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# RESEARCH AND EVALUATION OF TRADITIONAL MEDICINE

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# 1. Introduction

Several reviews and papers on methods for evaluation of traditional medicine and medicinal plants have appeared since WHO brought out "General guidelines for methodologies on research and evaluation of traditional medicine" in 2000[1]. Important among these are chapters on Standardization, pre-clinical toxicology and clinical evaluation of medicinal plants, including ethical aspects and "Research, drug development and manufacture of herbal drugs" in the book "Traditional Medicine in Asia" (2002)[2] and the chapters dealing with "Building the evidence base for traditional medicine practice" in the Proceedings of an International Symposium on Traditional Medicine held at Awaji Island, Japan[3]. The WHO document on general guidelines clearly states that "The quantity and qualify of the safety and efficacy data on traditional medicine are for from sufficient to meet the criteria needed to support its use worldwide. The reasons for the lack of research data are due not only to health care policies, but also to a lack of adequate or accepted research methodology for evaluating traditional medicine".

The standard of clinical trials and the methodology for evaluating traditional medicine remains, unfortunately, of a standard not acceptable to the scientific community. If the objective of studies is to carry out research of a quality acceptable to clinicans of the allopathic systems of medicine so that these medicines could be prescribed in their hospitals then the standards set out for such trials such as the controlled, randomized, double blind trial have to meet. There is still a long way to go. In an interesting paper Gyllenhal[4] (2002) points out the depressingly low standards of clinical trials carried out with (1) Panax ginseng for performance enhancement, diabetes and as an immunostimulant, (2) Zingiber officinale for treatment of nausea and vomiting, (3) a traditional Chinese herbal mixture for eczema and another (4) Chinese herbal mixture for atopic dermatitis was effective. A systematic review and twenty-six papers on these four Chinese preparations indicated that only the traditional Chinese herbal mixture for atopic dermatitis. The results on all the other three preparations indicated that effectiveness has not been conclusively shown. It is not that the preparations have been

shown to be ineffective. It is just that the clinical trials were carried out with a design that ended up with equivocal evidence regarding efficacy.

The results of trials on Indian plants indicate that only about 30% of the trials are carried out with a design and protocol which are acceptable. Results of clinical trials carried out with a faulty protocol are not acceptable. One would have accepted a surge in the quality of clinical evaluation after the different conferences, workshops and meetings conducted by WHO and other organizations on clinical trials methodology and the emphasis paid to this area of work. Unfortunately this has not happened.

At a meeting of this type being organized at Pyongyang in June 2005 by the South East Asia Regional Office of the World Health Organization it will be important to try and think why the problem of poor quality of clinical trials is not being resolved. There is some progress but this is very slow.

It is possible, as has been stated often, that there is a paucity of investigators who are skilled to carry out clinical trials with traditional medicines. The clinical pharmacologists and clinicians who could carry out such studies may not be interested in traditional medicines while those interested in carrying out such trials may not have the competence of carrying out the trials. An investigator may be very interested in studying the effects of a medicinal plant preparation in diabetes mellitus and he may have an adequate number of patients to carry out such a trial. However if he is not aware of the concepts of sample size, sample homogeity, randomization and double blindedness he will never be able to carry out a good clinical trial.

The other more interesting thinking which has developed in the last five years is whether the modern methods of clinical evaluation are really very appropriate for carrying out good and meaningful studies on traditional medicine. This has been brought out in a paper by Chaudhury[4] (1992) where he states that "the challenge of the twenty first century will be to carry out clinical evaluation of herbal remedies within the framework of rigid clinical pharmacological principles without trampling on the concepts of the traditional systems of medicine". This thought needs to be pursued further.

