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Review Article

Importance of Research Methodology in Homoeopathy: A Review

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Abstract Research is the fundamental attribute of any system of medicine. It is the basic needs to establish any system in scientific fraternity. The aim of this article is to highlight the controversy of Homoeopathic research, why research is important in Homoeopathy and understand the research in Homoeopathy. Drug proving protocol, which is designed by CCRH, Future prospective of research methodology in Homoeopathy and how will we have applied research methodology for the development of Homoeopathy.

Keywords *Research; Drug-proving; Research Methodology*

Introduction

Research is a process of collecting, analyzing and interpreting information to answer questions undertaken within a framework of a set of philosophies, uses procedures, methods and techniques that have been tested for their validity and reliability; The path to finding answers to your research questions constitutes research methodology. Research is a careful and detailed study into a specific problem, concern, or issue using the scientific method. Biomedical research (or experimental medicine) is in general simply known as medical research.

Homoeopathy is a form of complementary medicine based on treating 'like with like'. Its popularity with the public, and credibility with health professionals, has increased rapidly as a result of recent clinical trials demonstrating its efficacy. The results of a systematic review of clinical trials of homoeopathy are summarized. The main scientific obstacle to the acceptance of homoeopathy is its use of very high 'ultramolecular' dilutions. The action of these dilutions cannot be explained in terms of existing pharmacological concepts. This has lead to the 'information medicine' hypothesis, which postulates the storage of information in water and its transmission to sensitized biosystems. This hypothesis is starting to be supported by physics. 'Proving' drugs in order to determine their effects on healthy volunteers is a form of research practiced by homoeopaths for 200 years, the methodology is continuing to evolve. Clinical trials in homoeopathy are complicated by the fact that treatment is highly individualised. Various approaches to the problem of individualization in controlled trials, including 'homoeopathy as indicated', 'single homoeopathic medicine' and 'individualized isopathy' are discussed. To improve homoeopathic practice its results should be critically audited, a method for doing this is described.

Research in Homoeopathy

Controversy of research in Homoeopathy: MYTH & FACTS

Several of the presentations made at the FDA hearing (April 20-21, 2015) asserted that there is “no evidence” that homoeopathic medicines are effective for any condition. The information provided below will show this statement is not true.

Studies demonstrating the effectiveness of homoeopathic medicines have been published in leading medical journals, including the **Lancet**, **BMJ**, **Chest** (the publication of the American College of Chest Physicians), **Rheumatology** (the publication of the British Society for Rheumatology), **Pediatrics** (publication of the American Academy of Pediatrics), **Cancer** (journal of the American Cancer Society), **Pediatrics Infectious Disease Journal** (publication of the European Society of Pediatric Infectious Diseases), **European Journal of Pediatrics** (publication of the Swiss Society of Pediatrics and the Belgium Society of Pediatrics), and numerous others. Some researchers have chosen to create arbitrary guidelines that claim that no study is “reliable” unless it has greater than 150 subjects, No peer-review journal and independent research organization has ever claimed that these guidelines for determining “reliability” on research are valid or even reasonable.

Why research is important in Homoeopathy?

- There is little evidence to support homoeopathy as an effective treatment for any specific condition.
- Although people sometimes assume that all homoeopathic remedies are highly diluted and therefore unlikely to cause harm, some products labeled as homoeopathic can contain substantial amounts of active ingredients and therefore could cause side effects and drug interactions.
- Homoeopathic remedies are regulated by the U.S. Food and Drug Administration (FDA). However, FDA does not evaluate the remedies for safety or effectiveness.
- Several key concepts of homoeopathy are inconsistent with fundamental concepts of chemistry and physics. There are significant challenges in carrying out rigorous clinical research on homoeopathic remedies.
- A 2015 comprehensive assessment of evidence by the Australian government’s National Health and Medical Research Council concluded that there are no health conditions for which there is reliable evidence that homoeopathy is effective.
- Homoeopathy is a controversial topic in complementary medicine research. For example, it is not possible to explain in scientific terms how a remedy containing little or no active ingredient can have any effect. This, in turn, creates major challenges to rigorous clinical investigation of homoeopathic remedies. For example, one cannot confirm that an extremely dilute remedy contains what is listed on the label, or develop objective measures that show effects of extremely dilute remedies in the human body.
- Another research challenge is that homoeopathic treatments are highly individualized, and there is no uniform prescribing standard for homoeopathic practitioners. There are hundreds of different homoeopathic remedies, which can be prescribed in a variety of different dilutions for thousands of symptoms.

