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Title: **Transdisciplinary clinical research in Ayurveda using statistics**

**Abstract:** Ayurveda as a healthcare system has survived for thousands of years but continues to be dogged by reported lack of efficacy of the treatments in clinical trials. The lack of efficacy could be due to a real lack of efficacy (which then contradicts the survival of Ayurveda as a discipline) or could be attributed to inadequacies of trial design or in a larger context the overall scientific conduct of research in Ayurveda. There is a need for transdisciplinary research in trials of Ayurveda. To be able to benefit the scientific endeavors of researchers, it should allow the researchers to use Ayurveda’s multi-component, individualized and inherently holistic approach. Statistics is a scientific tool that allows research to be conducted in a scientifically unbiased manner, enforces transparency if used properly and enables for proper interpretation of results. The article argues that statistics can help the cause of research in Ayurveda.

**Introduction:** The western biomedical science is developed using a method that can be referred to as a *hierarchical method*, where it constructs theories to uncover new knowledge through a sequential process of answering specific questions e.g. what is the efficacy of a particular drug or what is the safety profile of a drug? [1] This method assumes a step wise approach and deals with the problem in successively conducted clinical trials in a specific sequence. The pharmacology of the molecule is ascertained at the very beginning through various studies on ‘in-vitro and in-vivo’ experimental models. These studies are followed by clinical trials in humans, quite a few are randomized clinical trials designed to study and test specific hypothesis. The RCTs are believed to provide data which is least biased and allows for maximum generalizability. These studies could be complemented by case studies, case series and observational studies. This ‘one step at a time’ approach has worked very well in the western medicine framework.

Ayurveda is open to acquiring and adopting knowledge from different streams, as the basis of *samsara* represents the inevitable law of change. Nothing, human body, nature around us, physical facts, remains completely static in this world. This means definitive conclusions drawn today become redundancies of tomorrow. This fits nicely into the 3 principles of *tatva*, *Shastra* and *vyavahara* [26]. The Ayurvedic system of medicine has been in existence for many years and there is a huge amount of evidence base. According to the laws of *samsara* would ayurvedic understanding need confirmation in modern form, as the *samhitas* contain the knowledge base of past? Are we even capable of undertaking such a task? Could some of it be achieved using statistics, even though there are shortcomings? The misuse or inaccurate use of statistical methods may point the research in the wrong direction and produce incorrect study results, artificial research and a waste of resources [27, 28, 29].

**Methodology:** Ayurveda uses complex treatment regimens which can consist of drugs, diet, exercise, etc. [2, 9]. The intervention is complex [5, 9] due to various reasons amongst which multiple component intervention and adjustment of the components depending on the individual being treated [6] are two which make designing of Ayurvedic clinical trials a complex task. Ayurveda continues to be a popular health system which is being used in India and the neighboring countries [4]. Clinical end points are specific states of homeostasis or physiological equilibrium [7]. In contrast, in western biomedicine to a large extent, the interventions have been ‘simple’ which have allowed double blind randomized clinical trials. Due to this, biases associated with selection of patients/subjects and with performance/evaluation of interventions are minimized. However there are many situations, even in the western biomedicine where these ‘ideal’ trials are infeasible and in these cases non randomized open label studies, observational studies, case studies and case series have been used. Some examples which come to mind are evaluation of public health interventions, trials in therapeutic areas such as cancer and psychiatry, medical device trials and trials which involve invasive interventions like surgery. It is understood now that trials in these areas have biases associated with them and a goal for these trials is as much about understanding the intervention as it is about understanding the limitations and biases associated with the trial itself. We can learn and adapt from existing examples in the fields mentioned above which have used non-randomized trials. Design, conduct, analysis and reporting of trials in Ayurveda using interventions that are holistic, not reductionist is difficult and as a result calls for some sort of guidance and standardization [8]. This need is further enhanced by the sheer number of Ayurveda trials being reported in the recent past as can be verified by using any medical databases and using ‘Ayurveda’ or ‘Ayurvedic’ as a search criterion. These reports could be using case series methodology or be reported as pure observational studies with the aim of understanding, evaluating and quantifying the effects of the Ayurvedic interventions. As such there would biases associated with these trials. Guidance and standardization including use of appropriate statistical methodology like design and analyses of trials can be used to understand these biases and in some case minimize it.

