SOCIETY FOR NEW AGE HERBALS

VIEWS & REVIEWS

Vol 2, No.5 **DECEMBER** **2009**

Clinical Research on Herbal Medicines- Issues, Perspectives and Way Forward

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A clinical trial (clinical research) is a research study on human volunteers to answer specific health questions. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people and ways to improve health. Interventional trials determine whether experimental treatments or new ways of using known therapies are safe and effective under controlled environments. However, these studies appear to be more relevant in case of new chemical entities where experience has to be generated. In case of herbal drugs, though, the purpose is validation of claims most of the times; however in case of new formulation (polyherbal most of the times), clinical trial will answer specifically whether this new formulation will be safe and effective in the desired indication or not.

Herbal medicines have not only been continuously in use for primary health care by the poor in developing countries, but have also been used in countries where conventional medicine is predominant in the national health care system. During the last decade, use of herbal medicine has expanded globally and has gained popularity. The World Health Organization (WHO) estimates that 4 billion people (approx. 80 per cent of the world population) use herbal medicine for some aspect of primary health care.

The potential benefits of herbal medicines could lie in their high acceptance by patients, efficacy, relative safety, and relatively low costs. Patients worldwide seem to have adopted herbal medicines in a major way. The efficacy of herbal medicines has been tested in hundreds of clinical trials, and it is wrong to say that they are all of inferior methodological quality, but this data is still

small considering the multitude of herbal medicines available; worldwide, several thousand different plants are being used for medicinal purposes.

In developed countries, majority of the clinical trials are double blind placebo controlled trials. However, among the clinical trials conducted in India, majority are randomized open trials, and very few double-blind placebo controlled trials. Further, majority of clinical trials conducted in India have shown significant efficacy and majority had no mention of the adverse events encountered during the course of the trial. After evaluating the collected data from the clinical trials funded/conducted on traditional medicine herbal products in India, the authors feel, that as far as trials conducted in India are concerned, majority of the trials seemed to be biased to prove efficacy whereas the trials conducted in other countries seemed to prove inefficacy of traditional medicine herbal products.

GUIDELINES / REGULATIONS FOR CLINICAL TRIALS ON HERBALS / ALTERNATIVE MEDICINE:

Currently there are no specific regulations or guidelines laid down that should be adopted to do clinical trials on herbals / Ayurvedic / alternative medicines. The guidelines available for allopathic stream of medicines may not be directly applicable to herbal medicines. However, a few organizations have developed broad directional guidelines, some of which are summarized below.

Indian Council of Medical Research (ICMR) guidelines

ICMR guidelines have classified herbal drugs into three categories and have suggested to follow different approaches for their clinical evaluation. The herbal products can belong to any of the three categories given below:-

- A plant or its extract the use of which a lot is recorded in the ancient Ayurveda, Siddha or Unani literature or the plant may actually be regularly in use by physicians of the traditional systems of medicine for a number of years.
- An extract of a plant or a compound isolated from the plant to be clinically evaluated for a therapeutic effect not originally described in the texts of traditional systems or, the method of preparation is different; it should be treated as a new drug
- An extract or a compound isolated from a plant which has never been in use before and has not ever been mentioned in ancient literature; it should be treated as a new drug

Clinical trials with herbal preparations should be carried out only after these have been standardized and markers identified to ensure that the substances being evaluated are always the same. The standard recommendations regarding informed consent, inducements for participation, information to be provided to the subject, withdrawal from study and research involving children or persons with diminished autonomy, all apply to trials on plant drugs also. These trials have also got to be approved by the appropriate scientific and ethical committees of the concerned Institutes. However, it is essential that such clinical trials be carried out only when a competent Ayurvedic, Siddha or Unani physician is an investigator or co-investigator in such a clinical trial.

