

**Training Workshop on  
Development of Protocols for Clinical Trials  
of Ayurvedic Drugs**

*Organized by the*

**Research Committee on Traditional Medicine**

*Of the*

**National Science Foundation**

21<sup>st</sup> March 2003

Auditorium, NSF

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# Training Workshop on "Development of Protocols for Clinical Trials of Ayurvedic Drugs"

Organized by

The NSF Research Committee on Traditional Medicine.

Programme

Venue : NSF Auditorium

Date : Friday, 21, March 2003

Time : 9.00 a.m. to 1.00 p.m

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9.00 a.m.	Registration	
9.30 a.m.	Welcome Address	Chairman, NSF
9.35 a.m.	Introductory Remarks	Dr S Sritharan, Chairman/RC
9.40 a.m.	General Overview on Research methodology	Dr Michael Eddleston
10.00 a.m.	<b>Discussion</b>	
10.10 a.m.	World situation on Traditional Medicine in Clinical Trials	Dr T Varugunam, Eastern University
10.30 a.m.	<b>Discussion</b>	
10.40 a.m.	<b>T E A</b>	
10.55 a.m.	Development of Protocols on Vitiligo for Clinical Trials of Ayurvedic Drugs	Dr H A S Ariyawansa, IIM
11.15 a.m.	<b>Discussion</b>	
11.25 a.m.	Appraisal of Protocol by Allopathic Dermatologist / Pharmacologist	Dr Ganga Sirimanna, NHSL
11.45 a.m.	<b>Discussion</b>	
11.55 a.m.	Development of protocols on Rheumatoid Arthritis for Clinical Trials of Ayurvedic Drugs	Dr Sarath Ranasinghe, IIM
12.15 p.m.	<b>Discussion</b>	
12.25 p.m.	Appraisal of Protocol by Allopathic Rheumatologist / Pharmacologist	Dr Lalith Wijeratne, NHSL
12.45 p.m.	<b>Discussion</b>	
12.55 p.m.	Final Discussion and summing up	

# General Overview on Research Methodology

*Michael Eddleston*  
*Dept of Clinical Medicine, Colombo.*



In this age of 'Evidence-based Medicine', both health care workers and researchers need to have a good understanding of clinical trial methodology. This will ensure that good studies are performed and that the end-users of the information are able to judge whether a trial's results are of good quality and valid to their clinical practice. This presentation will discuss the different types of study that can be performed, while concentrating on the good design of randomized controlled trials (RCT).

The best evidence for an intervention - Class I evidence – comes from *RCTs*. *RCTs* are one form of *Experimental* study, in which the investigator assigns exposures to a treatment. They must be differentiated from the lower quality *Non-randomized* or *Pseudo-randomized* controlled trials which are also experimental. Studies in which the researcher does not assign interventions but simply watches what happens are called *Observational* studies. There are a few types of such studies but none will give as accurate information as a *RCT*.

## Sources of error in Observational studies of a treatment

### *Systematic errors*

- Biases due to factors other than the treatment being offered

### *Random errors*

- Impact of chance on comparisons of outcome between those who did and those who didn't receive the treatment

## **RCTs can minimize such errors - issues with their design**

Examples illustrating each of these issues will be given during the presentation

### *Avoid systematic errors*

1. **Proper randomization:** ensures a similar likelihood of each type of patient being allocated to the different treatment regimens under investigation. Allocation must be made in ignorance of the next treatment option, otherwise health care workers will decide whether to recruit a patient or not, producing bias.

2. **Intention to treat analysis:** post-randomization exclusion of patients will produce bias. Best to include everyone randomized to each arm in the analysis. However, such an analysis will tend to underestimate the effects produced by full compliance with the study treatments.
3. **Do not do data-dependent analysis:** all major analyses should be stated in advance and not follow interesting findings!
4. **Sub-groups should be defined before randomization:** some features may be affected by the treatment under study.

***Avoid random errors***

1. **Size:** make sure that the trial is big enough (or can be incorporated into an individual patient meta-analysis). Do power calculations.

**Make the study *externally valid***

Try to include all possible patients into the trial – make entry criteria as wide as possible. If only a small group of patients are studied then the results of the trial will not be valid for most other patients.

## Reading

- Collins and MacMahon. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *Lancet* 2001; 357:373-79
- Grimes and Schulz. An overview of clinical research: the lay of the land. *Lancet* 2002, 359: 57-61.
- Schulz and Grimes. Generation of allocation sequences in randomised trials: chance, not choice. *Lancet* 2002; 359: 515-19
- Schulz and Grimes. Allocation concealment in randomised trials: defending against deciphering. *Lancet* 2002; 359: 614-18
- Schulz and Grimes. Blinding in randomised trials: hiding who got what. *Lancet* 2002; 359: 696-700
- Moher. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; 352: 609-13
- Jadad. Randomized controlled trials. BMJ publications.

All these papers and the book are available for free on the web.