Basic Classification of Research in Homoeopathy:

1. **Clinical trial and research**
- with individualised medicine
- without individualised medicine
2. **Basic research or laboratory-oriented research**
- In vivo Study
- In vitro Study

Clinical Trial and Clinical Research

To best understand the remaining part of this idea, some definitions are helpful:

- ***Single blind trial*** refers to experiments in which the subjects do not know whether a specific treatment was prescribe or a placebo.
- ***Double-blind trials*** refer to experiments in which neither the experimenter nor the subjects know whether a specific treatment was prescribe or a placebo.
- *Randomized trials* are those in which subjects of an experiment are randomly placed either in treatment groups or in placebo groups. The researchers attempt to place people with similar characteristics in equal numbers in treatment and placebo groups.
- *Crossover studies* refer to experiments in which half of the subjects of a study are given a placebo during one phase of a study and then given the active treatment during the second phase, while the other half begin with the active treatment and then receive the placebo during the second phase. Crossover studies sometimes do not test a placebo and instead compare one type of treatment with another type of treatment.

Clinical research is research that directly involves a particular person or group of people or that uses materials from humans, such as their behaviour or samples of their tissue. A **clinical trial** is one type of clinical research that follows a pre-defined plan or protocol. By taking part in clinical trials, participants can not only play a more active role in their own health care, but they can also access new treatments and help others by contributing to medical research.

People are often confused by research, not only because it can be overly technical but because some studies show that a therapy works and other studies shows that it doesn't. To solve this problem, a recent development in research is used, called a "**meta-analysis**," which is a systematic review of a body of research that evaluates the overall results of experiments. In 1991, three professors of medicine from the Netherlands, none of them homeopaths, performed a meta-analysis of 25 years of clinical studies using homeopathic medicines and published their results in the *British Medical Journal* [3]. This meta-analysis covered 107 controlled trials, of which 81 showed that homeopathic medicines were effective, 24 showed they were ineffective, and 2 were inconclusive. There are different types of homeopathic clinical research, some of which provide individualization of remedies; which is the hallmark of the homeopathic methodology; some of which give a commonly prescribed remedy to all people with a similar ailment.

Basic Research

They are mainly two variety in vivo (i.e. human experimentation and on lower animals,) and in vitro (in cultured media).

a) **In vivo study: -**

In vivo (Latin for "within the living"; often not italicized in English) are those in which the effects of various biological entities are tested on whole, living organisms usually animals including humans, and plants as opposed to a partial or dead organism

It may be further classified under two sub divisions

(i) Drug proving

Drug Proving now termed as Homoeopathic Pathogenetic Trials (HPT) is a process in which drug substances are put into trial over healthy human volunteers and their pathogenetic effects are observed, noted and compiled as the first step to introduce the drug in the Materia Medica. Proving of a drug substance is a unique process in

Homoeopathy. Unlike conventional medicine where animal experimentation forms the basis of evaluation of drug pathogenesis, homoeopathic medicines are proved on healthy human volunteers, including controls, from both sexes. The Central Council for Research in Homoeopathy since its inception in 1974, has adopted the Drug Proving Program as one of its primary research areas. The Council has focused on proving of indigenous drugs and also fragmentarily proved drugs. It is a double-blind, randomized, multicentric study and is being conducted at various centers. The various new drugs are being added in our Materia Medica.