Since this background paper deals not only with the methodology of clinical trials with medicinal plants but also with other aspects of traditional medicine it is pertinent to maintained that the results of clinical evaluation of the different systems of traditional

medicine also need refining and improvement. A systematic review and meta analysis of other traditional medicine therapies has been carried out on the basis of thirty six clinical trials[3]. The results obtained are shown below:

| | | | |
|---|---|---|---|
| 1. | Massage for low back pain | - | Insufficient evidence of efficacy |
| 2. | Spa treatment for various conditions | - | Insufficient evidence of efficacy |
| 3. | Spa treatment for rheumatoid arthritis and asteo arthritis | - - | Effective but studies are of poor quality |
| 4. | Yoga for Epilepsy | - | Insufficient evidence of efficacy |
| 5. | Homeopathy for Asthma | - | Insufficient evidence of efficacy |
| 6. | Homeopathy for Influenza | - | May shorten illness |

As can be seen, a lot of work is being carried out which will not yield unequivocal evidence regarding the efficacy of the system. Improvements in the methodology being used for such studies would yield result which are meaningful. This paper will look at some of the features which are essential for adequate clinical trials – and review whether any change is warranted – and then discuss a series of issues regarding such methodology which are being discussed today.

## 2. The Controlled Clinical Trial

The controlled clinical trial remains the cornerstone for clinical evaluation of traditional medicine for safety and efficacy. However in the field of traditional medicine there are several constraints in carrying out the methods of such a trial in all cases. The sample may not be large enough in numbers to carry out a large multicentred study. Double blind studies may not be possible. It is for this reason that the participants at the Hong Kong meeting stated "Single-case studies for the efficacy of a herbal medicine should not be ignored". Another type of study not usually carried out with synthetic compounds but which have a place in traditional medicine clinical trials are known as Observational Pharmacology Studies. In these studies the traditional medicine practitioners gives his treatment without modifying it in any way and the clinical investigator observes whether clinical improvement takes place. The data are recorded

by the traditional medicine practitioner and separately by the investigator carrying out these studies. More studies of this type should be carried out. It could provide a valuable model for studying both the efficacy and safety of herbal medicines[2].

## 3. Sample size

There can be no compromise, in a controlled, comparative clinical trial, in the size of the sample of the patients recruited for the clinical trial. The entire trial could result in an equivocal result unless adequate numbers are used. The number of subjects or patients need would depend on the significance of difference that the investigator or the pharmaceutical house is looking for or expecting.

## 4. Selection of patients

The patients who would comprise the two groups – controls on a standard drug – and patients on the herbal remedy being evaluated should be homogenous in character – i.e. the age, social status, economic background, state of health and other attributes should be similar. There is however a well established belief in traditional systems of medicine that the temperament or the "make up" of the individual also has a role to play in determining the actual medicine to be given. This concept has been mentioned earlier[2] and trials have been planned taking this into consideration. This temperament factor – for want of a better term is known as "prakrit" in the Ayurvedic System of Medicine "Mejaj" in the Unani System of Medicine and "Sho" in Kampo medicine.

This is not the place to give a lengthy background about this. It is something to be kept in mind, and taken care of, if possible, when selecting patients for the trial. The side effects of a herbal medicine also vary according to the temperament of the person. In Ayurveda there are three types of "prakrit", vata, pitta and kapha. The fresh juice of Momordica charantia, the bitter gourd used widely in South East Asia for diabetes mellitus would, according to Ayurveda, be effective in diabetic patients with a "kapha" or "pitta" temperament but should actually be avoided in patients with a "vata" temperament [5,6,7].

There is another concept in Ayurveda that the choice of therapy depends also on concomitant symptoms. The author planned a clinical trial of a herbal medicine used in bronchial asthma with two groups of patients – on the control drug salbutamol and on the herbal preparation. While this would be acceptable to any clinical pharmacologist or clinician in the modern system of medicine this was not acceptable to the experts in traditional medicine. This was because patients of bronchial asthma with gastrointestinal disturbances need a different herbal preparation than patients of bronchial asthma without gastrointestinal disturbances. These concepts are being brought out not to confuse the reader but to try and find explanations why clinical trials, planned by clinical pharmacologists, have very often failed to demonstrate efficacy of traditional medicines which are reported to be very effective for the same conditions in the traditional systems of medicine.

