Homeopathic Proving Guidelines

Harmonised by LMHI and ECH

Approved and published by the

Liga Medicorum Homoeopathica Internationalis

and the

European Committee for Homeopathy

First edition, May 2014

Visit www.lmhi.org or www.homeopathyeurope.org to download this document and French and Spanish translations.

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Foreword

The guidelines for homeopathic provings in this document are the result of a consensus process between the Liga Medicorum Homoeopathica Internationalis (LMHI) and the European Committee for Homeopathy (ECH) that took place between July 2013 and May 2014. All comments received prior to April 2, 2014 have been considered.

The LMHI and ECH have approved the current document on May 20 and April 4, 2014, respectively.

We cordially invite comments on these guidelines from all stakeholders, and will publish a revised document based on comments received until May 2016. Please send your comments to provings@homeopathyeurope.org or provings@lmhi.net.

For reference purposes, the individual ECH and LMHI Guidelines for Provings as they existed prior to this harmonisation process are available in English on the respective website, www.homeopathyeurope.org and www.lmhi.org.

Dr Jean Pierre Jansen
Chair of the Provings Sub-committee
European Committee for Homoeopathy

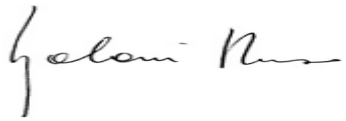
Prof. Ashley Ross
Chair of the Committee for Provings
Liga Medicorum Homoeopathica Internationalis

Preface

Dr Renzo Galassi, president of LMHI

When Hahnemann left us his theoretical and clinical will in the form of the Sixth edition of the *Organon*, one of the main insights was that of testing potential homoeopathic medicines on the healthy person, that today we call 'proving'. He, together with his first students, gave us an example of what it means to be a prover, being one of the main provers and proving supervisors in our history. Thanks to Hahnemann we understand that the only sure way of studying our medicines and discovering their true possibilities for healing patients, as homeopathic remedies, is through the well-conducted proving.

Proving is not a casual activity that anyone can organise according to his/her own rules or ideas. We have a protocol and procedures. Unfortunately these protocols and procedures differ a little in the minds of various experts or groups of experts. It is with great pleasure that the LMHI Proving working group, together with the ECH Subcommittee on Provings, decided to define these aspects for the future work of all those colleagues around the world who may decide to study new substances or to re-study old ones. As LMHI President, I am honoured to give my total support and approval to the result of this work and collaboration among the best-skilled experts in the world, headed by Prof. Ashley Ross for the LMHI and Dr Jean Pierre Jansen for the ECH.



Dr Renzo Galassi
President LMHI

Dr Thomas Peinbauer, president of ECH

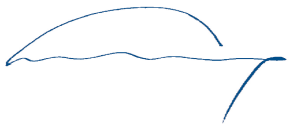
The European Committee for Homeopathy (ECH) represents nearly 45,000 medical doctors specialising in homeopathy in 25 European countries. As a representative body, the ECH promotes the scientific development of homoeopathy and the harmonisation of professional standards of homeopathic practice across Europe.

In 2004, the ECH published the first edition of its 'Homeopathic Drug Proving Guidelines'. In 2013, the Liga Medicorum Homoeopathica Internationalis (LMHI) and the ECH agreed on a collaborative process to harmonise proving guidelines towards a single global standard.

These harmonised Guidelines are the result of an exemplary collaborative and co-operative endeavour. After ten years of dedicated effort by Jean Pierre Jansen and the ECH Subcommittee on Provings, we, as the ECH, are proud to be able to present these new Guidelines in collaboration with the LMHI.

Homeopathic provings are essential to the progress of homeopathy. These Guidelines are intended to serve as a community reference for the improvement of the quality of homeopathic provings, and as a reliable reference to proving methodology and procedures for proving directors, ethical review boards and other authorities dealing with this subject.

