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Review Article

RCTs and other clinical trial designs in Ayurveda: A review of challenges and opportunities

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ABSTRACT

Currently, there is a paucity of clinical trial designs that comprehensively evaluate the efficacy of most complementary and alternative systems of medicine (CAMs) like Ayurveda. Several factors such as complex interventions, individualized therapy, etc., make designing Ayurveda clinical trials challenging. The prevalent randomized control trial (RCT) designs largely involve symptomatology/pathology-based recruitment and standardized interventions in carefully monitored trial environments. The present paper critically reviews the suitability of the dominant RCT model to Ayurveda and argues for newer, more sensitive trial models including modified RCTs and other clinical trial designs. It also explores the merits of a non-hierarchical approach to clinical evidence generation.

1. Introduction

Growing interest in the AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha, Sowa rigpa and Homeopathy) systems across India, led to the formulation of the Ministry of AYUSH's (Govt. of India) Good Clinical Practice (GCP) guidelines in 2013. These seem to have been largely derived from the Central Drugs Standard Control Organisation (CDSCO) proposed standard GCP guidelines [1], and recommend the randomized control trial (RCT) for clinical evidence generation in AYUSH systems [2]. While the move to regulate research in the AYUSH systems is commendable and necessary, the current guidelines do not adequately discuss the specific requirements of the AYUSH sector or trial modalities sensitive to the individualized nature of these systems. Correspondingly, most clinical trials in Ayurveda attempt to blindly replicate the dominant Western RCT model, in which there is a comparison of "groups of patients who differ only with respect to their treatment" [2]. This paper reviews the challenges associated with the dominant RCT model, and explores possible alternatives, with specific reference to Ayurveda.

2. The randomized control trial

The RCT is regarded as the 'gold standard' of clinical trials, and is considered the ideal research methodology to assess the efficacy of clinical interventions. It is a study in which patients/study subjects are randomly allocated to one or more study/control groups and is ideally blinded. The ability to infer causal relationships between an intervention and outcome under relatively controlled circumstances contributes to the high internal validity of RCTs, while randomization is claimed to balance confounders and 'equalize' the samples [3]. The most commonly used RCT design is shown in Fig. 1.

While the RCT would remain theoretically compatible as a trial format even for a large number of parameters, in clinical practice, it is virtually impossible to individually test and control for each of the complex and dynamic parameters that influence diseases. There is, therefore, a growing critique of the RCT as it is currently practiced, and numerous proposals for modified RCTs or context-specific designs that have greater external validity have been put forth. Houle [3] reported that RCTs were associated with limited external validity and consequently low generalizability due to the stringent inclusion, exclusion, and intervention criteria. She also reported the inefficiency of the RCT model to detect rare/delayed outcomes of interventions and the high costs involved in such trials. Deaton and Cartwright [4] argued that randomization does not, in fact, equalize confounders and other variables, particularly as most samples in a trial are age, and comorbidity exclusive, making them unrepresentative of the diversity of the population availing the intervention in the real world. They also claim that RCTs do not even, in most cases, provide a precise estimate of the average treatment effect.

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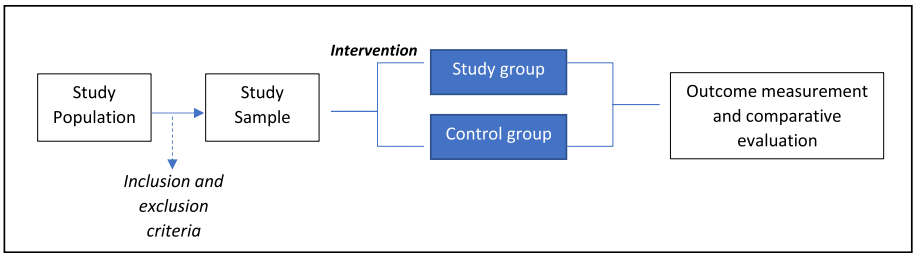

Fig. 1. A typical RCT design.