World Health Organization (WHO) guidelines

The WHO has published guidelines in order to define basic criteria for evaluating the quality, safety, and efficacy of herbal medicines aimed at assisting national regulatory authorities, scientific organizations and manufacturers in this particular area. Furthermore, the WHO has prepared pharmacopoeial monographs on herbal medicines and the basic guidelines for the assessment of herbal drugs. Originally, WHO guidelines for GCP have been adapted from ICH guidelines. These guidelines specify the requirements for clinical trial protocol and protocol amendment(s); background information about the name and description of the investigational product(s); trial objectives and purpose & trial design selection and withdrawal of subjects; treatment of subjects; assessment of efficacy & safety; statistics; direct access to source data/documents; quality control and quality assurance; description of ethical considerations relating to the trial; data handling and record keeping; financing and insurance if not addressed in a separate agreement; publication policy if not addressed in a separate agreement; pharmaceutical assessment of preparations; and stability and safety aspects.

AYUSH guidelines

Ayush is a nodal agency for coordinating all the works such as education, research and health care through Indian Systems of Medicine, viz. Ayurveda, Homeopathy, Naturopathy, Siddha and Yoga. This agency funds several extramural projects besides having a research council called Central Council for Research in Ayurveda and Siddha, dedicated to research in Ayurveda, through its several labs. AYUSH has recently published a draft on the broad guidelines for conducting clinical trials on AYUSH products. It is yet to come into force, though.

REVIEW OF CLINICAL TRIAL DESIGNS ON TRADITIONAL/ HERBAL MEDICINES

Globally, traditional /herbal medicines due to increasing popularity, have been under evaluation for both their efficacy and safety. Scientists who are undertaking/conducting clinical researches on them have limited knowledge on traditional/herbal medicines. Since they are trained in contemporary science and western medicine, they advocate a particular way of looking at herbal drugs, which includes the quality control, the toxicity, the proven efficacy through clinical trials using double blind placebo controlled methodology followed by post marketing surveillance with a view to monitor the adverse drug reactions. This approach was advocated by those countries, which do not have a rich tradition of healthcare like Ayurveda or Chinese medicine. This has necessitated a move from traditionally followed qualitative observations to the current concepts of quantitative research.

Single herbal drugs subjected to clinical trials using standard designs have recently been reported to be ineffective. This is in contrast to the several other studies on the same products proving their efficacy in earlier conducted clinical trials using almost similar designs. Moreover review of the trial methodologies and results obtained provided the debatable conclusion that none of the above methods followed for conducting clinical trials are foolproof with respect to traditional medicines which includes Ayurvedic/ herbal medicines as well. Numerous trials on even the same product using conventional design for clinical trials gave inconsistency in results. Therefore, the conventional approach of conducting clinical trials on single drug as a component of treatment may not be appropriate for traditional/ herbal medicines. The probable reason could be that “traditional medicine aims to correct maladjustments and restore the self-regulatory ability of the body, and not to antagonize specific pathogenic targets”.

One important factor should always work as a guiding principle while designing the protocol for clinical trials that single drugs are seldom used in practice and mostly a traditional medicine practitioner prescribes a regimen consisting of diet, multiple drugs and deeds--- to treat a particular ailment. In the trials analyzed in this study, trials had been conducted only on single drugs and not the actual whole treatment regimen, thereby doing injustice to the basic principles of traditional medicine as such.

NEED OF ALTERNATIVE APPROACH FOR CLINICAL TRIAL ON TRADITIONAL MEDICINE

The conventional methods of controlled and '*randomized controlled clinical trial'* is considered a Gold standard. However, while applying it to evaluate herbal/traditional medicine especially Ayurvedic medicines, its limitations come to fore. A careful study of holistic approach of treatment followed in traditional medicines suggests that the current method of conducting clinical trials have serious limitations in evaluating the evidence of efficacy of Ayurvedic or traditional medicine products and the reason being that the treatment regimens used by traditional medicines are holistic in nature; while the treatment approach in contemporary medicine is generally reductionist. Several limiting factors make the task of conducting clinical trials on traditional/ herbal medicines in conventional way, daunting; some of these issues are discussed below.

Trial design

Herbal / Traditional medicine presents special challenges in the design and execution of studies, with respect to both internal validity and generalizability. These problems relate to the tension between specifying the intervention sufficiently that others can apply it and desire to study traditional medicine as it is applied in traditional medicine practices. They also concern the difficulties in controlling expectation bias (the systematic effect on the results of the participants' belief that a certain therapy will help them). Most traditional medicine interventions are investigated only after they are so widespread that they can no longer be ignored, and by that time, the Traditional medicine practices are highly diversified in personal experiences, biases, and expectations. A single research strategy will not fit all circumstances and all traditional medicine interventions. Hence, there is need for flexibility in designing of trials likes' randomized trial, Single case, Black box, Ethnographic, etc. The study design may be chosen from a whole spectrum of clinical research designs which are suitable for assessing traditional medicine.

