

"Does one shoe fit all?"

THE RANDOMIZED CONTROLLED CLINICAL TRIAL (RCT) AS A MODEL FOR ASSESSING THE EFFICACY OR EFFECTIVENESS OF WHOLE SYSTEMS AYURVEDA OR OTHER TRADITIONAL MEDICINE (TM) TREATMENTS

The answer is self-evident in the title itself. We readily agree with Professor Patwardhan's editorial,^[1] and like him, we too commend the Department of AYUSH (Ministry of Health and Family Welfare, Government of India) to take steps to promote the research and development of treatments that have emerged from traditional medical practices in India. Quality assurance including, but not limited to, the standardization of herbal preparations (e.g. growing, harvesting, extraction, chemotype specificity), appropriate concentrations of the bioactive moieties,^[2,3] assessments for adulterants, batch to batch reliability of products, details of shelf life, stability, expiry dates, and product labels that disclose basic information to the public including the manufacturer's details will go a long way in allaying skepticism and fears of traditional medicine (TM) treatments.^[4,5] However, Kumar and Bhatnagar ask if the drive to "standardize" herbal products using modern chemical methods risks negating centuries of thoughtful cognitive processes that went into the testing of various products.^[6] So, there is little argument for evaluating the processes of Good Manufacturing Practices (GMP) or of assessing the safety issues of various TM treatments. On the other hand, what is the best approach to assess the efficacy or effectiveness of various treatments in TM?

Small molecules termed "New Chemical Entities" (NCEs) form the basis of most medical treatments licensed and approved for use in various medical illnesses. Since the publication of the use of streptomycin in pulmonary tuberculosis in 1948,^[7] the randomized control trial (RCT; double-blind, and often, placebo-controlled) has been used to test the efficacy and safety of NCEs in various medical disorders, and is considered the gold standard by which other treatments are judged. It is argued that successful randomization avoids (or minimizes) "bias",

facilitates concealment of the treatment assignment (e.g. "blinding"), therefore minimizing "expectancy bias", etc.^[8] In the modern clinical trial, randomization is considered the method (some would argue it to be the "only" method) to guarantee balance across treatment groups with regard to prognostic factors. Consequently, multiple RCTs with roughly equivalent positive results and approximately the same magnitude of treatment effects for an individual NCE (ideally from independent research groups) have increasingly come to represent the "evidence base" for recommending a particular treatment in modern medicine. Can we readily apply the RCT model to evaluate treatments in Ayurveda, Yoga or other TM?

Treatments emergent from Ayurveda have evolved over centuries, for example, herbal extracts may have many bioactive moieties from one plant, but typically and for a specific disorder may include the prescription of combinations of different plant extracts, and so are not "NCEs" as currently defined in biomedicine. Furthermore, practitioners in Ayurveda and other TM treatments take into account individual vulnerability or susceptibility to disease, and/or bodily constitution. For example, they may prescribe a specific diet (including fasting) or massage with an oil along with herbal extracts as part of the treatment regimen. In other words, it is a "selection bias" that in practice acknowledges individual differences due to genetic and/or environmental factors. In recent years, "biomarker" and pharmacogenomic research in biomedicine also acknowledges such genetic and environmental differences at the individual level.^[9] It is hoped that specific biomarkers will help select the "right" patients for the "right" drug, ideas that have been developed in Ayurveda and TM practice over several centuries.

One of the key drivers of the RCT design is what Professor Patwardhan has referred to in his editorial as "clinical equipoise", wherein the assumption is that the clinician genuinely does not know which treatment may be better. This state of affairs may not altogether be surprising given that the small molecule is a "new" chemical entity, and so it has not been utilized adequately in animals and/or humans. Whereas in Ayurveda, generations of humans (i.e. historical controls) have utilized various treatments, and it is argued that those that were harmful or ineffective were weeded out and those

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that were effective were kept and refined, though there are no systematic records of these processes.

