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Opinion Paper

How can traditional Chinese medicine trials achieve global credibility

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ABSTRACT

Traditional Chinese medicine (TCM) needs credible evidence that meets international evidence-based medicine standards to achieve global credibility and acceptance. A fundamental and crucial task is to conduct high-quality randomized controlled trials (RCTs). To achieve global credibility, TCM RCTs should meet universal standards of scientific rigor, such as addressing clinically important questions, achieving sufficient sample size and minimizing risk of bias, and enhance generalizability through appropriate multicenter and pragmatic designs, including Western centers, populations and trialists. In addition, TCM RCTs face unique challenges. Addressing these challenges through rigorous trial methodology and TCM-specific methodological innovation will be essential for establishing globally credible evidence and facilitating the international integration of TCM.

KEYWORDS

traditional Chinese medicine, evidence-based medicine, randomized controlled trials, global credibility, challenges

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Traditional Chinese medicine (TCM) and Western medicine operate under two distinct epistemologies—ways of knowing what is true. TCM rests on the teachings of ancient clinicians and centuries of accumulated clinical experience, with knowledge summarized from historical practice and transmitted through classical literature and master-apprentice mentorship. In contrast, Western medicine, particularly since 2000, has widely adopted evidence-based medicine (EBM) as a framework to evaluate the likely truth regarding the effectiveness of health care interventions, adverse effects of potentially harmful exposures, patient prognosis, and diagnostic accuracy. In particular, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach provides a detailed formal structure for EBM's approach to determining the truth regarding issues related to clinical decision-making.[1,2]

In recent years, leaders in TCM have become increasingly interested in applying the EBM epistemology to address the impact of health care interventions on patient-important outcomes. Even more recently, TCM leaders have developed a related interest in bringing TCM treatments to the West, allowing people residing there to receive the benefits of those treatments.

Success in bringing TCM to the West will require providing evidence that meets high EBM standards. A fundamental and crucial task is to conduct high-quality randomized controlled trials (RCTs). To achieve global credibility, TCM trials should not only meet universal standards of scientific rigor, but also demonstrate international relevance and address methodological challenges unique to TCM (Figure 1).

1. Meeting general standards of scientific rigor

TCM RCTs should be exemplary both in content and design. First, trialists should choose clinical questions that are important and sufficiently prevalent in both China and the West. Current management for the condition should not be completely adequate, leaving room for improvement. The chosen intervention should be promising but not yet established, with a systematic review confirming its potential.[3] Furthermore, the intervention must be feasible—practitioners must be available in the West—and acceptable to Western patients. Involving patients in trial design and other decisions can help ensure the question's importance and improve adherence.

Experienced trialists should lead the planning of the TCM RCTs and, along with skilled statisticians and data managers, work as a collaborative team to conduct the RCTs. To achieve optimal credibility, at least one of those trialists should have extensive experience in the West and be recognized there as outstanding in ensuring optimal trial design and implementation.

Trials sample size should be sufficient to achieve high statistical power to detect modest treatment effects and avoid prognostic imbalance between groups, on the basis of a formal and context-specific sample size calculation. For binary outcomes with event rates below 10% this will require sample sizes of several thousand patients.

TCM RCTs must adhere to methodological standards of rigorous RCTs and minimize risk of bias. This includes proper generation of random sequence and concealment, blinding of participants, clinicians, data collectors, and outcome adjudicators, and minimizing loss to follow-up.[4,5] Additional key issues include using intention-to-treat analysis, avoiding early termination for benefit, and documenting prognostic balance between groups in known prognostic factors.

2. Demonstrating generalizability

To convince Western clinicians and patients regarding the effect of TCM treatments and support their use in the West, TCM RCTs with a multicenter design—specifically including Western centers—is extremely helpful and essential to ensure generalizability to Western populations. The involvement

