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Clinical research in traditional medicine: Priorities and methods☆

Francesco Cardini[a,*], Christine Wade[b], Anna Laura Regalia[c], Suiqi Gui[d], Wang Li[d], Roberto Raschetti[a], Fredi Kronenberg[b]

[a] *Istituto Superiore di Sanità, Rome, Italy*
[b] *The Richard and Hinda Rosenthal Center for Complementary and Alternative Medicine, Department of Rehabilitation Medicine, College of Physicians & Surgeons, Columbia, University, New York, NY, USA*
[c] *Obstetrics & Gynecology Department, Hospital S. Gerardo (Monza), Milano Bicocca University, Milan, Italy*
[d] *Obstetrics & Gynecology Hospital, Fudan University, Shanghai, People's Republic of China*

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Summary This paper explores the challenges and opportunities associated with the evaluation of treatments arising from traditional medical systems (TMS). Globalization and popular consumer-and industry-driven market forces contribute to the spread of traditional treatments, techniques and technologies, but do not necessarily ensure their usefulness or safety. The international scientific community is obliged to evaluate the safety and efficacy of these treatments because of their potential impact on global public health. Clinical evaluations of traditional treatments, however, have complex methodological and practical challenges, depending on the goals of the research and the audience for the results (country of origin; or new host countries and new patient populations). To address these challenges, the authors offer the following recommendations to identify and prioritize treatments to study and how to design study protocols. Evaluations of traditional treatments are best addressed first by collaborative, international, pragmatic studies. Protocols for observational, prospective, pragmatic pilot study (randomized and controlled, when feasible) should be designed collaboratively and executed simultaneously in the culture of origin and in new contexts. This, in turn, could determine the acceptability, usefulness and feasibility of larger randomized controlled trials (RCTs). International multicentre RCTs would have the potential benefits of evaluating safety and effectiveness and also assessing the transferability of a traditional treatment across social and cultural contexts.

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* Correspondence to: Via Risorgimento 15, 37126 Verona, Italy. Tel.: +39 045 914266; fax: +39 045 8389990.
E-mail address: cardinif@internetstudio3.it (F. Cardini).

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Traditional medical systems (TMS): safety and efficacy

Traditional medical systems (TMS), of which the most aknowledged and investigated are Traditional Chinese medicine (TCM) and Indian Traditional Medicine (Ayurveda, Sitta, Unani), are used worldwide.[1–5] For centuries, TMS were the primary medical systems in their countries of origin. Despite the present dominance of the Western scientific medical model, TMS are still widely used. In countries such as China and India, where TMS rely on a theoretical literature-based structure, a materia medica and are practiced by a professional class of physicians, TMS are increasingly integrated into the general healthcare system.

Complementary and alternative therapies, which have been introduced more recently, were often created by individuals, or small groups of clinicians or scientists in opposition to and competition with the Western scientific medical model.

In contrast, the stability of TMS through linguistic continuity and durable infrastructures for teaching and practice enables a transfer of empirical knowledge over generations. Cultural rootedness and enduring and widespread use of TMS do not guarantee, but may indicate, the safety and efficacy of the treatments. Long-term and extensive use enables numerous observations of applications repeated over time and, moreover, it favours a process of selection (in a certain sense, ''Darwinian'') of successful treatments because at every transmission (''tradition'') from one generation of therapists to the next, treatments are at risk of adaptation or abandonment.

Treatment selection using traditional medical knowledge may be more efficient for safety (particularly short-term safety) than for efficacy.[6] For example, a traditional doctor's/healer's career would be compromised if prescribed treatments were noxious and such treatments would be abandoned. Treatment selection based on efficacy criteria is likely to be less direct considering the complexity of the concept of efficacy (for example, in cases of chronic or mental pathologies). The last considerations limit but do not eliminate the importance of the enduring and widespread use of traditional treatments. This feature should be required in establishing priorities for clinical research in traditional medicine (TM; see Section: Designs suitable for international multicentre studies of treatments from traditional medicine systems) and has consequences in setting up appropriate methods for this research (see Section: A rational sequence of study designs in traditional medicine).

Globalization of traditional medicine (TM)

The term ''globalization'' describes the increased mobility of individuals, information, goods, services, labour, technology and capital throughout the world. The pace of globalization has increased recently with the advent of new technologies, particularly in telecommunications and transportation.

One of the effects of globalization is the migration of TMS (or parts of them) from their original social and cultural contexts to those that are geographically distant and culturally removed. The pace of the movement of medical traditions has recently accelerated. Transferring a TMS to a new country may lead to modifications to the systems in response to local conditions. These modifications may vary in extent, but it is likely that a few decades after migration, a TMS will have absorbed cultural influences from the host country.[7] At the same time, TMS evolve in their country of origin.