## World situation on Traditional Medicine Clinical Trials

There is an increasing interest in all countries of the world in the use of Traditional Medicine for the treatment and prevention of illnesses. In the developing countries TM continues to be an important part of health care and is often the only form of health care available in many African countries. The World Health Organization launching its first global strategy for TM in May 2002 cites the following statistics as an indicator of this growing global interest. In France, 75% of the population has used complementary medicine at least once; in Germany, 77% of pain clinics provide acupuncture; and in the United Kingdom, expenditure on complementary or alternative medicine stands at US\$ 2300 million per year.

The United States of America has set up a National Centre for Complementary and Alternative Medicine(NCCAM) for the purpose of investigating the safety and efficacy of the therapies available in TM.

A doctors decision to prescribe a particular form of therapy is based on scientific evidence and not on anecdotal evidence. Scientific evidence is based on what is now termed the Randomised Clinical Trials(RCT). RCT has 4 phases.

- **Phase I:** What is the safe dose? How does the treatment affect the human body? How should the treatment be given?
- **Phase II:** Does the treatment treat the disease or cure the condition?
- **Phase III:** Is the treatment better than, the same as, or worse than the standard (or most widely accepted) treatment? If there is no standard treatment available, is it better than, the same as, or worse than a placebo?
- **Phase IV** After it has been approved for use are there any unanticipated side effects

Two precautions are taken to prevent biases creeping into the study in phases II and III studies

1. The patients are allocated, by chance using a random number table to the two groups; that is those receiving the drug and those receiving the placebo or another drug
2. The study is made double-blind; that is, neither the researchers nor the participants know who has been assigned to which group.

Following are examples of ongoing studies in TM, most of them being done in the USA. The use of acupuncture; herbs such as *Ginkgo biloba*; dietary supplements such as glucosamine, chondroitin, saw palmetto, and soy; and massage on diseases such as arthritis, neurological disorders, cardiovascular disease, and cancer.

Dr.T.Varagunam

## **Development of Protocol for Clinical Trials of Ayurvedic Drugs on Vitiligo (Switra)**

**1. PROJECT NAME:-** A clinical Study on the efficacy of an Ayurvedic drug on vitiligo (switra).

**2. AIMS AND OBJECTIVES :-**

2.1. To study and interpret aetiopathological and clinical profile in Ayurvedic view point.

2.2. To study and evaluate the efficacy of an Ayurvedic drug (single/ compound, External/Internal) on Vitiligo (Switra)

2.3 To study the trial drug in the Ayurvedic pharmacological Perspective and to understand the possible mode of action of the trial drug.

2.4 To study side effects of the trial drug.

**3. METHODOLOGY :-**

As this is a clinical study human models are subjected to drug trial.

Therefore patient's consent and the ethical clearance has to be obtained. The methodology is designed to highlight basic principles involved in vitiligo (switra) according to Ayurveda. Keeping Control is a must.

**(a) SELECTION OF PATIENTS :-**

Vitiligo (switra) patients are Selected for the clinical trial depending on the history , clinical signs and symptoms described in Ayurvedic texts. Chronicity and other prognosticating clinical features mentioned in texts also will be included in exclusion criteria. Eg. More than one year history of the disease can be considered as one exclusion criteria.

A clinical proforma specially prepared for the same will be used for recording data and observations of the patients. An out line of the proforma is given below:

Proforma should include –

I. Basic vital data: Bio data, dietary habits, Prakruthi, Saratha (body constituency) , Satmya etc. Purpose is to identify doshic involvement.

II. Etiological and Symptomatological data from Ayurvedic View point. Eg. History of rat bite, snake bite ect. Purpose is to identify and evaluate the possible causative factors and to understand the possible pathogenesis of switra in Ayurvedic perspectives.

III. Symptomatology – naked eye examination, of discoloration, Length and width (size) of the patches, Photo, naming the places of the patches etc.

**4. MATERIAL AND METHODS:-**

Selected cases using a special proforma are registered for the drug trial provided that they had given their consent and ethical clearance is got. Test drug is administered in planned way. Form of the drug, dosage, duration etc are as predetermined. During the drug trial patients are examined weekly and all the changes and new complaints are recorded. Time duration is one month. Followup will be done for 6 month.

## **5. OBSERVATIONS AND RESULTS:-**

All the observations are studied and evaluated (subjective and objective)

## **6. DATA ANALYSIS :-**

Collection of data is divided in to two main categories.

I Subjective.

II Objective.

## **7. TEST DRUG :- Single/ Compound.**

Test drug has to be studied in two ways.

I. According to Ayurvedic pharmacological principles Eg. Rasa, guna, veerya, vipaka, prabhava etc.

II. According to modern pharmacological principles. Eg. mode of Action, Analysis of chemical constituents etc.

## **8. DIAGNOSTIC CRITERIA :-**

Establishment of Diagnosis is done in either ways. Viz:

1. Ayurvedic approach.

2. Modern medical approach.

## **9. DIETARY AND BEHAVIORAL REGIMEN (PATHYAPATHYA).**

Avoid heaty foods – especially, Beef, pork, chillies, mustard etc.

