

Applying the Zelen design to real-world studies in traditional Chinese medicine: feasibility, ethical considerations, and methodological challenges

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Received: April 20, 2026; Revised: May 18, 2026; Accepted: June 3, 2026

ABSTRACT

Introduction In traditional Chinese medicine (TCM) clinical research, patients often have strong preferences for TCM therapies. In addition, non-pharmacological interventions such as acupuncture and tuina make effective blinding of patients and practitioners difficult, which may introduce Hawthorne effects and resentful demoralization. Conventional randomized controlled trials also face challenges, including poor recruitment, high dropout rates, and increased bias risk, which limit research efficiency and evidence quality. The Zelen design provides a promising methodological solution to these issues. **Methods** This study presents a methodological analysis of the Zelen design for TCM real-world studies, with three focal contributions: (I) in-depth feasibility analysis of the Zelen design tailored to the complexities of TCM interventions; (II) a simulated TCM trial including a worked example of complier average causal effect (CACE) analysis, with discussion of its idealized assumptions and the need for sensitivity analyses; and (III) an in depth examination of ethical safeguards and statistical methods for managing contamination. Key considerations reviewed include trial registration, ethical requirements, sample size calculation, blinding, appropriate applications, and TCM-specific outcome measures. **Results** This analysis identifies key barriers to broader implementation of the Zelen design for evaluating TCM efficacy evaluation, including ethical and regulatory uncertainty surrounding the randomization-before-consent process, a lack of dedicated methodological guidelines and statistical tools, and the inherent complexity of TCM interventions, which heightens contamination risk and complicates compliance definition, while also assessing the overall value of design. Despite these challenges, the Zelen design demonstrates clear advantages in improving patient recruitment and treatment adherence while preserving the benefits of randomization. **Conclusion** The Zelen design offers a balanced pathway that integrates scientific rigor with clinical practicality, and further refinement of design strategies tailored to TCM characteristics is warranted. Future efforts should prioritize methodological innovation and standardization to improve the overall quality of real-world studies in TCM.

KEYWORDS

Zelen design, real-world study, clinical study, traditional Chinese medicine, methodology, pragmatic clinical trial

CITE THIS ARTICLE

Wen YQ, Liu K, Zhang Y, et al. Applying the Zelen design to real-world studies in traditional Chinese medicine: feasibility, ethical considerations, and methodological challenges. Evidence-Based Chinese Medicine and Technology Assessment, 2026, 2: 9570037. <https://doi.org/10.26599/eCMTA.2026.9570037>

1. Introduction

Real-world studies (RWSs) have become an increasingly important focus in traditional Chinese medicine (TCM),¹ where they serve as a valuable complement to conventional clinical research paradigms.²⁻⁴ The Zelen design can be applied to pragmatic clinical trials (PCTs) conducted within the broader framework of RWSs.⁵⁻⁷ In TCM clinical trials, patients often resist randomization because of strong preferences for TCM therapies, leading to recruitment difficulties and reduced treatment adherence.⁸ Compared with traditional randomized controlled trials (RCTs),⁹ the Zelen design may help mitigate these challenges by improving recruitment rates, reducing preference-related bias, and facilitating participant enrollment.¹⁰

The Zelen design, proposed by the American statistician Marvin Zelen,¹¹ is also known as the randomized consent design or pre-randomized design. Its core feature is that eligible participants are first randomly assigned to different groups, after which informed consent is sought selectively according to the allocation result. This design can address problems such as high refusal

rates and poor adherence caused by patients' treatment preferences, although ethical concerns should also be carefully considered.¹² In addition, it helps avoid disappointment bias and Hawthorne effects, which can arise when patients are informed of their treatment allocation in advance. Depending on how informed consent is obtained, the Zelen design can be divided into two main types.¹³ The first is the single-consent design, in which informed consent is sought only from patients assigned to the intervention group; this type is suitable for comparing a new therapy with a standard therapy. The second is the double-consent design, in which patients in all groups are asked for consent regarding their assigned treatment; this type is appropriate for evaluating two standard therapies against each other. In addition, researchers have proposed several variants of the Zelen design for different study settings, such as the Zelen design nested within an observational study^{14,15} and the McNulty-Zelen design.¹⁶ These variants have further enriched the methodological landscape and have already been used in clinical practice.

