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COMMENTARY

Reconciling Methodological Paradigms Toward More Accurate Evaluation of Personalized Traditional Chinese Medicine (TCM) Intervention in Standardized Trials: Introducing the TRIPLE-TCM Trial Framework

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Abstract: Traditional Chinese Medicine (TCM) prioritizes highly individualized diagnosis and treatment, a principle that inherently conflicts with the standardized protocols of explanatory randomized controlled trials (RCTs). While pragmatic RCTs have been proposed to better reflect real-world TCM practice, their reliance on unblinded designs raises concerns about placebo effects and potential confounding biases, particularly for interventions like acupuncture. These methodological tensions highlight the need for innovative trial designs that can preserve TCM's personalized ethos while meeting the rigorous standards of evidence-based research. In response, we propose the ***T**rans-paradigm **R**andomized-**I**ndividualized-**P**reference-**L**inked **E**fficacy/**E**ffectiveness **E**valuation for TCM* (TRIPLE-TCM) framework—a hybrid trial design integrating explanatory RCTs, pragmatic RCTs, and partially randomized patient preference trials. TRIPLE-TCM employs a five-step procedure: (1) TCM pattern-guided recruitment to ensure diagnostic homogeneity; (2) hybrid randomization accommodating patient preferences; (3) semi-standardized interventions combining fixed core prescriptions with individualized adjustments; (4) a clinician-patient co-assessment model incorporating TCM-specific outcomes and validated biomarkers; and (5) cost-utility analyses to inform policy. This framework aims to balance internal and external validity while maintaining fidelity to TCM theory and clinical practice, providing a methodological bridge for TCM's broader acceptance. Further studies should validate its feasibility, reproducibility, and cross-cultural generalizability across diverse disease contexts and healthcare settings, advancing evidence-based integration of acupuncture and Chinese herbal medicine into global healthcare systems.

Keywords: explanatory RCTs, pragmatic RCTs, randomized controlled trials, evidence-based medicine, TCM standardization, efficacy and effectiveness

Research Background and Commentary Objectives

In traditional Chinese medicine (TCM) practice, clinical decision-making follows the principle of "Pattern Identification and Treatment" (known as "*Bian Zheng Lun Zhi*" in Chinese).[1] TCM theory posits that a single disease may present with multiple patterns. Using the four diagnostic methods—inspection, listening and smelling, inquiry, and pulse-feeling and

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palpation—practitioners identify the patient's specific TCM pattern and guide treatment.[2] Since these patterns evolve dynamically, herbal or acupuncture prescriptions are adjusted accordingly,[3] underscoring the highly individualized nature of TCM practice.

Despite millennia of practical application in China, TCM modalities such as acupuncture[4] and Chinese herbal medicine[5] have yet to attain broad global acceptance. This limited recognition largely stems from two factors: the scarcity of high-quality clinical evidence due to methodological flaws and the suboptimal implementation in earlier studies, and an incomplete understanding of their mechanisms of action.[4,5] In non-Asian cultural contexts, TCM encounters additional barriers to integration into mainstream healthcare systems, including unfamiliarity with its theoretical foundations, inconsistent regulatory frameworks, and divergent standards for scientific validation.[6] Consequently, research efforts have focused on generating robust evidence, accumulating empirical data, and elucidating mechanisms to inform clinical decision-making and policy development.[7] The rise of evidence-based medicine has offered a potential turning point, encouraging the use of explanatory randomized controlled trials (RCTs)—prioritized as the gold standard for generating high-level evidence[3]—to evaluate TCM interventions such as compound herbal formulas and acupuncture. Nevertheless, a fundamental tension exists: the standardized interventions and strict variable controls inherent in explanatory RCTs are misaligned with TCM's individualized approach.[3,8] Thus, while explanatory RCTs provide a structured method for assessing TCM efficacy, they fail to reflect its real-world clinical practice,[1,9] impeding progress in TCM research and international recognition of its therapeutic value.

Hu et al recently addressed this issue in an article published in this journal, proposing a new research paradigm centered on pragmatic RCTs.[8] Their paradigm emphasizes patient-preference-based randomization to gather real-world evidence. While we acknowledge this innovative contribution, we have reservations about certain aspects of their proposal.

This commentary aims to: (1) critically evaluate the paradigm proposed by Hu et al; (2) discuss whether TCM interventions are better suited to be evaluated in explanatory or pragmatic RCTs ; and (3) introduce an innovative RCT framework developed by our multidisciplinary research team to further reconcile the "Individualization/Standardization Contradiction" in TCM trials.

Divergent Perspectives on Hu et al's Pragmatic RCT Framework

Hu et al propose a research framework centered on pragmatic RCTs,[8] positioned in contrast to explanatory RCTs.[10] Both designs have been used in TCM research,[3] but differ significantly in attributes and inferential goals (see Table 1).

