Observational analysis of ayurvedic principles, ayurvedic hospital data, and patient outcomes

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Contents

[Statement of purpose: 3](#_Toc462647048)

[Title: 3](#_Toc462647049)

[Short background: 3](#_Toc462647050)

[Problem: 3](#_Toc462647051)

[What is the present status in understanding the problem? 3](#_Toc462647052)

[1. Literature review: 3](#_Toc462647053)

[2. Hospital data analysis methods: 4](#_Toc462647054)

[3. Data analysis of Treatment SOPs and implementation: 4](#_Toc462647055)

[4. Development of robust and replicable clinical documentation based on SOP: 5](#_Toc462647056)

[Expected outcomes: 5](#_Toc462647057)

[Introduction 9](#_Toc462647058)

[Chapter 1: Philosophical commonalities between the ICH and ayurvedic system: 11](#_Toc462647059)

[Chapter 2: Narrative reviews of the published trials 25](#_Toc462647060)

[2.1 Introduction 25](#_Toc462647061)

[2.2 The Consolidated Standards for Reporting of Trials (CONSORT) statement 27](#_Toc462647062)

[2.3 Jadad score 28](#_Toc462647063)

[2.4 Narrative review 28](#_Toc462647064)

[2.4.1 Objectives 29](#_Toc462647065)

[2.4.2 Search strategy and Selection criteria 29](#_Toc462647066)

[2.4.3 Main results 31](#_Toc462647067)

[2.5 Discussion 34](#_Toc462647068)

[2.5.1 Transparency issues 34](#_Toc462647069)

[2.5.2 Scientific issues 35](#_Toc462647070)

[2.5.3 Ethical issues 35](#_Toc462647071)

[2.6 Summary 36](#_Toc462647072)

[Chapter 3: Review of the hospital data analysis methods 38](#_Toc462647073)

[3 Background 38](#_Toc462647074)

[3.1 What is hospital data 38](#_Toc462647075)

[3.2 38](#_Toc462647076)

[Chapter 4: Hospital data descriptive analysis 39](#_Toc462647077)

[4 Background 39](#_Toc462647078)

[4.1 Hospital database INSTA 39](#_Toc462647079)

[4.2 Data collection methods 39](#_Toc462647080)

[4.3 Analysis plan 39](#_Toc462647081)

[4.4 Description of data 39](#_Toc462647082)

# Statement of purpose:

## Title:

Observational analysis of ayurvedic principles, ayurvedic hospital data, and patient outcomes By Vinay Mahajan, Girish Tillu, Ashwini Mathur, Darshan Shankar

## Short background:

Ayurveda has been practiced over many centuries in India. It will be safe to assume that the conceptual developments in ayurvedic knowledge base have taken place through every day observations and basic laws of nature. These fundamentals have been adjusted to the relevant times as per the passage of time, which is quite evident from vast literary history of Ayurveda which covers subjects like pharmacology, principle of diagnosis and treatment for all branches of medicine and surgery, philosophical framework and logic, pharmacy and numerous pharmacopeias. Traditional texts enumerate more than described for each disease condition (1).

Generating credible evidence for such a large pool only through modern experimental means such as trials is very challenging. Current hierarchical evidence model is being challenged by methodologists and the circular model comprising observational research methods are proposed for CAM research (2). Ayurveda like any other system of medicine, is practiced more in clinics than in clinical research setting, where there are no artificial restrictions on usage of medicines, duration of treatment or type of patients to treat, which is next to impossible in a protocol driven clinical trial setting. To plug the gap of missing empirical evidence, systematic analysis of observational clinical data is required. (3, 4) This project is focused on I-AIM clinical data for study of efficacy and safety trends. In our study of modern regulatory framework, we recognized similarity between concepts written by Charaka and ICH guidelines. This will form the philosophical basis for the research question.

## Problem:

To develop a replicable clinical documentation and HMIS system in I-AIM hospital setting, that can generate reliable data on disease classification, treatment protocols and outcomes. To test this system for assessing clinical and patient reported outcomes in musculoskeletal and metabolic diseases at I-AIM hospital.

## What is the present status in understanding the problem?

The problem of observational data analysis is split into 4 parts and is presented below. Each of the problem area is explained, the specific actions and possible outcomes are outlined.

### Literature review:

Philosophical commonalities between the ICH and ayurvedic system:

*Charaka Samhita* will be studied and interpreted on broad parameters used by ICH framework quality, efficacy and safety. This will provide philosophical connections between two systems and will create evidence base for the subsequent research work. This work is an effort to bridge the gap between ayurvedic and bio medicinal researchers. Furthermore, *Charaka Samhita* will be studied to understand diagnosis and treatment paradigm and outcome measures. To keep the work within practical limits we will focus on musculoskeletal and metabolic diseases. In depth study of various possible variations of the disease, treatment options, diagnostic and prognostic parameters will be carried out.

**Specific actions:**

1. Study ICH guidelines (quality, efficacy, safety) and *Charaka Samhita* (e.g. Vimana sthana) – see Appendix table 1 below
2. Diagnosis approaches (e.g. *Dashavidhapariksha*)
3. Treatment options (See Appendix figure 1)
4. Outcome measures (Ayurvedic as well as bio medicinal endpoints)

### Hospital data analysis methods:

Over the years, digitization of the hospital data has helped analytic discoveries, rather than only the straight facts. The day to day hospital settings generate a multifold data than clinical trials. This revolution has not been used by the ayurvedic medical industry. These advances should be used to improve patient wellness, better clinical decisions, better care coordination, cut down treatment abuse, and even to cut down costs.

**Specific actions:**

1. Review of the literature to understand the current methods employed across world
2. Check for potential solutions to be implemented at hospital (e.g. patient data dash boards)
3. Provide suggestions for improvements in day to day functioning at hospital

### Data analysis of Treatment SOPs and implementation:

The I-AIM hospital has generated 91,000 patient visits data over the years and perhaps the largest electronically available ayurvedic treatment database. What insights would come out of such a large database? A study will be carried out on patients in 2 disease areas musculoskeletal diseases, and metabolic diseases. This would provide us guidance for the future empirical research and analysis. The concepts explained in the ancient texts have not been proven empirically but have never been disproved either. The analysis of this database would present us with empirical insights never seen before.

**Inspection of the current database:**

1. I-AIM hospital database **INSTA** will be studied for
   1. What kind of data is collected?
   2. What are the issues with the current data
   3. Potential fixes for the future
2. Queries will be posted to the IT team
3. Specific reports or lists will be requested if considered necessary e.g. treatment data is not reported by INSTA reports fully.

Currently, as of August 2016, at IAIM hospital, treatment SOPs are written for musculoskeletal diseases, and metabolic diseases. Several modifications for diagnosis, treatment and outcome measures have been suggested. These will be implemented in the hospital practice over the coming months. The collected data based on these revised SOPs will be analyzed to validate the findings.

**Specific actions:**

1. Statistical methods to be employed:
   1. Graphical methods to display a lot of data in a concise form, trellis graphics, heat maps, etc.
   2. Pattern or trend analysis: to understand the underlying clusters within the data
   3. Decision theory analysis: to understand how the treatment gets assigned and what calculations, algorithms go through a doctor’s mind
   4. Multi-variate analysis: to model the data and gain more insights
2. Innovative and emerging tools and techniques from Omics / bioinformatics etc.

### Development of robust and replicable clinical documentation based on SOP:

**Specific actions:**

1. Define factors for the completeness, robustness of SOPs
2. Create a detailed analysis plan for analyzing the implementation
3. Analyze the results for completeness, robustness and replicability of the SOPs,
4. If any shortcomings are observed then revisions to the SOPs will be suggested

## Expected outcomes:

1. Philosophical linking between the ayurvedic scientific concepts and western medicinal concepts – building bridges between sciences
2. Baseline understanding of the data and descriptive analysis of the current facts of ayurvedic hospital data
3. Hospital data analysis methods development

**Reference:**

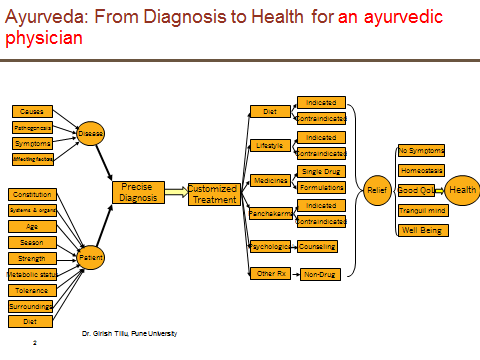
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3. Vaidya Rama, Observational therapeutics: Scope, challenges, and organization, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3255445/>
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**Appendix:**

Table 1: Cells highlighted in Green show similarities between ICH framework and *Charaka Samhita*.