On behalf of the ECH, I recommend these Guidelines to colleagues all over the world who are interested in the process of harmonisation and the progressive improvement of the quality of homeopathic provings.



Dr Thomas Peinbauer
President ECH

Introduction

Departure point

These guidelines have as their departure point the objective of conducting scientifically accountable provings that are in full agreement with homeopathic theory. These guidelines assume that all relevant national and international legislation and regulations will be considered in the formulation and conduct of the individual homeopathic proving.

Audience of the guidelines

The intended audience of these harmonised proving guidelines includes:

- Principal Investigators (P.I.) and sponsors
- ethical review boards
- regulatory authorities
- scientists
- publishers and editors of scientific journals
- homeopaths who will apply provings in their practice
- proving participants

Purpose of the guidelines

The purpose of these guidelines is:

- to assist proving directors and sponsors in their understanding of the basic structure and framework of a homeopathic proving, and the need to comply with regulatory /scientific standards
- to assist ethical review boards in their appreciation of the unique characteristics of homeopathic provings in contrast to other more conventional modes of scientific investigation
- to assist competent authorities in their understanding of the nature of homeopathic provings and their pivotal context within the practice of homeopathy
- to assist the various pharmacopoeias in their monograph approval processes, by providing a reference to a community standard for the conduct of homeopathic provings
- to provide to journal editors and medical publishers a reference upon which to develop a framework for the publication of provings.
- to provide a methodological base upon which to ensure inter-proving comparability and the progressive development of the understanding and methodology of the proving experiment, as first described by Samuel Hahnemann.

Scope of the guidelines

- This document is focused upon the various elements of proving design, and is intended to be applied within the context of broader ethical and regulatory

guidance. Notwithstanding this focus, it is not intended to specifically exclude other emerging proving design formats. Many elements of these guidelines may indeed be used to inform other proving designs, according to the preferences and requirements of the coordinator.

- These guidelines are developed from the accumulated expertise of two centuries of homeopathic proving practice, which, in turn, has formed the basis of the subsequent successful clinical utilisation of newly proved remedies.
- In accordance with modern clinical research and ethical requirements, these guidelines have deliberately been aligned with the requirements of the ICH- GCP and international ethical frameworks, as described, inter alia, in the Belmont Report, CIOMS Guidelines and the Declaration of Helsinki (as revised in 2013).
- The guidelines, as described, are both fully cognizant of mainstream ethical and regulatory frameworks (as cited above) and respectful of the unique approach and methodological imperatives of homeopathy as a medical system, and proving as a specific experimental mode within that system.
- The guidelines are not intended to describe the various details or variations. As a framework it is intended to be used as a basis for evaluation, whilst leaving sufficient freedom for experiment and variation.
- Specific guidelines are indicated to be either 'required' or 'recommended'.
- Guidelines are indicated as 'required' when they indeed are required by many national or international regulations, or when they are considered, by the homeopathic community, to be a minimum requirement for usefulness.
- Guidelines are indicated as 'recommended', when there is understood to be some room for variation, or when the specific guideline falls outside of regulatory or pharmacopoeial frameworks
- In those specific instances in which these guidelines are found to be in disagreement with specific national regulations, the specific national regulations are understood to take precedence over these guidelines. These guidelines are to be seen as best practices, and may be used to assist the formulation and adaptation of national and international regulations. The proving committees of the ECH and LMHI are committed to providing detailed assistance in such formulations and adaptation, should they be requested.
- This document is subject to revision in accordance with projected changes in scientific understanding and regulatory requirements.

Structure of the document

The 'required' and 'recommended' elements of each guideline are listed. The required guidelines are marked with a diamond sign ❖. Recommended guidelines are marked with a bullet sign •.

The rationale for specific guidelines is not provided. The bibliography does, however, provide a detailed list of sources and references that were consulted in the formulation of this document.