**Types of biases:** Bias is defined as any tendency which prevents unprejudiced consideration of a question. In research, bias occurs when ‘systematic error is introduced into sampling or testing by selecting or encouraging one outcome or answer over others’ [8]. Understanding bias allows readers to critically and independently review the scientific literature and avoid treatments which are suboptimal or potentially harmful [9] [Table 1]

**Statistics as a scientific tool:** In general, the framework for taking decisions can be represented by the following 2x2 table. [Table 2] The problem of un-knowingly taking the incorrect decision is a difficult one to solve but that is the problem we can attempt to solve by standardization.

Many problems in research including in Ayurveda have been tackled incorrectly and have resulted in sub-optimal and biased solutions. Many clinical researchers un-knowingly assumed that the best design for any clinical trial is a randomized clinical trial resulting in trials which have been reductionist in nature. They abandoned the multi-component, holistic approach of Ayurveda and blindly aped the much simpler single drug-single disease intervention models used in western medicine. The end-result of this approach has resulted in trials having interventions which are not used in normal clinical practice and use of clinical end-points which are not defined in terms of Ayurvedic clinical management principles [8].

One could argue that one of the major problems that is facing the Ayurveda research is the role of Type I and Type II errors and how the hypothesis for testing is articulated. For negative clinical trials, since most of the times a reductionist approach was used, the practitioners ignore the result stating that the full holistic treatment was never used and as such the results are not believable. This basically questions the role of Type I error. Clinical intervention giving rise to the negative clinical trials continues to be used in general practice, albeit in a form as given in classical texts and not based on a reductionist approach as was tested. Statistics discipline helps in decision making under uncertainty and possibilities of errors, even in the case of un-knowingly having to take certain decisions, would result in better decision making. If we keep ethics, transparency and scientific excellence as three pillars of taking correct decisions in clinical research, statistics lends itself admirably towards each of these three pillars [24]. Just as an illustration, the list below provides a connection between the three pillars and some commonly used statistical and programming principles. [Table 3]

In western biomedicine, statistics has played a pivotal role in better understanding of the medical phenomenon, the conduct of clinical trials and interpretation of clinical data; it may be desirable that some of these statistical principles are used for Ayurveda clinical research.

Standardization of clinical research through development of guidelines like CONSORT [10] or STROBE [11] is an effort that some agencies working in the sector are involved with. The immediate benefit of such a guideline would be of enabling the reach of Ayurveda to a wider audience and reducing the skepticism arising due to lack of a valid scientific process. Some high level problems that these guidelines could address from a statistical viewpoint could include:

* Appropriate trial design to include choice of control group, blinding, randomization (wherever feasible) and valid sample size calculations
* Statistical designs to address the issue of complex interventions that render randomization or blinding infeasible
* Studying interventions which could have synergistic effects (statistical interactions) and are individualized to each patient/volunteer in a clinical study
* Role of Type I and Type II error and articulating an appropriate hypothesis for testing
* Identifying a suitable approach to designing the trial. Should equivalence approach be used instead of superiority? If equivalence is used, what should be the choice of equivalence margin? How do you do equivalence testing when endpoints are not exactly the same for the Ayurvedic intervention and the gold standard treatment as given in western bio-medicine?
* Defining and measuring complex endpoints as ‘cure’ in Ayurveda which may be a specific state of homeostasis, hence difficult to measure due to its multivariate and composite nature
* Aid the study of correlation between complex endpoints defined based on Ayurvedic principles and western bio-medicine endpoints
* Enable appropriate definition of disease and inclusion/exclusion criterion based on Ayurvedic principles and analyze how it correlates to western bio-medicine definitions
* Analyze data from studies that are non-randomized and which can potentially result in ‘biased’ estimates

**Leveraging effective use of Statistical Methods:** Ideally statistical analysis should be driven by the statistical design used. Non-randomized trials having confounders and a control group, standard stratification and regression techniques will allow for assessment of the intervention which is adjusted for other confounders and strata rendering it less biased. For stratified analyses [14] study subjects are divided into strata with similar characteristics. Intervention effects are assessed within each stratum and then the overall effect can be calculated by averaging the within-strata estimates. Averaging is done using weighted average where some characteristic of the strata is used to determine the weight. Stratification is best used when there are only one or two confounders, for e.g. age, sex and/or in case of Ayurveda it could be the subject’s *prakriti*.

In regression techniques (linear regression if the outcome is continuous, logistic regression if it is binary and Cox regression if censoring occurs) estimates of each confounder’s relationship to outcome is estimated. For assessment of intervention effect, adjustments are added to or subtracted from intervention effect seen without the adjustments, to account for the impact of each of the confounders to the outcome or to account for the differences in the confounders between the treatment groups.