Another point to keep in mind when dealing with selection of patients is that very often, for ethical or other reasons, a new herbal preparation or traditional medicine is given to patients who are not responding to conventional therapies. Patients of diabetes whose blood sugar levels cannot be controlled are often given traditional medicines. This is not a good practice as it is choosing the patients not with the criteria of what would be the most appropriate sample but because these patients are available. If at all a trial is carried out on such non-responsive patients the objectives of the trial should be clearly delineated – i.e. a trial of a preparation on patients who have not responded to other treatments. Such a trial is in fact being carried out at the moment with Pterecarpus marsupium as a hypoglycemic drug. This study on non responders to other oral hypoglycemic drugs has been especially designed to study whether Pterecarpus marsupium is effective in such patients. This study, however, has been designed after a ten year study on patients with diabetes and after such an effort has been clearly demonstrated in Phase II and Phase III studies in diabetic patients[8]. This study on non responders is an extension of earlier studies.

## 5. Formulation, Dose and Regimen

Two important issues have emerged in the last five years which need to be taken into consideration when planning a clinical trial with a traditional remedy. The first is the

dose of the preparation to be used while the second is the importance of the stability of the plant material collected for the trial.

Several trials with traditional remedies and medicinal plants have not proved useful because the dose administered was inappropriate. The dose of the formulation has to be chosen with circumspection and care. If the substance is already in use then that dose should be used. If it is the first time that the formulation is to be used in human trials then, if there is animal data for efficacy the dose can be extra patented but with care as this may not always work this way[6]. The literature may often help by citing earlier studies, animal or human. Very often large doses have to be used. Patients do not like this and compliance becomes low. Clinical trials with herbal remedies would become much easier if the large bulk of the tablets could be compressed into smaller tablets. That is not being done at the present time.

Another point that needs to be emphasized is that the calculation of the dose should be carried out keeping in mind whether the crude form or extract is going to be used. The dose of the extract has to be calculated based on the extractive value, or better skill, on the quantity of the active marker present in the extract.

Standardization of the extracts and plant materials before the trials are initiated is essential. Experience has demonstrated that the importance of the material being active at the time of administration of the material is very important. There are two ways of approaching this universal problem. All the plant material could be collected for the entire trial – eighteen months to two years – and stored. The advantage of this is that there will be no variability in the effective concentration in the material because of collection of the material at different times from different places. The disadvantage is that there could be a reduction in the active constituents over the months. If this approach is used then the testing of the material has to be carried out whenever a new batch is sent out for clinical evaluation. This would ensure that the material would conform to the standards and that there is no deterioration of the quality of the material. A recent trial had to be stopped because of treatment failures whenever the combination product of herbs was used after three months of preparation. Laboratory studies were carried out. This demonstrated reduction in activity as time passed.

The other approach is not to collect the plant material at one time but to collect it at various intervals during the trials. This method would be acceptable only if the plant material is collected from medicinal plant cultivation in farms. This would reduce the variability in the active content of the plant due to variations in the location of collection, time of collection and other factors. These have been described in details elsewhere[9].

## 6. Design of the trial

The traditional design of clinical trials conforms to one of the following:

(a) Open trials

(b) Single blind trials and

(c) Double blind trials

Clinical trials with traditional medicines can be carried out within any of these designs. The difference between synthetic drugs and traditional medicine is that very often double blind trials are not possible. When a procedure like massage, yoga or meditation – common forms of therapy in many systems of medicine is being clinically evaluated it may be necessary to use the single blind technique or even carry out an open trial. Sometimes, even for trial with a herbal preparation it is not possible to have the preparation in a form – size, shape, volume, colour, consistency and taste – similar to the drug with which it is to be compared with. In these instances an attempt should be made to use the single blind design i.e. the doctor assessing the results of both treatments does not know at the time of assessment which patient was given which drug. If a single blind trial is not possible then an open trial could also result in scientifically acceptable results provided the parameters of assessment of the treatments are objective measurements which could be quantified. As much as is possible bias has to be ruled out. The message that appears to have come in the last few years is that the controlled, double blind, randomized, placebo controlled, multicentred clinical trial is not the only acceptable design. In trials of traditional medicines other designs could also be used. A very clear cut result was demonstrated in an open trial when the effects of a herbal coated medicated thread was found to be as effective as surgery in cases of anal fistula[10]. It was an open multicentred study.