3. Why current RCT models are incompatible with Ayurveda

While these general critiques of the RCT are pertinent, the issues with RCTs in Ayurveda are more specific and complex. Ram Manohar [5] reported two particular challenges associated with current RCTs in Ayurveda – a) complex diagnostic assessment in Ayurveda that significantly differs from Allopathic diagnosis, and b) the complexity of treatments offered in Ayurveda. He provides the example of two individuals presenting with cervical spondylosis showing identical disc bulge and degeneration reports. While both of them would receive the same standard Allopathic therapy, they would likely be prescribed different Ayurvedic interventions. The *Caraka Samhita* [6], a nodal Ayurvedic text, describes ten important patient assessment parameters, in addition to clinical assessment, including *prakriti* (physico-mental constitution), *agni* (metabolic profile), *samhanana* (anthropometry) etc., that help determine the individual disease states and their person-specific redressals. It is the person-specific variations evinced by these assessments that are responsible for different therapeutic interventions even in cases with identical clinical presentations. The number of parameters involved in patient assessment and intervention makes the design of an RCT in Ayurveda particularly difficult.

Patwardhan [1] emphasizes that RCTs in Allopathy are largely restricted to standardized single drug/therapy interventions, while Ayurveda interventions are complex and personalized, and often consist of multiple medications, physical therapies, and diet and lifestyle modifications. Over the past decade, several Ayurvedic clinical trials have attempted to blindly replicate the single disease-single intervention model of Allopathic RCTs. The issues associated with this approach are two-pronged. Take for example, two patients who have identical clinical and radiological presentations of osteoarthritis. Firstly, person-specific considerations such as *prakriti* etc. might cause an Ayurveda physician to treat both cases differently, as described earlier. Secondly, in the event that a single intervention (eg. *Sahacaradi Kasaya*) proves ineffective, or insufficient, the physician might choose to supplement/replace it with other treatments and complex interventions for more effective outcomes, making a single intervention study in such a case, is a poor indicator of clinical outcome. In such a case, the RCT design itself is responsible for forcing the adoption of a treatment protocol unrepresentative of treatment at point of care. Thus, regardless of whether associated with high success rates, or low success rates, the single disease-single intervention model is most often associated with poor/no external validity.

Ram Manohar [5] adds that this is further complicated by a dynamic assessment of progression and regression of disease in real-time clinical practice that requires a periodic assessment and modification of therapeutic interventions even during the course of the trial. This, he argues, in addition to the difficulties raised by the individualization and complexity of Ayurvedic treatment, makes the current RCT model a poor tool to assess clinical efficacy of Ayurveda therapies. Fonnebo et al. [7] highlighted the disparity between published studies claiming little/no efficacy of alternative medicine therapies, and reports of substantial benefits in real-time practice, supporting Ram Manohar's argument that there is a mismatch between current RCT evaluation of Ayurveda therapies and the way they are practiced at point of care.

Lastly, one of the biggest challenges associated with current clinical trials in Ayurveda is the lack of rigor and quality. One review showed that out of 225 published Ayurvedic clinical trials reviewed, 90% were associated with unsatisfactory diagnosis and ambiguous outcomes [8]. Adequate training in rigorous and Ayurveda-appropriate clinical trial models is vital if a robust evidence-base is to be developed.

4. Modified RCTs and other designs

In order to address the challenges raised above, several modified RCTs along with other trial designs have been proposed, for more appropriate clinical evaluation of Ayurveda. The Medical Research Council (MRC) of the United Kingdom published a series of experimental designs for complex interventions that include individually randomized trials, stepped-wedge designs, and N-of-1 designs [9]. Three modified RCTs that may be particularly relevant to Ayurveda are discussed below – the stepped wedge design, a novel 'black-box' model and the N-of-1 trial.

4.1. Stepped-wedge design trials

In stepped wedge designs, a sample is initially chosen, from which subjects/clusters move from control to intervention in a phased manner, as demonstrated in Fig. 2 If involving individual subjects, this design is particularly useful to comparatively evaluate the efficacy of an intervention over time. It is however, most often used as a cluster randomization trial, in which the sample population is broken down into smaller groups or clusters according to the parameters that are to be studied (age, disease severity, etc.). Alternatively, the sample population need not be clustered according to any of these parameters, and may only be randomly clustered [10]. Each of these clusters is then individually administered the standardized intervention(s) in a phased manner, as shown below in Fig. 2.