Table 1 Comparison of Key Features Between Explanatory and Pragmatic RCTs in TCM

Domain	Explanatory RCT	Pragmatic RCT
Primary Research Objective	Evaluate "efficacy"—determine the intervention's effect under ideal and controlled conditions, focusing on mechanistic outcomes	Assess"effectiveness"—measure the intervention's impact in real-world clinical settings, emphasizing practical applicability
Study Setting	Highly controlled environments (eg, specialized TCM research centers with standardized protocols)	Routine clinical practice settings (eg, hospitals, community clinics) with typical care conditions
Sample Size	Comparatively small	Comparatively large
Participant Selection	Strict inclusion/exclusion criteria; homogeneous sample with high adherence potential; excludes comorbid or complex cases	Broad, inclusive criteria; heterogeneous sample representing diverse patient populations, including those with comorbidities
Randomization	Highly stringent randomization (eg, centralized randomization systems, stratified randomization)	More flexible randomization (eg, cluster randomization, adaptive randomization)

(*Continued*)

Table 1 (Continued).

Domain	Explanatory RCT	Pragmatic RCT
Intervention Delivery	(1) Standardized and protocol-driven intervention (eg, fixed herbal formula or acupuncture technique) (2) Delivered by trained specialists (3) Strict adherence and fidelity monitoring	(1) Individualized or flexible treatment protocol (eg, individualized herbal prescriptions or acupoints) (2) Delivered by routine practitioners (3) Protocol deviations permitted with documentation
Control/ Comparator	Placebo-controlled (eg, inert herbal preparations or placebo/ sham acupuncture) to isolate intervention effects	Active comparator (eg, standard Western medicine) or usual care, waitlist control, or alternative usual practice
Outcome Measures	Emphasis on objective biomarkers, physiological parameters, or intermediate outcomes	Emphasis on patient-reported outcomes, functional improvements, and QoL measures
Study Duration & Follow-Up	(1) Short-term (eg, weeks to months) to capture immediate treatment effects (2) Patients are followed at frequent intervals and given detailed checklists of side-effects	(1) Medium- to long-term (eg, months to years) to evaluate sustained outcomes and safety (2) Patients are followed at very varying intervals according to haphazard practice
Internal Validity	High (ie, due to strict control of confounders and standardized procedures, strong causal inference is possible)	Relatively lower (ie, greater heterogeneity and flexibility in intervention may introduce bias and reduce internal control)
External Validity (Generalizability)	Limited generalizability due to artificial settings and strict controls (ie, primarily informs biological plausibility)	High external validity (ie, findings are applicable to everyday clinical decision-making and health policy)
Statistical Analysis	Emphasis on ITT or PP analysis to maximize internal validity	ITT analysis prioritized; may include subgroup analyses to address heterogeneity
Regulatory Relevance	Often used for initial proof-of-concept or regulatory approval (eg, FDA or NMPA)	Inform clinical guidelines and health policy decisions.

Abbreviations: ITT, Intention-To-Treat; PP, Per-Protocol; QoL, Quality-of-Life; RCT, Randomized Controlled Trial; TCM, Traditional Chinese Medicine.

Their model emphasizes: (1) patient-preference-based grouping, (2) standard Western medical treatment as the control, and (3) enhanced TCM intervention methods. Although this model demonstrates conceptual novelty and applied relevance, we identify methodological and practical limitations through a comparative framework analysis. This analysis involved evaluating Hu et al's model against existing explanatory RCT, pragmatic RCT, and patient-preference trial (PPT) framework across dimensions such as research design principles, clinical relevance, and practical feasibility.

Regarding "Grouping by Patient Preferences"

Hu et al advocate for group allocation based on patient preferences in TCM pragmatic RCTs,[8] representing a conceptual conflation between trial designs. Trials that assign participants according to preference, including partially randomized patient preference (PRPP) designs, fall under the category of PPTs.[11] Unlike pragmatic RCTs, PPTs do not adhere to the core principle of random allocation. Although PRPP paradigm incorporate patient preferences while guaranteeing group balance through partial randomization,[12] their primary aim is to improve recruitment and compliance and to minimize the influence of patients' preferences on study outcomes[13]—an objective distinct from that of pragmatic RCTs, which focus on estimating intervention effectiveness in real-world settings.[14]

We acknowledge that most TCM RCTs are conducted in TCM hospitals, where patients often hold strong preferences for TCM therapies,[8] making recruitment particularly challenging.[12] To address this, we recommend a phased methodological approach: initial implementation of a rigorously designed single-center trial within a TCM hospital setting, employing proactive management of patient preferences through transparent communication, waitlist-controlled designs, or guaranteed post-trial TCM access for control group participants. Our previous trial experience confirms that this approach enables feasible participant recruitment without substantial delays, even among populations with treatment preferences. Following demonstration of feasibility, safety, and preliminary efficacy outcomes, subsequent expansion to multicenter trials incorporating diverse settings (including Western medicine hospitals and community health centers)

would enhance generalizability and minimize selection bias. This sequential methodology ensures practical implementation while maintaining alignment with the ultimate objective of conducting methodologically rigorous and broadly representative RCTs.