Randomized controlled trials

The most powerful method for testing the effect of a conventional medical intervention is a Randomized clinical trial, which however is not suitable for many traditional medicines. Standard randomized controlled trials (RCTs) consisting of two or three study arms, large numbers of patients in each study arm, one specific, standard treatment or dose of treatment per study arm, and 1 or 2 years of follow-up may be ill-suited to answer questions about the long-term effects of complementary and alternative medicine. In many other traditional medicine therapies, however, the conceptual basis for the therapy requires an interaction between the practitioner and patient that

modifies the therapy specific to the individual. Indian traditional medicines, especially Ayurvedic medicine require individualization of treatment based on examination and understanding of the patient's condition using concepts that do not have an analogue in western allopathic medicine. Consequently, traditional medicine/ CAM advocates have criticized randomized clinical trials that reported no effect for not having allowed the necessary tailoring of the intervention.

Blinding:

Blind assessment is a critical component of conventional evaluation of therapeutic interventions. Treatment blinding in the evaluation of herbal medicines should adopt the approach of conventional medicines, e.g. using active and control formulations with similar colour, taste, aroma, etc. However, in the evaluation of efficacy of traditional therapies, it can be difficult, impractical or impossible for the practitioner to be kept ignorant of what treatment the patients are receiving. It is important, however, to reduce any bias introduced by non-blinded treatment by carrying out a blinded assessment of the primary outcomes of the study. If the herbal medicine cannot be administered in a predetermined standardized formulation, it will be impossible to keep the treatment blinded.

Placebo

Use of a placebo may not always be possible as this may involve ethical issues as well as technical problems. For example, it may not be possible to have a placebo control if the herbal medicine has a strong or prominent smell or taste, as is the case in products containing certain essential oils. In addition, patients who have been treated previously with the herbal medicine under investigation that has a characteristic organoleptic property, cannot be randomized into control groups. In the case of herbal medicines with a strong flavour, placebo substances with the same flavour may have a similar function. This problem may become more compounded in case of semi solid formulations like Chyawanprash. In such cases, it may be advisable to use a low dosage of the same herbal medicine as a control. Alternatively, a positive control, such as well-established treatment, can be used.

Clinical equipoise

Ayurveda or herbal medicine does not have another herbal clinical equivalent, rather clinical trials with herbal equipoise are discouraged. In herbal traditional medicine research, comparing the activities of the herbal remedies to standard care is paramount in order to achieve clinical *equipoise*. Without *equipoise,* the research will not be scientifically valid as some of the participants may

receive inferior treatment and the effort will not contribute to increasing knowledge about best treatment. The drawback in this approach is that some of the intangible holistic values of the herbal remedies are masked by the western approach and are not put into consideration. Therefore, the control group in herbal medicines research should be placed on the standard clinical care of allopathic medicines where it is available. Furthermore, the issue of continued care after completion of the study should be raised in such studies before commencement.

Polyherbal therapy

Ayurveda or other traditional systems of medicine seldom use mono herb based therapy. In most of the cases, traditional medicine physicians follow the approach of multiple therapies coupled with dietary and behavioral modalities to achieve therapeutic effectiveness. Rheumatoid arthritis is a typical example in which oral drugs (mostly polyherbal), topical application of medicated oils along with strict dietary restrictions are common features.

Standardization or Quality control

Plants are a polypharmacy in themselves containing hundreds of constituents and some of them are present at very low concentrations. Standardization of herbal products is a burning issue being discussed and debated from academic to regulatory fora. Quality of the finished product depends upon the quality and authenticity of the crude raw material, geographical location of collection, time of collection, method of harvesting, storage, processing, microbial load, heavy metal contamination, etc. Most critical point to achieve standardization is identification, isolation and characterization of the marker compounds. It is followed by developing appropriate analytical methods to test the qualitative and quantitative presence of the compounds not only in the crude plant material, but also in the intermediates like extracts and their finished formulations. Intense efforts are going on globally to evolve and develop the pharmacopoeial standards of the medicinal plants used in the traditional medicines.