(ii) **On lower animals / Animal experiments** –

Animal testing, also known as **animal experimentation**, **animal research**, and in vivo **testing**, is the use of non-human animals in experiments. It includes pure research (such as genetics, developmental biology, and behavioural studies) as well as applied research (such as biomedical research, xenotransplantation, drug testing, and toxicology tests, including cosmetics testing). [11]
Lower animal are used in homoeopathy for testing the efficacy of a drug as well gain the safety measure before applying a new medicine. It is always advocated before every clinical trial of a new drug whether homoeopathic or non-homoeopathic. Regarding homoeopathic drugs, these experiments should be conducted especially with the mother tinctures which are used in the crude forms to judge their complete safety & long-term usage. Also, there is much scope regarding the testing of homoeopathic potencies upon animals so as to obtain scientific acceptance & proofs as regard to their efficacy in the treatment of diseases.

b) **In vitro study: -**

In vitro (Latin for "within the glass") refers to the technique of performing a given procedure in a controlled environment outside of a living organism. In vitro pharmacokinetic models of infection can make an important contribution to the study of the pharmacodynamic properties of an antibacterial agent. In conjunction with animal and human pharmacodynamic evaluations, they provide data to allow for the optimization of drug dosing regimens. In vitro models can be used simply to describe the effect of a drug on a bacterial population as well as to provide data for more-analytical studies, including hypothesis testing drawn.

Drug Proving & Research Methodology

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Unlike conventional medicine where animal experimentation forms the basis of evaluation of drug pathogenesis, homoeopathic medicines are proved on healthy human volunteers, including controls, from both sexes. Drug proving is the best model for double blind placebo-controlled trial.

The Central Council for Research in Homoeopathy since its inception in 1973, has adopted the Drug Proving Program as one of its primary research areas. The Council over the years devised the methodology for Drug Proving and the first drug proving protocol of CCRH was published in 1987.In 2013, a second workshop was held at CCRH to develop the drug proving protocol in harmonization with the international guidelines being developed for drug proving. During this workshop the protocol of the Council was compared with the international guidelines.

Based on the outcome of this meet, a protocol for the drug proving program of the Council has been developed by combining the CCRH methodology with that detailed in internationally developed guidelines. This is a generic protocol, which will be applicable for the drugs being proved by the Council.

Protocol of HPT Based on Research Methodology (CCRH):

The study will be conducted in accordance with this protocol and will comply with all the requirements regarding the obligations of investigators and all other pertinent requirements.

1. Drugs and Cosmetic Act 1940 & Rules 1945 of Government of India.
2. Guideline for Good Clinical Practice (GCP).
3. Declaration of Helsinki.

Over the years, provings have been conducted by a number of authorities, most of whom have devised their own methodologies. Over the years, the term homoeopathic pathogenetic trials (HPT) is also frequently used for drug proving and these are considered to be clinical trials. Drugs and Cosmetics Rules 1945 (Rule 122 DAA inserted in 2005) of the Government of India defines clinical trial as “a systematic study of new drug(s) in human subjects(s) to generate data for discovering and/or verifying the clinical pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects with the objective of determining safety and/or efficacy of the new drug. Proving of drug substances in homoeopathy is done to identify their therapeutic potential and is primarily a study of action of these drugs on healthy human beings as such these studies fall under the purview of clinical trials, and therefore must confirm to the GCP guidelines issued by the regulatory authorities in the country.

HPT trials are similar to Phase I clinical trials with a major difference that the aim of the trial is not to elicit the therapeutic dosage (bio-availability) or pharmacokinetic response, but to elicit the pharmaco-dynamic (biological response) to ultra-high diluted, non-toxic doses of the intervention and are observed in terms of symptoms which are temporary and disappear after stoppage of intervention. Drug Proving was formally initiated by the Homoeopathic Research Committee. Since inception of the CCRH, the proving program has been continuing and is one of the most important research programs of the Council. The Council has over the years, devised a methodology for drug proving as detailed in the protocol. The drug proving program of the Council is conducted in coordination with homoeopathic medical colleges and a large number of provers are students of these colleges, apart from provers of non-homoeopathic background. In each program, it is attempted to include volunteers from non-homoeopathy background also, apart from the students. As such the proving team comprises of scientists from the institute/unit of the Council and academicians from the homoeopathic colleges.