Main proving guidelines

Provings as an experimental mode

Despite the existence of certain points of overlap between homoeopathic proving and early-phase clinical trial, provings cannot be defined as either a phase I or a phase 0 trial. The following table summarises the differences that justify a unique and specific definition of provings, as a mode of experimental enquiry.

	Phase 0	Phase I	Proving
Aim	Assess whether a high-risk drug behaves as would be expected from pre-clinical studies	Derive Pharmacokinetic and Pharmacodynamic data and determine safety	Collect subjective symptoms for formulation of a homeopathic drug picture
Volunteers	Patients, with few or no other therapeutic options	Healthy volunteers	Healthy volunteers, never patients
Number of volunteers	10-15	20-100	Any
Placebo control	No	No	Not essential
Dose	Micro-doses	Single ascending dose Multiple ascending dose	Repeated micro-dose until symptoms occur. Predefined maximum number of doses
Safety	Unknown, not a purpose	Variable, some risks prevented by pre-clinical studies	Almost perfect, toxic levels excluded. Concept of first safe dilution
GCP/ICH guidelines	Under development by EMA and FDA. Concept of IND (Investigational New Drug) studies	Exist, used by Ethical Boards	No official guidelines, but ECH/LMHI Guidelines conform to GCP/ICH guidelines
Indication specified	Yes	Yes	No
Demonstrative purpose	To confirm biological activity in line with early pre-clinical indications, ahead of formal phase I-IV studies	To ensure safety of drug in healthy human subjects, ahead of efficacy testing in subsequent phases	To investigate the therapeutic potential of a substance. No subsequent experimental phases

Purposes of proving

Homeopathic provings may be conducted for a range of purposes. The value of the proving experiment to the homeopathic and scientific community at large or the individual proving participant, and the restrictions imposed on the methodology will vary according to the purpose of the proving. The most prominent purposes of homoeopathic proving are:

- Extending the materia medica. This is the most common reason to conduct a proving. After the publication of the proving report, curative responses will further enrich the final materia medica. This results of provings conducted for this purpose may form part of the documentation that would be submitted towards market approval by a national authority, e.g. admission to a pharmacopoeia. In such cases, specific pharmacopoeial requirements in addition to those described in these guidelines, may exist.
- As a self-learning experience. In such proving experiments the principal objective is the experience of the action of a homeopathic potency on oneself. The focus is not on extending the materia medica, although this may occur.
- Evaluating the effectiveness of a potentised substance. Provings conducted for this purpose are designed to investigate the mechanism of action or other parameters related to the action of a homeopathic potency on the organism.

These harmonised guidelines are focused expressly on provings conducted for the purpose of extending the homeopathic materia medica.

The test substance

- ❖ The identity of the test substance, in terms of its scientific name and its common name(s) must be clearly defined. In the case of botanical and animal sources, it is advisable that these be accurately identified by an appropriately skilled botanist/zoologist.
- ❖ Where toxicological information on the test substance exists this is required to be included in documentation provided to the ethical review board and/or the proving report.
- Documented case experiences, where these exist within the literature, are recommended to be included.
- Where these are known and available, all previous provings and toxicological symptoms should be reviewed in the proving report.
- ❖ In all cases in which a part of a plant or animal is used as a source material, the part used must be accurately defined. In the case of plants, the stage of the plant's life cycle and time of collection are required to be described in the proving report.
- Details about the source, in terms of habitat and location, and the manufacturing process, manufacturer, and source of the potentised test substance are recommended to be included.

- The storage of vials (or powders) of the test substance and/or blanks in the same container should be avoided. Doses of respective test or blank substances should be mailed separately.
- ❖ The date and time of each dose are required to be recorded in the prover's diary and by the supervisor.

