

# Standards of reporting Ayurvedic clinical trials — Is there a need?

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## ABSTRACT

Reported lack of efficacy of Ayurvedic treatments in clinical trials is often not due to inefficacy of the treatment itself, but arises from inadequacies of trial design. This paper argues that trials of Ayurvedic interventions should exclusively use its multi-component, individualized and inherently holistic approach, and that general guidelines for rigorously reporting such clinical trials should be developed. Holistic Ayurvedic clinical trials, rigorously conducted and with high standards of reporting should translate into *good clinical science*, and may be expected to generate higher credibility for clinical studies of the Ayurvedic knowledge system.

## INTRODUCTION

Ayurveda as a medicinal system assesses deviation from health due to development of whole body system imbalance. These imbalances are among the basic concepts in Ayurveda which are now well understood, and which include the doshas and subdoshas in terms of which the imbalances are expressed.<sup>[1]</sup> It is now known that diet and lifestyle interventions derived from Ayurveda can help restore the system to balanced functioning and for these reasons Ayurveda interventions always have multiple components including diet and lifestyle components.

Ayurveda and other traditional medical systems often prescribe complex treatments<sup>[1]</sup> consisting of a combination of drugs, diet, detoxification procedures, lifestyle changes, and yoga practices, customized to the needs of individual patients.<sup>[2]</sup> Their end points are specific states of homeostasis or physiological equilibrium.<sup>[3]</sup> The question therefore arises, can one report the outcome of such multi-component, individualized interventions with unique end points, in a manner that is not merely anecdotal, so that the report contributes positively to the corpus of Ayurvedic clinical science?

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Various initiatives for methodological harmonization and quality improvement of clinical research have been published and are now widely accepted. The CONSolidated Standards Of Reporting Trials (CONSORT) statement offers a minimum set of recommendations for reporting Randomized Clinical Trials.<sup>[4]</sup> The CONSORT group also released guidelines on reporting of trials using Herbal products.<sup>[5]</sup> Recent work on the SPIRIT initiative<sup>[6]</sup> towards standards of designing protocols has been a welcome extension of reporting guidelines. In Epidemiology, the STrengthening the Reporting of OBServational Studies in Epidemiology (STROBE) statement similarly aims to strengthen reporting of observational studies,<sup>[7]</sup> while the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group has prepared checklists for meta-analysis of observational studies.<sup>[8]</sup> Transparent Reporting of Evaluations with Non-randomized Designs (TREND) statements concern methods of research design to eliminate biases in non-randomized studies.<sup>[9]</sup> The advantages of using such guidelines are well documented. Ayurveda would certainly benefit from similar guidelines.

Specifically related to Ayurvedic intervention, Narahari *et.al*<sup>[1]</sup> have provided a standard framework under which to develop protocols and subsequent reports. In addition, the Government of India has an official guidance on clinical trials of herbal remedies and medicinal plants,<sup>[10]</sup> which is a part of the more general guidance on conduct of clinical trials in India.

However, detailed development of guidelines for reporting of Ayurvedic clinical trials has not been done to the fullest

extent. This paper specifically considers the question of how to develop these standards of reporting of Ayurvedic clinical trials designed in accordance with its holistic theory and practice, so that objective lessons can be learned from the experience.

## STANDARDS OF REPORTING CLINICAL TRIALS OF AYURVEDA

To address the question of standards of reporting clinical trials of Ayurveda, one must ensure adherence to the three essential pre-requisites of good clinical science. Firstly, reporting must be transparent, honest and accurate; secondly, it must be scientifically unbiased; and thirdly, all interventions used in the trial must be ethical.

In the recent past, design of clinical trials for Ayurvedic interventions has abandoned its multi-component, holistic approach. Instead, trials have blindly emulated the simpler *single drug-single disease* intervention models used in western medicine. The limitations of this approach have been two-fold: (1) Ayurveda's complete interventions as used in normal clinical practice have not been put to the test; rather, what has been tested has only been some part of the whole intervention normally prescribed; (2) end-points used to signal positive outcome have not been defined in terms of Ayurvedic clinical management principles; nor have creative efforts been made to measure them. This mismatch between Ayurvedic principles and scientific trial design has resulted in conclusions about treatment efficacy that are not in accord with the clinical experiences of practitioners of authentic Ayurveda. These differences have in turn resulted in skepticism concerning Ayurveda's clinical claims in the world of professional medicine.

In the context of developing *standards* for Ayurvedic clinical trials, it must be firmly asserted that expertise in the use of Ayurveda interventions lies solely with *Ayurvedic knowledge holders*, and not with their collaborators, including statisticians. It is not wise to advise Ayurvedic physicians on how to conduct Ayurvedic clinical management of any particular health condition. However, fellow scientists and statisticians who are interested in appreciating the Ayurveda knowledge system are fully justified in insisting on honest, accurate, scientifically unbiased, transparent and standardized reporting of all Ayurvedic clinical trials.

Guidelines on reporting (as opposed to conducting) trials will play a major role in establishing credibility of Ayurvedic clinical management. Such guidelines, for example, will require transparency in reporting details for the following points :-

- Reasons for conducting the clinical trial, its underlying

rationale? This is important in establishing the ethics, and in ensuring that all human experimentation is in line with the Helsinki declaration<sup>[11]</sup> on human experimentation.