Regarding "Control with Standard Western Medical Treatment"

While we endorse Hu et al's recommendation to use standard Western medical treatment as control in pragmatic RCTs,[8] their supporting citation requires careful consideration. The cited RCT regarding electro-acupuncture for female stress urinary incontinence (SUI) employed a Streitberger-like placebo needle[15]—contradicts their argument.[8] Such placebo devices[15,16] do not constitute standard Western care control. Evidence-based treatments for female SUI include pelvic floor exercises (Kegels), topical estrogen, neuromodulation, and/or surgical options such as sling procedures or urethropexy.[17]

Regarding "Enhancing TCM Intervention Methods"

Hu et al propose converting TCM decoctions into granules or capsules to address challenges such as preparation time, storage challenges, and strong taste, thereby standardizing interventions and reducing patient burden.[8] While this perspective holds merit, we offer several counterpoints.

First, encapsulated TCM formulations are typically highly processed commercial Chinese polyherbal preparations (CCPPs) produced by pharmaceutical companies.[18] Unlike individualized decoctions, CCPPs follow fixed formulas, potentially undermining the personalized therapeutic approach central to TCM practice.[19]

Second, the use of dispensing granules (single-herb extracts) in clinical trials remains contentious due to ongoing concerns regarding their therapeutic equivalence with traditional decoctions.[20] The efficacy discrepancies may stem from chemical differences rooted in divergent preparation methods: Traditional decoctions involve co-boiling herbs, whereas dispensing granules are individually extracted and later combined, potentially altering bioactive profiles.[21] For instance, a Hong Kong study comparing *Sanhuang-Xiexin-Tang* in decoction and granule form revealed significant compositional differences, with key compounds (eg, berberine, epiberberine, baicalin, wonogoside and emodin) present only in the traditional decoction.[20] Additionally, TCM theory emphasizes herb-herb compatibility achieved through co-decoction, which may enhance efficacy and reduce toxicity—an effect not replicable with single-herb granules.[21] Whether the lack of this process compromises safety remains unclear.[21] Therefore, granules may not accurately represent the clinical effects and safety profile of traditional decoctions in TCM trials.

As an alternative, commissioned decoctions may better balance intervention standardization and patient convenience in the trial. Unlike self-prepared decoctions which are labor-intensive and prone to variability affecting therapeutic outcomes,[22] commissioned decoction services—typically conducted by certified dispensers using automated decoction equipment and standardized extraction parameters—ensure both consistency and convenience. These decoctions are vacuum-packed under sterile conditions, allowing for improved storage and portability.[22,23] By maintaining fidelity to traditional methods while eliminating subjective preparation factors,[23] commissioned decoctions offer a viable solution for clinical trials without compromising therapeutic integrity.

Explanatory vs Pragmatic RCTs: Which Trial Design Suits TCM Evaluation?

Analysis of *ClinicalTrials.gov* data (2021–2024) indicates that most registered TCM RCTs employ explanatory RCT designs, adhering to randomization, parallel control, and blinding principles.[8] The explanatory RCT approach rigorously controls confounders to test causal hypotheses under idealized settings, thereby assessing intervention efficacy.[24] However, this design often overlooks the individualized, pattern-based modifications inherent to real-world TCM practice, compromising external validity.[24]

Pragmatic RCTs enhance the generalizability (external validity) of results through broad eligibility criteria and real-world clinical settings, and systematically address patient-centered outcomes by focusing on clinically meaningful endpoints and patient-reported outcomes (PROs) as core measures (Table 1). However, relying solely on pragmatic

RCTs also presents challenges. Specifically, while pragmatic RCTs better reflect clinical reality,[24] the frequent absence of placebo controls and blinding procedures obscures the distinction between specific and nonspecific treatment effects.[25,26] This is particularly problematic for acupuncture, whose therapeutic legitimacy remains debated, with critics attributing its effects to placebo.[27] Placebo controls additionally mitigate confounding factors such as statistical regression to the mean and spontaneous remission.[26] Furthermore, pragmatic RCTs require large sample sizes and extended follow-up to generate reliable evidence, substantially increasing costs.[28] These challenges are exacerbated in non-East Asian contexts, where limited familiarity with TCM complicates recruitment and implementation.[29]

Given these constraints, neither explanatory nor pragmatic RCTs alone suffice for robust TCM evaluation. A sequential design offers a viable alternative:[30] an initial explanatory RCT establishes efficacy under controlled conditions, followed by a pragmatic RCT to evaluate real-world effectiveness. This approach positions the pragmatic RCT as a complement to, rather than a substitute for, explanatory RCT, offering a more comprehensive evidence base.[30,31]

Beyond sequential application, we propose—primarily for cost-efficiency—integrating explanatory and pragmatic RCT elements into a unified hybrid framework. This model, detailed subsequently, aims to incorporate classical TCM diagnostic and therapeutic features within an RCT structure, capturing both the strengths and weaknesses of TCM interventions from a "real world" perspective.

In addition, several studies have examined trial designs that transcend the traditional "explanatory-pragmatic" dichotomy to better accommodate the inherent complexity of evaluating TCM interventions. Beyond the PRPP designs discussed earlier, other approaches such as cluster RCTs (suitable for clinic-based TCM services),[32] N-of-1 trials (appropriate for highly individualized TCM treatments),[33] and adaptive trials (enabling predefined modifications based on interim results, thus facilitating efficient evaluation of multicomponent TCM interventions)[34] have been implemented in specific contexts. These methodological innovations underscore that no universally "perfect" trial design exists; rather, design selection or integration should be guided by the research question, intervention characteristics, and implementation context.