A mention has been made earlier in the paper to Observational Pharmacology studies. More studies of this type should be carried out especially as a prelude to the carrying out of international studies. Much information could be obtained from studies of this type. It is indeed surprising that even though the WHO meeting at Hong Kong in 2000[1] highlighted the usefulness of these studies there have hardly been any published studies of this type in the last five years. The WHO Report states quite clearly "Observational studies have specific advantages in studying aspects of clinical safety. The use of such studies to prove efficacy is limited because bias in patient selection may occur. Nevertheless, the level of evidence on efficacy of traditional medicines can be significantly increased by well-designed observational studies". It is hoped that there will be, in the next few years, more use of this non interventional, cost effective approach towards collection of information on the safety and efficacy of traditional medicines being used.

There has also not been much activity towards carrying out the randomized single case design study mentioned at Hong Kong[1]. The benefits of this type of study has also been listed by Thatte; Single case design studies should have a common protocol which should be the basis of collaborative research between practitioners[6].

## 7. Randomization

Randomization of groups to eliminate bias has been a major advance in therapeutic evaluation of both synthetic and traditional medicines, and unlike "blind" studies is nearly always possible in clinical trials with traditional medicines. Randomization should therefore nearly always be incorporated into the methodology of clinical trials with traditional remedies. Randomization has however to be carried out in a proper manner. The quality of randomization of Chinese randomized trials on herbal medicines for hepatitis B has been reviewed[11]. Only ten per cent of the studies involving 176 randomized controlled trials on 20,452 patients represented the method by which these investigators randomized the patients. There were other major flaws in the randomization technique.

## 8. Use of the placebo

The use of an inert placebo is decreasing in comparative clinical trials because in most clinical conditions there already exists a treatment. The new herbal drug should therefore be compared against the existing drug. It would be unethical to withhold any treatment to a group of patients – if such treatment exists – for the sole purpose of investigating whether traditional medicine is effective. Some design of the study should be selected where this does not happen. It would probably always be possible to randomly allocate the patients even though it may be an open study[11]. Some investigators however feel that if herbal remedies are being used for relieving minor symptoms or for enhancing the quality of life then the use of the placebo in one of the groups would pose no greater risk and could be justified[12]. Although the author of this paper does not believe that placebos are needed today it would be only fair to state that placebo controlled trials have demonstrated the clinical efficacy of St. John's Wort in mild or moderate depression[13]. Ginkgo bitoba for dementia[14] and for Saw palmetto in benign prostate hyperplasia[15].

## 9. Phases of Clinical trials

A clinical trial of any new drug under trial, synthetic or herbal, goes through the following stages of clinical trials:

Phase I Studies - to determine the safety of the maximum tolerated dose and pharmacokinetic studies if possible.

Phase Ii Studies - to determine efficacy of the product being evaluated and record any side effects.

Phase III Studies - expansion of the efficacy and safety of the product in a larger number of patients at a larger number of centres.

Phase IV Studies - to study the safety/efficacy of the product after approval has been given for marketing the product in the first persons receiving the product.

Phase V Studies - studying the efficacy and side effects of the product when it is used by the community without the strict conditions which prevail in Phase II and Phase III clinical trials.

The special features regarding clinical evaluation of traditional medicines as related to these Phases of clinical trials are discussed below:

Determination of the dose to be used in Phase I studies with traditional medicine always poses a problem. This has been discussed earlier in this paper. Pharmacokinetic studies with herbal preparations are difficult and may not be possible even though a beginning has been made at a few centres in the region to carry out such studies. Generally the traditional medicine goes on to Phase III trials without having had pharmacokinetic studies carried out.