## **10. ANALYSIS OF DATA :-**

Data included in proforma has to be analyzed by a qualified statistician following standard methods.

## **11. DISCUSSION :-**

Discussion has to be developed on the results obtained . This need a very careful interpretation of results depending on Ayurvedic principles. Similarly it should be discussed whether the proposed objectives were achieved or not. If not problems have to be highlighted. Main points on which discussion must be developed are,

11.1 Relation ship of vitiligo (swithra)and it's causative factors.

11.2 Possible pathogenesis of swithra in ayurvedic view point.

11.3 Response of the test drug on vitiligo (swithra) .

11.4 Evaluation of the efficacy.

11.5 Significance of the test drug and it's scope.

## **12. CONCLUSION :-**

Final assessment of the efficacy of the test drug and projection of it's results for future researches.

Dr. H. A. S. Ariyawansa.

Senior Lecturer I.

Institutes of indigenous Medicine,

Ragagiriya.

# DEVELOPMENT OF PROTOCOLS FOR CLINICAL TRIALS OF AYURVEDIC DRUGS - RHEUMATOID ARTHRITIS –AMAVATA

## 1. Project Name:

The effect of an ayurvedic drug on Rheumatoid Arthritis (Amavata)

(a Clinical Trial)

## 2. Aims and Objectives:

2.1 To Study the aetiopathological and symtomatological background of R.A.

in ayurvedic stand point (Research on Disease)

[Roga Paryeshanaya]

2.2 To study the therapeutic efficacy of an ayurvedic drug on R.A

(Research on Treatment)

[ Chikitsa Paryeshanaya]

2.3 To Study the drug used in the treatment for R.A. (Research on the Drug)

(Oushada Paryeshanaya)

## 3 Methodology :

It is proposed to carry out a clinical trial Methodology of the research is based to highlight the basic principles involved in R.A. with special reference to Ayurveda.

### a. Selection of Patients

R A (Amavata) patients are selected for the clinical trial depending on the history, symptomatology and clinical picture they present. Chronically ill patients with severely deformed joints are liable to be excluded.

A specially prepared pro-forma, high lighting ayurvedic principles will be used to record data and observations of patients. The pro-forma will constitute of the following items among others.

### i. Basic and vital data.

Vital statistics (sex, age, occupation, dietary habits, prakrithi etc.)

ii. Aetiological and symptomatological data with special reference to Ayurveda.

ii.i To identify and evaluate the predominant dostic involvement.

ii.ii. To identify and evaluate the Ama condition involved, at its two broad aspects, i.e.,

a. apakva annarasa

b. apakva rasadhathu

iii.iii To identify and evaluate the involvement of dushya, ashaya, srothes in the disease

iii.iv To understand the aetiopathogenesis (samprapthi) in relation to intermediate aetiopathogenesis ( Anthar Samprapthi avastha )

### iii. Methodology proper ( Materials and Methods)

Please see No.6

iv. Data on the therapeutic efficacy of the experimental drug ( Results and observations)

**The assessment of above data to be carried out as follows;**

iv.i. By using subjective parameters such as pain, loss of

appetite, body aches, stiffness of joints etc.,

iv.ii By using objective parameters such as fever, oedema, grasping power, walking ability

iv.iii Biochemical parameters, such as Rheumatoid factor, ESR

etc. (with ayurvedic explanation based on Ama and Dosha Dushya Sammurchana principles)

#### **4.Experimental Drug**

With special reference to Rasa, Guna, Veerya, Vipaka and Prabhava concept of Draviya-guna in ayurveda.

#### **5.Diagnostic Criteria**

Diagnosis will be done on

a. Ayurvedic criteria of Amavata

b. Modern medical criteria of R.A.

6.Suitably prepared form(s) of the drug (decoction, powder, tablet etc.) is administered to registered cases and efficacy is recorded at measured intervals upto 3 months.

A six months follow-up period is proposed.

7.Advocacy on dietary and behavioral aspect (i.e. pathya-pathya) is carried out.

8.Use of a control group(s), placebo(s) and other research methodological aspects such as double blind techniques etc., could be used as required.

#### **9.Recording of Data**

Proforma will provide required means and facilities to record observed and biochemical data.

#### **10.Analysis of Data**

Statistical and other accepted methods of analysis will be used in analysing data.

11.Discussion on the analyzed data is effected on the lines with special reference to Ayurveda as follows,

11.1 The relationship of the disease with the Ama conditions

11.2 The effects of Ama and its definite role in precipitating the disease.

11.3 The effect of the experimental drug on the Ama condition.

11.4 The effect of the experimental drug on the disease

11.5 The ability of the experimental drug in curbing or controlling the signal and symptoms of the drug.

11.6 The effect of the drug on biochemical parameters

11.7 Offer an explanation to the action of the drug in terms of ayurveda such as shamana, shodana, pachana etc.

11.8 On the significance (statistical or otherwise) of the effectiveness of the experimental drug.

11.9 The projection of the results obtain for future research.

11.10 On the application or the potential benefits the R A patients could reap from the current trial.

#### **12 Conclusion.**

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2003.03.11.