Study Objective

To identify pathogenetic effects of a Homoeopathically prepared drug substance (investigational proving substance IPS) on healthy human beings.

Inclusion criteria

c) Healthy individuals with no apparent disease and normal routine
d) Laboratory parameters during screening
e) Healthy individuals identified as fit for proving by experts Intelligent enough to record carefully the facts, subjective and objective symptoms generated by the IPS during proving
f) Able to be informed of the nature of the study and willing to give written informed consent

Exclusion criteria

a) Any disease or condition that might compromise the haematopoitic, renal, endocrine, pulmonary, central nervous system, cardiovascular, immunological, dermatological, gastro-intestinal or any other body system
b) Persons with colour blindness
c) Persons who have undergone surgery in last two months
d) Planned medical/dental treatment during the proving period including herbal or dietary supplements, procedures, or medications that are likely to interfere with, or substantially alter, responsiveness to the proving substance
e) Volunteers on regular medication (Allopathic, Ayurvedic, Homoeopathic, Naturopathic, Unani etc.) for any acute or chronic disease
f) Participant must not be on any homoeopathic remedy in the preceding one month and have had no significant change in health status in last one month
g) Emotionally disturbed, hysterical or anxious persons
h) Persons having known history of allergies, food hypersensitivity, etc
i) Women during pregnancy, puerperium and while breast-feeding, and women who have undergone hysterectomy
j) Smokers who smoke more than 10 cigarettes per day
k) Recent history of alcoholism/drug addictions or unlikely to refrain from excessive alcohol consumption/drug intake during the study period
l) Participation in another clinical or proving trial during the last six months

Sample Size

Each drug will be proved on a minimum of 30 participants, including 30% control. Adding 20% dropout, minimum volunteers needed to enroll in proving becomes 40. Each center must enroll minimum 15 to a maximum of 25 volunteers in proving. Efforts are to be taken to include at least 20% volunteers from non-homoeopathic background.

Dose & Potency

The provers will be instructed to take (no.30 size globules) 4 pills, 4 times a day at four hourly intervals for 7 days. In each proving study, the IPS will be proved in at least 2 potencies and maximum 4 potencies used in ascending order

Data Recording

The prover will be expected to make a daily record of the date and time of intake of study medication in the prescribed proforma. During the 7-day study medication intake period, the prover will report to the investigator daily. The investigator will interrogate the prover about the change in health status/sign and symptoms if any during this period and will record his/her observations in the symptom elaboration proforma Each symptom must be completed with respect to order of appearance, time of appearance & disappearance, location, sensation/character, modalities, concomitants, direction/extension of symptoms, etc.

Clinical examination findings will also be recorded. Appropriate pathological investigations if required would also be advised and the report will be added. For each symptom, the investigator on detailed interrogation with the prover, will classify and mention their symptoms as follows:

a) **NS** - New symptoms, not previously experienced.

b) **C-** - Unexpected change representing worsening or aggravation of ongoing or recurring symptoms.

c) **C+** - Unexpected change representing an improvement of ongoing or recurring symptoms.

d) **RS** - Unexpected recurrence of past symptoms.

The investigator will also record his/her observation about the possible causality of symptoms with the drug intake.