Another method which is very useful is the propensity scores method [15] and is useful where many confounders need to be controlled for but the data is limited. The principle is based on the fact that propensity scores capture the information about the relationship between confounders and treatment allocation (not the outcomes as is the case in stratification and regression techniques), so that selection bias is removed when comparisons are made between groups with similar propensity scores. In many Ayurveda trials, selection bias could be a major component of the overall bias due to non-randomized nature of allocating the interventions. If confounding variables or characteristics which determine the allocation are captured correctly, then the bias associated with the selection could be removed using the propensity score method [16].

The method involves calculation for each subject their chance of receiving the experimental intervention from their baseline characteristics or in other words estimates a subject’s propensity of receiving the experimental intervention based on his or her characteristic. In a randomized trial with two equal sized treatment groups, the propensity will be the 0.5 for each subject and will not depend on his or her characteristic. In non-randomized trials, for example for an Ayurveda intervention where two treatment groups are Ayurveda whole system intervention and normal western biomedicine intervention, it is likely that treatment assignment will depend on baseline characteristics. It might be that patients with diagnoses of the disease which is closer to how it is described in traditional Ayurveda texts may be more likely to receive Ayurveda intervention. In this case the average propensity score in the Ayurveda intervention group will differ from the average in the western biomedicine group. In this case selection bias is a problem that needs to be addressed and propensity score method can be used to do that [16].

All of the methods mentioned above, namely stratification, regression and propensity score techniques require that key confounders are measured and are measured accurately. Irrespective of which method is used, investigators must include detailed description of the methods thoroughly and be conscious and critical of the assumptions they must make whenever they use these methods [17]. All these need to defined and described in the protocol before the trial is conducted.

**Statistical Design Methods:** Randomized clinical trials are a preferred method for assessing intervention effects and more generally assessing causality, especially when they can be implemented and all assumptions required for conducting these trials are met. When they are infeasible, alternative designs permit a wider range of research questions to be answered and permit more direct generalization of intervention effects; however, when using such designs, estimates of the magnitude of the effect may be more uncertain and could result in biased conclusions. The broad aim of clinical trials within the Ayurvedic context could be split into following types:

* Category 1: To provide evidence of effectiveness
* Category 2: To provide evidence of safety
* Category 3: To provide reference/evidence for existing practice
* Category 4: To enhance the existing knowledge base for a known intervention.
* Category 5: To further the science (in case of new or modified interventions or approach)

Above aspects if stated clearly upfront will allow the choice of the right design which could very well be a non-randomized study. Some of the more popular designs which could help in answering anyone of the above mentioned objectives are being listed here.

**Conclusions:** Clinical research methods in Ayurveda need to be adopted to suit the purpose. Statistics as a science and statisticians as partners can play a significant role in this endeavor. The statistical principles that are alluded to and problems that are highlighted - Are they new or theoretically difficult to solve? The answer is clearly no. The issue is of creating a transdisciplinary framework which utilizes all the existing statistical techniques and computing power to move Ayurveda research forward. The framework should be such that the Ayurveda researches feel fully empowered to do a trial as they see is the best for their interventions and do not do trials which are forcibly fit into the framework of randomized clinical trials. Statisticians through their consulting skill and their ability of going into the fundamental details lend themselves as key partners in progressing Ayurvedic clinical research. Let us move towards turning the famous Mark Twain quote ‘Lies, Damned Lies, Statistics’ into ‘Lies, Damned Lies and therefore statistics’. This hopefully will ensure that instead of getting a correct answer for the wrong question, an approximate answer to the right question for Ayurvedic trials would be is obtained.

**Two illustrations that demonstrate the challenges in clinical research in Ayurveda**

Example 1: During a review of a grant proposal for ‘Integrative Research on Aging and Regenerative Biology’, criticism was received on design of clinical trial for a specific disease, which was equivalent to Osteoporosis in modern medicine. The proposed design just said that a pragmatic clinical trial design which incorporates holistic intervention in about 500 patients would be used. The question or comment that was made on this was ‘**Nonspecific complicated** and **diffuse** with respect to clinical trials…without any **rationally designed protocols** under the **pretext of holistic approach** … focusing on **individualized medication**’. The challenge in this case is how do you rationally design a study which gives statistically unbiased results especially in cases where randomized, double blind studies are not possible?

In this case designs such as cluster trials where Ayurveda centers are randomized, preference trials and randomized consent designs, observational studies and before and after designs could be used. Analyses of such trials using methods as adjusting for covariates or propensity scores method have been suggested. Sample size calculations for such designs remain a challenge and need to be resolved. Practical implementation of such trials including drug supply management and data management issues need to be worked out.