|  |  |  |  |
| --- | --- | --- | --- |
| Quality | Efficacy | | Safety |
| Q1A – Q1F Stability | E1 Clinical Safety for Drugs used in Long-Term Treatment | E14 Clinical Evaluation of QT | S1A - S1C Carcinogenicity Studies |
| Q2 Analytical Validation | E2A – E2F Pharmacovigilance | E15 Definitions in Pharmacogenetics / Pharmacogenomics | S2 Genotoxicity Studies |
| Q3A – Q3D Impurities | E3 Clinical Study Reports | E16 Qualification of Genomic Biomarkers | S3A - S3B Toxicokinetics and Pharmacokinetics |
| Q4 – Q4B Pharmacopeias | E4 Dose-Response Studies | E17 Multi-Regional Clinical Trials | S4 Toxicity Testing |
| Q5A – Q5E Quality of Biotechnological Products | E5 Ethnic Factors | E18 Genomic Sampling | S5 Reproductive Toxicology |
| Q6A – Q6B Specifications | E6 Good Clinical Practice |  | S6 Biotechnological Products |
| Q7 Good manufacturing practice | E7 Clinical Trials in Geriatrics Population |  | S7A - S7B Pharmacology Studies |
| Q8 Pharmaceutical Development | E8 General Considerations for Clinical Trials |  | S8 Immunotoxicology Studies |
| Q9 Quality Risk Management | E9 Statistical Principles |  | S9 Nonclinical Evaluation for Anticancer Pharmaceuticals |
| Q10 Pharmaceutical Quality system | E10 Choice of Control Group |  | S10 Photosafety Evaluation |
| Q11 Development and manufacturing of Drug Substance | E11 Clinical Trials in Pediatric Population |  | S11 Nonclinical Safety Testing |
| Q12 Lifecycle Management | E12 Clinical Evaluation by Therapeutic Category |  |  |

Figure 1:



# Introduction

The practice of medicine has a history of three thousand years in India. Ayurvedic medicine is one of the world’s oldest medicinal systems. Caraka samhita and Sushrut samhita, two of the ancient texts written in Sanskrit are considered to be the back bone of the ayurvedic medicines. But there is a belief that these practices would have started much before these two samhitas were written. Ayurveda combines a number of approaches, such as changes in lifestyle, Ayurvedic medicines, cleansing or detoxifying, massage, exercise, and meditation. Overall, it aims to strengthen and purify the body and mind and increase spiritual awareness.

Modern medicine took giant strides in the 19th century with advances in chemistry and laboratory equipment. The western medicinal system has surged ahead and has witnessed many fantastic breakthroughs which are helping human kind. For any science to remain relevant to the era there should be ongoing research activities. Any science which is stagnant cannot remain attractive and will soon lose its usefulness. This is even applicable to Ayurvedic medical science.

Ayurveda is considered to be a science based on pure logical explanation. These are called Darshana. But in more than 2000 – 3000 years there have not been major conceptual additions to the science. The concepts written in samhitas are lagging behind compared to the present knowledge base. But this does not make the science less important. There is a huge opportunity to use the traditional understanding in combination with newer available technology like x-rays, ECGs, CT scans, biomarker understanding, etc. to achieve cure for diseases.

Ayurvedic medical system has always been an individualized therapy due to its very nature. For this to have worked, there would have been very good scientific basis. Traditionally, “one fits all” or “big block buster drugs” has been the approach in western medicine system. But with the scientific advances and many biomarkers coming into existence, the focus is moving towards customized medicine, which only seemed possible in sci-fi movies.

There is no documented reference within the samhitas or other historic texts about how did the great sages understand the intricacies of treating different diseases, identifying the medicinal plants, their formulations, etc. Could we assume that did they conduct experiments to understand these properties and somehow that did not get documented at all? Or could it be attributed to our inability to understand the cryptic nature of the shlokas? Could we even dare to assume that there were clinical trials conducted? If not then, could we put a concerted effort on gaining more understanding via good quality clinical trials?

One should not go with the impression that classical Ayurveda has no evidence base. In fact, Ayurveda has always been evidence conscious, and most of the principles and treatment modalities seem to have been critically tested and validated for the conditions existing in their own time frame. The ancient concept of evidence is based on fourfold testing, viz., (1) Pratyaksha pramana (direct observation), (2) Anumana pramana (inferential evidence), (3) Aptopadesa (scriptural evidence) and (4) Yukti pramana (planned rational experimental evidence).

This fourfold battery of testing new knowledge is classical of ancient Indian scientific tradition, which seems to be highly contemporary.

The evidence base of contemporary Ayurveda is to be visualized in several forms, including (1) Textual evidence and folklore claims, (2) Experience-based evidence, (3) Longstanding traditional use, (4) Mass acceptability and (5) New scientific evidence. It cannot be overemphasized that in spite of all the strengths of primary evidence, one cannot deny the need to develop new supportive scientific evidence without which contemporary Ayurveda cannot attain the status of a real global science accessible for the larger benefit of humanity at large. WHO also holds a similar view. However, it must be emphasized that fruitful strategies for developing new scientific evidence cannot succeed if traditional primary evidence is ignored. New research is to be planned on the foundations of existing textual and experience-based evidence. The frequently used term "evidence" essentially means a relevant and reasonable proof for a fact or truth; such a proof need not be necessarily in words or terms of today's science alone.

Even after accepting major differences, there are quite a lot of similarities in the principles of the traditional ayurvedic medicine and western medicine. What *Charaka* and some of the earliest “doctors” defined in the historical texts still holds validity in today’s world.

# Chapter 1: Philosophical commonalities between the ICH and ayurvedic system:

Big pharmaceutical companies have become one of the targets of critics for high prices and not doing enough for society. The health authorities are becoming more stringent in their safety review which has also resulted in less drug approvals and many drugs withdrawn from the market. To add to this the insurance companies are becoming stricter in their coverage making it difficult for a common man to afford lifesaving drugs.

We have a generic market which again base their studies on the big pharmaceuticals and keep battling for a good market price. With innovation taking a back seat here there is only a mad run for money.

In this rage for drugs v/s money v/s life can we look at any alternate solution to combat the prevailing situation? Is there no means of getting the need identified through means which are less invasive and much affordable?

Why do we not look at our own long historic tradition of medicine “The Ayurveda”.

Approximately 3000 – 5000 year old Indian traditional medicinal system is based on 2 major treaties *Charaka Samhita* (for physicians) and *Sushruta Samhita* (for surgeons)Earliest texts date on Ayurveda, which is written by *Charaka,* back to 760 BC, around 660 BC Sushruta wrote *Sushruta Samhita,* a medical text about the surgical approaches used in that period.

Ayurvedic medical system is a world of medicine and the most holistic system available. *Charaka Samhita* is considered to be a very highly technical text, which deals with 8 branches of *ayurveda*. (1) Internal medicine (*kayachikitsa*), (2) Ear, nose, throat (*Shalakya Tantra*), (3) Toxicology (*Vishagara-vairodh Tantra*), (4) Pediatrics (*Kaumara bhritya*), (5) Surgery (*Shalya Tantra*), (6) Psychiatry (*Bhuta Vidya*), (7) Aphrodisiacs (*Vajikarana*), (8) Rejuvenation (*Rasayana*). These details point to holistic approach. These could rival various franchisees.

*Rig-veda* (a lot of things, a lot of medical content), *Sam-veda* (Soma sacrifice), *Yajur-veda* (entire sacrificial rite), *Athar-veda* with a lot of medical text are the 4 vedas which could be considered to be the first of its kind encyclopedias written by human kind. These are considered to be written around 1500 to 2000 BC. *Athar-veda* is considered to be written in 1200 BC. Ayurveda is considered to be based on these vedas.

Under the rule of king *Ashoka* Ayurveda flourished. The ayurvedic treatment was in use till 12th century, but the decline started after the invasion of India by the Muslims.

No documentation of any major development on ayurvedic text or ayurvedic discipline has been documented post 12th century.

Similar developments have been seen happening in China around 300 BC and few evidences of medicinal science development in Middle East around 980 AD known as Unani medicine are also seen.

Physician Hippocrates of Kos (ca. 460 BC – ca. 370 BC), is considered the “father of modern medicine”. The Hippocratic Corpus is a collection of around 70 early medical works from ancient Greece, associated with Hippocrates and his students. Hippocrates and his followers were first to describe many diseases and medical conditions.

There are major differences in ayurvedic medicinal system and western medicinal system, in terms of what is the origin of the disease, what causes it, how to treat the same? But the ultimate aim in both the systems is to have disease free existence for human beings. Modern medicine took giant strides in the 19th century with advances in chemistry and laboratory equipment. The western medicinal system has witnessed many fantastic breakthroughs which are helping human kind. Some of these have come at a huge cost not just monetary but sometimes at a cost of ethics and integrity.