This discussion does not suggest abandoning the RCT in evaluating Ayurveda or other TM treatments altogether, but recommends a thoughtful dialog of what may be an appropriate approach to assess the efficacy or effectiveness of these treatments for a certain disorder. Professor Patwardhan has provided suggestions, for example, therapeutic equivalence. Many placebo-controlled RCTs are designed for superiority of an NCE and often require smaller numbers of participants to answer the question of efficacy. Some regulatory agencies prefer non-inferiority RCTs, that is, the new treatment is not inferior to standard allopathic treatment, but this design typically requires very large sample sizes especially for small therapeutic gains and may be cost prohibitive. Therapeutic equivalence may be appropriate for certain illnesses; therefore, is the TM treatment equivalent to the available standard treatment for specific primary and secondary endpoints? Example: Does Yoga provide relief of symptoms in persons with Generalized Anxiety Disorder compared to serotonergic anti-depressants in an RCT? (as “blinding” is difficult, all efforts to mask the assessor of primary or secondary outcomes could be undertaken). If the result is therapeutically equivalent for both treatments, and if there are far fewer side effects for the Yoga treatment group, then a low-cost, “do it at home”, and non-pharmacological option would become available to patients. Nonetheless, other questions may arise: What is a good control group for Yoga, what is the “dosage” of Yoga that is needed to achieve good results, what forms and elements of Yoga are both necessary and sufficient? How do we achieve standardization of Yoga therapy across sites conducting studies, such that eventually when it is disseminated and implemented in practice, the key elements of Yoga are in fact undertaken by the individual practitioner and the patient. Additional issues should be taken into account – what is the therapeutic margin that would be equivalent, for example, $\pm 5\%$ or $\pm 20\%$? Another issue: Scales developed for concepts in Allopathy (e.g. Generalized Anxiety Disorder) may not be appropriate for Yoga and so should alternative Ayurvedic or other TM endpoints be developed instead? Finally, the equivalence trial versus the superiority or non-inferiority trial still does not address the issues of randomization or blinding.

One type of randomization procedure that may be suitable for some Ayurveda and TM treatments, is adaptive randomization, especially outcome-adaptive randomization.^[10] So, for instance, certain herbal extracts were combined with a specific diet and lifestyle changes for some chronic but not imminently life-threatening condition (e.g. chronic medical disorder) and all patients

were assigned to this treatment. Patients could be followed clinically for specific endpoints indicating response and/or remission, then one or more elements of the treatment could be withdrawn in a controlled manner and compared with the group that continues to receive all elements to assess relapses and/or recurrences. This design may especially apply to waxing and waning clinical conditions with multiple episodes. Finally, treatment outcomes in the practice of TM may also be determined by Patient–Provider–Remedy (PPR) entanglement. As has been shown in the practice of Homeopathy, a relationship between all three components must exist for the “curative” response to occur.^[11] It can be argued that practitioner–patient–treatment relationships are important in most systems of health-care practice. This triadic relationship cannot easily be simulated within the confines of an RCT. The alternatives to RCT-based methodologies endorsed by the Cochrane Effective Practice and Organization of Care (EPOC) Group that may be relevant for the evaluation of TM include (1) the non-RCT, (2) the controlled before and after (CBA) study design, and (3) the interrupted time series (ITS) design.^[12] Yet, other pragmatic clinical trial designs which reflect “real world” practice have begun to emerge including the Point-of-Care Trial.^[13,14] Such alternative designs do not solve selection bias but are considered more effective than non-randomized studies. Aicken has argued that randomization brings with it inefficiencies, especially when several prognostic factors are involved.^[15] This can be a serious issue for small sample size studies, and may be especially relevant in Ayurvedic and TM studies where funding constraints may exist. He cogently presents an alternative to randomization – design adaptive allocation, a method that provides balance between treatments and is exceedingly efficient even with multiple prognostic factors.^[15] Importantly and critical to the ongoing development of Ayurveda and other TM treatments is a sound understanding of the biological mechanisms underlying these treatments on various disease parameters; such science needs to be nurtured and fostered in India.

Disease prevention and/or modification (with the exception perhaps of vaccines) have not been the focus of global pharmaceutical company research as the financial rewards are mostly in the area of acute conditions and tied closely to the Intellectual Property protections afforded to NCEs. Here, there may be a significant opportunity for Ayurveda and TM treatments. By way of example, The Orphan Drug Act and the creation of an office within the FDA in 1982 resulted in the US government providing financial and marketing incentives to smaller pharmaceutical companies, grants to academia, and involved professional and patient organizations, and research groups.^[16] The implementation of this legislation resulted in a highly successful program of over 300 drugs or biological products coming to

market for rare diseases, whereas the large pharmaceutical companies had little, if any, monetary interest in developing products for these disorders. In the decade prior to this legislation, only 10 products were brought to market.^[16] If a similar model were to be established for Ayurveda and TM treatments in India, and not necessarily just for “rare” diseases, for example, to test the effectiveness of TM treatments for chronic medical conditions, it could serve as a “game changing” health-care delivery model for these traditional whole system treatments in India. If the Government of India were to assemble a working group of all stakeholders (patients, Ayurvedic and other TM treatment manufacturers, academia, researchers, Ayurvedic and Allopathic hospitals and practitioners among others), such dialog and action could serve as the basis for a successful transformation of the health-care landscape in India. The models of health care in the West with an emphasis on large medical hospital complexes concentrating on acute medical conditions may not be sustainable in India or for that matter even desirable, especially for chronic medical conditions. India with its long history in Ayurveda and TM treatments, and also a strong tradition in biomedicine, is uniquely positioned to “think outside the box”, and institute an effective low-cost health-care delivery model incorporating elements of both biomedicine and TM, especially for chronic medical disorders. Going forward, we hope such innovative thinking will inform regulatory guidelines for Ayurvedic, TM or Allopathic products in India.

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