Ayurveda GCP Guidelines: Need for freedom from RCT ascendency in favor of whole system approach

As a result of the significant interest and growth in Ayurveda, Siddha, and Unani (ASU) medicines and other aspects of the Traditional Medicine (TM) sector, the Department of Ayurveda, Yoga, Unani, Siddha, and Homeopathy (AYUSH), Government of India, is planning to introduce a regulation for Good Clinical Practices (GCP) under Schedule T of the Drugs and Cosmetics Act, 1940. Guidelines are being drafted for the evaluation of ASU medicines and other TM, to encourage Research and Development (R and D) activities in the sector. The purpose of the guidelines is to develop methodologies for research and evaluation; to improve the quality and value of research; to provide appropriate evaluation methods to facilitate the development of regulation and registration in ASU medicines and other TM in a phased manner; and to help promote a better understanding of ASU medicines and other TM. These guidelines are intended to serve as a reference source for research scientists, registered medical practitioners, manufacturers, and health authorities. This exercise initiated by the Department of AYUSH is timely and commendable. However, the proposed guidelines seem to have been drawn up on the basis of Western biomedical approaches, including randomized controlled trials, as necessary evidence. These are mainly related to evaluation of New Chemical Entities (NCE). They appear to be largely based on the standard GCP guidelines previously proposed by the Central Drugs Standard Control Organization and need more attention to the special needs of the ASU sector.

In fact, we need to evolve appropriate guidelines based on the basic principles of Ayurveda where due weightage is given to empirical evidence. The black box approach, pragmatic trials, and the whole system approach of Ayurveda needs to be maintained rather than accepting reductionist methods of treating any symptom or disease condition in isolation. Although safety and quality assurance should not be compromised, the new guidelines need to be revised in light of the debate on the ethics of randomized clinical trials (RCTs) recently published in The New England Journal of Medicine. Miller and Joffe suggest a solution that gained widespread acceptance appeals to the ‘equipoise’, which has assumed canonical status in research ethics (see News and Comment 44 a-b). They suggest five conditions, for which when satisfied, an RCT should not be deemed necessary. Interestingly, their conditions can be generalized and applied to Ayurveda treatments of chronic diseases.

These suggestions have a significant relevance for Ayurveda, especially because of its potential efficacy against chronic diseases, of which some, but not all, may be fatal. Also, Ayurveda advocates the personalized approach in treatment of patients. Moreover, instead of using single chemical entities, Ayurveda uses herbal medicines, and more complex, yet systematically determined regimes of diet (ahara) and lifestyle (vihara), based on increasingly well-understood Ayurvedic physiological principles such as Prakriti. Clearly, the question of the ethical appropriateness of a particular kind of trial to evaluate a given treatment is completely independent of the kind of treatment being considered. Miller and Joffe’s criteria may be generalized to Ayurvedic treatments. The question of whether treatment is drug-based, or herbal, or other is irrelevant.

The first criterion requires compelling arguments, or reasons supporting a hypothesized efficacy of the treatment in question. In the case of Ayurveda, its dosha prakriti theory of disease susceptibility and dosha vikriti approach to etiology are increasingly well understood. These concepts and practices provide well-positioned arguments and reasoning in support of complex Ayurveda treatments. The second criterion requires evidence for large effect sizes from earlier studies. Ayurveda has long-standing historical evidence of safety and efficacy of treatments judged in terms of its own endpoints. This strong empirical evidence may be considered in Ayurveda’s favor. In the case of chronic diseases, the effect size for systematic remission or cure using the present drug treatments is very low. Applications of Ayurveda to chronic disease therefore satisfy the third criterion. The fourth criterion requires a historical control group. The ancestral and present populations receiving traditional treatments provide better clinical assessment than carefully selected members of some contemporary RCT. Finally, the fifth criterion requires recent advances in the scientific appreciation of the theory of Ayurveda’s
fundamental concepts. It is reasonable to judge the success of Ayurvedic treatments in terms of Ayurvedic endpoints and not be limited to endpoints selected by the western biomedicine approach.

Ayurveda treatments have produced significant remission of certain chronic illnesses such as cancer\[12\] and rheumatoid arthritis (RA), where Western medicine has limitations. It is noteworthy that the outcomes of the pilot whole system study comparing the classical Ayurvedic treatment and methotrexate in the management of RA, with funding from National Institutes of Health, has been recently published by *Annals of Rheumatic Disease.*\[13\] Similarly, a systematic RCT of certain Ayurvedic preparations with celecoxib and glucosamine have suggested that equivalence and not superiority is a better study design.\[14-18\] Use of effective and safe Ayurvedic treatments become more important, particularly in cases like RA, where long-term support by single chemical drugs of choice can lead to life-threatening damage to vital organs.\[16\] RA in itself is only life-shortening and not life-threatening. However, it still needs safe and effective options on a fast track. In case of many chronic diseases, life expectancy and quality of life are reduced with a risk of iatrogenic disease. In light of this rationale, RCTs for Ayurveda treatments of chronic disease may not be relevant as Ayurveda satisfies the five criteria proposed in Miller and Joffe’s *NEJM* article.