TRIPLE-TCM: A Trans-Paradigm Framework for TCM Clinical Trials

To bridge the gap between individualized care and scientific validation in TCM clinical research, our team proposed a conceptual research framework—**TRIPLE-TCM** (**T**rans-paradigm **R**andomized-**I**ndividualized-**P**reference-**L**inked **E**fficacy/**E**ffectiveness **E**valuation for **TCM**, see Table 2). This conceptual framework integrates key elements from three established RCT designs: explanatory RCT, pragmatic RCT, and PRPP trial. As outlined in Figure 1, TRIPLE-TCM

Table 2 Definition of the "TRIPLE" Acronym

Letter	Term	Definition/Explanation
T	**T**rans(-paradigm)	Integrates key elements from three research classical RCT paradigms: • *Explanatory RCT* (Causal inference under highly-controlled conditions) • *Pragmatic RCT* (Ecological validity in real-world settings) • *Partially Randomized Patient Preference* (patient-centered individualized care) *This hybrid approach bridges methodological gaps between controlled and real-world evidence
R	**R**andomized	Embeds the gold-standard explanatory RCT component: • Central randomization • Double-blind design (patient/assessor-blinded) using matched placebo (placebo decoction/Streitberger acupuncture)
I	**I**ndividualized	Reflects treatment individualization in real-world TCM practice (*Pattern Identification and Treatment*) as advocated by pragmatic RCT

(*Continued*)

Table 2 (Continued).

Letter	Term	Definition/Explanation
P	**P**reference(-embedded)	Embeds a non-randomized preference cohort to model authentic patient choices behaviors in clinical settings
L	**L**ongitudinally-linked	Tripartite data linkage analysis (2 randomized arms + 1 non-randomized cohort) via • Baseline Characteristic Matching • Mixed-effects Modeling • Time-Effect Curve Comparisons
E	**E**fficacy/**E**ffectiveness (**E**valuation)	Assesses both: • Efficacy (Controlled trial outcomes) • Effectiveness (Real-world performance)

Notes: "TRIPLE" also signifies the number "3", representing that this research framework is an innovative design integrating elements from three classic RCT paradigms (*Explanatory RCT, Pragmatic RCT* and *Partially Randomized Patient Preference*). Additionally, it indicates that three study arms (2 Randomized + 1 Non-Randomized Cohort) require integrated data analysis.
Abbreviations: RCT, Randomized Controlled Trial; TCM, Traditional Chinese Medicine.

offers a five-step procedure for trial design and implementation, which was developed through a systematic and multi-stage process. Initially, our core multidisciplinary team—including TCM clinicians, educators, methodologists, and clinical psychologists—identified key methodological challenges in current TCM RCTs through an interdisciplinary workshop. Building on this, we drafted the fundamental components of the TRIPLE-TCM framework based on our team's prior clinical trial experience and extensive literature review. To ensure the framework's rigor, generalizability, and feasibility, we expanded the discussion by forming an extended expert consensus panel. In addition to the core team