Currently, the applications of the Zelen design in TCM remains at an early exploratory stage, with methodological introduction and clinical attempts advancing in parallel. Two systematic reviews have explored the principles, key implementation elements, and value of the Zelen design in RWSs, offering methodological guidance for subsequent TCM research.¹⁷ Zeng et al.¹⁷ presented its basic framework at academic conferences, raising awareness of the Zelen design in TCM clinical research. Sun et al.¹⁸ used the Zelen design

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to validate the efficacy of Guige Lingxian decoction combined with through-moxibustion at cervical Jiaji points (EX-B2) for cervical radiculopathy. Two studies by Liu¹⁹ and Xiang²⁰ respectively applied this design to efficacy observation and mechanistic studies of acupuncture for perennial allergic rhinitis, offering a novel design approach for acupuncture clinical research. In recent years, multiple TCM trials using the Zelen design have been registered in the Chinese Clinical Trial Registry. These trials cover herbal medicine, acupuncture, tuina, external therapies, and traditional exercises. Most adopt the single-consent design and are small-sample, single-center studies. Overall, the published literature remains limited, involves few disease areas, and consists largely of methodological introductions or small-scale validations. A standardized implementation framework has not yet been established. Nevertheless, interest in applying the Zelen design in TCM is growing. In this context, analyzing the methodological feasibility and applicability of the Zelen design for TCM efficacy evaluation has practical value for improving the clinical research design system in TCM.

Given these considerations, this study explores the potential application of the Zelen design in RWSs and aims to offer clinical researchers a new methodological perspective. Although previous reviews have introduced the Zelen design,^{4,7} the present work offers a distinct and deeper contribution by systematically analyzing the feasibility and methodological considerations of the Zelen design specifically for TCM, providing a simulated TCM trial with a detailed complier average causal effect (CACE) calculation while critically discussing its idealized assumptions, and examining key implementation challenges, including ethical guidance and contamination, in greater depth than previously available.

2. Methods

This study employed a two-phase methodological approach to evaluate the feasibility of applying the Zelen design in TCM real-world studies. Phase 1 comprised a systematic methodological analysis of the Zelen design tailored to TCM interventions. Phase 2 involved the design and analysis of a simulated TCM trial to demonstrate operationalization of the Zelen design in a TCM context.

2.1. Phase 1: a systematic methodological analysis

2.1.1. Clinical trial registration and ethical considerations

All interventional trials must be registered on a public platform, with the study design disclosed before recruitment begins.²¹ When registering a Zelen design, particular care is needed to ensure transparency and accuracy. Because this design uses a randomization-before-consent process, the protocol should be explicitly labeled as a Zelen design or pre-randomized design in the public registry, accompanied by detailed descriptions of the randomization method and any blinding procedures. In the informed consent section, simply selecting “yes” is insufficient; the specific steps for obtaining consent must be described. Although no independent registration guidelines currently exist specifically for this design, the standard requirements for clinical trial registration remain applicable.

Ethically, the main controversy surrounding the Zelen design centers on the single-consent approach, in which control-group patients are enrolled without prior knowledge or consent. Traditional RCTs, in accordance with the declaration of Helsinki, require full informed consent from all participants before randomization. When a placebo control is used, additional attention must be paid to the risk of ineffective treatment and the provision of effective rescue measures. The ethical issues associated with the Zelen design are more complex,²² as the control group receives standard care without being informed, a situation described as uninformed participation. However, this design is not entirely infeasible. The U.S. Revised Common Rule permits institutional review boards to waive informed consent under conditions of low risk, legal permissibility, and practicability.²³ Similarly, Ethical Review Measures for Ethical Review of Life Science and Medical Research Involving

Human Being allows exemptions from informed consent requirements upon ethics committee approval.²⁴

2.1.2. Sample size calculation

The Zelen design explicitly adopts the intention-to-treat (ITT) principle as the basis for statistical analysis, and sample size calculation must be performed within this framework. Because all randomized participants, regardless of whether they provide consent or receive the assigned intervention, must be included in the final analysis, researchers need to account for the expected post-randomization consent or refusal rate during the design phase. Accordingly, the initial sample size should be inflated to ensure that the final sample available for analysis retains adequate statistical power. Currently, sample size estimation for PCT designs is based on methods used in traditional RCTs. Within this framework, the Zelen design further incorporates the expected refusal rate as a key parameter and adjusts the sample size accordingly to determine the final required sample size.¹

Assume a two-group Zelen design in which participants in both arms provide informed consent and the aim is to compare the effectiveness of two standard therapies, Drug A and Drug B. The sample size calculation proceeds as follows.