The proposed ASU guidelines are expected to generate a body of clinical research based on bioethics, transparency in reporting, and lack of scientific bias. Bioethics emphasizes that patients come first and proper efforts are made to ensure respect, justice, and beneficence. Transparency implies a factual reporting of everything that was done in the planning and conducting of the specific clinical research. This is difficult, as factual reporting could result in biased, under-powered or ethically unacceptable research. Scientific unbiasedness is different from unbiasedness that is used generally. As long we know and acknowledge that a designed trial is biased, we have created a body of work that is scientifically unbiased. In other words acknowledging the shortcomings of any trial and transparency in reporting greatly enhances the value of the trial. The Ayurvedic system of medicine has survived and thrived over a long period of time, which is an indication that it works. We need better record keeping to track the effectiveness and safety of the treatment regimen supported by a robust pharmacovigilance program.\[19\] The Ayurvedic pharmacovigilance program should be focused on effectiveness rather than on safety, as is the case with western medicine programs.

Therefore, Indian scientists and regulators should design GCP guidelines after considering the epistemological differences between Ayurveda and Western biomedicine. The conceptual framework for new models of integrative medicine\[10\] and Indian guidelines for GCP must stem from the principles and practices of Ayurveda. If we attempt to do so, the global scientific community should also benefit, where the relevance of RCTs in the light of integrative medicine has already been greatly debated for better alternatives.

We sincerely hope that the Department of AyUSH and other authorities may like to reconsider the proposed GCP guidelines in the best interest of Ayurveda and Traditional Medicine. To foster good clinical research, it is greatly desired that the principles driving these guidelines should be ethics, transparency and scientific unbiasedness. A lot more people are seeking Ayurveda and TM as a treatment system, as it is clinically practiced. Generally, in whole system trials, patients are randomly assigned to treatment alternatives, which may include essentials of *ahara, vihara, panchakarma,* and *ausbudhi,* as prescribed by Ayurveda. Such trials may also evaluate whole system interventions implemented under defined manuals and protocols, to specify individualized treatments based on specific patient characteristics. In such cases, double blinding of the physicians and patients to treatment allocation may not be feasible. However, blinding of the outcomes to the evaluators can ensure an unbiased comparison.

In the conventional RCT model, efficacy is often determined before assessing effectiveness, which is now considered unethical. In case of Ayurveda for instance, patients are already using its treatments and therefore effectiveness studies can guide the necessity of studying the efficacy of specific components. Researchers have voiced this view in several countries over the last few years.\[19,20\] It is also important to note that RCTs are typically designed to minimize Type 1 error and maximize power. Type 1 error minimizes the chances of releasing a bad drug into the market and power maximizes the chance of discovering a good drug. The case of Ayurveda, however, is different as the treatment regimen is already in use. The questions of Type 1 error and power in the traditional sense do not apply. As such observational studies, meta-analyses, case studies and case series, and an effective pharmacovigilance program are much more in keeping with the needs of the situation, it is important to note that even though observational studies or case studies or case series could be biased, as a body of knowledge they are scientifically unbiased. Therefore, rather than performing RCTs of Ayurveda treatments, future research efforts should focus on robust documentation and understanding their mechanisms and their importance as an affordable and safe healthcare system.
Typically, Ayurveda treatments should not need Phase 4 trials. Instead, a robust assessment through systematic documentation and pharmacoepidemiological evidence[21] should suffice. We should learn and quickly adopt appropriate reporting standards on lines similar to Consolidated Standards for Reporting Trials (CONSORT)[22] and several other guidelines, including those for observational studies on traditional medicine research such as Traditional Chinese Medicine (TCM), meta-analyses, and herbal medicines.[23] It is important, however, to recognize that results from such research cannot be used to prove or disprove the effectiveness of ‘whole system’ treatments. Understanding the underlying Ayurvedic biology, physiology, pathology, pathways, and mechanisms through which treatments exercise their benefits is far more important.[24] We need to be certain that these treatments are effective and safe, so it may not be so critical to know their mechanistic aspects at the very beginning. This is how many drugs have found place in modern medicine, the best example being aspirin, where its anti-inflammatory and analgesic properties were recognized long before its mechanism of influencing prostaglandin synthesis was understood.

To summarize, when the world is waking up and seriously debating the need for newer models for clinical research, Indian guidelines for ASU should not get overwhelmed by the RCT approach of biomedicine. Such approaches and protocols for TCM have already been developed and whole systems trials have been attempted.[25] It would be prudent to form a serious working group to evolve appropriate guidelines for clinical revalidation of ASU systems, and not just herbal drugs in isolation. Such Indianized, innovative guidelines on GCP for ASU would not only give due respect, leadership, and a major boost to this sector, but also offer freedom from the over-dominance of RCTs. In addition, patients would gain solace from being given rightful access to safe and affordable healthcare.

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