At the Phase II stage it may be preferable to carry out an exploratory OPEN study first before going on to blind studies. This pertains only to herbal preparations and traditional medicines which have never before been administered to humans. The pharmacokinetic properties are also not known. If the traditional medicine is in widespread use this is not necessary.

There does not appear to be any special problems relating to Phase III studies with traditional medicines.

At the Phase IV stage information about other drugs used concomitantly with the product should be carefully recorded as this may lead to side effects caused by interactions. For the first time the product will be used together with other drugs which the patient would be using for either minor or major problems.

It is, of course, necessary to ensure that the product is evaluated toxicologically in the laboratory and literature about the medicinal plants being used before initiating Phase I studies. A shorter limited toxicology study profile first described[9] in 1980 has now been broadly adopted by the World Health Organization. Regulatory approval from the

national government and ethical approval from the Institute Ethics Committee, and if necessary from the government, have to be obtained before initiating the trial.

## 10. Multicentred Clinical Trials

Multicentred studies need to be carried out at several centres using the same protocol for several reasons. The first is that multicentred studies add to the numbers of patients being administered the traditional medicines and thereby enhancing the value of the studies. Sometimes it is not possible to find the number of patients needed for analysis at one center. Carrying out the trial at four or five centres will enable the trial to be carried out on the requisite number of patients. A second reason for multicentred study is that it provides an opportunity of studying the effectiveness and side effects of the traditional medicine in different cultured settings and different ethnic population. When the product is eventually released it would be used in all these settings. Finally it is now known that there are differences in different populations and this may influence the effectiveness of the preparation being tested or its side effects. The recent discovery of the effects of Hypericum perforatum on drug metabolism makes systemic studies of herbal medicines in different ethnic groups an added on very useful factor[3].

This is not the place to describe how multicentred studies should be carried out. One of the most effective networks for carrying out multicentred studies on herbal medicines has been established by the Indian Council of Medical Research. Investigators interested in establishing multicentred studies need to review this model which, in its short life has been responsible for three treatments and medicinal plants being evaluated in this network before going on to industry. These are the use of medicated thread for fistula-in-ano, of Pterecarpus marsupium in diabetes mellitus and Picrorhazia kurroa in hepatitis disease[2,8].

## 11. Quality of Life Assessment

Traditional Medicines are reported to have an immunostimulant property which enhances the quality of life and provides a satisfaction which is difficult to measure and

is never included as a parameter to be studied in clinical trials with synthetic drugs. The WHO "General guidelines for methodologies on research and evaluation of traditional medicines"[3] suggested that the WHO Quality of Life user manual could be used to help evaluation of the results of clinical research on herbal medicines and traditional procedure – based therapies. Roy Chaudhury and Chaudhury in their chapter on preclinical toxicology and clinical evaluation of medicinal plants in the book Herbal Medicine in Asia by Ranjit Roy Chaudhury and Uton Muchtar Rafei[2] also said "In addition to studying the efficacy of the plant and the side effects included by it, the amount of Satisfaction felt by the plant and the Quality of Life parameters could also be studied". This is particularly important when a herbal remedy is being assessed alongside a synthetic drug. However, this is not being done. Some studies in this direction would provide evidence that many of the plants enhance the Quality of Life and event this by their immunostimulant action.

## 12. Concomitant Administration of Traditional and Allopathic Drug

There has been a change in the thinking about administration of both a traditional medicine and an allopathic drug concomitantly in a clinical trial. Earlier it was felt that such a trial should not be undertaken unless animal toxicology studies are carried out before such trials are undertaken. Clinical trials of concomitantly administered medicines are carried out to assess whether the dose of the allopathic drug could be reduced or whether specific side effects induced by the allopathic drug could be reduced. If the effects of the herbal medicine are well known or if it is being used widely then it may be justifiable and ethical to plan a trial with medicines from different systems of medicine. This issue will become important in the near future when antiretroviral medicines would be used widely for the treatment of HIV carriers. These drugs are potentially toxic drugs. However, there are claims from different parts of the world that these side effects of antiretrovirals could be reduced by herbal remedies and traditional medicines. Clinical trials would be needed to produce evidence based results to support this important contention. In addition there is an additional benefit in patients with AIDS taking also traditional medicine. This has been summed up by an investigator with the statement

"The psychologic benefits of taking herbal medicine in HIV-AIDS patients should not be underestimated [16].