(I) Calculate the effective sample size ($N_{\text{per group}}$).

Based on the expected effect size, the specified significance level, α , and the desired statistical power, $1 - \beta$, the total number of effective analytic individuals theoretically required is calculated as follows:²⁵

$$N_{\text{per group}} = \frac{p_1(1-p_1) + p_2(1-p_2)}{(p_1 - p_2)^2} (Z_{\frac{\alpha}{2}} + Z_{\beta})^2 \quad \text{Eq. (1)}$$

where assuming response rates of 70% in Group A (p_1) and 60% in Group B (p_2) with a two-sided significance level of $\alpha = 0.05$ and 80% power, the required sample size is 353 patients per group, giving a total of $N_{\text{basic}}=706$ patients to be enrolled.

For a continuous outcome, the same inflation method described below applies; the only change is that the basic sample size formula should be replaced with the standard formula for comparing two means.

(II) Estimate the anticipated consent rate (P_{accept})

Following Jia et al.¹ and Zelen,¹³ θ_0 is defined as the probability of no patient preference, while θ_a and θ_b are defined as the probabilities of preferring treatment A or treatment B, respectively, with $\theta_0 + \theta_a + \theta_b = 1$. For a double-consent design, the probability that a patient accepts the assigned treatment is:

$$P_{\text{accept}} = \theta_0 + \frac{1}{2}(\theta_a + \theta_b) = \frac{1}{2}(1 + \theta_0) \quad \text{Eq. (2)}$$

where assuming $\theta_a = 20\%$, $\theta_b = 10\%$, and $\theta_0 = 70\%$, the consent rate P is 85%.

For a single-consent design, in which consent is sought only from the intervention group, the acceptance rate for the intervention group equals θ_0 , $P_{\text{accept}} = \theta_0$.

(III) Inflate the sample size (M)¹

$$M = \frac{N_{\text{basic}}}{(2P_{\text{accept}} - 1)^2} \quad \text{Eq. (3)}$$

where based on Eqs. (1)-(3), the final inflated sample size is calculated to be 1441.

In the single-consent design, informed consent is obtained only from patients in Group A. The final sample size can be calculated using the formula:¹

$$M = \frac{N_{\text{basic}}}{P_{\text{accept}}^2} \quad \text{Eq. (4)}$$

Where based on Eqs. (1), (2), and (4), the final inflated sample size is calculated to be 872.

2.1.3. Statistical analysis

• CACE analysis

In the Zelen design, the primary analysis follows the ITT principle, which estimates the effect of offering the treatment. A per-protocol (PP) analysis may be conducted as a secondary supportive analysis; nevertheless, it is susceptible to selection bias arising from post-randomization non-adherence. Because non-adherence attenuates the ITT estimate, the CACE approach is further used to estimate the causal effect of treatment receipt among those who actually comply, using randomization as an instrumental variable. The CACE is identified under two core assumptions:²⁶ exclusion restriction (randomization affects the outcome only through actual treatment receipt) and monotonicity (no patient assigned to the control group receives the experimental treatment). Both assumptions are untestable but can be assessed through sensitivity analyses. Estimation methods include the Wald estimator, two-stage least squares (2SLS), two-stage residual inclusion,^{27,28} and G-estimation.²⁹

• Missing data handling

In the Zelen design, missing data arise primarily from post-randomization informed refusal, loss to follow-up, and incomplete routine medical records for the control group. Missing data can be addressed using multiple imputation or inverse probability of missingness weighting. For CACE analysis, the outcome variable should first be multiply imputed, with the imputation model including randomization assignment, actual treatment receipt, and baseline covariates. 2SLS estimation is then applied to each imputed dataset, and the results are pooled using Rubin's rules.³⁰ Regardless of the method used, the missing data rate by arm and the assumed missingness mechanism should be clearly reported, and sensitivity analyses should be conducted to assess the robustness of findings to deviations from the missing data assumptions.

2.1.4. Methodological adaptations for TCM research

• Blinding strategies

TCM clinical interventions encompass physical therapies, herbal medicine, and mind-body or dietary approaches. Acupuncture and tuina are difficult to blind because of their operational nature. Herbal decoctions also pose challenges for credible placebo control because of their distinctive formulation characteristics. The Zelen design offers an alternative path: instead of attempting to blind the intervention itself, it evaluates the intervention's overall effectiveness in real-world clinical settings.^{31,32} This reflects the total effect of the complete intervention, including cognitive and interaction effects, under conditions in which both practitioners and patients are aware of the assigned treatment.

