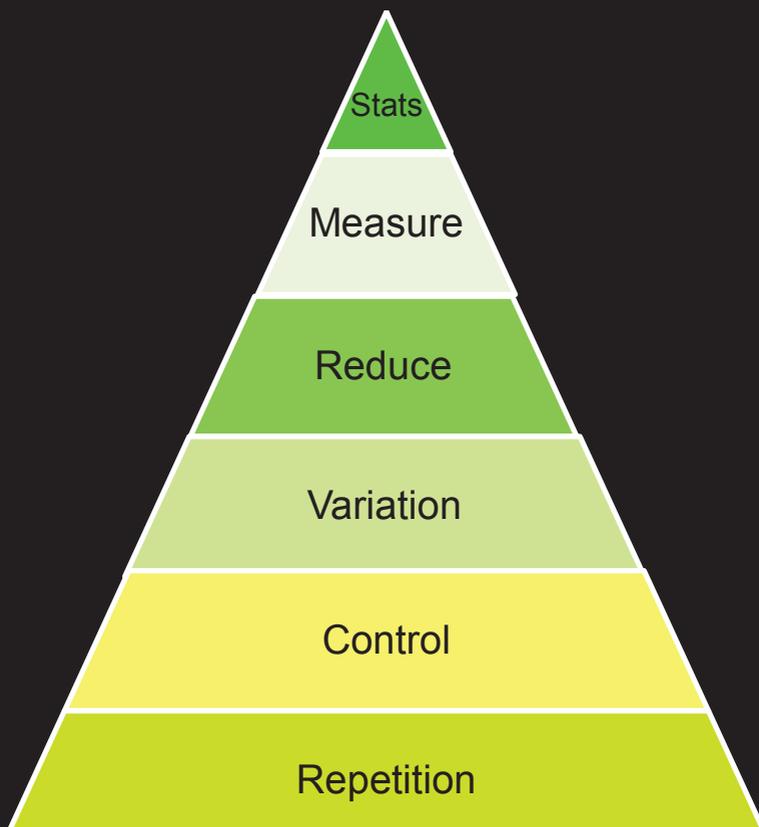


Quantitative Homeopathic Research: Seven Simple Steps

The Little Black Book



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Introduction

This book was written to assist in conducting quantitative homeopathic research. There is a need for definitive research data in homeopathy, and it is hoped that these steps will help those setting out on the research path. Furthermore, the reader should gain a better understanding of the limitations of various types of experimental designs and the interpretation of data derived from them.

The aim of quantitative clinical pathophysiological research is to determine whether the response to an experimental treatment is greater than that which would occur by chance. In the scientific method, the response must be quantifiable. It must be a response that can be measured objectively, and the treatment that caused the response must be defined prior to starting the study. A variable is a value that is allowed to change or vary within the scope of the experimental design. Measureable pathological variables are used to assess differences in responses between treatment and control (non-treatment) groups. They can also be used to compare baseline values (measured before a treatment) with the values after the treatment.

The production of quantitative clinical pathophysiological research data capable of withstanding rigorous scientific and statistical interrogation is essential if homeopathy is to take its place in the mainstream of modern medical and veterinary science. Careful planning is a critical element of the research process.

There is a place, between deciding what specifically a scholar wishes to research and setting out on the experiment, at which these seven steps become the foundation of the

experimental work. The steps have been designed to facilitate strong experimental design and useful, defensible results. Hahnemann set unusually high standards of medical practice in his time; it is up to present day homeopaths to do the same.

Step 1. Statistical procedures

A good understanding of the fundamentals of statistical methods is essential for analysis of research data. If this is done, interpretation of results has meaning. Many researchers only resort to statistical procedures when confronted with the task of analysing the results of their experiment. As well, the use of statistical methods before commencement of the trial to assist in the design of the experiment will ensure that the data so produced are amenable to analysis and appropriate to the question being asked by the trial (i.e., the hypothesis under investigation).

Assistance with statistical design and analysis may be provided by the institution with which the researcher is affiliated or may be obtained for a fee from a consultant statistician. Either way, the researcher will be required to prepare data in a form suitable for input into a statistical software programme, and should be capable of interpreting the statistical output of the programme. Therefore, it is important that the researcher attend a course in the fundamentals of statistics and a course in the use of the relevant statistical software package before commencing the trial. Such courses are available at most universities and technical colleges and take 3 to 6 months to complete. The acquisition of a good understanding of the principles and practicalities of statistical analysis is the *single most important step* in the entire research process.