Acupuncture, a technique commonly utilized in TCM, has been extensively investigated,[8] and provides useful information for prioritization in TM research. Acupuncture was introduced to Europe several times as from the 13th Century, if not before,[9] but its use remained limited and did not endure. The practice of TCM acupuncture has become popular in only the last four decades in Western societies. Consequences of transcultural migration include new proposals for mechanism of action and investigative research, innovations and variations in technique, elaboration of styles, divorce from traditional theoretical constructs, application without TCM diagnosis, and adaptation to the values of conventional medicine and/or host cultures. Acupuncture is not currently a uniform practice delivered in the context of classical TCM, but a technique that has been integrated in various forms into a range of medical arenas.[10] Acupuncture styles around the world, and within TCM, have evolved simultaneously. Visitors to TCM hospitals in the People's Republic of China can appreciate the extent of TCM use and its adaptation to a modern medical setting. The integration of TCM with Western medicine in China over the past half century has highlighted the strengths of working within the theoretical structures of TCM, and has brought about useful innovations in the technology of acupuncture, such as acupuncture point injection.[11]

To evaluate the safety and efficacy of such a variety of traditional and traditional-derived treatments initially requires answers to two basic questions: (1) which treatments should be studied? and (2) where should the treatments be studied (i.e. in their country of origin or a new setting)?

How should the study of traditional treatments be prioritized?

Comprehensive investigation by Western clinical researchers of the current state of TMS requires adequate methods to be developed and priorities to be established. Documented history of enduring use in significant segments of the population is a starting point. Moreover, to investigate TM treatments with integrity, collaboration is required between TM clinicians and researchers practising within the traditional social and cultural environments, and those practising within other (''adoptive'') contexts.

Several factors are important in determining the outcome of any treatment, both in clinical practice and in experimental settings, including forma mentis, beliefs, knowledge and practical abilities of the provider, as well as the positive or negative prejudices of the patient with respect to the provider or the therapy, cultural differences in the acceptability of the treatment and adherence to it, the patient—doctor encounter, and differences in access to other treatments. Consequently, in the age of globalisation, assessing transferability of treatments is a relevant goal for clinical research in TM, alongside the common aims of assessing safety, efficacy and public health cost—benefit ratios. International collaborative studies that use a single research protocol to evaluate a treatment in different populations in a variety of settings, including the original setting, are needed to assess transferability.

In countries with integrated conventional and traditional medical systems (like China and India), integrated medical education and research infrastructure, together with increasingly efficient electronic communication, provide a supportive environment for the development of international scientific collaboration. Collaborative studies conducted in multinational research settings with a high degree of scientific integrity, i.e. settings that ensure adherence to defined procedures, adequate sample size and follow up periods, and have knowledge of both TM and Western scientific methods, may become a reality. Ideally, well-conducted and highly regarded published studies with clinically relevant results could influence clinical practice globally.

Research resources for studies of non-conventional medicine are meagre, and defining priorities for the utilization of funds is an arduous task.[12—14] Nahin and Straus[15] from the National Center for Complementary and Alternative Medicine (NCCAM) at the NIH proposed a pragmatic schema for allocation of resources in the United States, which is currently the Western nation with the highest investment in the study of CAM. The authors recommended five criteria: quantity and quality of available preliminary data to help determine the most appropriate type of research; extent of use by the public; public health importance of the disease being treated; feasibility of conducting the research; cost of the research.[15]

These criteria are non-specific and are potentially inclusive of any treatment. To create an agenda that makes sense for treatments coming from TMS, additional criteria for establishing priorities are required (Table 1). The first criterion (see Table 1) is inspired by the characteristics of TMS discussed in Section: *Traditional medical systems (TMS): safety and efficacy* (social and cultural acceptance, widespread and enduring use). The other criteria are specifications for feasibility and are particularly relevant for international multicentre studies and for studies in which verification of the transferability across cultures is an objective.