In implementing the Zelen design, patient unblinding is accepted. However, measurement bias due to knowledge of group assignment must be carefully controlled. The following standardized procedures are recommended.

(I) Prioritize objective indicators. Whenever feasible, primary outcomes should be objective, such as laboratory tests, imaging findings, electronic health record-derived endpoints, or registry data. Subjective outcomes should be complemented by objective validation.

(II) Ensure blinded outcome assessment. Data collectors, outcome assessors, and statisticians must remain blind to group allocation. In the single-consent Zelen design, control patients are naturally blinded. Outcome assessors, however, must not access treatment assignment information; this can be achieved by separating the teams responsible for intervention delivery and outcome measurement.

(III) Establish third-party endpoint adjudication. An independent endpoint adjudication committee, comprising clinicians and methodologists not involved in patient management, should evaluate all outcomes using predefined criteria, with members blinded to group allocation. Disagreements should be resolved by consensus or by a prespecified voting procedure.

(IV) Standardize training and data collection. All data collectors must receive uniform training on case report form completion, scale administration, and objective measurement protocols. Regular quality checks, including inter-rater reliability assessments, should be conducted.

• Defining the research question for TCM

The single-consent Zelen design is suitable for comparisons between an experimental therapy and a standard therapy, whereas the double-consent design is appropriate for head-to-head comparisons of two standard treatments. In TCM research, the design applies to three scenarios: TCM versus standard therapy, direct comparison of two TCM regimens, or TCM as an add-on or alternative strategy. Many TCM trials compare integrative medicine with standard Western therapy.³³ However, such designs cannot isolate TCM's independent contribution, nor can they determine whether pure TCM is non-inferior or superior to standard Western therapy under equivalent conditions. The National Administration of Traditional Chinese Medicine calls for higher-level evidence generated within the TCM theoretical framework to support the development and optimization of standard TCM protocols.³⁴ The Zelen design, while preserving randomization, enables a fair and feasible comparison between TCM and standard therapies.

• Selection of outcome measures

A valid outcome measurement system is key to the validity of a study.³⁵ The Zelen design does not allow blinding of patients or practitioners, which creates a risk of measurement bias. Therefore, a robust outcome measurement system with blinded assessment mechanisms is necessary. Priority should be given to objective indicators, such as laboratory tests or imaging findings. For patient-reported outcomes, researchers should use standardized scales with proven validity and reliability and ensure that data collectors and analysts remain blinded.

A TCM-specific evaluation system should be established, including an independent blinded endpoint adjudication committee. TCM syndrome scores provide one example. Following the TCM Diagnosis and Treatment Guideline for Chronic Heart Failure issued by the China Association of Chinese Medicine,³⁶ core heart failure patterns should be quantified using standard grades. Based on a unified four-examination information collection form, independent blinded assessments should be conducted before and after treatment. Initial discrepancies should be resolved through consensus meetings to obtain final syndrome scores. This approach provides valid evidence that reflects both scientific rigor and the unique characteristics of TCM.

2.2. Phase 2: a simulated TCM trial

To illustrate the application of the above methodological principles, a simulated single-consent pragmatic clinical trial was designed as a worked example. This simulated trial was not intended as an independent study but served to demonstrate how the Zelen design can be operationalized in a TCM context.

(I) Study design: In this simulated trial, we compared Chinese herbal medicine with a standard Western regimen for mild to moderate active ulcerative colitis of the damp-heat type in TCM. The herbal formula was not fixed; instead, a predefined algorithm allowed individualized adjustments based on changes in TCM patterns. All adjustments were documented in a treatment log.

(II) Participants and randomization: Eligible patients were randomized 1:1 to the herbal treatment group or the standard treatment group. Only the herbal treatment group provided informed consent; the standard treatment group was not informed of the trial assignment.

(III) Outcomes: The primary outcome was the clinical remission rate at 8 weeks, assessed by the modified Mayo score.³⁷ Secondary outcomes included a standardized TCM syndrome score, endoscopic mucosal healing rate, inflammatory biomarkers such as C-reactive protein, quality of life score, and safety indicators. Concomitant medication was recorded at each visit, and a binary variable, major co-intervention, defined as the use of any extra therapy for at least 7 consecutive days, was included for sensitivity analyses.