Traditionally, “one fits all” or “big block buster drugs” has been the approach in western medicine system. But with the scientific advances and many biomarkers coming into existence, the focus is moving towards customized medicine, which only seemed possible in sci-fi movies. Today the western medicine is aiming towards customized therapies for patients by thinking in terms of disease and patient as one constraint and solution very patient centric i.e. one patient – one solution.

Ayurvedic medical system has always been an individualized therapy due to its very nature. For this to have worked, there would have been very good scientific basis.

Despite of these major differences in their ideologies, there are quite a lot of similarities in the principles of the traditional ayurvedic medicine and western medicine. What *Charaka* and some of the earliest “vidyas (doctors)” defined in the historical texts is still valid in today’s world. The concepts defined in the Helsinki declaration, GxP guidelines and the ICH guidelines concur with what is in the historic books.

- What is a hospital?

- Who is a doctor?

- How to treat patients?

- Who should be treated, how much money should be charged?

- How should the special populations (e.g. pediatric population, geriatric population) be treated?

These questions have similar answers in both the worlds. Why is it important to know this? This could be a very crucial step in order to achieve the evidence which western world is expecting. The similarities are very stark and would even prompt us to think “are we trying to re-do what we know for so many years?”

It is up to us now to expedite this process of finding similarities and identify strategy to capitalize on the same. This step would help in building confidence amongst the two medicinal systems. Below are few examples of the like mindedness of the two systems:

|  |  |  |
| --- | --- | --- |
| Topic | Modern guidelines | Historic text |
| Well-being of patients | Helsinki declaration:  The first and foremost thing in a clinical practice or a clinical trial would be of patient safety. World Medical Health (WMA), in their 18th General assembly, 1964 came up with “Ethical Principles for Medical Research Involving Human Subjects”. The declaration covers various principles of medical research and medical care. Focus on protection, well-being of the human beings participating in the clinical research.  As per the current version of the declaration, 59th WMA General Assembly, Seoul, October 2008, there are 35 sections across 3 major headings A. Introduction, B. Principles for all medical research, C. Additional principles for medical research combined with medical care.  One of the most important sentences: The health of my patient will be my first consideration and a physician shall act in the patient’s best interest when providing medical care.  This declaration protects various types of vulnerable populations. | Ayurveda is considered to be eternal in nature. As a part of “study” in *Charaka Samhita*, the ayurvedic physician was taught to keep all the living things before. He was taught to make all the efforts to provide health to the patients. He was taught to think about the welfare of society and not to think ill about any of the patients.  The physician should not treat female patients or kids (pediatrics) without the required consent, which could be a parallel to the “vulnerable population”.  The physician is expected to keep all the data about patient confidential. *Charaka Samhita Viamansthana* *8 #13*  Page 113 of part I has explanation related to what should be done |
| Qualifications of a doctor and concept of a hospital | In this world of documentation and audit trails, every single item needs to be documented. This evidence has to be submitted along with each and every Clinical Study Report to various health authorities around the world.  ICH E6 “Guidelines for Good Clinical Practice”, outline international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.  Section 4 of the guidelines focuses on “INVESTIGATOR” which is defined as in section 1.34 of the guideline: “A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.”  Section 4.2 talks about “Adequate Resources”. | *Charaka* defined how a hospital should be in *Sutrashtan adhyaya 15 shloka 7* According to *Charaka,* thehospital should be designed by an architect, someone who is trained in “*vastu shastra*”.  The concept of a hospital defined in the texts is in line with the modern thought process. The thought process of having a clean place which is accessible to common man, a pharmacy with abundant medicines and availability of medicinal equipments still holds good in these times.  There are references to the number of attendants (16 in number), furniture, livestock, fixtures which should be available in the hospital “house”.  The building should be strong and well-built in  a location free from high winds, although it should be constructed in such a way that gentle winds can pass through it if desired, freshening the interior environment. The building should not be built in  mountainous places (for lack of accessibility), and  nor should it be located next to a bigger building (which brings misfortune upon it). Dusty locations, wet environments, or locations with foul or toxic smells should be rejected as building sites. The attendants that work in the clinic or hospital should be enthusiastic, skilled and compassionate. Caraka states that people well versed in music and poetry should also be encouraged to participate in the healing centre. Outside the building a herb and vegetable garden should supply medications and food for the clinic or hospital, and certain animals, such as a cow and her calf, and birds such as quail and partridge, should be kept by the facility for the benefit and enjoyment of the patients and faculty.  He defined quadraple concept for successful medical practice which included *vaiyda* (the doctor), *paricharika* (a nurse), good medicine and good patient. *Sutrashtan adhyaya 15 shloka 9*  In *Sushruta samhita Sutra sthan adhyaya 2 shloka* |
| Informed use of treatment | As per ICH E6 guidelines, section 4.6.6, it is important to tell a patient about what is being administered to him or her.  4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.  This is a very important GCP constraint before administering any kind of a drug to any patient or a subject. | There are a lot substances used as medicines in the ayurvedic treatments, documented in various texts. Different types of flora, fauna, poisonous materials, meat, etc. are used. It is a *vaidya’s* duty to inform the patient what is being administered before administering the medicine. A drug, if unknown, is fatal like poison, weapon, fire and thunderbolt while, if known, is vitalizer like nector, as per *SutraSthan adhyaya 1 shloka 124-125*. |
| Pediatric population and concerns | The pediatric population represents a vulnerable subgroup. Therefore, special measures are needed to protect the rights of pediatric study participants and to shield them from undue risk.  ICH E11 guideline “CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION” is designed to provide an outline of critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population.  There are very limited number of medicinal products available labeled for pediatric usage. Ages are defined in completed days, months, or years.   * 1. Preterm newborn infants   2. Term newborn infants (0 to 27 days)   3. Infants and toddlers (28 days to 23 months)   4. Children (2 to 11 years)   5. Adolescents (12 to 16-18 years (dependent on region))   This kind of classification is very important to correctly identify the dose level.  Similarly, these are covered under Helsinki declaration. | *Charaka* specifically talks about the pediatric diseases in one of the 8 branches of ayurveda, *Kaumarabhrtya.*  Some of the diseases which are seen in adults are the same in pediatrics, but only in less quantity. These are very difficult to identify as pediatric patients are unable to express what they are going through. Smaller doses should be given and formulations of drugs should be sweet and soft. These are the problems which are still worked on even in the modern times.  *Charaka* defines age groups in *vimansthan adhyaya 8 and shloka 122.* He has classified life into 3 age groups, childhood (up to 16 years), middle age (up to 60 years) and old age (up to 100 years). |
| Ethnic suitability | ICH guideline E5 “ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA” outlines guidelines for usage of a medicinal product across various parts of the world. It provides a framework for evaluating the impact of ethnic factors upon a medicine’s effect, i.e., its efficacy and safety at a particular dosage and dose regimen. | *Chikitasasthan adhyaya 30 and shloka 316-328* in these shlokas Charaka has written about the benefits of using suitable foods.  A drug could fail if the doctor does not take age, sex, strength, body, etc. into account before prescribing it.  There is a reference to different parts of “India” and what kind of food and drugs could be suitable to them. Madhya desa, south region, eastern region, Chinese parts.    For patients, the drug should be administered along with the items suitable to them because the suitable medicine provides strength quickly and does not harm even if taken plentiful. [Even if taken in large dose.]  Other than just ethnic suitability there are references to how males should be treated differently than females. |
| Formulations, route, type of doses, frequency, Food effect | In the development cycle of a drug, there are different type studies conducted to understand the properties of the drug. These could be bioavailability, formulation-route-dosing frequency studies, drug-drug interaction studies, food effect studies, QT studies, organ impairment studies (renal, hepatic, etc. impairment studies)  These studies help in making the label of the drug. | There are a lot of references in various texts about when should drug be given, how much should it be given, and so on.  They had understood the importance of considering route of administration, time, place, suitability and dose.  “*anupana*” is a special category of the Ayurvedic pharmacy which relates to the usage of certain additional substances given along with the medicines. Water, milk, *ghee*, *jaggery,* honey,fresh plant juices, meat broths, etc. could be some of the examples.  Dosing strategies: *Abhakta* (dosing on empty stomach), adhobhakt (dosing after meal), *muhuh muhuh* (multiple times a day), *nisa* (dose to be taken before sleeping) etc.  The following shlokas from *Chikitasasthan adhyaya 30 and shloka 298-300,* explain time of administration, which could be equated to Food effect.  (page 550 in part I)  ebooksclub[1].org\_\_Ayurveda\_\_The\_Divine\_Science\_of\_Life.pdf: page 93, 6.13 dosing strategy. |
| Dose toxicity (under dosing and over-doing) | In the modern day medicine, finding the right dose is a huge problem. There has been considerable amount of research which is ongoing.  Under dosing is not going cure the disease and over dosing may end up creating significant side effects.  This problem is a very important problem in cancer trial as the drugs can be very toxic. | *Chikitasasthan adhyaya 30 shlokas 313-314* in *Charaka Samhita,* talk about under dosing or over dosing of the drug and what are the consequences.  Very less dose of any medicine is ineffective and too much of it could prove harmful. |
| Commercial aspect: |  | In ChikistaSthan  The doctor should not use his knowledge of medicine to make money to wealthy. Instead, the powers which he has gained through studying ayurveda should be used for welfare of the society. Someone who helps patients come out jaws of death enjoys maximum happiness.  Page 467 of Part I book talks about the non commercial aspect: |
| Repeatability | Clinical trials are nothing but experiments conducted on human beings. For any scientific experiment to be considered as reliable, is should have the property of producing similar results time and again. | Page 114 su29#7, page 133 Vi8#101 |
| Classification of diseases (Girish) | > 4500 type of disease | ICD 10 |
| Sushruta’s concept of sterlization |  |  |

