Biotherapy: * exact origin and identification of source material.

Manufacturing process

In the pharmacopoeias or monographies several items of the manufacturing process are stated incomplete (e.g. Pharmacopoeia of the U.S./HPRS-2001-General Pharmacy p.41: for Hahnemannian attenuations is stated that the “mixture is succussed thoroughly” but not if it is done by machine or by hand and how many times it is done). Therefore additionally to the statement of the pharmacopoeia or monographies, the following items should be checked:

* Elapsed time from harvesting to preparation and storage of source material and potencies.

* Preparation of the attenuations/potencies:

- Hahnemannian potencies – Multiple flask method of preparation – Succussion by hand or by machine – Number of succussions
- Korsakovian potencies – Single flask method of preparation – Starting from Mother Tincture, Hahnemannian or others – Numbers of succussions / fequency / upstroke. Different machine are used to prepare Korsakovian potencies. Their performance varies with respect to frequency, amplitude of upstroke, power and duration of succussion. Therefore the exact mode of preparation should be stated.
- Fluxion attenuations – Starting from Mothjer Tincture, Hahnemannian, Korsakovian potencies – Continuous flux / frequensy / discontinuous flux.
- High potencies above C1000 – Which modes of attenuations (starting from Hahnemannian or Korsakovian) have been used and starting from which number of attenuation.
- Q potencies (LM) – Hahnemann prescribes the trituration of the source material until C3, therefore it should be stated if the source material has been triturated or diluted until C3.
- Preparation of blanks (placebos, inert control substance) – It would be prepared in another room and/or at another timeframe than the verum to avoid distant contamination – Proposal for 2 different kinds of blanks 1) substance vehicle only (i.e. plain globule) 2) globules sprayed with non succusses 83% alcohol.
- Samples of the source material, placebos and proving medicine kept by:
.....
- Manufactured by:
.....
- Charge N°: Date of production:

Note: details about storage and packaging in “Protocol HDP - Trial (proving) design d”



Appendix 2 (Example)

CURRICULUM VITAE of Principal Investigator

Name Address

Title
Current field(s) of action

SKILLS AND EXPERIENCE

Medical practice

Locality/ Site of practice
Specification of kind(s) of work with dates of beginning and ending

Administration (i.e. member of Homeopathic Medical associations, member of other associations).

Homeopathic research

i.e. Consultant in research projects on homeopathy. Conducting of homeopathic drug provings.

Teaching

Teaching activities supervision activities.

EDUCATION

Homeopathy

Courses in homeopathy – Teachers of homeopathy.

General Medicine

From to education in general medicine, surgery, internship etc.
At University “x”

EMPLOYMENT(S)

From to
From to

PUBLICATIONS AND PRESENTATIONS

List of publications, courses given etc.



Appendix 3

Internet addresses of important institutions (in alphabetic order)

Adverse Drug Reaction

Reporting system, see www.fda.gov

Formblatt Bericht über unerwünschte Arzneimittelwirkungen ist erhältlich über

<http://www.akdae.de/UAW-Meldung>

Declaration of Helsinki – current version: The World Medical Association www.wma.net

German version: Informationen siehe: Homepage der World Medical Association

<http://www.wma.net> (nur die englische Fassung wurde in Edinburgh beschlossen – inoffizielle, nicht offiziell autorisierte) deutsche Übersetzung:

<http://www.bundesaerztekammer.de/30/Auslandsdienst/92helsinki2000.pdf>

Directive on good clinical practice

Search for: Directive 2001/20/EC. It is published in Official Journal of the European Communities.

European Committee for Homeopathy (ECH)

To contact subcommittee Drug Proving go to the website www.homeopathyeurope.org

European Legislation

Search for “Eur-Lex” or “europa.eu.int”

European Pharmacopoeia

www.pheur.org

Federal Institute for Drugs and Medical Devices

BfArM – Bundesinstitut für Arzneimittel und Medizinprodukte www.bfarm.de

Only few documents in english.

German version

Search RICHTLINIE 2001/20/EG DES EUROPÄISCHEN PARLAMENTS UND DES RATES

GIRI Groupe International de Recherche sur l’Infinitésimal.

<http://www.entretiens-internationaux.mc/giri.html>

HMA Head of Medicines Agencies including **HMPWG** Homeopathic Medicinal Products Working Group.

<http://www.hma.eu/79.html>

InHom

<http://www.homoeopathie-stiftung.de/Hom-Stiftung/festschrift/Hom-Stiftung.pdf>

International Conference on Harmonization (ICH)

www.ich.org Search Guidelines / Efficacy. Only in english.

LMHI Liga Medicorum Homeopathica Internationalis

www.lmhint.org

Organon

<http://www.homeoint.org/books> Search Hahnemann - Organon – English. Presented by the Institute for the History of Medicine of the Robert Bosch Foundation, Stuttgart, Germany.



CONCLUSIONS

The definition of a homeopathic drug proving can be synthesized in the following sentences:

A homeopathic drug proving (HDP) is done by the defined administration of a proving medicine in a safe dilution, prepared according to a homeopathic monograph, to healthy persons (volunteers, provers). The proving medicine causes reversible symptoms on the physical, mental and psychic level of volunteers, which are systematically observed and recorded by the volunteer(s) and the investigator(s).

A HDP is done in order to use it as a homeopathic remedy, according to the principle of similarity, in a sick person.



Glossary:

Adverse Drug Reaction (ADR): In homeopathic drug proving a conventional ADR will not occur, because there are no toxicological effects of the proving substances, since they are administered in at least a first safe dilution.