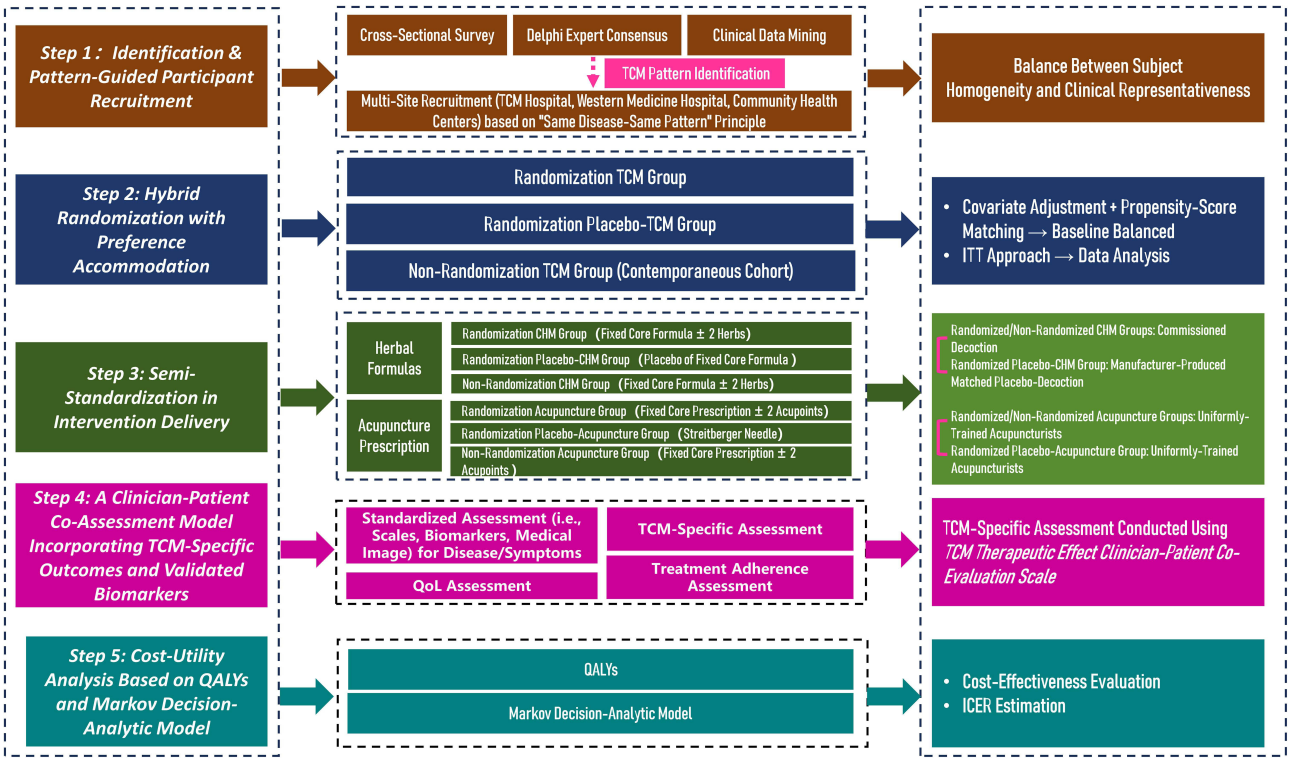

Figure 1 Implementation Process of TRIPLE-TCM.
Abbreviations: CHM, Chinese Herbal Medicine; ICER, Incremental Cost-Effectiveness Ratio; ITT, Intention-To-Treat; QALYs, Quality-Adjusted Life Years; QoL, Quality of Life; TCM, Traditional Chinese Medicine.

members, this panel included biostatisticians, Western medicine physicians, health economists, evidence-based medicine specialists, health policy makers, clinical research managers, and patient representatives. Through three rounds of online interdisciplinary workshops, the five-step procedure and its core elements were iteratively reviewed and refined, resulting in a high level of consensus.

Step 1: TCM Pattern Identification & Pattern-Guided Participant Recruitment

To enhance diagnostic objectivity in TCM trials, TRIPLE-TCM begins with an integrative identification of core TCM patterns for a target disease through cross-sectional surveys, Delphi expert consensus, and clinical data mining techniques such as machine learning–based clustering. Patient recruitment is then guided by a strict "Disease-Pattern Model", requiring participants to share both the same biomedical diagnosis and a standardized TCM pattern.[24] This "One-disease–One-pattern" framework ensures a highly homogeneous sample while allowing for the presence of a single minor concomitant pattern per participant to preserve clinical representativeness. These secondary patterns are treated as stratification variables in subsequent statistical analyses.

Step 2: Hybrid Randomization with Preference Accommodation

A hybrid randomization scheme is adopted to preserve scientific rigor while accommodating patient preferences. Eligible participants are encouraged to undergo randomization into either an active TCM group (herbal or acupuncture) or a corresponding placebo control group. Those declining randomization due to strong treatment preferences are assigned directly to a non-randomized active TCM arm. This results in three parallel cohorts: randomized TCM, randomized placebo-TCM, and non-randomized TCM. Baseline imbalances between groups are addressed through both covariate adjustment and propensity-score matching.[35] All arms are analyzed under an intention-to-treat approach, with the non-randomized cohort providing additional insights into how patient preference may moderate treatment outcomes, including potential dose–response effects based on preference strength.

Step 3: Semi-Standardization in Intervention Delivery

Interventions are delivered using a semi-standardized protocol, combining a fixed core prescription targeting the primary TCM pattern with up to two individualized adjustments (herbs or acupoints) based on each participant's minor pattern. In both randomized and non-randomized active TCM arms, clinicians are permitted to modify herbal formulas or acupuncture prescriptions within predefined limits. The placebo arms receive a standardized, non-modifiable sham intervention. Herbal treatments are prepared through commissioned decoction to ensure consistency, while matched placebo decoctions employ GMP-certified, sensorily indistinguishable preparation (ie, plant-flavored solution without any pharmacological activity). For acupuncture, two to three experienced practitioners—trained to adhere to a standardized protocol (eg, consistent needle placement, depth, and manipulation techniques in accordance with STRICTA guidelines[36])—administer the treatments to ensure consistency while accounting for practical constraints such as clinical duties and leave. Patient blinding is achieved using Streitberger placebo needles inserted at non-acupoint locations, positioned 0.5 *Cun* lateral to the real acupoints (see Figure 2).

Step 4: A Clinician-Patient Co-Assessment Model Incorporating TCM-Specific Outcomes and Validated Biomarkers

Outcome evaluation encompasses clinical efficacy, quality of life (QoL), and treatment adherence.