All of the above points contribute to the analyses which is performed for the modern medicines and submitted as a part of the submission dossiers. Could this help change the perception of Ayurveda being only “evidence based” or “nonscientific” to something better? Could these potential similarities help lessen the gap?

Ayurveda to further focus on the treatment therapies has been split in to 8 branches which are very closely related to the branches of western medicine. Below is the list of the 8 branches of Ayurveda and its equivalent in the western medicine.

|  |  |  |
| --- | --- | --- |
| Ayurveda Branch | English translation | Branch in Western medicine |
| Kayacikitsa | medicine | General Medicine |
| Salakya | dealing with diseases of supra-clavicular  region | ENT |
| Salyapahartrka | dealing with extraction of foreign bodies | Surgery |
| Visa-gara-vairodhika-prasamana | dealing with alleviation of poisons, artificial  poisons and toxic symptoms due to intake of  antagonistic substances | Toxicology |
| Bhuta vidya | dealing with spirits or organisms | psychology and psychiatry |
| Kaumarabhrtya | pediatrics | Obstetrics, Gynecology and Pediatrics |
| Rasayana | promotive measures | Therapies on wellbeing and wellness |
| Vajikarana | aphrodisiacs | Fertility and Sexual studies |

It is very well known and understood that Ayurveda is an observational science and there is no scientific evidence to its outcome/benefit. But on further reading of the Charaka Samhita on the evaluation of the treatment effect we can see that it closely comparable to how treatment effect is statistically evaluated in the western medicine.

All the factors that could cause an interaction effect during treatment evaluation can be seen below in the means of success in treatment.

(Charaka Samhita 2003rev2vol1 , Edited by Gabriel Van Loon)

The following properties are known as “Paradi” (“Beginning with Para”). They

**are the means of success in treatment:**

paratva (excellence)

aparatva (non-excellence)-- These 2 are used in relation to place, time, age,

measure, vipaka, virya, rasa etc.

yukti (rationale)-- is the rational planning of therapeutic measures

sankhya (enumeration)-- is mathematics including statistics

samyoga (conjunction)-- is the joining together of entities. It is of three types

according to the active participation of both, all or only one partner. It is non-eternal.

[this last statement is a profound philosophical one; no union is permanent, but rather

only temporary. All entities are made of the temporary bonding of other entities. All

living creatures are only the temporary union of the foods they have eaten, and will

eventually disperse to become the foods of a different union or creature.] [Samyoga also

refers to conjunction of herbs into formulas, of doshas and dhatus into disease, of

multiple etiologies into single etiology, etc.]

vibhaga (disjunction)-- it is also of 3 types; vibhakti (excision), viyoga

(disjoining) and bhagaso graha (division).

prthaktva (separateness) – is of 3 types; asamyoga (spatial separateness),

vailaksanya (class separateness) and anekata (individual separateness).

parimana (measurement)-- denotes measures (of all types- including weights).

samskara (processing)-- this is processing

abhyasa (practice)–is regular use of substance, habituation and practice.

–Thus all the paradi properties are said with their definitions, which if

unknown, do not let the therapy proceed properly.

The historic texts are indicative of the fact that the doctors practicing Ayurveda somehow knew these things. Only thing lacking here is the supporting data to confirm these claims.

Our aim here is not to outdo or supersede one system over the other but rather to bring about awareness and change in our thought process by moving from calling “Alternative” to “Supplemental” in both ways?

Appendix:

1. Well-being of patients: 
2. Qualifications of a doctor and concept of a hospital
3. Informed use of treatment



1. Pediatric population and concerns









1. Formulations, type of doses, frequency, Food effect (page 550 in part I)



1. Ethnic suitability



1. Dose toxicity (under dosing and over-dosing)





1. Commercial aspect: Page 467 of Part I book talks about the non-commercial aspect:





1. Repeatability: Page 114 su29#7, page 133 Vi8#101

These texts have extensive references to various disease areas. E.g. Cancer—an ayurvedic perspective (\*), in this paper, the authors have elaborated about integrated approach towards management of cancer.

# Chapter 2: Narrative reviews of the published trials

# 2.1 Introduction

Use of Ayurveda and other traditional medicines has expanded globally not only in the poor countries but also in the developed countries where conventional medicine is predominant. Due to this expansion documentation of the safety and efficacy of Ayurveda and other traditional medicines has become an important concern

As per Ayurvedic philosophy the entire cosmos is made up of energies of five elements: air, water, fire, earth, ether (space). The human body is also made up of these elements. These elements form the cognitive aspect of human beings. Ayurvedic medicine is oriented toward prevention, health maintenance, and treatment. The belief in Ayurvedic medicine is that a disease is the product of an imbalance in the body and mental elements that reduce the body’s resistance to diseases. If the imbalance is corrected and the body’s defense mechanisms are strengthened, then the body will resist a disease with a goal of eliminating it. The first goal is health promotion and disease prevention. The second goal is to treat physical, mental and spiritual illness. [3]

As the basic principles of Ayurveda and other Traditional systems are different from the Western medicine there is a perceived lack of evidence for all Traditional systems of medicine including Ayurveda. This has resulted in a situation, where in we see that a large section of the population is using these systems of medicine, but it is not accepted as a part of mainstream health care.

The western medicines are developed using a method called as hierarchical method where it tries answering the questions with limited scope e.g. what is the efficacy of a particular drug, what is the safety profile of a drug? This method assumes a step wise approach and deals with the problem in successively conducted clinical trials of various types in a specific sequence. The pharmacology of the molecule is ascertained first at the very beginning. These studies are followed by cohort studies, Open-label randomized studies. The process ends with the blinded, randomized, placebo controlled trials (RCT). The RCTs offer most internal validity and reduce the bias. These studies could be complemented by then moving onto case studies, case series. This “one step at a time” approach has worked very well in the western medicine framework.

There are some other models proposed by various authors to handle complex and tricky situations arising in defining and understanding the action of mechanism of Ayurvedic intervention.

Huge observational data for ayurvedic medicines [9]: There are more than 1,00,000 books and manuscripts, 57 authentic books (Drug and cosmetic act 1940), > 4500 diseases including subtypes and conditions (Ayusoft database), > 81,000 formulations (TKDL database), > 4,00,000 Practitioners (Planning Commission - 11th Plan) in India, Infinite documents, references, experiential data, Living tradition and knowledge in public domain. Dravyaguna (Pharmacology), Bhaisajya Kalpana (Pharmaceutics), Nidana (Diagnosis) and Chikitsa (Management principles), this data points to a validated knowledge base and it is acceptable that Ayurveda is an evidence based knowledge system.

Dr. Ashok D. B. Vaidya has explained the concept of reverse pharmacology to understand the action mechanism of Ayurvedic intervention. Reverse pharmacology is the science of integrating documented clinical/experiential hits, into leads by trans-disciplinary exploratory studies and further developing these into drug candidates by experimental and clinical research. It comprises of three stages - experiential, exploratory and experimental.

* Experiential robust documentation of clinical observations of the biodynamic effects of standardized ayurvedic drugs by meticulous record keeping.
* Exploratory studies for tolerability, drug interactions, dose range finding in ambulant patients of defined subsets of the disease and para-clinical studies in relevant in vitro and in vivo models to evaluate the target activity.
* Experimental studies, basic and clinical, at several levels of biological organization, to identify and validate the reverse pharmacological correlate of ayurvedic drug safety and efficacy.