Step 2. Measurement

Many clinical trials have been published in which subjects have participated in their own assessment (e.g., the degree of pain experienced after a remedial surgical procedure). Although such reports have their merits, their credibility is often diminished by an inability to prove that the results are free of subjective bias. Therefore, it is highly recommended that measurement of the outcome variable of interest be conducted independently of the subject of the investigation. In other words, an observer should conduct the measurement and record the result and the subject should not contribute to this process.

Response variables should be quantified in terms of discrete units of measurement, preferably using an instrument. When reporting the methods used in a trial, it is important to specify the model and manufacturer of the instrument used (most scientific journals require specification of the name, city and state for manufacturers in the USA and specification of the name, city and country for manufacturers elsewhere). Other relevant information that could affect the accuracy of the equipment used, such as whether a thermometer is of the digital or mercury type or whether blood pressure is measured using a mechanical or a mercury manometer, should be included. Analytical methods should be referenced or, in the case of commercially available kits, described in terms of type and manufacturer as for instruments. It is sometimes useful to consider sending samples to an independent, accredited pathology laboratory for analysis, in which case, details of the methods used should be obtained and reported.

Step 3. Expansion, reduction and the middle-of-the-road approach

When designing a research project, it is important to critically examine the scope of the question or hypothesis and the associated measurement protocol (experimental design) in terms of whether they would benefit by being reduced or expanded.

If the scope of the question and thus the design is reduced, the results become more specific. Although such findings may be useful as a basis for further research, their scope of application may be limited.

If the scope of the question is expanded, the unavoidable inclusion of confounding variables that cannot be negated by the experimental design may occur. This may make analysis difficult and decrease statistical power. Statistical analysis is based on the concept of a null hypothesis, which states that there are no differences between treatments. If the probability of the null hypothesis being true is less than 5% ($P < 0.05$), it is usually rejected and we conclude that the null hypothesis is false (i.e., that there are differences between treatments). Statistical power is the likelihood that a statistical test will not fail to reject a null hypothesis when in fact we should have rejected it and is a function of the sample size, the magnitude of the difference of interest, variation associated with the variable of interest, the accuracy of measurement and the statistical significance level used in the test.

The results of expanded research may be useful for identifying aspects deserving of investigation at a more reduced level; conversely, the results of research at a reduced level may be useful as a platform for investigation at a more expanded level.

Although the benefits of reductionism vs holism have been debated for many years, it is advisable to adopt a middle-of-the-road approach if the aim of the research is to provide data that has immediate practical value.

For example, one may wish to determine whether a homeopathic treatment has an effect on the severity of diarrhoea. If scope of the experiment were to be expanded to include all cases of diarrhoea, it would have to include not only people but also animals with this condition as well as a wide variety of causes of diarrhoea. Although the results of such expanded research may yield interesting results and stimulate further research, the trial would be expensive and time consuming and the results could not be applied to specific practical conditions without a large degree of uncertainty. The last-mentioned problem is often encountered in interpreting the results of homeopathic trials as a guide to treatment regimens in the clinical setting (1).

On the other hand, the scope of the research could be reduced to subjects suffering from diarrhoea caused by infection with a rare protozoan found only at the peak of Mt Warning. Although such a reduced design would severely limit general application of the results, it may find application as a design for studies of protozoan diarrhoea in other regions – or it may be useful to solstice celebrators!

A middle-of-the-road trial would involve one cause, clinic, shed, paddock or population, sex and age group. Such a trial would be easy to conduct and to repeat, and subjects could be selected from practice records if an initial diagnosis was performed.

Step 4. Variation

Variation should be restricted to the factor that is being assessed. Should this not be possible, variation in other factors should be minimised and accurately recorded. For example, climatic variation should be recorded when conducting field trials. This enables repetition and acts as a check for the validity of replications.