Efficacy is assessed using both standardized biomedical instruments and questionnaires (eg, polysomnography and PSQI for insomnia; FPG, PPG and HbA1C for diabetes) and a novel TCM-specific scale—the "TCM Therapeutic Effect Clinician-Patient Co-Evaluation Scale", which was proposed by our team (see Table 3). This instrument, jointly completed by patients and clinicians, captures both subjective and objective dimensions of therapeutic response. Patients self-report their primary and secondary symptoms along with vital functional indicators central to TCM diagnostics (eg, appetite, pain, bowel and urinary habits, sleep, sweating, and, for women, menstruation and leukorrhea). Clinicians contribute structured assessments of clinical signs, tongue and pulse manifestations, overall condition,

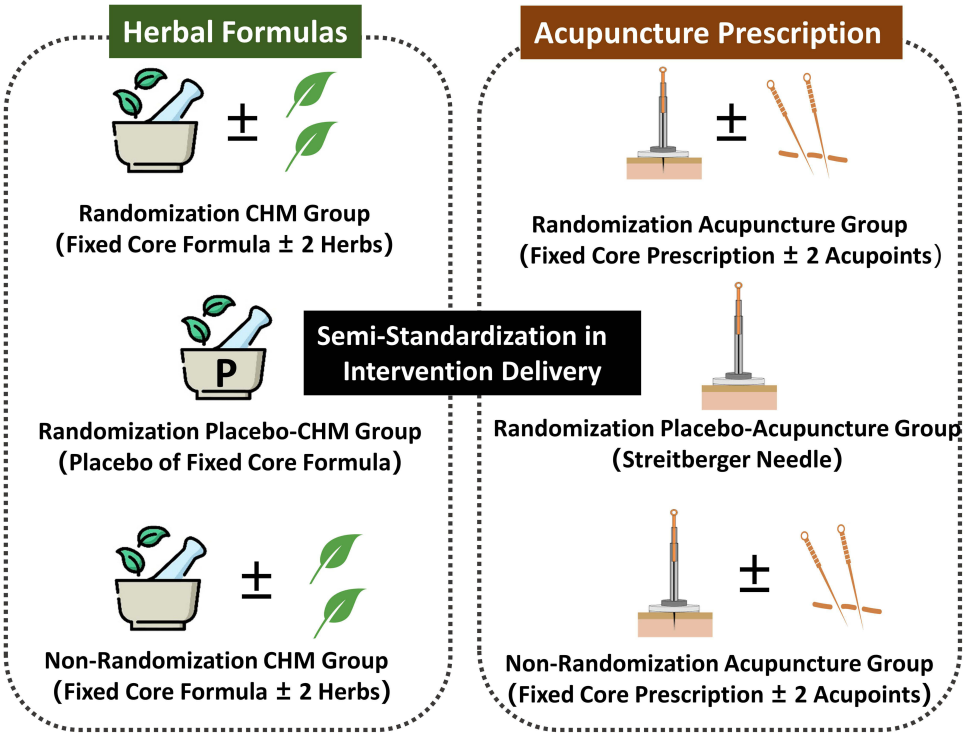

Figure 2 Protocol for Delivering Semi-Standardized Interventions. The images have been adapted from *Vecteezy* under the *Creative Commons CC-BY license*.
Abbreviation: CHM, Chinese Herbal Medicine.

therapeutic response, and any adverse events observed. The integration of patient-reported components aligns with contemporary trends emphasizing PROs.[37] Given that many complementary and alternative therapies are designed to alleviate symptoms and enhance overall well-being, PROs are particularly well suited for evaluating their effectiveness.[38]

Table 3 TCM Therapeutic Effect Clinician-Patient Co-Evaluation Scale

Patient-Reported Section	***Instructions***: Please complete the "Patient-Reported Section" based on your experience over the past 2 weeks. (1) In the "**Main Symptoms**" section, list 1–3 of your most bothersome symptoms (physical or psychological). Additional symptoms can be listed under "**Secondary Symptoms**" (unlimited entries). Rate each symptom's severity using the 0–5 points. (2) In the "**TCM Vital Functional Indicators**" section, rate the severity (0–5 points) of symptoms related to pain, bowel/urinary function, appetite, sleep, sweating, and (for women) menstruation or vaginal discharge. ***Notes***: Scoring Criteria (0–5 points) for *Main/Secondary Symptoms* and *TCM Vital Functional Indicators* 0 - Asymptomatic: Complete absence of symptoms with no impact on daily activities. 1 - Minimal: Barely noticeable symptoms under specific conditions (eg, when focusing); no impact on daily function. 2 - Mild: Noticeable but transient symptoms; no significant disruption to daily life. 3 - Moderate: Obvious symptoms that interfere with certain daily activities, but remain tolerable. 4 - Severe: Persistent symptoms with significant impairment to daily function; medical attention required. 5 - Very Severe/Disabling: Intolerable symptoms completely preventing daily activities; urgent care needed.					
Main Symptoms	Baseline/Pre-Treatment	The n^{th} Intervention	End of Treatment	1^{st} Follow-Up	2^{nd} Follow-Up	n^{th} Follow-Up
(1) X X X	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
(2) X X X	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
(3) X X X	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
Secondary Symptoms	Baseline/Pre-Treatment	The n^{th} Intervention	End of Treatment	1^{st} Follow-Up	2^{nd} Follow-Up	n^{th} Follow-Up
(1) X X X	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
(2) X X X	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5

(*Continued*)

Table 3 (Continued).