Based on the huge observational data and the relatively low rate of side effects, it is rather easy to test Ayurvedic intervention in larger clinical trials. This would help build the required safety and efficacy information relevant to the Ayurvedic intervention under question. Once these key parameters are established, the pharmacokinetic properties can be understood. This process is economical may take lesser amount of time when compared with the hierarchical model used in western medicine.

Harald Walach et al. [8] have discussed a circular method to develop medicines. This would imply a multiplicity of methods, using different designs, counterbalancing their individual strengths and weaknesses to arrive at pragmatic but equally rigorous evidence which would provide significant assistance in clinical and health systems innovation.

Experimental methods that test specifically for efficacy have to be complemented by observational, non-experimental methods that are more descriptive in nature and describe real-life effects and applicability. The latter can range from retrospective audit studies, prospective case series to one armed to multiple armed cohort studies. Matched pairs studies can be conducted as experimental studies, by forming first pairs and then randomizing them, or as quasi-experimental studies by forming pairs from naturally occurring cohorts according to matching criteria.

ICH guidelines E2E for Pharmacovigilance planning, and E9 for statistical principles of clinical trials, provide a lot of different study designs to build the necessary evidence base either in form of a RCT or in any other form deemed fit for purpose. Case series, active and passive surveillance, sentinel site surveillance, drug and exposure registries are a few types of study designs to generate necessary data. Comparative observational studies like cross sectional survey, case-control study, cohort study, descriptive study and drug utilization study have been suggested. This is not an exhaustive list, but should be considered as a good starting point.

Similar to the Traditional Indian Medicine, there are other medicinal systems in existence e.g. traditional Chinese medicine (TCM), herbal medicines, etc. These systems are complex and they face similar sort of questions. TCM individualized its treatment protocol or clinical practice without considering the principles of modern medicine. The standard methodology of random selection, blinding and placebo control, followed by statistical analysis was generally overlooked. This had a negative effect on the development of TCM. Since 2000 onward, the volume of applied research in Chinese medicine is growing rapidly and the quality is improving. There is good evidence supporting the use of some Chinese patent medicine treatments. Further, there is a more open attitude to Chinese medicine among conventional health professionals, partly explained by the rise of evidence-based medicine (EBM). They have been reasonably successful in developing CONSORT like standards to define the quality, improve the standard of reporting.

On the other hand, the Western medicine is primarily oriented toward the treatment of disease. The drugs are developed based on the concept that the elimination of specific causes of a disease will cure a disease. Western medicine has been the dominant medical system of the world of the last century due to various reasons. Hence, there has been a tendency to test the effectiveness of all other medical systems and the cures they offer using the framework and methods of Western medicine which rely heavily on pharmacology, safety and efficacy of the drugs in principle. Those molecules which meet these criteria are allowed to be marketed as the drugs. The methods to come up with and test western medicines have undergone a lot of improvements and have developed validated methods which cater to the specific needs e.g. CONSORT, Jadad Score, ICH, GCP guidelines to name a few.

It is very evident that generating evidence which fits into the western medicine frame-work for Ayurvedic system is the need of the hour. But it is a very complex task as Ayurvedic intervention is just not a tablet or a capsule but is a holistic approach towards life. In order to achieve this seemingly very difficult task, it is important to find correlation between different systems. The efforts should be made to convert the evidence which is rooted in Ayurvedic discipline to be converted into “trans-disciplinary” evidence.

2.2 The Consolidated Standards for Reporting of Trials (CONSORT) statement

To comprehend the results of a randomized controlled trial (RCT), readers must understand its design, conduct, analysis and interpretation. That goal can only be achieved through complete transparency from authors. Despite several decades of educational efforts, the reporting of RCTs needed improvement. Investigators and editors developed the CONSORT (Consolidated Standards of Reporting Trials) statement to help improve reporting by using a checklist and flow diagram. The CONSORT statement was developed to assist investigators, authors, reviewers and editors on the necessary information to be included in reports of controlled clinical trials [4]. It is intended to improve the reporting of a Randomized Control Trial, enabling readers to understand a trial’s conduct and to assess the validity of its results. The checklist items includes 25-items selected because empirical evidence indicates that not reporting the information is associated with biased estimates of treatment effect or the information is essential to judge the reliability or relevance of the findings. The flow diagram depicts the passage of participants through an RCT.

The CONSORT statement was first published in 1996, revised in 2001, and 2010[4]. This statement consists of a checklist and flow diagram to guide writers and reviewers on the information that should be available from published reports of two-group parallel RCTs [4]. The CONSORT statement has been endorsed by many leading medical journals, editorial associations, professional societies, and funding agencies [4]. Since its inception, several extensions of the CONSORT statement have been developed [4]. CONSORT was extended to cluster randomized trials [4] and for trials examining harms [4]. Also, an international group of acupuncture researchers developed a set of recommendations for improving reporting of the interventions in parallel group trials of acupunctured the Standards for Reporting Interventions in Controlled Trials of Acupuncture or STRICTA [4].

# 2.3 Jadad score

A numerical score between 0-5 is assigned as rough measures of study design/reporting quality (0 being weakest and 5 being strongest). This number is based on a well-established, validated scale developed by Jadad et al [5]. This calculation does not account for all study elements that may be used to assess quality. A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point towards an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

|  |  |
| --- | --- |
| **Jadad Score Calculation** |  |
| **Item** | **Score** |
| Was the study described as randomized (this includes words such as randomly, random, and randomization)? | 0/1 |
| Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)? | 0/1 |
| Was the study described as double blind? | 0/1 |
| Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)? | 0/1 |
| Was there a description of withdrawals and dropouts? | 0/1 |
| Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc). | 0/-1 |
| Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy). | 0/-1 |

# 2.4 Narrative review

In order to understand the existing practices of Ayurvedic therapy the following systematic review was done.

## 2.4.1 Objectives

The objective of the report was to conduct a search of published literature on how the clinical trials are conducted and reported for Ayurvedic medicines.

## 2.4.2 Search strategy and Selection criteria

This search result could be biased as it was only electronic and restricted to language English. As this research is aimed for academic purpose, no papers were bought.

As per figure 1,

Broad search:

* Cochrane library database was used as a search engine with the key word “Ayurved” OR “ayurvedic” OR “traditional Indian” for papers published on or before 2nd August 2016. 397 potentially relevant papers were retrieved.
* 123 paper were eliminated for the following reasons: 61 duplicate entries, 37 non-interventional studies, 23 studies irrelevant to the study and 2 non-ayurvedic papers.
* Thus, there were 274 papers left for analysis.

Narrowed to specific necessity:

* 274 studies satisfied the inclusion criteria of which for 147 (53.65%) trials were fully available, for 119 (43.43%) trials abstracts were available and 8 (2.92%) trials had no info available in the papers.

These 274 trials were used in the following analyses.

Major versions of CONSORT statements were published in 2001 and 2010. For any new guidance to come in full effect, it usually takes a couple of years, hence the analysis will be done on the overall studies, as well as studies conducted on or before year 2003, between years 2004 and 2012 and 3rd category is between years 2013 and 2016.

Status of each of the paper

Full text available = 147 (53.65%)

Abstract available = 119 (43.43%)

Not available = 8 (2.92%)

Time frame = Till August 2016

Database searched = Cochrane library

Number of studies published before

On or before 2003 = 52 (18.98%)

Between 2004 and 2012 = 130 (47.45%)

Between 2013 and 2016 = 92 (33.58%)

Potentially relevant papers identified

Search words used: ayurved\* OR ayurvedic OR traditional indian\*

(N = 397)

Papers eliminated from the analysis

(N=123)

Non Ayurveda = 2

Non interventional = 37

Non relevant = 23

Duplication = 61

Papers (studies) used in the analysis

(N=274)

Figure 1: Search strategy and Selection criteria

## 2.4.3 Main results

1. Publication trend: Till the year 2004 the number of studies published was in single digits, but post 2004, the publications have reached 20 to 30 studies per year. The following show the trend of the published clinical trials. Increased publications are a positive sign as the overall research efforts are increasing.

|  |  |
| --- | --- |
| Year | Number of studies published |
| Till 1980s | 6 |
| 1981 to 1990 | 3 |
| 1991 to 2000 | 28 |
| 2001 to 2005 | 24 |
| 2006 to 2010 | 85 |
| 2011 to 2016 | 128 |

52 (18.98%) papers were published before or within 2 years the publication of 2001 version of CONSORT. 130 (47.44%) papers were published within 2004 and 2012, remaining 92 (33.58%) papers were published between 2013 and August 2016.