Ayurvedic perspective

The word Ayurveda is derived from *Ayu* (life) and *Veda* (knowledge) therefore, it is knowledge of life. Its objectives are two fold viz. to maintain the health of a healthy person and if by chance despite following all the instructions of leading a healthy life, somebody falls ill then cure the disease. With a view to remain healthy for 100 years in order to achieve *dharm, arth, kama and moksha* (Charak Samhita, 2000), Ayurveda prescribes both non-therapeutic and therapeutic measures. Therapeutic measures again are of two types (i) life sustaining and (ii) disease alleviating.

Both of the above include three fold measures

- Dietary regimen
- Behavioural modalities
- Drugs

PROPOSED METHODOLOGIES

The authors propose that the proper method of conducting clinical trials in case of Ayurvedic medicine is to subject the whole treatment regime to the test rather than its individual components and best way to achieve this is to follow the concept of observational research rather than double blind placebo controlled clinical trials.

One strategy could be to use pragmatic trial approach, which however has its own problems. In a pragmatic trial, patients are assigned to a traditional practitioner rather than a tightly specified traditional therapy. The traditional practitioners can provide their treatments in their usual fashion, individualizing the therapy for each particular patient. While this strategy allows the conventional practice to take place in its traditional fashion, it makes blinding or otherwise controlling expectation bias very difficult.

Furthermore, while in one way individualizing the therapy increases generalizability, it also increases the sensitivity of the results to the skill of the practitioners. Since the intervention relies on practitioner expertise in understanding the patient and delivering the therapy, the study results are more difficult to apply to other practitioners. Thus, pragmatic trials should discuss the training and experience of the traditional practitioner. Large pragmatic trials that include many practitioners and that compare a traditional therapy with a credible control or alternative therapy would be particularly useful in assessing traditional medicine.

The most appropriate method of generating efficacy data on classical Ayurvedic therapeutic regimen appears to be observational research as it involves:-efficacy of whole treatment regimen; it is conducted in real life situation; data generated by this method can be used by other physicians as well. Change in mind set is required among traditional medicine physicians to start proper documentation of their practice to generate the data. It will be acceptable to both WHO and to drug regulatory agencies as documented evidence of traditional use.

Observational studies collect findings on a therapeutic or prophylactic treatment under routine conditions. The special feature of these studies is that they seek, as far as possible, not to influence the individual doctor–patient relationship with respect to indications, and the selection of

and carrying out of the treatment. These studies may be conducted with or without a control group. The specific details of the study (e.g. the time and extent of examination for each individual patient, the number of patients involved) and the envisaged methods (e.g. data recording and evaluation) must be adapted to the question investigated in the study (e.g. safety or appropriate posology). 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 medicine can be significantly increased by well-designed observational studies.

Some of the methodological approaches specific to the assessment of traditional medicines through clinical research are given below.

- Evaluate traditional medicine in its own theoretical framework - this approach is related to clinical evaluation of holistic multi-pronged therapeutic approach the traditional system of medicine practices.
- Evaluate traditional medicine in the theoretical framework of conventional medicine - this approach refers to certain cases of Ayurvedic drugs where single herbs are used as stand alone medicine in traditional medicine
- Compare the efficacy of different traditional practices within the system of traditional medicine - this approach refers to clinical evaluations of non-therapeutic or semi-therapeutic practices. For eg. Panchkarma, which involves use of medicated oil or Yogic practices which do not involve any medicine.
- Evaluate the efficacy of pure active phytochemicals under the rigorous current scientific procedures or conventional methods for clinical trials

CONCLUSION:

To conclude, we propose a paradigm shift in approach to conduct clinical trials of traditional medicines. There is huge difference right from objective to evaluation parameters when it is compared to clinical trials on modern synthetic products. Even if we assume that there is need of double-blind placebo-controlled trial, its methodology needs significant modification. There is, therefore, an urgent need to do brainstorming and evolve a harmonized guideline for clinical trials to be conducted on traditional medicine herbal products.

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