(IV) Assessments: performed at baseline, week 4, week 8, and week 12, the follow-up point.

(V) Statistical analysis: The primary analysis followed the ITT principle. CACE analysis was conducted using random assignment as an instrumental variable, primarily via 2SLS, adjusting for baseline disease activity, disease duration, baseline TCM syndrome score, and other key covariates. Sensitivity

analyses included: (i) inverse probability weighting within the herbal group to predict adherence probability; (ii) repeating CACE analysis after excluding patients with major co-interventions; and (iii) alternative models (G-estimation) to examine consistency under different statistical assumptions.

3. Results

3.1. Phase 1: methodological feasibility findings

Ethical and regulatory considerations are novel in TCM because of the randomization-before-consent process. While the U.S. Revised Common Rule and Ethical Review Measures for Ethical Review of Life Science and Medical Research Involving Human Being permit waiver of informed consent under specific conditions, application in TCM requires careful intervention-specific risk stratification. For acupuncture, large-scale prospective registry studies support low-risk classification; for oral herbal medicines, safety evidence is often incomplete, requiring strengthened monitoring plans. Given that some TCM interventions are not inherently low risk, including herbal medicines, which carry risks of hepatotoxicity or herb-drug interactions, and acupuncture, which is not devoid of risk, researchers and ethics committees are advised to use a structured checklist, as shown in Table 1, to evaluate the appropriateness of a Zelen design. A single-consent design may be adopted only when all criteria are satisfactorily met, and the ethical justification must be explicitly documented in the study protocol.

Lack of dedicated guidelines remains a challenge, as no standardized implementation framework or statistical tools specifically tailored to TCM under the Zelen design currently exist.

The inherent complexity of TCM interventions, such as herbal formulas and acupuncture, poses an additional challenge. These treatments are often modified during therapy, requiring protocols to specify core components,

permitted adjustments, and process indicators. This complexity increases contamination risk, as control-group patients may freely seek external TCM therapies, systematically diluting treatment effects.

Despite these barriers, the Zelen design demonstrated clear advantages: lower recruitment barriers, improved treatment adherence, and preserved randomization benefits. The comparison with RCTs and trials within cohorts (TwICs) (Table 2) highlighted the Zelen design suitability for standard therapy comparisons and unblinded or high-contamination settings, with high external validity.

3.2. Phase 2: simulated trial results

CACE analysis for the simulated data was performed using formula-based methods (Table 3).

Based on the simulated data in Table 3, the CACE was calculated as follows.

- (I) Estimate the ITT effect:
ITT = 68.0% – 62.0% = 6.0%
- (II) Estimate the proportion of compliers:
 P_1 (the compliance rate in the TCM group) = 70%; P_2 (the crossover rate in the standard treatment group) = 0%, because patients in this group were unaware of the TCM regimen and therefore none received TCM.
- (III) Calculate CACE:

$$CACE = \frac{ITT}{(P_1 - P_2)}$$

Eq. (5)

Among compliers, pure TCM therapy increased the clinical remission rate by 8.6% compared with standard Western therapy. This effect is larger than the ITT estimate of 6% because the ITT effect is diluted by the 30% of patients in the TCM group who refused treatment. Notably, the CACE estimate

Table 1 A checklist for ethical approval of single-consent Zelen designs in TCM research

Key consideration	Item No.	Specific questions for researchers and ethics committees
Necessity	1a	Can the research question be practicably answered using a conventional consent design?
	1b	Is the waiver of consent essential to avoid significant recruitment or selection bias?
Control group justification	2a	Does the control group receive the current standard treatment rather than placebo alone?
	2b	If sham acupuncture or placebo controls are used, is the same standard treatment provided to both the intervention and control groups?
Risk assessment	3a	Is the intervention qualified as low risk (e.g., acupuncture with established safety data, or herbal formula with prior hepatotoxicity surveillance)?
	3b	Has a risk justification been documented for the ethics committee?
Patient protection and emergency protocol	4a	Has an independent DSMB been established?
	4b	Does the DSMB have the authority to request unblinding?
	4c	Have predefined stopping rules been specified?
	4d	Has a 24-hour contact been provided for treating physicians to request emergency unblinding?
	4e	Have the procedures and documentation requirements for emergency unblinding been clearly defined?
	4f	For control patients, has a rescue plan been described?
	4g	If standard care fails, how will clinical management be conducted without unblinding?
	4h	Under what circumstances may the DSMB recommend unblinding?
Post-trial debriefing and objection handling	5a	After trial completion, is there a plan to inform control patients of their participation?
	5b	Have the method, timing, and content been specified?
	5c	If a control patient objects to having been enrolled without prior consent after debriefing, has a protocol been established to handle such objections?
	5d	Will the patient be allowed to withdraw their data from future secondary analyses?
	5e	Will the primary ITT analysis remain unchanged?
Transparency	6a	Is the use of the Zelen design and the waiver of informed consent clearly justified in the registered protocol?
	6b	Does the ethics committee have documented experience in reviewing Zelen designs or waiver-of-consent protocols?

