Clinical Research Management & Ayurveda

Contributed By : Dr. Tanuja Nesari  Inputs By : Dr. Narendra S. Bhatt

Introduction

Ayurveda has been practiced in this country since ages and has stood the taste of time. Thus as efficacy and safety of Ayurvedic drugs is already proved through clinical experiences, This itself proves its evidence; however for wider applicability and acceptance of these drugs in current sophisticated era of science and technology, there is a strong need to reassess the efficacy of these drugs through scientific clinical research.

Likewise, efficacy of Ayurvedic therapeutics is yet to be established in today’s medical challenges, e.g. various types of Cancers, Aids, D.M, and Degenerative diseases, Atherosclerosis, Allergic skin disorders, Stress disorders etc.

Charaka in the 1st chapter of Sootrashana has paid utmost importance to Clinical Drug Research to determine the specific areas and mode of drug action i.e. 'Success in the treatment signifies the Samyaka Prayoga' (Rational use ) of medicine (Ch.Su1/135).

Hence, to prove the rationality of Ayurvedic drugs, Clinical Drug Evaluation is necessary. Ayurvedic Medicine is designed as per patient’s condition, constitution and acceptability, where in importance is paid to an individual as a whole and not only to a disease, hence holistic approach of this science has made this medicine as a ‘tailor made medicine.’

Ayurveda has vast resources of drugs from herbal, mineral and animal origin. Which are used as single or polyherbal; herbo-mineral compounds.

Recent survey by All India Co-ordinated Research Project on Ethno Biology (AICRPE) of Government of India, has revealed that, about 2000 plants species are used in Ayurveda, for varied usage in human and animal health care, encompassing preventive, promotive and curative aspects and also as ingredients in cosmetics and as fertilizers and safe biocontrol agents in agriculture.

Several medicinal plants are attracting global attention in the context of search for safe, curative or preventive drugs. These plants are considered as knowledge source for biological activity to develop NCE. (New Chemical Entity) for modern medicine.

If level of international trade in medicinal plants is considered, the export of indigenous formulations including Ayurvedic, Unani and others, although still very small (6% as compared to 36% of china) show an upward trend having risen from a modest beginning of 16 corers in 1990-1991 to approx Rs 450 corers in one decade (UNCTAD database, international center, Geneva).

Considering the global scenario of Clinical Research Managements and Clinical Data management in Modern Medicine, Clinical Research has become multidisciplinary, multibillion and multinational industry governed by many complex and interrelated complex guidelines.

Many CROs (contract Research Organizations) have been emerged since 1990s and out sourcing of clinical trials has led to the growth of CROs and there has been a corresponding shift away from permanent inhousing clinical research staff in a pharma industry to an environment in which temporary staff are contracted in, or studies or
whole development project are contracted out.

India has great potential for effective clinical Research Management and Clinical Data management due to following reasons-

A. Rich Tradition and Biodiversity in Ayurveda Modern drug development process needs approx 350 million US $ and minimum 10 years. However, search of experience-based medicine from Ayurvedic Material Medica saves time and money.

B. Moreover India has more scientific manpower in terms of English graduates (3 million) Doctors (7 Lacs) and IT professionals.

C. Compared to other countries Labor cost in India is low and

D. Unfortunately India has more number of patient populations. (Estimated 20% in 2010)

This opportunity should be exploited by conducting good clinical trials on Ayurvedic medicines.

However GCP guidelines on which CRM is conducted e.g. ICH, GCP, ICMR, WHO, European clinical trial Directives, Human Rights act etc are designed for modern drug development Process and in search of pure compound (NCE).

Sometimes in hurry of global acceptance, and to get place in global market and to fit in the above guidelines, Ayurvedic principals of Clinical Management are compromised.

Ayurvedic Clinical Research cannot be fitted in these guidelines. Therefore there is an urgent need to find out correlates between the GCPs of the two systems the and to evolve a new Ayurvedic Clinical Research Practice guidelines (AGRP), which will

1. Be an international ethical and scientific quality, Standard for designing, Conducting, recording and reporting trials, that involves the participation of human subjects. Compliance with these trials provides public assurance that the right safety and well being of trial subject are protected.

2. Work on areas of national interest (e.g. Malaria, Leprosy, etc) to promote the need based research in India.

3. Useful to work on research areas of global interest, i.e. Stress Disorders, Diabetes Mellitus, Arthritis, Degenerative Diseases, Heart Diseases etc.