Observer variation can be controlled by using the same observer for each measurement or, if this is not possible, by using observers of similar dress, genotype, age, shape and behaviour. Phenotypic variation between subjects can be controlled by selecting subjects of the same sex with similar ages, weights and occupations. Genotypic variation between subjects can be controlled by using subjects with similar genetic backgrounds. For example, it would be of little use to randomly allocate German shepherds and Red Setters to the same treatments even if they were of the same age, sex and weight because their genetics differ too widely. Hybrids should be avoided because their genotypic variation is great despite their phenotypic similarity. In such cases, gene mapping may assist with the selection of appropriate subjects (see reference 4 for an example of the use of genotypically similar mice in a trial).

Variation is reduced by random allocation of subjects to treatments, and many books have been written on methods of randomisation. Independent random allocation of subjects means that the allocation of subjects to treatments is not biased by the observer. Currently, computer-generated random numbers constitute the most effective means of subject randomisation.

Treatments should be administered consistently according

to a predefined protocol, unless the mode of administration is part of the treatment, e.g., when the effectiveness of liquids is compared with that of pillules. In all other instances, a similar mode of administration is unacceptable – administration of treatments must be identical, e.g., when homeopathic liquid is administered to cats by placing a drop of liquid on the head, an anatomically defined and identical position on the skin of the cranium should be used for administration of the treatment to each subject.

Step 5. Control

All quantitative trials should include a control group consisting of subjects that are exposed to the same experimental conditions as the treatment group, except for the treatment under investigation. It is assumed that factors other than the treatment that affect the variable of interest will affect the control and treatment groups equally, ensuring that any difference between these groups can safely be ascribed to the treatment and not the environment (5).

The range in age, sex, occupation, weight, genotype and other relevant factors should be identical in the control and treatment groups. If the treatment involves an intervention such as dosing liquid from a bottle, a placebo dose containing all the ingredients of the liquid preparation except the active ingredient should be administered to the control group to eliminate the possibility that the act of administering the dose has an effect on the variable in question (3, 4). If a large group is treated, the controls should be randomly distributed amongst the treated subjects so that they are exposed to the same environment. This is a point of weakness in some homeopathic trials.

If possible, the observer should not know whether a subject is receiving the placebo or the treatment. This is another way of preventing observer bias, and is called blinding. As a further precaution against observer bias, it is useful to use one independent person to administer the treatments and another to record the results .

Step 6. Repetition

In modern science, no matter where you are in the world, the scientific project must be repeatable in another country or area for it to be valid. This should be possible if the variables and measurements are well documented.

Repetitions are defined as repeat experiments at different times or places. Seven repetitions are advisable, although the most stringent current standards for approval of the release of drugs for general use require 10 repetitions. Repetition is expensive. When the research is supported by limited or private funding, it is better to design a very simple trial and to repeat it 10 times in succession than to design a complicated trial that will require extensive funding to enable simultaneous or subsequent repetition.

Repetitions within a trial are called replicates, e.g., the individuals within a group are replicates. The number of replicates required is not fixed but depends on the variation intrinsic to the variable of interest. When the intrinsic variation is high, the power of statistical methods is diminished, and many replicates will be required to detect statistically significant differences. The likelihood that a certain number of replicates will be sufficient to detect statistically significant differences can be determined from reports of similar research trials but is difficult to predict in the absence of previous research data.

Animals are only considered replicates if they are individually identified and share the same environment. If six animals are not individually identified but share the same environment, they constitute one experimental unit, not six replicates. If the pen environments differ or are not monitored, this unrecorded variation may make differences between

replicates difficult to interpret. In many research trials, insufficient attention is paid to the pen environment. If it is not possible to record all factors that may affect the environment, the likelihood of such causes of variation should be considered when interpreting the results.

Step 7. Economics

Research should be affordable and costs should be projected forward when drawing up a budget. For example, future increases in the prices of consumables over the period necessary to complete the trial should be taken into consideration.

Budget for the purchase of a statistics software program or the cost of employing a statistician to analyse the results if you do not intend doing the analysis yourself. Universities usually provide access to statisticians, but it is wise to clarify to what extent statistical support is available, as universities may wish the student perform the statistical analyses themselves or may charge students for assistance with statistics.

Other hidden costs include:

- measurement devices or laboratory fees
- hire of premises, changes to premises, the cost of food...even coffee costs
- labour and experimental animals
- transport of people, equipment and animals
- writing materials, postage, computer, telephone
- time lost from present occupation
- time spent at libraries and seminars
- the isolation factor – research is by nature solitary and can reduce efficiency
- supervision or assistance – no-one does it alone, and

the institution may not pay for unexpected repetitions caused by floods and other disasters.