Potencies to be used

- ❖ It is required to use potencies above, and including, the C12 or equivalent (i.e. D24 or LM4), because these are considered safe.
  - ❖ Lower potencies above the First Safe Dilution (FSD), if known, are allowed. The use of potencies below the FSD is considered unsafe.
- Potencies between C12 and C30 (or their equivalent dilutions) are recommended. Potencies above C30 are allowed at the Principal Investigator's discretion.
- In view of the existence of a range of systems, including using more than one potency in the same volunteer, in various orders, it is recommended that the rationale for the employment of a particular potency, or range of potencies, should be described in the report.

Posology

- Oral doses are recommended.
- ❖ If any other route of administration is used, the rationale for such should be provided.

Dose

- The timeline for the repetition of doses shall be established prior to the initiation of the proving. These should include:
  - Frequency of dosing
  - Maximum number of doses
  - Criteria for stopping the dosing (non-repetition)
  - It is recommended that doses are repeated until symptoms appear.
- There should be no repetition of dosing if proving symptoms appear.
- It is further recommended that dosing should not be repeated when symptoms have disappeared.
- The rules for stopping should also be defined for those cases in which no symptoms appear.

Adverse events

- Provings using test substances according to the guidelines provided in 'Potencies to be used', above, are considered to be safe.
- In the case of an adverse event (AE), the HPCUS guidelines are to be followed. This reporting system is informed by generally accepted regulations for the handling of AE's.

- The Principal Investigator decides which AE are to be included as a proving symptom. It is recommended that the reasons for the inclusion or exclusion of these should be documented and described in the proving report.

Duration of the proving

- The following phases with duration are recommended:
  - Pre-observation phase: the prover is recommended to journal daily for one week (7 days) immediately preceding the first dose.
  - Observation phase: the prover is recommended to journal and be observed until the disappearance of the last new symptom
  - Post-proving phase: the prover is recommended to journal and be monitored for an additional 2 weeks after the disappearance of the last new symptom, or a minimum of 6 weeks after the first dose.
  - Exit interview: an exit interview if to be conducted 3 months after the first dose.

Pre-observation

- It is required to include a Pre-observation period for the following reasons:
- ❖ to establish rapport between the prover and the supervisor.
- ❖ to ensure that the prover understands all proving requirement and procedures (including accurate and detailed journaling) and to check for prover compliance.
- ❖ to establish a baseline of existing symptoms for validation of experimental symptoms.

Control group

- The inclusion of a control group is recommended. If this is not an element of the design of the proving, the blinding for name and potency employed should be rigorous.
- The term 'blank' is recommended for 'lookalike' doses employed in the control group within provings, the purpose of which is to induce a more focussed awareness in all provers. This purpose is fundamentally different to the use of 'lookalike' doses in experimental controls to eliminate matching symptoms that might occur in both verum and placebo groups. The term 'placebo' is appropriate to the latter purpose, whilst 'blank' is appropriate to the former.
- The use of blanks is recommended. If this is not an element of the design of the proving this should be explained in the report.
- When blanks are used, it is recommended that 10%, or a minimum of 2 volunteers are assigned to the control group.
- Reporting and analysis of the verum symptoms and the 'blank' symptoms are presented separately in the proving report.
- Verum symptoms that have been excluded because they match a symptom in the control group, should be clearly indicated.
- ❖ The Principal Investigator, all supervisors, and all volunteers are required to be blind to the assignment of blanks.

Blanks

- ❖ Where the use of blanks is part of the proving design, these should be indistinguishable in all respects from the verum.
- ❖ All operations performed in the preparation of blanks, particularly in respect to use of the same solvent as verum and/or whether such was subjected to serial dilution and/or succession, are required to be accurately described.
- A description of the rationale for the use of blanks is recommended. Where blanks are used as a means of eliminating matching verum symptoms, the criteria for exclusion should be defined in advance.
- ❖ It is required that the randomisation and allocation procedures are accurately described.