1. Journals: Majority of the papers were published in Indian based journals (173 out of 274). Total 19 different counties were identified to have journal offices. The list of countries is displayed below.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Count of Journal type** |  |  |  |  |
|  | **Abstract** | **Available** | **Not available** | **Grand Total** |
| Indian | 57 | 112 | 4 | 173 |
| American | 25 | 13 | 1 | 39 |
| UK based | 6 | 10 | 2 | 18 |
| Irish | 4 | 6 |  | 10 |
| German | 8 | 2 |  | 10 |
| Dutch | 4 | 1 |  | 5 |
| Pakistani | 3 |  |  | 3 |
| \*\* Unknown | 2 |  | 1 | 3 |
| Bangladeshi | 2 |  |  | 2 |
| Irani |  | 2 |  | 2 |
| Turkish | 1 |  |  | 1 |
| Swiss | 1 |  |  | 1 |
| Canadian | 1 |  |  | 1 |
| Japanese | 1 |  |  | 1 |
| Thai | 1 |  |  | 1 |
| Croatian |  | 1 |  | 1 |
| Belgian | 1 |  |  | 1 |
| Romanian | 1 |  |  | 1 |
| Sri Lankan | 1 |  |  | 1 |
| **Grand Total** | **119** | **147** | **8** | **274** |

Papers were published in 119 different journals. AYU had 58 studies, International Journal of Research in Ayurveda and Pharmacy had 47 studies, Journal of Ayurveda and Integrative Medicine had 15 studies and Journal of ethnopharmacology had 9 studies published.

1. ICD-10 has 22 major categories listed, out of which for 21 categories at least 1 study was conducted. This is an indication that Ayurveda as a medical science even though is ancient still is relevant in today’s modern world.

Traditional areas managed by ayurvedic treatments appear as the most frequently disease areas. E.g. Endocrine, nutritional and metabolic diseases, Diseases of the musculoskeletal system and connective tissue, Mental and behavioural disorders, Diseases of the genitourinary system, Diseases of the digestive system make the top 5. There are 5 studies done for Neoplasm, but mostly in the palliative setting.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Count of Disease area** | **Column Labels** |  |  |  |
| **Row Labels** | **Abstract** | **Available** | **Not available** | **Grand Total** |
| Endocrine, nutritional and metabolic diseases | 19 | 22 |  | 41 |
| Diseases of the musculoskeletal system and connective tissue | 18 | 19 | 1 | 38 |
| Mental and behavioural disorders | 13 | 13 | 2 | 28 |
| Diseases of the genitourinary system | 10 | 13 |  | 23 |
| Diseases of the digestive system | 12 | 10 |  | 22 |
| Diseases of the respiratory system | 4 | 12 | 1 | 17 |
| Diseases of the skin and subcutaneous tissue | 3 | 13 |  | 16 |
| Certain Infectious and parasitic diseases | 5 | 7 | 3 | 15 |
| Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | 2 | 9 |  | 11 |
| Diseases of the circulatory system | 8 | 2 |  | 10 |
| Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified | 3 | 6 |  | 9 |
| Diseases of the eye and adnexa | 7 | 1 |  | 8 |
| NOT APPLICABLE (studies on healthy volunteers) | 4 | 3 |  | 7 |
| Diseases of the nervous system | 3 | 4 |  | 7 |
| Pregnancy, childbirth and the puerperium | 1 | 4 |  | 5 |
| Neoplasms | 3 | 1 | 1 | 5 |
| Injury, poisoning and certain other consequences of external causes | 2 | 3 |  | 5 |
| Factors influencing health status and contact with health services | 2 | 1 |  | 3 |
| Diseases of the ear and mastoid process |  | 2 |  | 2 |
| Certain conditions originating in the perinatal period |  | 1 |  | 1 |
| External causes of morbidity and mortality |  | 1 |  | 1 |
| **Grand Total** | **119** | **147** | **8** | **274** |

1. Location of studies: Most of the studies 227 out of 274 were conducted in India, for 17 studies the location was Unknown, 7 studies were carried out in Sri Lanka, 4 in Australia and 3 in the USA. Overall 16 countries have conducted at least 1 study.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Count of Location** | **Column Labels** |  |  |  |
| **Row Labels** | **On or before 2003** | **Between 2004 and 2012** | **Between 2013 and 2016** | **Grand Total** |
| India | 38 | 107 | 82 | 227 |
| \*\* Unknown | 4 | 9 | 4 | 17 |
| Sri Lanka | 1 | 6 |  | 7 |
| Australia | 2 | 1 | 1 | 4 |
| USA | 1 | 1 | 1 | 3 |
| Germany | 2 |  |  | 2 |
| Pakistan |  | 2 |  | 2 |
| UK |  | 1 | 1 | 2 |
| Bangladesh | 2 |  |  | 2 |
| Canada | 1 |  |  | 1 |
| Thailand |  | 1 |  | 1 |
| Switzerland |  |  | 1 | 1 |
| Iran |  |  | 1 | 1 |
| Singapore | 1 |  |  | 1 |
| Norway |  | 1 |  | 1 |
| Italy |  | 1 |  | 1 |
| Japan |  |  | 1 | 1 |
| **Grand Total** | **52** | **130** | **92** | **274** |

1. What kind of trial designs are used in the clinical trials: Out of 274 studies, there were 127 (46.35%) of studies did not mention study design or noted it as “Randomly”. 126 (45.99%) studies mentioned word “randomized” in the study design. Remaining 21 studies were “Open label”, “Double blind”, “Series”, “Observational”, “Single blind”.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Count of Design** | **Column Labels** |  |  |  |
| **Row Labels** | **Abstract** | **Available** | **Not available** | **Grand Total** |
| Randomised Double Blind | 33 | 33 | 3 | 69 |
| Unknown | 36 | 26 | 4 | 66 |
| Randomly | 18 | 43 |  | 61 |
| Randomised Open label | 10 | 12 |  | 22 |
| Randomised | 6 | 15 |  | 21 |
| Randomised Single Blind | 5 | 8 |  | 13 |
| Open label | 3 | 8 |  | 11 |
| Double Blind | 4 |  | 1 | 5 |
| Series | 2 |  |  | 2 |
| Observational |  | 2 |  | 2 |
| Single Blind | 1 |  |  | 1 |
| Randomised Triple Blind | 1 |  |  | 1 |
| **Grand Total** | **119** | **147** | **8** | **274** |

The number of studies noting “Randomly” or “Unknown” has not gone down as the years have passed by. Researchers should make efforts to document and use the correct study design to make the results reproducible.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Count of Design** | **Column Labels** |  |  |  |
| **Row Labels** | **On or before**  **2003** | **Between**  **2004 and 2012** | **Between**  **2013 and 2016** | **Grand Total** |
| Randomised Double Blind | 24 | 31 | 14 | 69 |
| Unknown | 13 | 36 | 17 | 66 |
| Randomly | 5 | 31 | 25 | 61 |
| Randomised Open label | 4 | 9 | 9 | 22 |
| Randomised |  | 8 | 13 | 21 |
| Randomised Single Blind |  | 6 | 7 | 13 |
| Open label | 3 | 5 | 3 | 11 |
| Double Blind | 2 | 1 | 2 | 5 |
| Series | 1 | 1 |  | 2 |
| Observational |  | 1 | 1 | 2 |
| Single Blind |  |  | 1 | 1 |
| Randomised Triple Blind |  | 1 |  | 1 |
| **Grand Total** | **52** | **130** | **92** | **274** |

1. Most of the study designs were parallel group 228 (83.21%), only 11 (4.01%) studies were cross over in nature. 24 (8.76%) studies did not mention or is not applicable due to single arm study.
2. 241 studies out of 274 were carried out in single center, 16 were multicenter studies (all conducted in India) and for 17 studies, it was not clear if the studies were carried out in a single center setting or a multi-center setting.
3. Duration of studies and the size of the studies: 211 (77%) of the trials reported duration of the trial and 250 (91%) trials reported number of patients in the trial. There were nearly 17,637 patients/healthy volunteers treated in more than 42 years of treatment duration in all these studies put together. In general, the studies were of short duration (median 8 weeks) with lesser patients (median 46 patients). The duration may not be reflective of the true clinical setting, giving rise to meaningless results. Smaller studies tend to overestimate the treatment effects.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Duration (weeks) | Total patients | Males | Females |
| n (%) | 211 (77%) | 250 (91%) | 94 (34%) | 93 (34%) |
| Mean | 10.4 | 70.5 | 28.5 | 28.8 |
| SD | 9.78 | 118.85 | 32.07 | 34.69 |
| Median | 8 | 46 | 20.5 | 19 |
| Minimum | 0.1 | 8 | 0 | 0 |
| Maximum | 74 | 1646 | 180 | 214 |
|  | Total duration =  2199  ~ 42.28 years | Total patients  = 17637 | Total males  = 2683 | Total females  = 2678 |

1. There were 105 (38.32%) papers/studies discussed the Ayurvedic definition of disease, or ayurvedic endpoint. There were 216 (78.83%) of studies used Western end points. 31 (11.31%) studies used both ayurvedic and western endpoints. This data reflects the attempts made by various people to force fit traditional medicine in western framework. There is a huge scope for improvement in order to develop alternative methods to test the traditional medicines in modern scientific ways.