… …	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
TCM Vital Functional Indicators	Baseline/Pre-Treatment	The n^{th} Intervention	End of Treatment	1^{st} Follow-Up	2^{nd} Follow-Up	n^{th} Follow-Up
(1) Pain	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
(2) Constipation/ Diarrhea	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
(3) Urinary Symptoms	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
(4) Appetite	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
(5) Sleep Quality	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
(6) Spontaneous Sweating	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
(7) Night Sweats	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
(8) Menstrual Characteristics (if applicable)	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
(9) Vaginal discharge (Leukorrhea) (if applicable)	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5	0 1 2 3 4 5
Physician Evaluation Section	***Instructions:*** (1) In the "**Clinical Signs**" section, list all observable clinical signs relevant to the patient's condition (unlimited entries). Rate each using the following 0–4 points: 0 - Absent: No abnormal findings. 1 - Minimal: Subtle findings not requiring treatment. 2 - Mild: Detectable findings not requiring urgent intervention. 3 - Moderate: Clinically relevant abnormalities requiring monitoring. 4 - Severe: Life-threatening signs needing urgent intervention. (2) In the "**Tongue and Pulse Characteristics**" section, score based on the following (*Notes*: Tongue Diagnosis should be evaluated comprehensively, taking into account tongue body, coating, color, shape, etc.): 0 - Normal: No abnormalities. 1 - Mild Abnormality: Slight deviations. 2 - Moderate Abnormality: Clear pathological signs. 3 - Marked Abnormality: Typical pathological presentation with TCM pattern correlation. 4 - Severe Abnormality: Critical presentation, indicating severe disease progression. (3) In the "**Overall Impression on Patient's Changes**" section, (a) Evaluate patient's "**Severity of Condition**" based on your overall clinical impression using the following: 0 - Asymptomatic: No signs of illness; completely healthy state 1 - Mild: Minimal disease impact; no functional limitations. 2 - Moderate: Clear disease manifestations with partial functional restrictions. 3 - Marked: Significant disease burden impairing most daily functions. 4 - Severe: Critical illness causing complete functional disability. (b) Rate the "**Therapeutic Effect**" based on your overall clinical impression using the following: 4 - Excellent improvement: Complete resolution of symptoms with full functional recovery. 3 - Significant improvement: Marked alleviation of symptoms. 2 - Moderate improvement: Partial symptom relief. 1 - Minimal improvement: Slight symptomatic benefit. 0 - No effect/Worsening: No observable improvement or disease progression. (4) In the "**Adverse Events (AEs)**" section, record all AEs (unlimited entries) that are either reported by the patient or observed by the clinician and deemed related to the treatment. Score each as follows: 0 - None: No AEs detected. 1 - Mild: requires no intervention (continue monitoring). 2 - Moderate: Tolerable but necessitates trial discontinuation. 3 - Severe: Medically significant; requires hospitalization or urgent treatment.					

(*Continued*)

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Table 3 (Continued).

Clinical Signs	Baseline/Pre-Treatment	The n^{th} Intervention	End of Treatment	1^{st} Follow-Up	2^{nd} Follow-Up	n^{th} Follow-Up
(1) X X X	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
(2) X X X	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
… …	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Tongue and Pulse Characteristics	Baseline/Pre-Treatment	The n^{th} Intervention	End of Treatment	1^{st} Follow-Up	2^{nd} Follow-Up	n^{th} Follow-Up
(1) Tongue Appearance	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
(2) Pulse Manifestation	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Overall Impression on Patient's Changes	Baseline/Pre-Treatment	The n^{th} Intervention	End of Treatment	1^{st} Follow-Up	2^{nd} Follow-Up	n^{th} Follow-Up
(1) Severity of Condition	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
(2) Therapeutic Effect	N/A	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Adverse Events	Baseline/Pre-Treatment	The n^{th} Intervention	End of Treatment	1^{st} Follow-Up	2^{nd} Follow-Up	n^{th} Follow-Up
(1) X X X	N/A	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
(2) X X X	N/A	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
….	N/A	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3

While PROs are increasingly adopted in TCM trials for decision-making and policy guidance,[37] their standalone reliability for accurately capturing disease activity or severity remains debated.[39] To address this limitation, our co-evaluation scale integrates both PROs and clinician-assessed outcomes into a single instrument, enabling a more comprehensive and balanced appraisal of therapeutic effects.

QoL assessment incorporates well-established instruments such as the MOS 36-Item Short-Form Health Survey (SF-36), EuroQol-5D (EQ-5D), and/or the WHO Quality of Life Questionnaire (WHOQOL), consistent with the patient-centered emphasis of pragmatic trial conventions, where changes in symptom and functional status constitute key outcomes.[40]

Treatment adherence monitoring constitutes an essential third component. Despite initial randomization, protocol deviations (eg, nonadherence, cross-over, or dropout, etc.) may introduce confounding. As treatment effect estimates that ignore adherence patterns can misinform real-world therapeutic decisions,[41] systematic tracking of compliance is mandated throughout the TCM trial period to ensure the interpretability of results.