## 13. Ethical considerations

The ethical aspects of clinical evaluation of traditional medicine remain broadly the same as for synthetic drugs. Issues such as Informed Consent, Compensation for injury during the trial, selection of Special Groups, Privacy and Confidentiality, functioning of Institutional Ethics Committees are as important for traditional medicine research as far any other clinical research. This is not the place to discuss each of these issues as Ethics of Clinical Trials could rightfully be the subject for another meeting. In this paper a few issues which appear to be more important for clinical trials with traditional medicines would be discussed. The four issues to be dealt with are (1) Responsibility of the Investigator in undertaking clinical trials, (2) Informed Consent, (3) Ownership of data and (4) Sharing the benefits of the research with the original keepers of the knowledge.

## 14. Responsibility of the Investigator in undertaking the clinical trials

The clinical investigator who undertakes a clinical trial has much more preclinical data than an investigator taking the responsibility of a trial with a traditional medicine. The structure of the active substance will probably not be known, bioavailability students would not have been conducted and pharmacokinetic studies would not have been possible. The quality of the active substance is always a cause for concern It is therefore a more difficult decision for a clinical investigator to agree to become the coordinator of a trial with herbal remedies. It is an ethical judgement for him to take up the trial.

## 15. Informed Consent

Very often clinical trials with traditional medicines would be carried out in the rural areas in subjects who are uneducated, illiterate and poor. It is difficult to provide

the information on any trial to a prospective participant in the trial. It is doubly difficult to do the same to people who are illiterate. An appropriate Informed Consent form should be designed for these persons so that they can understand what they are doing and what they are agreeing to do. It would be unethical to take advantage of their ignorance and obtain signed Ethical Consent forms. Herein lies the ethical issue for the chief investigator.

## 16. Ownership of data

The issue of ownership of the data generated in the trial should be discussed with the sponsers of the trial before the trial is initiated. This is much more complicated problem than what appears. Pharmaceutical houses sponsoring the clinical trial may not like to publish the results of trials where the new drug being tested was much less effective or induced side effects. On the other hand, it is important to disseminate these results to other investigators about these results. The dilemma here can only be resolved by a dialogue before the trial. The issue as to who actually owns the data and thereby have the right to use the information is one that can be discussed.

## 17. Sharing the benefits

Very often the knowledge which has led to work culminating in a clinical trial has come from folk lore, from the indigenous population or from tribal knowledge and forest dwellers. If the clinical trial and the research carried out on the medicine leads to financial profits in the shape of a drug being developed then that local population have the ethical right to receive a share of the benefits. This should be worked out so that the possessors of the knowledge benefit also. This is the ethical issue involved.

## 18. Conclusions

The quality of clinical evaluation of traditional medicines needs to be improved. The weaknesses in this area have been recognized by scientists and investigators both from "modern" medicine and also from the traditional systems of medicine. This feeling has been very aptly described by a thinker and researcher from the Ayurvedic system of medicine who has stated "Ayurvedic clinical research has been going on for the last 50 years. However, hardly any studies have applied real tests of scientific enquiry to its full conceptual understanding. This is why the results of clinical research in Ayurveda so far have not received due recognition from the scientific world"[17].

Scientists from the different systems of medicine have to work together to develop a methodology of clinical research which will allow traditional medicine to be researched within its own paradigm, which will respect the concepts and fundamental values of traditional medicine and yet will provide evidence so that there is development of evidence – based clinical practice. This indeed is the formidable challenge ahead.

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