Application of the seven steps in practice

In this section, a selection of published trials relevant to homeopathy is discussed in the context of the seven steps. Some of these reports were chosen to illustrate how experimental design can limit the usefulness of results despite considerable expenditure of effort, time and money. It is important to note that no research is without fault; faultless research is a concept akin to God. Each research trial is a contribution to knowledge and should be valued within the boundaries of its limitations. A summary of these reports in terms of the seven steps is presented in Table 1. High cost is defined as that which could not be easily paid by a student with a \$40,000/year income in Australia.

Table 1. Comparison of selected published reports in terms of compliance with desirable attributes for successful research.

Attribute	Reference number				
	1	2	3	4	5
Statistical analysis	Yes	Yes	Yes	Yes	Yes
Instrument measurement	No	No	Yes	Yes	Yes
Middle-of-the-road design	No	No	Yes	Yes	Yes
Hidden variation	Yes	Yes	No	No	No
Repetition	Yes	No	No	No	No
Control	No	No	Yes	Yes	Yes
Cost	High	High	High	High	High

Example 1.

The report of Witt et al. (2008) (reference 1) was included as a demonstration of research that falls outside the definition of pathophysiological quantitative research and because it demonstrates that homeopathic medicine has positive effects. This trial was a cohort study in which the subjects' own observations over a long period were analysed. The aim of the study was to evaluate health status changes in chronically ill patients after 8 years of homeopathic treatment. It did not show that the pathophysiological effects observed were caused by homeopathy alone, but showed that the health status of patients who were treated by homeopathic physicians was likely to improve. Thus, it was successful in answering the question that it was designed to answer.

The discussion of the results of this expanded study was confined to answering whether homeopathic physicians provide an effective service in terms of health status and no attempt was made to relate the observed effects to homeopathy alone.

The sample population was not standardised; there was a bias towards educated females among those selected. Outcomes were used to assess the efficacy of standard drug treatments, as is common in medical practice. As large numbers of patients (3709) were enrolled in the study over a long period (8 years) (replication), not all variation could be controlled. The constant factor was the prescription of homeopathic treatment by physicians, as would occur in clinical practice. Variation due to differences in sociodemographic factors and patient histories was recorded using a questionnaire and taken into account in the statistical analysis.

Care should be exercised in interpreting this study as proof of the efficacy of homeopathy because all of the actions of

the doctors may have contributed to the result – not just the administration of homeopathy.

Although the statistical methods used were appropriate, the measurements were not objective, many variables were present and there was no control group. The study must also have been costly in terms of time and effort. However, it is an accurate clinical record of the effects of homeopathic physicians and is of value in that it indicates that further investigation of homeopathic physicians' practices is warranted. It would be of interest if the study could be repeated several times in other countries. This is not the type of research described in the seven steps. Dr Witt has previously participated in other trials, which are enlarged by the information in this trial.

Example 2.

Birnesser et al. (2004) (reference 2) conducted a simple quantitative trial to compare the effects of Traumeel S with those of NSAIDs on epicondylitis. Although the hypothesis was reduced to a simple comparison, the experimental design was expanded to include a broad base for examination.

The measurements were not conducted by the subjects, but they were not obtained using instruments and were therefore subject to observer bias. Furthermore, the observers differed, which would have increased variation. The trial involved two variables (pain and flexibility) and two treatments (Traumeel S and NSAIDs), and outcomes were assessed at three intervals (0, 1 and 2 weeks after administration of the treatments).

The treatments were confounded by the effects of optional oral analgesics and physiotherapy, which would have increased the variation. Thus, the trial had an extended base, consistent with practical conditions. However, the subjects were not randomly selected, and were allocated to the treatment protocol preferred by them. There was considerable variation in subject variables, and there were no controls.

There was repetition, as 184 people at 30 clinics were enrolled. Differences between the effects of the two treatments were not statistically significant. This means that the two preparations perform to the same standards in the real world. This finding answered the question asked. This trial did not test whether either medicine is effective, but whether their effects differ, and conclusively showed there is no difference. This trial showed that the results are worthy of retesting using a more stringent experimental regimen.