This design, however, still requires a standardized intervention protocol, and is therefore incapable of assessing efficacy of variable individual-specific therapies in clinically similar conditions. An instance of individualized Ayurveda intervention is described below. Take a case of *Prameha* (a spectrum of diseases including diabetes). After detailed initial assessments and history-taking, the treating physician may decide to only administer internal medications (eg. *Asanadigana kasaya* + *Katakakhadiradi kasaya* along with Tab. *Nisamalaki*), together with diet and lifestyle modifications. However, if no improvement is observed after the duration of initial treatment, the physician may reconsider the intervention, deciding upon a mild/strong *sodhana* (whole-body purification), in

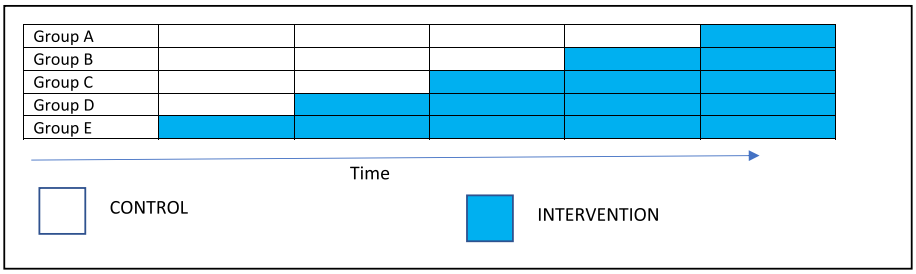

Fig. 2. Stepped Wedge Design.

addition to internal medications. Such an eventuality would require the adoption of protocols for *snehana* (medications, their doses and durations for oleation therapy), *abhyanga* (oils for massage), *pancakarma* etc. specifically designed for the patient, together with decisions regarding their internal medications. Further, daily assessments and follow-up visits to the patient would naturally result in minor prescription modifications even during the course of the treatment – for example, if the patient develops a headache after two days, the physician may decide to add *Rasnadi curna lepa* application on the forehead for a few days. Assessment of such a protocol using the stepped wedge-design would be impossible. In contrast, other Ayurveda procedures that are not constrained by individual variations, would lend themselves more easily to evaluation by this trial design.

For instance, the *Niruha basti* procedure (medicated decoction enema) has very particular specifications regarding the treatment room, patient position, size of nozzle, proportions and materials of enema bag, method of nozzle insertion, duration of medicine retention etc., irrespective of any individual specific variations, making it a good example of a standard Ayurvedic therapeutic protocol. Testing the efficacy of such standard protocols in individuals is constrained to an extent by individual variations, along with concurrent medications and therapies even in identically diagnosed conditions. However, such standard protocols are undoubtedly easier to test using the dominant RCT model and modified RCT designs such as the stepped-wedge, than individual-customized protocols, as discussed above.

The phasing of intervention in sample clusters in the stepped-wedge design has a two-pronged benefit – it allows within-cluster and between-cluster assessment and eliminates the need for a control group, since individual clusters act as their own controls. Testing of the AYUSH Ministry mandated COVID-19 preventive and therapeutic protocol would lend itself ideally to the stepped-wedge design. It would be particularly useful to study population-wide/public health Ayurvedic interventions, that have so far eluded robust clinical trial validation.

4.2. A black box RCT model

Furst et al. [11] conducted a modified RCT trial in Ayurveda that compared methotrexate against complex Ayurveda treatments for rheumatoid arthritis (RA). In this study, patients were randomly allocated based on biomedical diagnoses (showing radiological evidence of RA) to the Allopathic intervention group (methotrexate), the Ayurvedic intervention group (in which the physicians were given freedom to diagnose and treat individual cases with no restrictions on medicine/modality), or an integrated intervention group (Ayurveda and Allopathy). Following this, purely Allopathic clinical outcomes were evaluated in all groups to allow for comparative outcome analysis and clinical efficacy assessment. This study, was given the Excellence in Integrative Medicine Research by the European Society of Integrative Medicine, and recommended as a blue print for future clinical studies in complementary and alternative systems of medicine by Ernst and Furst [12]. Witt et al. [13] used a similar model in a multi-centre trial to assess the comparative clinical efficacy of Ayurveda and Allopathy in osteoarthritis.