The standard ways of data collection forms should be one important aspect taken up at the national level. The way CDISC group is driving standardized data collection forms for western clinical trials, similar efforts should be made. TCM is making a lot of progress in this area and has started working with CDISC team for standard data collection pages. <https://www.cdisc.org/system/files/all/standard/CFAST-TA-Project-Status.pdf>

1. The quality of 126 Randomized Clinical Trials was assessed based on Jadad score and only 34 (26.98%) trials had a score of greater than or equal to 3. This reflects areas of improvements from methodological stand point. This is very essential to improve the credibility outside the fraternity.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Count of Jadad Score** | **Column Labels** |  |  |  |  |
| **Row Labels** | **Abstract** | **Available** | **Not available** | **Grand Total** | **%** |
| 0 | 3 | 4 |  | 7 | 5.56% |
| 1 | 18 | 16 | 2 | 36 | 28.57% |
| 2 | 28 | 20 | 1 | 49 | 38.89% |
| 3 | 6 | 20 |  | 26 | 20.63% |
| 4 |  | 6 |  | 6 | 4.76% |
| 5 |  | 2 |  | 2 | 1.59% |
| **Grand Total** | **55** | **68** | **3** | **126** |  |

The quality of reporting is going up across the time frames. There were only 8 studies on or before 2003 with a Jadad score of 3 or more, this has gone up to 16 in years between 2004 and 2012, and 10 studies between 2013 and 2016.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Count of Jadad Score** | **Column Labels** |  |  |  |
| **Row Labels** | **On or before 2003** | **Between**  **2004 and 2012** | **Between**  **2013 and 2016** | **Grand Total** |
| 0 | 3 | 3 | 1 | 7 |
| 1 | 3 | 13 | 20 | 36 |
| 2 | 14 | 23 | 12 | 49 |
| 3 | 8 | 11 | 7 | 26 |
| 4 |  | 3 | 3 | 6 |
| 5 |  | 2 |  | 2 |
| **Grand Total** | **28** | **55** | **43** | **126** |

1. Further analysis was carried out to check if there is any publication bias towards only reporting positive findings. There was a huge difference in published studies with positive results (62.77%) vs. negative results (6.93%). It is very important to build the correct scientific basis for future, to be open about what has worked and what has not. Across different periods, the tendency to report only positive studies continues as is.
2. CONSORT scores: CONSORT scores were determined based on the 25 point checklist version 2011. 126 studies with design identified as “randomized” were analyzed. 67 studies had scores of less than or equal to 10. 47 studies had scores going from 11 to 15 both inclusive. 12 studies had scores of greater than or equal to 16, with 2 studies having maximum score of 22 out of 25. These 2 studies were conducted between 2013 and 2016.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Count of CONSORT Score** | **Column Labels** |  |  |  |
| **Row Labels** | **On or before 2003** | **Between**  **2004 and 2012** | **Between**  **2013 and 2016** | **Grand Total** |
| 1 |  | 1 |  | 1 |
| 2 | 1 | 3 | 1 | 5 |
| 3 | 1 |  |  | 1 |
| 4 | 1 | 1 |  | 2 |
| 5 | 4 |  |  | 4 |
| 6 | 2 |  | 4 | 6 |
| 7 | 4 | 4 | 3 | 11 |
| 8 | 3 | 5 | 7 | 15 |
| 9 | 1 | 5 | 1 | 7 |
| 10 | 3 | 5 | 7 | 15 |
| 11 | 1 | 4 | 6 | 11 |
| 12 | 1 | 8 | 5 | 14 |
| 13 | 2 | 7 |  | 9 |
| 14 | 4 | 3 | 1 | 8 |
| 15 |  | 2 | 3 | 5 |
| 16 |  | 3 | 1 | 4 |
| 17 |  | 1 |  | 1 |
| 18 |  | 1 |  | 1 |
| 19 |  | 1 | 1 | 2 |
| 20 |  | 1 |  | 1 |
| 21 |  |  | 1 | 1 |
| 22 |  |  | 2 | 2 |
| **Grand Total** | **28** | **55** | **43** | **126** |
|  |  |  |  |  |
| <= 10 | 20 | 24 | 23 |  |
| Between 11 and 15 | 8 | 24 | 12 |  |
| Greater than equal to 16 |  | 7 | 5 |  |

In 3 different reporting periods, the scores are going up. Studies reported on or before 2003, has the maximum score of 14, and 20 out of 28 studies have scores of <= 10.

When the full study details are available the COSNORT scores are higher than when only an abstract is available. If all the complete papers were available then there would certainly have been improvement in the scores, but would not have been drastic either.

The consolidation of scores across 274 studies and in the 126 randomized trials.

|  |  |  |
| --- | --- | --- |
| CONSORT point | Total Overall | Only randomized (N=126) |
| Title & abstract | 118 | 59 |
| Introduction | 170 | 83 |
| Trial Design | 101 | 50 |
| Participants | 166 | 84 |
| Interventions | 158 | 79 |
| Outcomes | 169 | 82 |
| Sample size | 8 | 2 |
| Sequence generation | 3 | 3 |
| Allocation concealment | 10 | 7 |
| Implementation | 3 | 2 |
| Blinding | 44 | 20 |
| Statistical Methods | 47 | 23 |
| Participant Flow | 10 | 6 |
| Recruitment | 72 | 36 |
| Baseline Data | 68 | 34 |
| Number Analyzed | 50 | 27 |
| Outcomes and estimation | 154 | 76 |
| Ancillary Analyses | 2 | 2 |
| Harms | 65 | 34 |
| Limitations | 20 | 13 |
| Generalizability | 14 | 10 |
| Interpretation | 141 | 71 |
| Registration | 54 | 25 |
| Protocol | 11 | 6 |
| Funding | 38 | 15 |

Explanation of trial design, sample size calculations, sequence generation, allocation concealment and implementation has not been done in majority of the studies. Blinding and statistical methods are 2 other major areas requiring a lot of detailed attention. Participant flow diagram has been prepared only for 10 out of 274 studies and 6 out of 126 studies. The baseline data is not presented. Limitations and generalizability related points have been overlooked.

1. How many treatment or groups or conditions tested in a study? 175 out of 274 studies had 2 treatment groups, with 1 study having 7 treatment groups, for 25 studies the number of treatment groups was not clearly defined.
2. 93 (33.94%) studies reported adverse events. This number is considerably low. This should be improved to build transdisciplinary trust.

# 2.5 Discussion

## 2.5.1 Transparency issues

The sample of trials may not have been representative. Our search would not have located all published trials. But there are trials published in many journals not indexed by the databases chosen for the search. The trials conducted could have been reported in language other than English. There seems to be tendency of publishing more positive studies vs. negative studies. This publication bias would result in building biased scientific literature.

## 2.5.2 Scientific issues

The published studies were of short duration with lesser patients. The duration may not reflective of the true clinical setting, giving rise to meaningless results. Smaller studies tend to overestimate the treatment effects. Methodological quality of the trials was suboptimal. There is a scope for improvement in designing and conducting clinical trials which will improve credibility.

## 2.5.3 Ethical issues

Smaller sample sizes, unpublished work, application of western endpoints to traditional methods would all raise some question or the other. We observed that the basic principle of clinical trial; randomization, was never explained in most of the cases; leading to concerns on reproducibility and bias.

A high chance of fraud during the conduct of the clinical trial due to no standardized process for diagnosis, dosing, follow up and conclusion.