In a clinical situation, pain experienced by human subjects constitutes an ethical problem and precludes the inclusion of

an untreated control group in trials in which pain could be alleviated. It is possible that useful results could be obtained using broiler chickens, which also suffer from this disease. The inclusion of a control group would not be considered unethical and post mortem examinations could yield valuable information.

Example 3.

Biswas et al. (2005) (reference 3) investigated whether two homeopathic remedies ameliorate cancer. This research addressed a simple question and as such was a reduced trial. Do the treatments ameliorate cancer? The answer was simple: yes, they do. Observers were blinded and did not know which treatment the mice had received. The animals were randomly allocated to the groups.

As the measurements were made objectively during pathological examination, this trial qualifies as a quantitative pathophysiological trial. There were three controls, Groups 1, 2 and 6, and it is most likely that the environment was standardised, as this is routine laboratory practice although it is not described. Individual records of each mouse were kept, and the standard errors generated were small, meaning that replication was adequate. Repetition would have been of value to show that these significant results are not just a feature of this laboratory.

The findings of this trial are important enough to warrant investing more funds in testing these medicines in a wider clinical setting. If such simple remedies have the potential to provide valid alternatives to expensive and sometimes harmful chemotherapy, further research should be conducted. There are cases where the chemotherapy provides no relief, or has been refused by the sufferer or animal owner. In such cases, the ethical use of these medicines is a valid, possibility in an experimental situation.

Example 4.

Pedalino et al. (2004) (reference 4) asked a question: Can the efficacy of homeopathic medicines on inflammation be evaluated according to macrophage activity in experimental peritonitis? In my opinion, this question was a middle-of-the-road type of question, but it was still too expanded or general to be answered by the specific nature of the trial. Inflammation is a wide topic.

The variable of interest consisted of the number and behaviour of white blood cells in the peritoneal cavity and was measured objectively using pathological tests that were independent of the animals. Moreover, positive and negative controls were included to test the effect of injection into the peritoneum. This was a quantitative pathophysiological experiment. Mice were randomly allocated to treatment groups. Saline was injected into the peritoneums of control mice to negate any effect caused by the act of injecting the animals. There was no non-treated control group, although this may not have been necessary, as it is already known that saline will not have an effect.

This trial was conducted in a laboratory, where the environment is usually controlled. Numbers were sufficient, that is, there was sufficient replication and individual identification to produce statistically significant differences.

The results of this experiment would have been more useful if the trial had been repeated in another laboratory at another time. Although the use of statistics was extensive, the findings were inconclusive, and this is stated by the researchers who use the word “suggest” when describing the positive nature of their findings. This trial paves the way for further research. Medicines such as these are needed where there is antibiotic resistance or poverty; this trial showed that it would be worth

conducting further trials, which could result in their use in mainstream medicine.

Example 5.

The trial of Schuberth et al. (2002) (reference 5) was designed to determine whether a homeopathic preparation affects the behaviour of cells according to flow cytometric analysis. This trial involved a reduced question and was conducted *in vitro*, i.e., outside of the body, using a simple reduced design.

In vitro experiments are not directly applicable to clinical situations. They pave the way for clinical trials designed according to the seven steps. For example, demonstration that a homeopathic medicine alters the behaviour of cells *in vitro* could be sufficient evidence to warrant a clinical trial to determine whether it is useful in treating diseases in which altered cell behaviour contributes to the healing process, e.g., in bovine mastitis and human staphylococcal infection.

The aim of this trial was to determine whether flow cytometric analysis could be used to study homeopathically-induced changes in cell behaviour. Thus, the specific effect of the preparations on cell behaviour was secondary to establishing the validity of the method used. The trial was successful in answering the question – this is an excellent method for assessing the effects of medicines. In doing so, it conclusively showed that these medicines affect cell behaviour. Further repetition is required.

Such trials are cost- and labour-effective and are amenable to large numbers of measurements (10,000 in this case), which enables large numbers of replicates. The control in this experiment was normal culture medium and the treatments consisted of culture medium to which the compound of interest had been added. The measurements involved assessment of growth of the bovine leucocytes and their ability to kill their target cells.

Conclusion

This publication was written in the hope that it will assist other researchers and homeopaths who wish to validate their clinical successes. Much more research is needed, both in homeopathic and non-homeopathic disciplines, and more open acknowledgement of the limitations of research results can only have a positive outcome.

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