Blinding

- Different levels of blinding are to be maintained.
  - Blinding for the name of the remedy is ideally recommended to be maintained until the analysis of the symptoms has been finalised. Minimally blinded for name is recommended to be maintained until the last exit interview has been completed.
  - Blinding for allocation to blank or verum is recommended to be maintained until closure of the observation phase and all diaries have been handed in.
  - Blinding for the level of the potency or potencies, when more than one potency is used, is recommended to be maintained until after finalisation of the analysis.

Volunteers

- The recruitment of volunteers is required to be accurately described:
  - It is recommended that not only homeopathically literate volunteers be recruited.
  - No volunteer should be coerced into participating in a proving.
- The criteria for the inclusion and exclusion of volunteers must be defined before the initiation of a proving.
- The following requirements are only valid inasmuch as confidentiality is able to be maintained.
- Inclusion criteria: The inclusion criteria are recommended to be formulated so as to:
  - reasonably estimate the prognosis of well-being and observational skills of the volunteer, and their ability and likelihood to comply with the proving plan.
  - ensure that volunteers are capable of providing accurate information while recording their subjective symptoms.
- Exclusion criteria:
  - ❖ It is required to exclude volunteers who are not healthy, or who present possible confounding factors to the proving, and who may not be in a

position to report / record symptoms accurately. These criteria would, therefore be required to exclude mentally incompetent volunteers, pregnant volunteers, volunteers with serious emotional disorders, volunteers who plan medical / dental treatment during the test period, those under current homeopathic treatment (30 days), and volunteers anticipating a change in lifestyle habits which is likely to alter results.

- It is recommended that volunteers <18 years and >75 years be excluded.

- Prover demographics
  - ❖ It is required to include both male and female provers and to document demographic characteristics, which would include details of ethnicity and location, and homeopathic literacy.
- Initial interview:
  - ❖ It is required that a face-to-face interview, that includes age, gender, past medical history, medications, allergies, current conditions, prior symptoms that required treatment, clinically important symptoms occurring in the past 3 months, is conducted on all volunteers.
  - A full homeopathic history and physical examination with the development of the homeopathic picture as baseline is recommended.
- Journaling and Symptoms:
  - ❖ It is required that volunteers receive instruction on how to record symptoms and report on their general well-being, and the format and frequency of contact with their supervisor.
  - ❖ It is further required that a coded list of volunteers, that enables the direct linking of each symptom to a specific volunteer is compiled and provided in the report.
- Exit interview
  - ❖ It is required that an exit interview, to ensure the return of the prover to their former healthy state and to check each symptom for accuracy, is conducted on every prover, prior to closure. Such exit interview is recommended to be conducted in person.

Optimal number of provers

- A minimum of 10 verum provers at closure of the observation phase is recommended.
- An experimental group of more than 20 verum provers is not recommended, as this would reflect a negative burden/benefit ratio.
- Notwithstanding the above recommendation, it is recognised that a proving employing fewer than 10 verum provers may contribute significantly to clinical practice.
- The expertise of the Principal Investigator, supervisors and volunteers will affect the optimal number of provers in a particular circumstance.

Informed consent

- ❖ It is required that all participants complete and sign informed consent forms (ICFs). Such ICF is mandatorily to include clear statements of the purpose and expected effort/burden of the proving, and the right to withdraw at any point without prejudice or consequence.
- ❖ It is further required that the confidentiality of provers is protected. The Principal investigator is ultimately responsible for the protection of prover privacy.
- It is recommended that an independent and informed advisor should be available to volunteers before the signing of informed consent
- It is recommended that insurance be provided to all volunteers
- Submission of a proving protocol for approval by an ethical review board is recommended