Aims

1. Aim of Ayurvedic clinical research should be to make this indigenous system of India self-reliant in primary health care and lead the country on a course of becoming a world leader in Natural Product Industry.

2. Aim of Ayurvedic Research should be to find out safe and cost effective medicine on priority research areas like stress disorders Arthritis, Jaundice, Ca, DM, Arteriosclerosis, Allergic skin disorders, Peptic Ulcers, Irrritable bowel disease, Aids etc.

3. Aim of clinical research is to conduct experimented and control clinical studies for

   a) Standardization and quality control of Ayurvedic medicines and

   b) ADR monitoring of traditional medicines.

Issues in Ayurvedic Clinical Research Management
Issues

1. Currently available GCP guidelines, cannot be applied as it is to the Ayurvedic Clinical Research as there are certain differences in Ayurveda and modern trial design. These are due to difference in basic principles of management of diseases.
   A. In Ayurveda, effect of therapy is assessed in Toto (Holistic approach). More then one intervention for e.g. Drug therapy, Diet advice, Change in life style, and Panchakarma procedures etc. are used in management of diseases.
   Where as, modern medicine is evolved on molecular reductionist approach.
   B. It is considered that, Ayurvedic medicines are experiential based (Experiential) whereas, modern medicine are evolved experimentally (experimental).
   C. Ayurveda has individualized approach towards management whereas modern medicines aims at curing the Disease.
   D. In Ayurveda, medicine is selected, as per individual’s constitution acceptability, age, condition and type of disease etc. Likewise many other factors like season, collection, habitat of plant, formulation, dosage form, dose as well as vehicle and time of drug administration and duration of administration, modifies effect of Ayurvedic medicines. In this way, Ayurvedic medicines are called as Designer / Tailor made medicines. However Allopathic drugs are developed as per target action and screened biological activities
   E. In Ayurveda, many a times whole plant or its extract or polyherbal extract compounds are used. It is the synergistic effect of phytoconstituents in a plants which exhibit their action, where as in modern medicine, ‘Pure compound’ active molecule is used to treat the disease.

Therefore the guidelines for design of research for both the systems should be distinct which will incorporate fundamentals of Clinical Research of respective science.

2. Bottlenecks in herbal medicine research according to modern technologies are as follows
   - Pharmokinetics of plant substances not known
   - Pre clinical toxicology requirements
   - Metabolites and half-life in man not known
   - Cross over studies not possible.
   - Washout period cannot be calculated
   - Difficulty to prepared identical placebo
   - Sample needs to be fully collected before start
   - Physio chemical and Pharmacological Characteristics may change during storage
   - Plant to plant interaction
   - Effect of plant being tested on other system

3. As per modern drug development process, there are certain pitfalls in research on Ayurvedic medicines with respect to their identification, Authentication, Standardization of raw material and processing as well as finished products. Hence Standardization and quality control of Ayurvedic medicines has become mandatory before initiating clinical trials

4. Different approach to diagnostic levels.
Modern Medicine
Clinical Symptoms and signs
+ Lab investigations
Radiology
+ Special Test
+ Biopsy

Ayurved
Clinical Symptoms and signs
This can be incorporated for diagnosis.
+ can not form the baseline for diagnosis only supports
It as Ayurvedic Diagnosis method
(Nidan) is totally different.

Strategy
1. Development of new guidelines of Good Clinical Practice as per Ayurvedic principles; which will be internationally excepted.
2. Development of new research streams with multidisciplinary approach. Research process will involve a team of experts from different faculties. However it would be divided into three subgroups.
   1. Team involved in standardization and preclinical studies.
   2. Team involved in actual clinical trial process
   3. Team involved in data management
   a) Areas of National Health Care interest
   b) Areas of Global Health Care interest
4. Research with the integration of academics & industries as well as inclusion of p.G. Scholars in research.