One significant advantage of this trial design, is that it makes allowance for complex individual-specific interventions, even in similar clinical presentations. Further, giving Ayurveda physicians the freedom to diagnose and treat presenting patients in their own ways, is fully representative of real time Ayurvedic practice.

While this modified RCT design, seems to currently be one of the best for Ayurveda, the mode of action of the Ayurvedic interventions remain a 'black box', – i.e. unmeasurable. It also does not assess the efficacy of a particular Ayurveda intervention (since the protocol consists of a group of complex individually varying interventions), but rather *whether* or not an Ayurvedic approach is effective in the management of the biomedical disease under consideration.

4.3. N-of-1 RCTs

N-of-1 trials are single subject RCTs in which the subject undergoes alternating intervention pairs (two different interventions, or an intervention and placebo), separated by a suitable wash-out period, until such time as both the physician and subject are able to determine whether or not outcome variations are present between the interventions. Ideally, both the subject and physician are blinded to which component of the pair is being administered [14].

However, N-of-1 trials are only administered when there is reasonable certainty that an intervention has quick-onset of action that ceases on discontinuation of intervention [15]. It may be noted in the context of Ayurveda, that such trials would therefore be restricted to medications or procedures such as *agnikarma* (thermal cautery) or nebulization with Ayurveda medications etc. that possess rapid action. For example, an N-of-1 trial to evaluate the efficacy of *agnikarma* in *gṛdhrasi* (correlated by some with sciatica), would involve alternating periods of intervention and no intervention with periodic outcome assessment. The efficacy or lack of it of *agnikarma* would be determined by variations in subjective and objective parameters observed during the trial and control phases. As such, blinding would be almost impossible in these trials, owing to the distinctive tastes/smells etc. of Ayurveda medications as well as the frequent use of physical therapies.

A significant advantage of N-of-1 trials is that subjective patient assessment, diagnosis and treatment can all be carried out and presented in accordance with Ayurvedic principles. However, they are considered by some as having low validity due to the very

low sample size, which may be offset to a certain extent by sensitive replication.

A contrast of conventional RCTs with modified RCTs has been presented in Table 1.

5. Other trial designs: observational studies, adaptive trials and single subject research

5.1. Observational studies

Graz et al. [16] recommend that observational studies should play a much larger role in clinical evidence generation for traditional healthcare systems like Ayurveda, particularly considering the long history of use and the diverse usage pattern. They suggest several observational trial designs including a) a retrospective treatment outcome (RTO) study and b) a comparison of prognosis and outcome (CPO). The RTO involves the analysis of patient records and progress to document the plethora of interventions prescribed, their effectiveness (based on documented outcomes) and any correlations between intervention and outcome. An important example of an RTO is the case report that retrospectively analyses and reports clinical outcomes. The CPO investigates whether the efficacy of traditional interventions for a particular biomedical condition are comparable with modern medical interventions. In this study, patients with similar diagnosis are sent to both a modern medicine practitioner and a traditional healer, and their prognosis (predicted degree of improvement prior to treatment) and actual treatment outcome are documented and compared, providing information regarding the effectiveness of the traditional healing approach and methodology.

For instance, if a researcher wished to study the efficacy of various Ayurveda approaches used in the management of *Kitibha kustha* (a spectrum of skin disorders), a retrospective treatment outcome modality could be used to analyze records of various successfully treated *Kitibha* cases to identify which interventions were most commonly prescribed, which, if any, intervention(s) were associated with best treatment outcome etc. Further, causal relationships may also be tentatively drawn, from these and hypothesized for further investigation in larger observational studies as well as prospective interventional clinical trials.