Symptoms: Recording, analysis

- ❖ Both subjective and objective data are required to be included.
- Where objective data are recorded, the relationship of the observer of such objective data should be recorded.
- In transcription of the subjective journal record, the expression of the individual prover should be preserved as accurately as possible (i.e. verbatim).
- ❖ Each symptom is required to be traceable to a specific volunteer.
- ❖ Within the journal record, all physical, mental and emotional symptoms, with an indication of the day of occurrence are required to be recorded.
- ❖ Symptom parameters that define the nature of the time relationship of a proving symptom to an earlier occurrence of the symptom, viz. new, recent, existing, old, altered, or cured are required to be defined before initiation of a proving. All existing symptoms prior to administration of the first dose and recurrences of recent symptoms should be excluded. An existent symptom is present when the observation phase started, a recent symptom was absent when the observation started, but was present within a predefined relatively short time before the observation phase, e.g. 1 year is recommended.
- Symptom qualities:
  - ❖ It is required that provers will be encourage to record complete symptoms, which include location, time of occurrence, duration, frequency or periodicity, relation to other symptoms, modalities related to amelioration/aggravation, and identifiable potential aetiological factors
- ❖ Other symptom qualities: It is required to determine whether a presumed proving symptom arises from factors outside of the proving or the administration of the test substance:
  - accident
  - intercurrent acute disease
  - symptoms due to other changes in circumstances, e.g. in the workplace or within the family.
- Where the intensity of a symptom is recorded, it is recommended that this should be according to a predefined scale.

- ❖ It is required that all corrections and editorial changes be logged with recording of the editor, date and time.
- ❖ It is required that all symptoms of provers are included in the proving report.
- If a prover is excluded, for any reason, all symptoms recorded by that prover prior to the exclusion should be considered for analysis.
- Existing and recent symptoms should be excluded.
- All differences in text between the original recording and later editing should be logged.
- After final editing by the prover, the text is recommended to be locked. Subsequent editing for purposes of improved reading, provided such editing does not result in a change of meaning, is allowed and is also recommended to be logged.
- ❖ Where these are used, the reasons for the recording and interpretation of biomarkers should be defined prior to the start of a proving.
- The use of questionnaires to detect predefined symptoms is not recommended.
- The choice of recording in handwriting or typing is recommended to be left to the volunteer.
- ❖ Each volunteer is required to be assigned a code, so as to ensure continuity of data and the ability to track each symptom recorded by an individual volunteer, as well as their assignment of a specific potency or blank.

Supervisor's tasks

- ❖ The supervisor is required to be responsible for monitoring the safety and well-being, compliance, and self-observational ability of the prover.
- ❖ He/she is required, also, to decide on the stoppage and/or further repetition of the dose.
- ❖ He/she is further required to support the observation and recording of symptoms.
- ❖ It is required that the supervisor ensure twice-a-day contact with each volunteer until the day after their last dose. Daily contact until symptoms abate and less frequent contact are sufficient thereafter.

Withdrawal criteria for volunteers

- ❖ It is required to withdraw volunteers when the well-being, compliance or self-observational ability of the prover is compromised.
- Therapeutic interventions, whether or not related to the remedy, may be grounds for withdrawal, depending on an estimation of their impact on the symptoms.
- Likewise, large excesses in lifestyle, e.g. getting unusually drunk, that may negatively impact on the symptoms may serve as grounds for withdrawal.

Reporting

- In this version no detailed guidelines for the compilation of a proving report are defined.
- It is recommended that the Consort guidelines, extended with RedHot additional guidelines be followed.

- It is recommended that detailed references for any reviewed information (cases, previous provings, toxicology) be provided.

❖ Not withstanding the above recommendations, it is required that a proving report should include the following additional information:
  - a list of missed appointments, or record of doubt about proper self-observation.
  - the day number and time of the day of each dose.
  - a record of any concomitant interventions.
  - a list of cured symptoms and/or a list of persisting symptoms.
  - a list of reported adverse events.
  - a tabulation of the reason(s) for the withdrawal of volunteer(s)

- It is recommended that the proving be translated to a reportorial format and that such repertory by included in the proving report, and subsequently submitted to repertory publishers.