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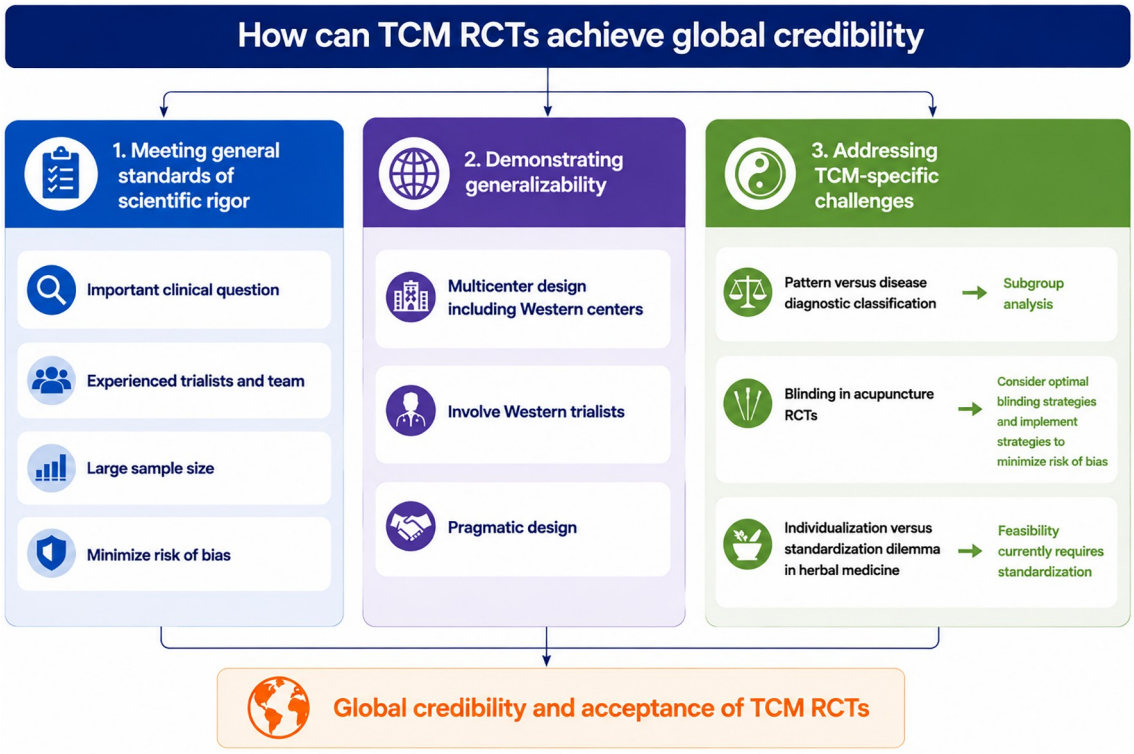

Figure 1 How can TCM RCTs achieve global credibility

Notes: RCTs: randomized controlled trials; TCM: traditional Chinese medicine.

of credible Western trialists provides methodological oversight and local trust, both of which are vital for the trial's acceptance.

The China Tongxinluo Study for Acute Myocardial Infarction (CTS-AMI),[6] the first large (3797 patients), multicenter (124 Chinese hospitals), randomized, blinded, placebo-controlled trial evaluated the effect of Tongxinluo capsules as adjunctive therapy for patients with ST-segment elevation myocardial infarction (STEMI). The CTS-AMI trial reported that Tongxinluo group had lower rates of major adverse cardiac and cerebrovascular events and cardiac death at 30 days and 1 year, with no increase in major bleeding. Although this result suggests the possibility of major benefit, an editorial raised doubts about the use of Tongxinluo outside of China.[7] First, as the CTS-AMI trial enrolled only Chinese patients, the editorialist challenged the generalizability of its findings to non-Chinese populations. In addition, the study population—of which over 90% were classified as Killip class I, with a very low incidence of heart failure or cardiogenic shock—may not represent typical STEMI populations elsewhere. The low rates of recurrent myocardial infarction and emergency revascularization in the placebo group reflect this low-risk population. Furthermore, the editorial raised concerns regarding the adequacy of background medical therapy in the study population, as the reported use of beta-blockers (57%) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (approximately half) appeared relatively low compared with contemporary Western practice. This has raised the question of whether the observed benefit of Tongxinluo would be attenuated in settings where patients receive more comprehensive implementation of guideline-directed medical therapy. Finally, because Tongxinluo is a complex mixture of multiple plant and animal-derived components, its active ingredients, mechanisms of action, potential interactions with conventional therapies, and long-term safety profile remain uncertain.

This example demonstrates that convincing evidence supporting the integration of TCMs into global clinical practice will require conducting multicenter RCTs that include Western populations and centers enrolling representative patients and undergoing optimal Western patient management. It is also likely to require, in addition, understanding of the mechanisms of Chinese herbal medicines, particular ones with multiple potentially active ingredients (the rule among such interventions).

However, conducting multicenter RCTs that include Western centers involves logistical and financial challenges. These challenges may be particularly relevant for TCM interventions, which often involve complex treatment procedures and require appropriate training to ensure consistency across centers. A staged approach, in which promising TCM interventions are first evaluated in rigorous RCTs and subsequently undergo broader international validation when sufficient evidence and resources are available, may represent a pragmatic strategy. However, trialists adopting such a strategy should be aware that, until the RCTs in the West are undertaken, skepticism is likely to persist.

Trialists classify RCTs as explanatory (aim at ideal or optimal setting) or pragmatic (aim at replicating all aspects of how clinicians and patients would use them in clinical practice).[8] If the goal is to inform clinical decision and expand the clinical application of TCM, pragmatic designs are optimal. Pragmatic TCM RCTs should enroll a heterogeneous group of patients varying in age, sex, severity, comorbidity and use of other interventions, should administer the intervention as it will be used in practice rather that how it should ideally be administered, and focus on patient important outcomes. When the trial primarily takes the individual patient's perspective, seeking to inform patients regarding the potential benefits of treatment under conditions of adherence, trialists should implement strategies to optimize adherence, such as use of a run-in period to exclude non-compliant patients.

3. Addressing TCM-specific challenges

TCM RCTs face special challenges that arise from the unique nature of TCM diagnosis and TCM interventions. Here we discuss three major challenges, as well as their possible solutions.