Follow Up

a) If sign(s)/symptoms(s) appear…

The prover is asked to stop taking the drug as soon as he/she feels any change or any sign(s) &/or symptoms(s) develop during the trial. The prover notes down the sequence of the appearance of new sign(s) &/ or symptoms(s), their progress and the number of doses after which each sign &/or symptom appears with date, time of onset and duration for which it persists. The intake of drug remains suspended till the sign(s) &/or symptoms(s) totally disappear. Each prover is interrogated by the Proving Master/Proving Associate to verify the sign(s) &/or symptom(s) recorded by him/her in Prover's Day Book Proforma every day. The verified symptoms are recorded in 'Symptoms Elaboration Proforma' with complete details in respect of their location, sensation, modalities and concomitants by the Proving Master.

During the course of proving, the prover is referred for specific laboratory investigation(s) to rule out any pathological cause for appearance of new symptom(s)/sign(s). Laboratory tests are performed to facilitate observation of any correlation between the subjective and objective changes during the course of proving. The opinion of the experts is also taken, on the appearance of new sign(s)/symptom(s), wherever needed. Photos of objective findings (e.g. skin eruptions, swellings, etc.) will also to taken and to be kept along with the prover record.

Steps of Study Design of RCT In Homoeopathy

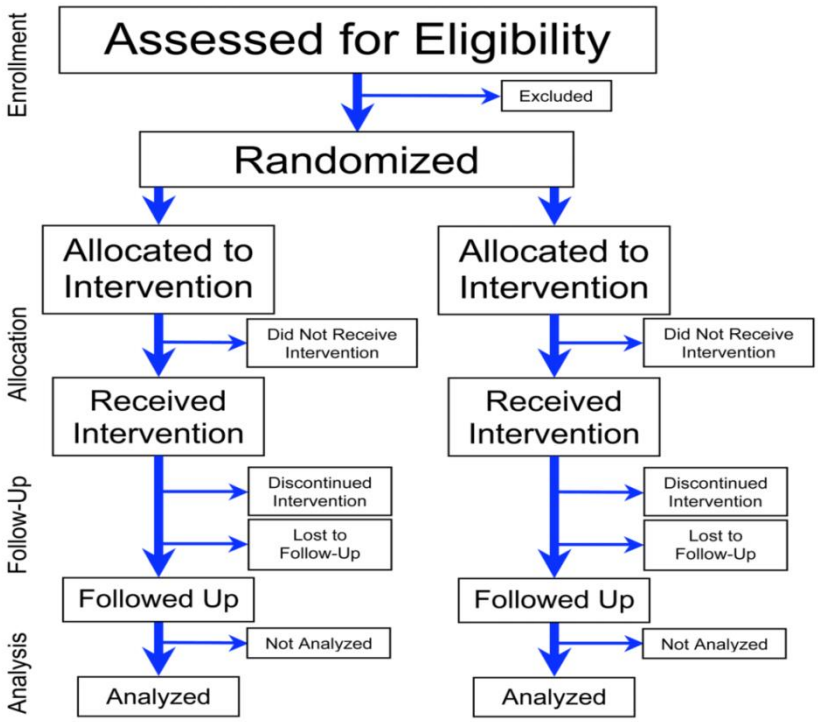

Figure: Schematic of RCT

Future Prospective of Research Methodology in Homoeopathy

Areas which must be explored: The clarity must prevail

1. Drug standardization: Aphorism 122 quotes, "In these experiments - on which depends the exactitude of the whole medical art, and the weal of all future generations of mankind - no other medicines should be employed except such as are perfectly well known, and of whose purity, genuineness and energy we are thoroughly assured." The aim of drug standardization is to ensure quality, genuiness, and authenticity of raw drugs and to evaluate the safety and efficacy of drugs. This aspect is of prime importance for all our future confrontation with the scientific fraternity. We must be familiar with the common question every intellectual asks us- What this drug contains or made up of?

2. Homoeopathic pathogenetic trials (HPTs): Drug proving or human pathogenetic trial is the core area we aim for. Drug proving techniques have been elaborated by Hahnemann some 200 years ago and have been rectified and updated time to time. In the recent times, the process and methodology of HPTs has improved greatly. Recent published guidelines 22, 23 on drug proving have strengthened HPT practices around the globe. The technique must be unified to yield & replicate true symptomatology of drugs.