However, observational studies possess little control over trial environments, as a result of which the quality of data obtained could potentially be affected. Graz et al. [16] suggest methods by which observational studies can be made more rigorous. For instance, they suggest that observational studies and their follow-ups be carried out using the same inclusion and exclusion criteria as are employed in experimental trials. They further suggest that the same statistical tools used in RCTs be applied to observational studies as well, particularly including adjustment for variations in base-line susceptibility of individual to outcome post-intervention, adjustments for confounding factors (such as concurrent medication) and the 'intention to treat' analysis, in which all participants of the trial are included in statistical evaluation and analysed in accordance to the group to which they were initially allocated, irrespective of intervention received. They also recommend that the study sample chosen be large enough for suitable correlational tests (eg. Chi-square or Fisher's) to be run. In addition to the above, Graz et al. [16], highlight that observational study designs provide viable low-cost, low-input, high-validity methods of clinical evidence generation for Ayurveda.

5.2. Adaptive clinical trials

Adaptive clinical trials are those that involve planned and structured modification of one or more elements of the study design during the course of the trial. For example, if a particular medication/intervention is found inadequate/ineffective during the course of the trial, it may be changed or modified [17]. A study attempting to evaluate the efficacy of *Parnayavani Arka* (an aqueous distillate of the drug *Coleus aromaticus*) in *Tamaka svasa* (a spectrum of respiratory disorders associated with wheezing sounds) at a dose of 5 ml per nebulization would benefit from a pilot adaptive trial. If during the trial, the dose is found inadequate, it may be increased to 8 ml, or 10 ml, or qualified as 5 ml in moderate cases and 10 ml in severe cases. Alternatively, it might be found that a combination of *Parnayavani* and *Bharngi* (*Clerodendrum serratum*) *Arkas* provide far better outcome than the *Parnayavani Arka* alone. This can also be incorporated into the trial.

One of the advantages of this model is that it factors in the dynamic modification of interventions that take place in real-time clinical practice [17]. They have also been shown to augment efficiency of clinical trials by facilitating precise dose fixation, and allow for significantly improved patient outcome. While these would be particularly helpful to assess interim outcomes, they still mandate some form of group specific intervention.

5.3. Single subject research

This method involves the clinical evaluation of an intervention in a single subject, or a small group of subjects, in which each subject serves as his/her own control [18]. Such a study would typically consist of a baseline observation phase for a specific period followed by an intervention phase. Identical before-after repeated measurements of a minimum of five data points are taken. Graphical representation of results obtained helps to clearly identify before after changes [14].

In Ayurveda, such designs would be useful to understand the clinical efficacy of a particular treatment/treatment combination in a disease. Take for example a study to evaluate the efficacy of *kati basti* in *kati sula* (lower back ache). A minimum of five data points

Table 1
Conventional vs. modified RCTs.

Conventional RCTs	Modified RCTs
Do not allow for patient-specific variations in treatment in accordance with *prakriti* etc. assessments in conditions with identical biomedical diagnosis/ similar clinical presentations.	The Black Box design allows for patient specific intervention variations, even in conditions with identical biomedical diagnosis/similar clinical presentations. To a limited extent, N-of-1 trials also allow for this provided the intervention is fast acting.
Subjects do not act as their own controls	In the N-of-1 trial, the subject acts as his/her own control, therefore eliminating usual confounders.
Are not ideal when assessing public health interventions due to: a Small sample size b No time-dependent analysis	The stepped wedge cluster randomization model is particularly useful when assessing large sample interventions (such as public health interventions). It is also useful to assess between-cluster and within-cluster variations that are more truly representative of population dynamics. Further, time-dependent analysis of intervention is also possible.

(range of motion, distance walked during the heel-toe-test, number of squat-raise done, straight leg raise, and pain reduction) are observed for a suitable baseline phase after preliminary patient analysis consisting of *prakriti* etc. assessments, followed by *kati basti* intervention for a specific duration. The above data points are observed for using both subjective and objective (X-Rays etc.) clinical evaluations. Assuming a small group of three individuals were selected for this study, individual and group comparisons of outcome measures may be drawn (based on hypothetical presentations and numbers) as shown in Figs. 3,4.