One challenge in all TCM RCTs comes from diagnostic divergence: TCM relies on "patterns," whereas Western medicine uses "disease" classification. Pattern differentiation and treatment, which refers to diagnosing based on a

comprehensive analysis of symptoms and selecting treatment based on the patterns, constitutes a core principle of TCM. In TCM practice, the same disease in different patients, or even in the same person at different stages, may represent different underlying patterns requiring different treatments.

If the goal is to help TCM gain acceptance in the West, enrolling patients in a manner that Western population can understand and accept—that is, adopting the Western disease classification for eligibility criteria in RCTs, would be optimal. This also aligns with the pragmatic design. TCM experts may argue that a TCM intervention is only effective for specific patterns and including patients with different patterns would dilute the treatment effect and may lead to false-negative results and they may be right. To address this issue, a possible solution is to conduct subgroup analysis by patterns. When patterns are both possible effect modifier and prognostic factor, trialists may conduct randomization stratified by patterns.

Trialists can also perform subgroup analysis based on regions, in particular China and other east versus west. Patients in different regions may differ substantially and the skill and training of practitioners who give the intervention (especially acupuncture) may differ. If subgroup analysis suggests similar effect in the two settings, this would strongly support uptake of the intervention in the West. Since patient characteristics are seldom true effect modifier and the credibility of subgroup analysis diminishes with multiplicity,[9] researchers should limit the analyses to only those they truly consider important with clear prior hypotheses, and those particularly relevant to sceptics regarding applicability of TCM to Western settings.[10]

The second challenge, particularly in acupuncture RCTs, is blinding. Constructing a sham acupuncture control that is both indistinguishable from true acupuncture and physiologically inert remains difficult.[11] Superficial needling or needling at irrelevant acupoints, while providing a relatively realistic sensation through skin penetration, may themselves exert therapeutic effects by activating local nerves, and therefore may lead to underestimation of the effect of acupuncture.[12] Non-invasive sham needles can simulate the appearance of real needling, but they are not suitable for acupoints requiring transverse needling (e.g., on the scalp or face). Moreover, the lack of actual skin penetration makes them easily detectable, especially by patients with prior acupuncture experience, leading to failure of blinding.[13] Even the non-penetrating placebo needles may not be fully physiologically inert.[14] Blinding operators who actively deliver acupuncture is even more difficult. Although people have designed a few devices aiming for achieving blinding of both patients and operators, they have not been widely used or validated.[15,16] Researchers have proposed approaches to testing blinding success; however, due to methodological uncertainties regarding the interpretation of these assessments, their use remains controversial.[17]

Since blinding is inherently challenging in acupuncture RCTs, trialists should implement strategies to minimize the risk of bias arising from unblinding. When participant blinding cannot be maintained, standardized communication and follow-up procedures may help reduce differential expectations and patient-initiated co-interventions. Because blinding of operators is generally infeasible, trialists should limit unnecessary interactions between the operators and patients outside intervention delivery. Data collectors who follow up the patients, outcome assessors, statisticians, and investigators interpreting the results should remain blinded.

The third challenge, particularly in Chinese herbal medicine trials, arises from the individualized nature of TCM practice.[18] Traditionally, TCM practitioners often prescribe Chinese herbal medicine as multi-herb formulas tailored to each patient's specific pattern and constitution, and adjust preparation methods accordingly,[19] a level of personalization that is, at least for now, nearly impossible to replicate in Western clinical settings. Currently, a growing number of TCM products are manufactured as standardized finished dosage forms, including pills, granules, and tablets, known as proprietary Chinese medicines. The standardization ensures consistency, reproducibility, and regulatory acceptability, prerequisites for conducting RCTs in Western countries. However, this standardization comes at the cost of the individualized flexibility inherent in traditional decoction-based practice, which may be necessary for optimal benefit.

4. Conclusions

For TCM to achieve global credibility and acceptance, researchers need to embrace rigorous EBM epistemology and conduct high-quality RCTs that meet internationally recognized standards, including choosing appropriate clinical questions, involving experienced trialists, enrolling large number of patients and minimizing risk of bias. To ensure generalizability of the trial results to the West, a multicenter design that includes Western centers and Western trial experts is crucial. In addition, TCM RCTs should use pragmatic design in which patients and interventions simulate those seen in practice, and outcomes are those most important to patients.

Beyond these general requirements, trialists and methodologists need to address TCM-specific challenges, including the pattern versus disease diagnostic classification (subgroup analysis presents a possible solution), the blinding in acupuncture RCTs (careful consideration of optimal blinding strategies), and the individualization versus standardization dilemma in herbal medicine (accepting that feasibility currently requires standardization). Meeting general scientific and global credibility requirements and addressing TCM-specific methodological innovation will be the key for TCM to successfully integrate into global community.

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Data Availability

Not applicable.

Author Contribution Statement

Ying Wang: Conceptualization, writing – original draft, visualization, and writing – review & editing. **Gordon Guyatt:** Conceptualization, supervision, writing – original draft, and writing – review & editing.

Use of AI Statement

None.

Declaration of Competing Interest

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