Step 5: Cost-Utility Analysis Based on QALYs and Markov Decision-Analytic Model

In recent years, pharmacoeconomic studies have increasingly assessed the efficacy, safety, and affordability of Chinese herbal medicine to inform evidence-based decisions regarding essential medicine lists, national reimbursement policies, and drug price negotiations.[42] However, acupuncture remains underrepresented, with limited studies yielding inconsistent conclusions regarding its cost-effectiveness.[43]

To ensure policy relevance, TRIPLE-TCM incorporates comprehensive health-economic assessments. Quality-adjusted life years (QALYs) serve as the primary outcome measure to assess both clinical effectiveness and cost-effectiveness. For long-term projections, a Markov decision-analytic model will be constructed using trial-derived direct costs and QALYs to estimate incremental cost-effectiveness ratios. These data will inform clinical guideline development, optimize treatment strategies, and provide policymakers with robust evidence for resource allocation within the TCM system.[42–44]

Key Insights and Conceptual Contributions

The evaluation of TCM interventions demands a nuanced approach that reconciles the inherent tension between its individualized clinical practice and the standardized methodologies of evidence-based research. Through a critical assessment of the pragmatic RCT framework proposed by Hu et al and comparative analysis with explanatory RCT principles, we demonstrate why the traditional "explanatory-pragmatic" dichotomy—when applied in isolation—fails to capture the complexity of TCM intervention evaluation. While explanatory RCTs provide rigorous efficacy data under controlled conditions, their artificial settings often compromise external validity, failing to reflect real-world TCM applications. Conversely, pragmatic RCTs, though more ecologically valid, struggle with confounding factors such as placebo effects and lack of blinding, particularly in therapies like acupuncture. We endorse Hu et al's emphasis on incorporating patient preferences into trials and further argue that, in TCM research, such preferences should not be treated merely as confounders to eliminate, but rather strategically integrated and managed.

These insights constitute the central conceptual contribution of this commentary—introducing the TRIPLE-TCM framework, a trans-paradigm model integrating explanatory RCTs, pragmatic RCTs, and PRPP to simultaneously assess efficacy and effectiveness while accommodating TCM's personalized diagnostics. TRIPLE-TCM embodies not only a theoretical advance but also a systematic operational scheme composed of multiple interrelated modules, including pattern-guided recruitment, preference-embedded randomization, semi-standardized interventions, and clinician-patient co-assessment.

This hybrid framework balances scientific rigor with clinical relevance across multiple levels:

- At the "Diagnostic" level, the "disease-pattern model" standardizes TCM diagnoses across participants, establishing a homogeneous basis for comparison.
- At the "Treatment" level, the semi-standardized protocol of "core formula + individualized modifications" accommodates both consistency in the intervention and necessary clinical flexibility within the same trial.
- At the "Assessment" level, the "clinician-patient co-assessment model" integrates biomedical indicators, PROs, and TCM-specific measures, offering a multidimensional and standardized tool for evaluating the effects and safety of complex TCM interventions.

Summary and Research Outlook

This study introduces the TRIPLE-TCM framework, a novel trial design that ensures the internal validity of therapeutic effects through randomized cohorts; it also analyzes, through non-randomized preference cohorts, the potential moderating effect of patient preference on treatment outcomes, thus enhancing both external validity and recruitment feasibility. Nonetheless, the framework remains in its early conceptual stage.

For future work, we propose the following steps:

First, the "TCM Therapeutic Effect Clinician-Patient Co-Evaluation Scale" embedded in the TRIPLE-TCM framework should undergo rigorous psychometric validation to ensure reliability and validity, providing a robust tool for subsequent empirical studies.

Second, once the scale demonstrates satisfactory psychometric properties, pilot feasibility studies should be initiated to evaluate the framework's real-world implementation. Initial trials may focus on diseases with well-defined TCM syndrome patterns and established therapeutic advantages. For instance, our team's prior meta-analyses and clinical trials on acupuncture and CCPP for conditions like primary insomnia[45,46] and depressive disorders[47] suggest significant therapeutic potential, albeit the need for improved evidence quality. These conditions are therefore well-suited for validating the TRIPLE-TCM framework.

Finally, the framework's applicability in cross-cultural contexts, especially in non-Asian regions, must be assessed. These settings may present specific challenges, including limited TCM awareness, a scarcity of qualified practitioners, low cultural acceptance of diagnostic methods such as tongue and pulse examination, and difficulties in designing and implementing sensory-matched placebo controls.

Through these systematic efforts, we hope TCM research can better align with global evidence standards while preserving its holistic principles, ultimately enhancing its credibility and integration into mainstream healthcare.

Abbreviations

CCPP(s), Commercial Chinese Polyherbal Preparation(s); EQ-5D, EuroQol-5D; FPG, Fasting Plasma Glucose; GMP, Good Manufacturing Practice; HbA1C, Hemoglobin A1C; PPG, Postprandial Plasma Glucose; PPT(s), Patient-Preference Trial(s); PSQI, Pittsburgh Sleep Quality Index; PROs, Patient-Reported Outcomes; PRPP, Partially Randomised Patient Preference; QoL, Quality of Life; QALYs, Quality-Adjusted Life Years; RCT(s), Randomized Controlled Trial(s); SF-36, The MOS 36-Item Short-Form Health Survey; STRICTA, STandards for Reporting Interventions in Clinical Trials of Acupuncture; SUI, Stress Urinary Incontinence; TCM, Traditional Chinese Medicine; TRIPLE-TCM, **T**rans-paradigm **R**andomized-**I**ndividualized-**P**reference-**L**inked **E**fficacy/**E**ffectiveness **E**valuation for TCM; WHOQOL, The WHO Quality of Life Questionnaire.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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