Process

ACRM PROCESS CAN BE CONDUCTED AS PER FOLLOWING GUIDELINES

1. ICMR guidelines.

2. Ayurvedic guidelines.
   - ICMR guidelines for research on traditional medicine
   - Indication cited in ancient text. Limited toxicity studies for 4-6 wks in a diff species.
   - New herbal drug IND extensive pre clinical & clinical testing.
   - Non-documentated new indication / use of a plant known since ancient time extensive pre clinical and clinical testing.
The team involved clinical research process would be
1. Basic scientist
2. Ayurvedic Experts and medical experts.
3. Investigator
4. Bio statisticians
5. IT Professionals
6. Investigating Specialists

Clinical research process should be conducted as follows.
ACRM
1. Phases/Development
2. Clinical Trial Design
3. Protocol Components
4. CRF Design
5. Ethical Consideration
6. Data management
7. Preparation and submission of Dossier.

For each of the above process, inputs from Ayurvedic fundamental of clinical research should be incorporated.

1. PHASES

Phase I

Clinical Pharmacology -
Tolerability, metabolism and acute toxic effect,
The effective dose (i.e. matra) should be specified on the basis of above parameters.
No. of subjects 10-20
Closely observed.
Duration: 10-30 days

Phase II
Dosage finding & efficacy toxicity
No. of Subjects : 30-50 closely observed :
Duration - 1-6 months.

Phase III
Effectiveness, side effects
Comparison with controls
No. of subjects 1000-2000
Duration 6 months - 1 year
Phase IV
Effectiveness under field conditions
Rare side effect or complication
Drug interactions
e.g. ghrut + madhu --> toxic effect
No. of sub. Very large
Duration - Very long

2. Clinical Trial Design

A document that describes the objective design methodology, statistical considerations and organization of trial.

Elements in Clinical Trial Design

- Types of Control
  - Active
  - Placebo

- Types of Trial design
  - Parallel
  - Cross over
  - Other trial design

- Patient Population
  - indication being treated
  - concurrent diseases
  - concomitant medication

- Level of blinding

- Randomization

- Indication for Treatment
- Duration of dosing
- Methods of Clinical trial

3. Protocol COMPONENTS: -

1. Introduction
2. Objectives
3. No. of subjects
4. Subject selection
5. Exclusion Criteria
6. Trial Design
7. Study Period
8. Discontinuation
9. Investigation
10. Follow ups
11. Drug, dosage
12. Adverse Event
13. Primary end point
14. Secondary end point
15. CRF
16. Laboratory Methods
17. Statistical Methods
18. Ethical aspects
19. Informed consent
20. Monitoring
21. Compensations
22. Time flow chart

For each point Ayurved inputs are needed, e.g
1) Objectives:
- to ensure safety & efficacy of the Ayurvedic drug
- to show the specific effect of the drug
- to find adverse effects if any

Inclusion criteria
Should be determined depending upon the topic for trial and the drug selected for the trial.
- For Panchakarma therapy the "Arha" i.e the inclusion criteria for panchakarma therapy should be considered.
  Patient of jaundice can be treated by Virechana therapy.

Exclusion criteria:
Patient who do not meet eligibility criteria are excluded.
Anarha are excluded from the study
E.g. (1) Patient of piles is not fit for Virechana therapy
     (2) Anarha for Hartaki

4. CRF Design

Clinical Exam. of the patient.
The CRF for Clinical exam. should be designed according to Ayurvedic guidelines for case taking and it should be prepared at the outset of the study.

It comprises of -

Roga Pariksha - Nidan Panchak

Hetu - cause of disease. Ayur consider the causes of disease to a great extent. Once the cause of disease is identified and stopped, half the treatment is done.

Purvarupa - is the pre symptom exposure stage
Rupa - is the stage at which the symptoms are clearly exposed.
Upashaya -
Samprapti - the disease process or pathology.

The progress of disease can be arrested at any of these levels.

Rogi Pariksha - Dashavidhana, Ashtavidhan Pariksha.

1) Prakruti - It is the base for treatment. It forms the indication for prescribing a specific drug.
2) Vikruti - comprises Rog Pariksha
3) Sar - to assess the 'bala' of the patient.
4) Sanhanan -
5) Praman - Sharirpraman
5. Ethical Considerations

6. Data Management

7. Preparation of Dossier should be properly and carefully observed in Ayurvedic Research Process

Outcome

(1) Ayurvedic drugs are still to be accepted in some part of the world. Though they are accepted in some nations, but all drugs especially of mineral origin are still not accepted worldwide. The newly evolved Ayurved guidelines would help to prepare globally accepted drugs.

(2) The guidelines may give a way to interpret the present illnesses (e.g. Ca, AIDS) in Ayurvedic form.