Example 2: A recent preliminary abstract on a study on lower back problem was written as such. ‘’It is estimated that approximately 80% of the human population will suffer from lower back pain, at some point of their lives. Back ache symptoms are the most common cause of disability in those in the age group above 45 years. Modern medical treatment has its limitations in managing lower back pain. Ayurveda adopts the whole system approach and different treatment measures are planned to disrupt the pathology. Internal medications (individualized), external therapy, diet and regimens are employed. To create an evidence base, determination of optimal Ayurveda treatment, documentation of cases using standard diagnostic and assessment procedures has been taken up. Based on an open label prospective study with 54 patients getting treated for lower back pain, it was seen that 27 patients responded and 27 were non-responders which included patients who dropped out or had missing data. More chronically ill patients (17 of 29 (58%) responded compared to acutely ill patients (10 of 25 (40%)). The median duration of treatment was 4.57 vs. 3.14 weeks for responders vs. non-responders, (4.57 chronic vs. 4.14 acute). 11 responders were given physiotherapy vs. 4 for non-responders (7 chronic vs. 4 acute). Responders were suffering from lower back problem for more time compared to the non-responders (median of 12 months vs. 3 months, 24.00 months chronic vs. 1.00 month acute). The drop-out patients who did not come after baseline visit were more ill than any other group with median at 15.00 months. The median improvement for responders on a Quality of Life questionnaire was 50% vs. 16% for non-responders (median 56% chronic vs. 40% acute). There are a lot more patients treated in acute category who are treated for longer period but have failed to respond’.

As can be seen from the abstract, the results are complicated and difficult to summarize for recommending an optimal Ayurvedic intervention. The problem becomes more complicated as the internal medicine that is used is also individualized. Based on Ayurvedic principles they can be classified into certain categories. How do these categories influence the results needs to be determined. This is a case of complicated statistical analyses which is needed for a small experiment. Can modern statistical analyses techniques play a role?

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**Table 1: Types of Bias**

|  |  |  |
| --- | --- | --- |
| **Phase** | **Type of bias** | **How to avoid** |
| Pre-trial | Flawed design | Clearly defined risk and outcome, preferably with objective or validated methods. Standardized and blinded data collection. |
| Pre-trial | Selection bias | Select patients using rigorous criteria to avoid confounding results. Patients should originate from the same general population. |
| Pre-trial | Channeling bias | Assign patients to study cohorts using rigorous criteria. |
| During trial | Interviewer bias | Standardize interviewer's interaction with patient. Blind interviewer to exposure status. |
| During trial | Chronology bias | Avoid using historic controls (confounding by secular trends). |
| During trial | Recall bias | Use objective data sources whenever possible. When using subjective data sources, corroborate with medical record. |
| During trial | Transfer bias | Carefully design plan for lost-to-followup patients prior to the study. |
| During trial | Exposure misclassification | Clearly defined exposure prior to study. |
| During trial | Outcome misclassification | Use objective diagnostic studies or validated measures as primary outcome. |
| During trial | Performance bias | Use blinded evaluators to assess performance. |
| After trial | Citation bias | Register trial with an accepted clinical trials registry. Check registries for similar unpublished or in-progress trials prior to publication. |
| After trial | Confounding | Known confounders can be controlled with study design (case control design or randomization) or during data analysis (regression). Unknown confounders can only be controlled with randomization. |

**Table 2: Decision making matrix**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **What decision was taken?** | |
|  |  | **Correct** | **Incorrect** |
| **How decision was taken?** | **Knowingly** | Good Science | Fraud |
| **Un-knowingly** | Luck | Bad Science/Bad Luck |

**Table 3: Statistical programing principles and Good Science**

|  |  |
| --- | --- |
| **Statistical Programming Principles** | **Clinical Research Principles** |
| Hypotheses Testing | Scientific excellence and Transparency |
| Confidence Intervals | Scientific excellence |
| Sample Size | Scientific excellence and Ethics |
| Randomization and Blinding | Scientific excellence and Transparency |
| Bias and Bias reduction | Scientific excellence and Transparency |
| Statistical interpretation of data | Scientific excellence and Transparency |
| Meta-analyses | Scientific excellence |
| Design of experiments | Scientific excellence, Transparency and Ethics |
| Good programming principles | Scientific excellence and Transparency |
| Validation and Quality Assurance | Transparency |