- Whether the goals of the clinical trial correspond to its stated rationale. This consistency will address the issue of 'internal validity' of the trial.
- Whether the trial's design elements ensure that its goals can be achieved. This guideline should include discussion on how the patients/subjects were selected (inclusion and exclusion criteria), how many (to ensure lack of scientific bias), duration of the intervention, and the experience and qualifications of Ayurvedic practitioners conducting the trial. If addressed transparently, the design elements lead to clear understanding of biases.
- Whether the disease under study was appropriately defined i.e. based on Ayurvedic knowledge (listing all end-points associated with the disease with due weightages). Clarity of disease definition helps minimize subjectivity in patient selection, as well as biases in assessing end-points related to the disease.
- Were the various components prescribed for the intervention based on customized diagnosis? Were all details of its complexity included? Clear and full definitions of the interventions used, including placebo or comparator interventions allows others to assess reasons for the trial's failure or success, and will help them replicate the trial should they be interested in doing so.
- Definitions of the end-points indicating a positive outcome for the patient, and how to measure them - success or failure of an intervention depends on objective definitions of the presence or absence of pathology. Along with the previous point on definition of the disease, this helps make reports clearly unbiased in assessing an intervention's success.
- Actual patient history during the trial, including details of patient selection procedures, patient drop-out and associated reasons, and all records of adverse reactions or events? Transparency in reporting individual patient flow during the trial helps in assessing the internal validity of the trial, which is a first step to establishing its external validity.
- Discussions of net results obtained, keeping in mind the original rationale for conducting the trial. Discussions should include points on (1) the internal validity of the trial including clear discussion on how closely conduct of the trial followed its written protocol; (2) external validity of the trial including analyses of results vis-à-vis the latest scientific indicators (e.g. bio-markers, state of the art scientific breakthroughs) and extrapolations of results to a wider population than that studied in the trial.

As previously emphasized, demand for standardization in reporting should in no way restrict Ayurvedic physicians from practicing their art faithfully. Guidelines only go to promote the report's objectivity, scientific validity and ethical considerations. In other words, 'standards of reporting' are not about clinical management, but offer guidelines on how to report faithfully, comprehensively and accurately on what actually occurs during trials. Such standards of reporting will allow all readers to enjoy objective conclusions, and obtain better pictures of detailed strategies and ethical norms used in trials.

Various issues concerning clinical trials can be resolved by reporting them completely and accurately. For example:

- A report may state, '*the inclusion criteria for subjects and choices of end-points are based on western definitions of the disease, only treatment is based on Ayurvedic principles*'. Such an admission will encourage the reader to ask how the western definition correlates with the corresponding Ayurvedic definition, and the extent to which the Ayurvedic end-points would correspond with western ones. (One-to-one correspondences are unlikely; generally, the relationship will be many-to-one.)
- An unclear rationale may raise questions about the ethics of conducting the trial. If the statistical reasoning used to determine the number of subjects is inadequate, it may prove impossible to draw conclusions from the resulting trial. Using patients as subjects for such a trial could become an ethical issue, quite apart from being a scientific problem.
- Any mismatch between the definitions of a disease and its 'cure', will cause problems in interpreting results. Ensuring that both are clearly defined should eliminate them.
- State whether blinding was, or was not, carried out. Blinding is conducted to eliminate performance or assessment bias. In Ayurvedic trials, it is often inappropriate and not done. Explicitly reporting this to be the case, and listing associated reasons, may stimulate readers to think of alternative strategies to minimize performance bias.
- Similarly, randomization should be reported, as should the method of carrying it out, since randomization reduces biases arising in patient selection. Any selection bias can be reduced by having a comparison group, and randomly assigning patients between intervention and comparison groups. The comparison group can be a placebo group or a standard treatment group, or, if neither is feasible, it could even be historical data (clearly identified and defined in the protocol) from previous studies.
- Patient flow: all details of patients enrolled for the trial whether or not they completed it, inform the reader

about deviations from the written protocol during implementation, so reporting them is important.

All the points and examples emphasize the three basic principles under which reporting should be done - transparency, scientifically unbiased and ethically strong.

## DISCUSSION

Various initiatives for methodological harmonization and quality improvement of clinical research have been published and are now widely accepted. The advantages of using such guidelines are well documented. Ayurveda would certainly benefit from similar guidelines.

Guidelines suggested by Narahari and developed in CONSORT for Herbal medicines are good building blocks. Narahari's paper emphasizes the steps necessary for ensuring that good clinical science is practiced through a specific example. By building on his ideas and generalizing them, a good start can be made. The CONSORT statement for herbal medicine is also a good building block and needs to be enhanced with Ayurvedic specific definitions of interventions and disease cures. Complexity arising due to these difficult issues needs to be added for reporting of Ayurvedic clinical trials.

The recent work of Bian *et. al*<sup>[12]</sup> is an adaptation of CONSORT statement for the Chinese traditional medicine. This work clearly highlights the complexity involved in Chinese interventions and definitions of disease state and cure. Adaptations of CONOSRT principles, which allow for traditional Chinese interventions offer guidance for Ayurvedic scientists.

An added complexity for an extensively practiced healthcare system like Ayurveda is that various forms of clinical data are generated in large amounts daily. However, neither data collection nor reporting of any of these clinical data are standardized. Currently generated reports include:

- Data from single case studies, generally reported as anecdotes.
- Data from observational studies reported without addressing their limitations, such as performance and selection biases and consequent shortcomings.
- Data from clinical trials which are improperly designed or have interventions based on a reductionist approach.

In western bio-medicine case studies, observational studies, clinical trials and meta-analyses are used for specific purposes at successive stages of drug development. In contrast, in Ayurveda all four kinds of study can be used to establish its evidence base. Ayurveda should adopt them all because of the need to generate evidence. In

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particular, well-defined meta-analyses should be carried out to summarize clinical results across multiple trials. We need to develop guidelines for each one of them, namely, Ayurvedic case reports, Ayurvedic observation studies, and Ayurvedic clinical trials.

As has been seen in the western biomedicine case, standardizing reporting guidelines will ensure that good clinical science is practiced and reported. The time is now right to build on existing guidelines and, where none exist, develop them.

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