Alternatively, this study design could be used to evaluate the clinical efficacy of a particular complex intervention. One of the main drawbacks of this design is that it requires a dramatic change in outcome from observation to intervention phase in order to be able to establish a causal relationship between intervention and outcome. Another is the lack of generalizability, which may be offset to a certain extent by further studies [19] – a) direct replication of the intervention in individuals with similar baseline conditions (including *prakriti* profile etc.) and clinical presentations, or b) systematic replication of intervention in individuals with similar *prakriti* profiles, but varying *kati sula* presentations, or vice versa to evaluate clinical efficacy of intervention in differing conditions. Meta-analysis of such replication studies could provide valuable insights into how different clusters of subjects (stratified according to *prakriti*, *sara*, *vaya*, clinical presentation, etc.) respond to an intervention.

6. Non-hierarchical models – A possible way ahead

From the discussions presented above, it is evident that there is no single trial design that is universally applicable for systems like Ayurveda. Questioning the general validity of the evidence pyramid (N-of-1 trials at the bottom and RCTs at the top), Walach et al. [20] argue for a non-hierarchical approach to clinical evidence generation. Extending this thought to Ayurveda, it becomes clear that study designs can only be decided based on trial objective(s). For instance, if the objective is to understand whether or not a disease can be cured/improved using an Ayurvedic approach, the ideal study design would be the modified RCT proposed by Furst et al. [11]. In the absence of resources to carry out such an RCT, the scope for multiple case reports, N-of-1 trials or single subject research designs always remain. However, if the study objective is to evaluate the efficacy of a particular single/complex intervention, three types of studies could be carried out – a) observational studies to assess retrospectively the effectiveness of said intervention, b) single subject research or N-of-1 trials, c) other suitably designed RCTs. Further, if this intervention is intended for a larger population, as with Ayurveda interventions for COVID-19, a stepped wedge design trial could also be carried out. If the study objective includes precise dose fixation of a medication, the adaptive trial design could be incorporated.

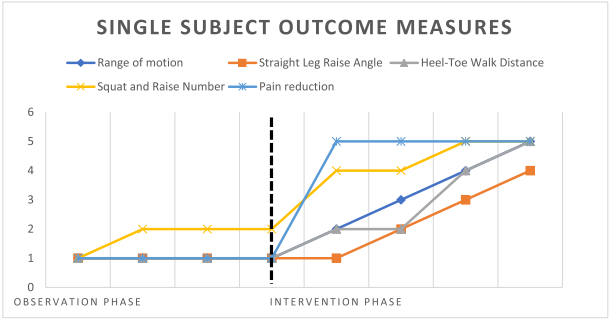

Fig. 3. Sample single subject outcome measure.

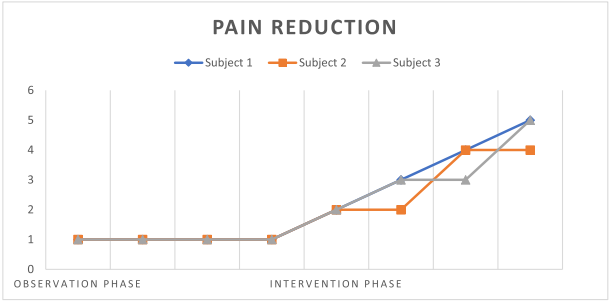

Fig. 4. Sample Multiple Subject Outcome comparison.

Objective driven focus on study designs does away with dogmatic insistence upon the RCT as the most valid source of evidence generation in Ayurveda, and pragmatically incorporates the best available designs to answer the questions at hand. This non-hierarchical approach to clinical evidence generation is not only context-specific, but also incorporates different types of evidence that are more truly representative of Ayurvedic practice at point of care.

7. Conclusion

In summary, many aspects of real-time Ayurvedic clinical practice such as person-specific care, and complex interventions need to be factored into the design of clinical trials in Ayurveda, rendering the dominant RCT model often inadequate. In order to overcome these issues, many researchers have proposed modified RCTs and other trial designs such as the 'black-box' RCT, N-of-1 trials, observational studies, etc. It is clear, however, as discussed above, that study designs must only be selected in accordance with study objectives. There is plenty of scope for newer, more sensitive trial designs, which may also include a combination of methods. In this regard, it is essential that suitable training in research methods and designs be made available to Ayurveda researchers and other concerned stakeholders.

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Conflict of interest

None

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