Adverse Proving Symptom: An adverse Proving Symptom is defined as a symptom, which is likely to be caused by the administration of the proving medicine and adversely affects the well being of a volunteer, disturbs the normal daily routine and may require the withdrawal of the volunteer from the homeopathic drug proving. It will be recorded on the Adverse Event Form, attached to the Case Report Form (CRF) of each volunteer as SUSAR (Suspected Unexpected Serious Adverse Reaction).

Proving Symptom: 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 the volunteer, shown during the taking of the case history. Proving symptoms are generally temporary symptoms, lasting for several hours or days.

Adverse Even (AE): 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 unfavourable and unattended sign, symptom or disease temporally associated with the administration of a proving medicine, whether or not related to it.

Applicable Regulatory Requirement(s): Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products (proving medicine). A homeopathic drug proving is legally considered to be a clinical trial.

Blinding/ Masking – Placebos/Blanks: Whereas the meaning of “placebo” is different in conventional clinical trials and homeopathic drug provings (HDP), it is proposed to use “blanks” as an own term for “homeopathic placebos”, as described in the protocol. In HDP blinding is not restricted to getting the medicine or not, but also to the identity of the medicine and potency, because the administration of the proving medicine is not a treatment, but will produce proving symptoms, which may affect the whole organism. In case of blinding of investigator and/or principal investigator they should not know, which proving medicine is under control.

Clinical Trial/Study: The aim of a homeopathic drug proving is not the proof of efficacy but to gain knowledge about the innate character of a drug, the “remedy picture”, which is more an aspect of quality, than of quantity. Thus a HDP is an investigational clinical trial designed to gather information on the potential areas of application for homeopathic remedies.

Clinical Trial/Study Report: The report of a HDP requires specific items, which are not mentioned in the ICH Guideline for Structure and content of Clinical Study Reports. Therefore a specific structure for HDP has to be applied.



First Safe Dilution (FSD): The FSD is the first dilution safe for any human, it is responding to the HMA decision tree. See :

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/HMPWG/2010_05_HMPWG_First_Safe_Dilutions.pdf

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 investigator too –after having taken the case history and done clinical examination– does not see an indication for medical treatment.

HPUS: Homeopathic Pharmacopoeia of the United States of America.

Independent Ethics Committee (IEC): To review HDP, an IEC which also includes homeopathic professionals is necessary.

Investigational Product: A proving medicine (drug), prepared according to a Homeopathic Monograph or a Placebo/Blank administered or used as a reference in HDP. Packaging must prevent “contamination” and “deterioration” during transport and storage (including protection against electromagnetic waves).

Investigator: In literature on HDP also referred as Observer, Supervisor, Proving Doctor, is a person responsible for the direct contact with the volunteer(s). He reviews diaries (journals) together with each volunteer in order to clarify and if necessary amend the symptoms. For HDP the following qualifications are considered to be adequate: “All investigators, who are in direct contact with volunteers, must have a qualified education in homeopathy, must have had at least 5 years of experience in Homeopathic practice (treating patients) and must have proven at least 3 Homeopathic remedies personally.

The **Principal Investigator:** In literature on HDP also referred as Master Prover, Coordinator, Director of Proving, is a person responsible for the conduct and organization of the HDP following GCP Guidelines, e.g. contact with IEC and the report of severe adverse events, storing of study documents. Above the requirements as investigator the principal investigator must additionally have at least 2 years of experience in HDPs. The **Volunteer:** In literature on HDP also referred to as Prover, is a person who takes the proving medicine and reports any symptoms that occur by keeping a diary and direct contact with the investigator.

Law of similars: see under Principle of similarity.

Monitoring: Usually monitoring is not applicable in HDP because of the small number of volunteers taking part in a proving, nevertheless, it would be helpful to have independent international peer groups for quality insurance.

Potentized Medicines: Medicines processed in a specific way, namely by succession or trituration of serial dilutions. The diluting procedure specific to homeopathy is called potentisation or dynamisation. With steps of 1 part of Mother Tincture or previous dilution and 99 parts of solvent for “C” (centesimals) potencies and 1/9 for “D” (decimals) potencies. The number of steps usually defines the degree of dynamisation, e.g. “C 12” or “C 30”.



Principle of similarity: A substance, capable of provoking symptoms in a healthy organism, acts as a curative agent in a diseased organism in which similar symptoms are manifested (e.g. the dilution of “onion” or *Allium Cepa* cures a coryza with symptoms like those that occurs when cutting onions).

Proving symptom: 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 the volunteer, shown during the taking of the case history. Proving symptoms are generally temporary symptoms, lasting for several hours or days.

Principal Investigator: see Investigator.

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

Qualitative data: Data that approximates or characterizes but does not measure the attributes, characteristics, properties, etc., of a thing or phenomenon. Qualitative research is based on individual, often subjective analysis. A general description of properties that cannot be written in numbers, that cannot be reduced to something that can be enumerated. Related to or based on the quality or character of something, often opposed to its size or quantity.

Serious Adverse Events (SAE) or Serious Adverse Drug Reaction (Serious ADR): Since HDP are done with non-toxic dilutions of a proving medicine, it is very unlikely to have serious adverse drug reactions.

Source data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a HDP necessary for the reconstruction and evaluation of it. Source data are contained in source documents (original records or certified copies).

Sponsor: An individual, company, institution, or organization 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.

Sponsor-Investigator: If the HDP is done with several investigators, the sponsor-investigator takes the role of the principal investigator.

Sub investigator: In HDP usually the investigators (proving doctors) have no sub investigators.



Subject/Trial Subject (Volunteer): An individual who participates in a clinical trial (HDP), either as a recipient of the investigational product(s) (proving medicine) or as a control.