Designs suitable for international multicentre studies of treatments from traditional medicine systems

Rigorous clinical research methods should be applied to research in TM, as they are in biomed-

Table 1 Criteria for prioritizing international collaborative research opportunities in traditional medicine

Continuous documented use of the treatment in its original social and cultural context, for an enduring period of time and by large segments of the population
Quantity and quality of available preliminary data to help determine the most appropriate type of research
Public health importance of disease being treated
Feasibility of conducting the research (availability of clinical research infrastructure and trained practitioners both in the original and adoptive cultural context)
Low complexity of the treatment
Repeatability of the research design
Cost of research

Adapted from: Ref. [15]

Table 2 Rational sequences of research in conventional and traditional medicine

	Conventional treatment	Traditional treatment
(1) Requirements for consideration	Strong physio-pathological basis (''it could work'')	Widespread and enduring use in clinical practice (''it seems to work'')
(2) Next step	Evaluation of safety and efficacy (''does it work in experimental settings?'')	Pragmatic evaluation of safety and effectiveness (''does it work in clinical practice?'')
(3) Next step (if found safe and useful at step 2)	Introduction in clinical practice; evaluation of effectiveness (''does it work in clinical practice?'')	Evaluation of efficacy; research on mechanism (''has it specific actions? why and how does it work?'')

ical research; however, a broad range of methods should be considered,[16] keeping in mind the differences between explanatory and pragmatic studies, and between the concepts of efficacy and effectiveness.[17]

Explanatory trials evaluate the efficacy of a treatment under controlled conditions that optimize isolation of the treatment effect through design features, such as a control or placebo condition, randomization, standardized treatment protocols, homogeneous samples, and blinding of subjects, providers, and evaluators. These studies often require substantial deviations from ''usual practice'' conditions; for example, by eliminating treatment preferences, or by using specialized providers and settings.

Pragmatic studies,[18–23] unlike explanatory studies, do not provide conclusive information on the specificity of the treatment effect, but they have some interesting characteristics. These studies:

(a) Compare treatments provided in actual clinical settings and not in (partially or totally) artificial ones (as in explanatory trials).
(b) Are more adherent to the routine practice (i.e. potentially more faithful to the tradition) of the treatment under investigation.
(c) Are usually simpler and cheaper than explanatory trials, thus they generally enable longer follow up.
(d) Directly answer the question (fundamental for the clinician): ''should I propose this treatment to a patient for condition X?''
(e) Evaluate the effectiveness of a treatment, rather than its efficacy.

An international multicentre pragmatic study of a traditional therapy (which includes a study site in

Table 3 Phases of clinical research and models for study of traditional medicine

Phase	Purpose	Tool
I	Documentation and description of a traditional treatment	Surveys, ethnomedical research, case studies and review of the available observational data
II	Preliminary evaluation of safety, effectiveness and transferability on a small group of subjects with a defined indication	Observational, prospective, pragmatic, intercultural pilot study — randomized and controlled, if feasible — oriented to set up an RCT protocol
III	Comparative evaluation of safety, effectiveness and transferability	Pragmatic multicentre RCT, versus conventional treatment or no treatment (if no treatment is available)
IVa	Research on efficacy and on mechanism of action	Explanatory RCT, basic science research
IVb	Surveillance after acceptance in the new clinical setting either as an additional option for patients or as integrated part of conventional clinical practice	Long term follow up, pharmacological surveillance, risk-benefit studies

the country of origin of the therapy) could evaluate effectiveness, safety and transferability to other countries/cultures while preserving authentic practice. A Chinese-Italian pilot study on Vitamin K acupoint-injection for primary severe dysmenorrhoea, conduced by the authors, is an example of this research strategy.[24]

Pragmatic studies of treatments selected according to the criteria listed in Table 1 could be used to screen for traditional therapies worthy of further research resources (see Tables 2 and 3). This point of view does not contradict the need for quality studies of TM treatments, such as explanatory randomized trials, placebo controlled when possible.[25,26] Such trials would certainly produce a higher level of evidence, but, given their cost and complexity, should be implemented only when favourable pragmatic evidence has accumulated.

A rational sequence of study designs in traditional medicine

To create a model for integrating TM treatments into evidence-based clinical practice, we should acknowledge that these treatments have been widely used for years in humans. For this reason, the usual procedure of conceiving, evaluating and introducing a new treatment is inverted (Table 2).

Table 3 shows a rational sequence for the evaluation of safety and effectiveness/efficacy of a TM treatment. In this model, clarification of the mechanism of action of a TM is not an essential requirement for its utilization in an integrated system of conventional and traditional medical care. Resources for research on efficacy and on the mechanism of action (the importance of which remains crucial), should be allocated only for treatments with solid pragmatic evidence of safety and effectiveness. The sequence described in Table 3 is hypothetical, and its ability to promote a model of integration that is socially useful and accepted by the scientific community should be adequately tested.

Finally, the authors are aware that there are different opinions about what ''integration'' means and what is the most advantageous and ethical model for the relationship between conventional Western biomedicine and other medical systems. As an example, the concepts of integration and pluralism have been recently discussed and countered.[27] Although it is not an aim of this paper to deal with this important issue, the rational sequence of study designs proposed here could be useful in both perspectives.

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