Analysis

❖ It is required that the results of a proving be presented in a standard and accessible format – i.e. conventional head-to-toe format with grouping of all modalities; concomitants; causalities, etc.

- It is recommended that the following analytical features be included to facilitate appreciation of the unique features of the proving:
  - grouping of symptoms by intensity
  - extraction of generalities, based on repeating patterns (modalities, sensations, alternations, concomitants and causations or triggering factors) across several local and particular symptoms
  - a tentative compilation of characteristic symptoms, based upon the Principal Investigator's subjective evaluation of the proving data. Whilst it is acknowledged that there is currently no established, objective or reproducible method of establishing characteristic symptoms in a new proving, where such insights are possible, it is recommended to be included in the publication of a proving.
  - descriptive statistics

Qualifications of Principal Investigator and supervisors

- The Principal Investigator and supervisors are required to have sufficient experience in homeopathic practice to be able to:
  a. look after the well-being of the volunteer
  b. judge symptoms if they can be considered complete, and recognise if a symptom is strange, rare and peculiar.
- A Principal Investigator should have at least 5 years of experience in homeopathic practice, and have participated, if possible, as a volunteer in at least one proving and as supervisor in another proving.

- ❖ It is required of the Principal Investigator, and recommended for all supervisors, that a formal ethics course should have been completed. (e.g. NIH online course, 4 hours).
- A supervisor should have at least 5 years of experience in homeopathic practice, and participated, if possible, as volunteer in at least one proving. In those cases in which a proving is conducted within the context of the education of homeopathic students, a lesser criterion is allowed, if this is described in the report

Terms, definitions and abbreviations

Allocation - The procedure of assigning a certain numbered vial to a particular prover.

Blank - A look-alike vehiculum, which is identical in all observable respects (including taste) to the medicated vehiculum.

ECH - European Committee for Homeopathy. See www.homeopathyeurope.org

FSD - First Safe Dilution: The minimal molecular dilution that is considered safe

HPCUS - Homeopathic Pharmacopoeia Convention of the United States. See www.hpus.com

HPUS – Homoeopathic Pharmacopoeia of the United States. See www.hpus.com

Informed consent – A written and signed statement that the volunteer has received and understood all relevant proving information, including the aim, purpose, benefits, risks of the project and the right to withdraw without prejudice or any other consequence. The researcher should be convinced that this is correct.

LMHI - Liga Medicorum Homoeopathica Internationalis. See www.lmhi.org

Principal Investigator (P.I.) - The researcher who assumes ultimate responsibility for all aspects of the proving.

Placebo – An inert look-alike vehiculum, used as a control for purposes of eliminating symptoms that match a symptom produced in the verum group

Randomisation - The procedure of randomly assigning a verum potency or a blank to a specific numbered vial.

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Appendix I: Adverse event form [example]

Prover code:
Sex: M / F
DOB:
Code and nature of IMP unblinded by (name) on (date):
Potency / Blank / Placebo

Description of complaint or problem:
Date, duration:
Time since last dose:
Nature of event: Intercurrent disease / Accident / Serious adverse event
Description:
Intensity:
Diagnostic and therapeutic actions:
Hospitalisation: Y / N
Outcome: Full recovery / Not yet recovered / Unknown / Other

Name and phone number of treating doctor
Principal investigator informed on date and time:

Other relevant information:

This form is completed by: (name)

Appendix II: Document history

Version	Date	Description
0.1	2-1-2014	Initial version, based on meeting in Barcelona
0.2	16-1-2014	Corrections
0.3	20-3-2014	After internet comment round January-March 2014
0.4	2-4-2014	Approved by ECH
0.5	13-4-2014	Clean version, based on approved version 4
0.6	4-5-2014	Draft edited English version, based on version5
0.7	10-5-2014	Unused version
0.8	20-5-2014	Approved by LMHI
0.9a	1-6-2014	Final English version
0.9b	20-6-2014	French and Spanish translations