# 2.6 Summary

1. There is a need to be more systematic in reporting the clinical studies in the journals which are available electronically. There is a need to database the existing vast pool of data.
2. There is a need to come up with guidelines to conduct, design and report clinical trials for the Ayurvedic interventions to enhance the credibility of the already existing vast pool of data.
3. As per the proposals made in the “hierarchical view”, “reverse pharmacology view”, various methods suggested in ICH guidelines and “circular method view” there is a need to define what kind of clinical trials could be performed at what point of time in the whole drug development process for Ayurveda. Internal validity has to be balanced by external validity, and this can rarely be achieved with one single research method such as the RCT, but involves other strategies such as outcomes and cohort studies. In order to answer the questions about the safety, efficacy of a drug, there is a need to optimize the use all three approaches.
4. There is a need to standardize the following:

* How to write a protocol, what type of information should go in and how much detail
  + Rationale for a specific study
  + Ayurvedic definition of disease
  + Ayurvedic definition of patient / how to identify the patient?
  + Ayurvedic interventions (treatments and duration)
  + Ayurvedic endpoints
  + Inclusion and exclusion criteria for patients
  + Visit schedule
* How to collect the data based on the protocol?
  + How to capture required information?
  + Categorical variables?
* How to define the statistical analysis plan?
  + Tables, Listings and Figures how many? Is it possible to follow various ICH guidelines (E3)
  + Statistical methods
  + Derivations of the required variables
  + Imputation rules for missing data

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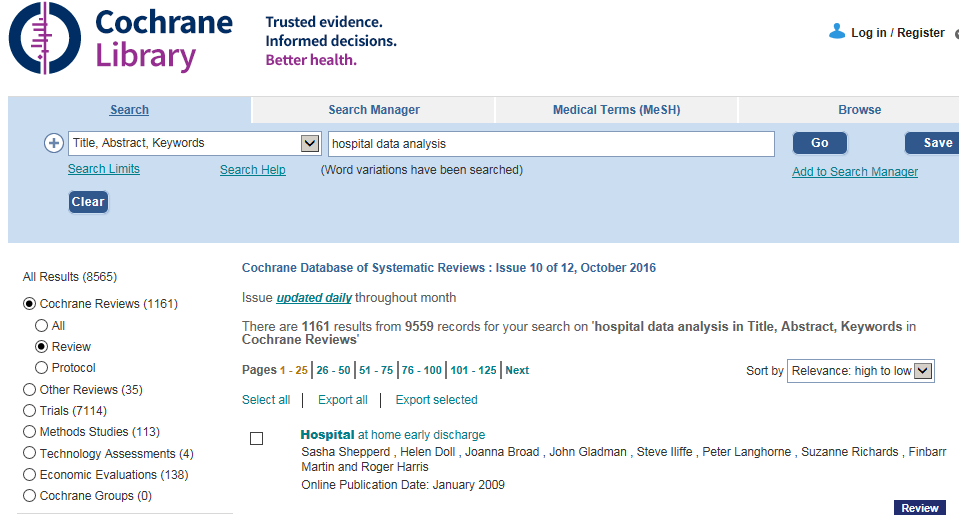
# Chapter 3: Review of the hospital data analysis methods

# 3 Background

# 3.1 What is hospital data

# 3.2 Review

On 4th Oct 2016, Cochrane library review was done for “Hospital data analysis”. There were 113 method studies, 4 technological assessments and 138 economic evaluations identified. There were no time limits imposed.



# Chapter 4: Hospital data descriptive analysis

# 4 Background

# 4.1 Hospital database INSTA

# 4.2 Data collection methods

# 4.3 Analysis plan

# 4.4 Description of data

# Total number of distinct patients

Based on the Vitals sign, Lab results and diagnosis report data dated 31st July 2016, the following numbers are derived:

|  |  |
| --- | --- |
| All patients present in the database | 41,094 |
| Only In-patients | 4,016 |
| Only out-patients | 33,709 |
| Common patients with in-patient and out-patient | 3,368 |

Summary statistics of the patient’s age (years) in 3 types of patient categories:

|  |  |  |  |
| --- | --- | --- | --- |
| Age (years) | Only in-patient | Only out-patients | Common |
| n | 4017 | 37077 | 3368 |
| Mean | 51.98 | 44.88 | 51.09 |
| SD | 17.89 | 18.48 | 17.99 |
| Median | 53 | 45 | 52 |
| Minimum | 2 | 1 | 2 |
| Maximum | 103 | 108 | 98 |

The median age for in-patient (53 years) is greater by 8 years than that for the out-patient group (45 years).

Summary statistics of age by gender and type of patient:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Age  (years) | Only  in-patient  (Male) | Only  in-patient  (Female) | Only  out-patient  (Male) | Only  out-patient  (Female) | Common  (Male) | Common  (Female) |
| n | 1959 | 2058 | 19021 | 18057 | 1652 | 1716 |
| Mean | 51.85 | 52.10 | 45.08 | 44.68 | 50.77 | 51.40 |
| SD | 17.76 | 17.01 | 18.93 | 17.98 | 18.79 | 17.18 |
| Median | 53 | 54 | 45 | 45 | 51 | 53 |
| Minimum | 2 | 3 | 2 | 1 | 2 | 3 |
| Maximum | 103 | 94 | 108 | 101 | 98 | 90 |

The age for males and females did not differ a lot in each of the 3 categories. The ratio of male to female patients is approximately 50% across each of the 3 categories.

Age group frequency by 10 year age categorization:

Only in-patients:

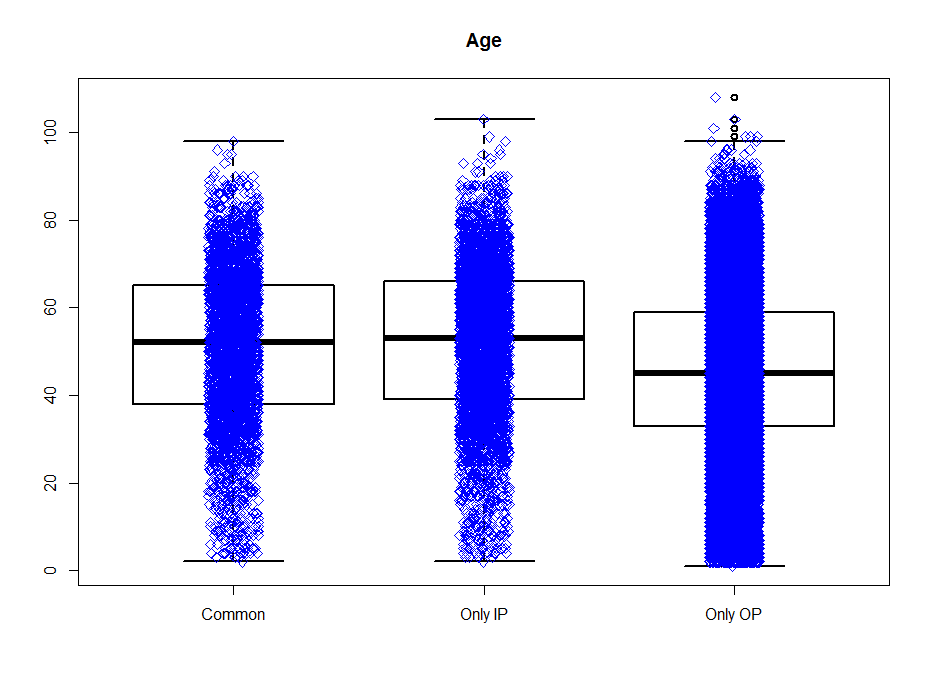
Only out-patients:

Common patients:

There is 1 patient above 100 years in Only IP group and 3 patients above 100 years in Only OP group, not displayed on the histograms.

All 3 categories on the same graph:

Boxplot representation of the age summary statistics and the individual age values overlayed is displayed below. Age categories are statistically significantly different in 3 groups. The number of patients in “Only IP” category under age of 20 is less than for the other 2 categories.



Patients’ residential status: Majority of patients were from Bengaluru city (~ 75% of overall patients).

Patients’ blood group: For 19,500 (47.45%) out of 41,094 patients the blood group has been captured. These numbers are quite consistent with the proportions reported for India. The cells in yellow should be checked.

|  |  |  |
| --- | --- | --- |
| A- | 258 | 1% |
| A+ | 3708 | 19% |
| A1 -ve | 2 | 0% |
| A1 +ve | 25 | 0% |
| A1B +ve | 6 | 0% |
| A2 +ve | 1 | 0% |
| A2B +ve | 1 | 0% |
| AB- | 94 | 0% |
| AB+ | 1152 | 6% |
| B- | 326 | 2% |
| B+ | 5730 | 29% |
| O- | 518 | 3% |
| O+ | 7679 | 39% |

Analysis on the diseases experienced by patients in 3 groups by age categories is done as follows. The patients are categorized into 3 age group categories: Age <= 18 years, age in between 18 and 65 years and age >= 65 years. The following tables display cross tabulation of ACD code and 3 groups (Only IP, Only OP and Common) for different age categories.

Expectation: The diseases requiring hospitalization should be different from the diseases not requiring hospitalization. The most frequently occurring diseases should be different across age groups.

Check the 2 csv files created with the frequency counts and distinct patients having the disease at least once.

Total number of patients in Outpatient section

Total number of patients in Inpatient section

Total number of patients only in Outpatient section

Total number of patients only in Inpatient section

Total number of patients present in both Outpatient and Inpatient sections

Demographics of patients

Number of patients checked by different departments