3. Clinical research: Clinical research is one of the growing activities in Homoeopathy in the past few years. The concept of "Evidence based medicine" has evolved in conjugation with clinical research. In the past few years many clinical research papers have been published in peer reviewed journals (references cited elsewhere in article), thus by supporting Homoeopathy at global level.

4. Clinical verification: To make clinical proving and research more authentic and scientific, clinical verifications are now carried at multicentric levels. This helps us to gain finer shades of remedies in terms of ethnicities, climates, populations etc.

5. Fundamental or Philosophical research: This is one of the areas of interest for historians and many clinicians. These 200 years of evolution of Homoeopathy have been in turmoil for such a vast concept. Evolution in these years is really an area of interest for many. Hahnemannian writings, case studies, his mode of living etc are now studied with in-depth scientific attitude to extract finer information he applied. This will help us to present our concepts in more audacious manner.

Challenges (Past, Present and Future) in homoeopathy

Challenges keep us moving and must be taken with wisdom. There are some fundamental challenges in front of us now and they must be encountered to make future better. The inherent challenges which Homoeopathy has been facing are:

• High quality clinical trials and verifications
• Replication of HPTs, clinical trials and verifications to support results obtained earlier
• Rational, multi-centric, large sample size studies
• Publication bias,
• There is a need of extensive research based upon individualised treatment planning in Homoeopathy
• Selection of isopathic studies for meta-analysis (i.e. studies using a Homoeopathically prepared specific agent that triggers specific local symptoms, as it is not Homoeopathy by definition18) may affect the level of comparison with conventional RCTs. There must be separate RCT guidelines for Homoeopathy and also comparing RCTs of Conventional and Homoeopathic medicines.
• Global guidelines for clinical research
• Centralized database of research activities accessed globally • Promotion of primary health care research in conjugation with Homoeopathic practices • Funding and resource related challenges

What should we have done for HOMOEOPATHY

- If a science exists there exist routes to prove it. Scientific research is the next decade challenge for all of us. It must comply with the nature's law, survival of fittest.
- We must be able to find the hidden treasures of Homoeopathy and present them to scientific fraternity in a comprehensible manner. Research studies must be taken on a larger sample size at multi-centric levels to better understand Homoeopathy.
- Every generation must be inspired and motivated to contribute towards the development of science first. There is a need to "re-searched" and "revalidation" of the existing work with newer outlooks and thoughts.
- We must inculcate reading and forming libraries at our own level. There is a strong need of platforms dedicated to deliberate and open discussions on research related activities. • Evidenced based medicine standards must be amended and made mandatory at every level of Homoeopathic practices, be it individual, clinical, hospital, Institutional, or research level.
- The main aim of research is to look into the matter in a scientific and "rational" attitude and the conclusions and benefits must be used for the development of skills, clinical practices, repositories and growth

Conclusion

Man is the constant investigator and experimenter; his reason gifted mind always provoked him to search explanation for every statement. The constant why and how helped him to enlarge the field of

science. Homoeopathy too belongs to this field. Though based on fixed principle but still it creates many queries in the mind of most intelligent creature of nature.

Although our master said “it matters little what may be scientific explanation of how it takes place” [21] but in today’s scenario its mandatory to collect the evidence of homoeopathic effect. Since the birth of homoeopathy till now the controversies are never ending. Starting from Hufeland’s comment, many of dignities like Prof. Ernst of Australia has raised comments like homoeopathy is dangerous and should be banned by NHS. WHO too warns against the use of homoeopathy? It is the duty of homoeopathic neonates to come forward explore the research, enlarge the science, collect the evidence and proof the world that homoeopathy is scientific method of treatment, which can cure, manage, or prevent the disease. Homoeopathic tenets should never be compromised for research methodologies. Research methodologies should be design as per the requirements of Homoeopathic philosophy.

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