Notes: DSMB: data safety monitoring board; ITT: intention-to-treat analysis; No.: number; TCM: traditional Chinese medicine.

Table 2 Differences among Zelen design, traditional RCTs, and TwiCs

Feature	Zelen design	Traditional RCT	TwiCs
Core process	Randomization before consent	Consent before randomization	Broad consent from cohort; intervention-group consent after randomization
Participant source	Directly from the target population	Directly from the target population	From an existing prospective cohort
Ethics	Controversial, as some participants are unaware	Clear and respects autonomy	Multistage consent, with low controversy
Sample size	Adjusts for non-adherence, much larger than in an RCT	Based on the ITT effect	Complex, adjusts for cohort eligibility
Statistical analysis	ITT, CACE, and sensitivity analyses	ITT	CACE
Bias control	Avoids disappointment bias in controls	Risk of disappointment bias and high dropout	Controls are aware of the study but blinded to intervention details
Recruitment efficiency	High and fast	Low, often limited by refusal	Moderately high, depending on the cohort
Research goal	Real-world effect of offering treatment	Biological efficacy	Effectiveness of offering treatment in a near-real-world setting
Best suited for	Standard therapy comparisons and unblinded or high-contamination settings	Confirmatory trials	Real-world evidence, chronic diseases, and large cohort platforms
External validity	High	Low	Moderate to high

Notes: CACE: complier average causal effect; ITT: intention-to-treat; RCT: randomized controlled trial; TwiCs: trials within Cohorts.

Table 3 Simulated trial data: compliance and outcome rates by group

Group	Sample size	Compliers (received assigned intervention), <i>n</i> (%)	Clinical remission rate (%)
TCM group (A)	550	385 (70%)	68.0
Standard treatment group (B)	550	550 (100%)	62.0

Notes: TCM: traditional Chinese medicine.

applies only to the complier population and cannot be directly generalized to all patients. Furthermore, this estimate relies on the exclusion restriction and monotonicity assumptions. Sensitivity analyses, such as G-estimation, are recommended to assess its robustness.

4. Discussion

4.1. Summary of key findings

This paper systematically introduces the Zelen design into the context of real-world studies in TCM. The main contribution is the provision of a comprehensive methodological framework that addresses feasibility, ethical safeguards, and statistical challenges specific to TCM interventions. Through this framework, the paper demonstrates that the Zelen design fits the real-world context of TCM. By carefully defining the research context, adhering to ethical standards, optimizing outcome selection, and applying rigorous statistical methods, this design can effectively evaluate the real-world effectiveness of TCM interventions and generate evidence that traditional RCTs often cannot provide. The simulated trial further illustrates that among compliers, pure TCM therapy increased the clinical remission rate by 8.6% compared with standard Western therapy, which is larger than the ITT estimate of 6% because the ITT effect is diluted by non-adherence.

4.2. Advantages of the Zelen design over traditional RCTs in TCM

Traditional RCTs face specific limitations when applied to TCM research. In clinical trials, ideal randomization assumes that all participants strictly adhere to the assigned protocol and complete follow-up, thereby ensuring comparability and unbiased effect estimation. In practice, however, patient populations often have clear treatment preferences. Such patients tend to have strong inclinations toward specific interventions and may refuse randomization.³⁸ For example, patients seeking TCM care often have inherent preferences for TCM therapies or turn to TCM after experiencing poor out-

comes with conventional medicine. This preference creates dual challenges during randomization: reduced adherence due to refusal and ethical concerns about overriding patient wishes.³⁹ Moreover, patient preference for TCM limits the external validity of RCTs, as enrolled participants often represent only a small subgroup willing to accept randomization, making findings difficult to generalize to real-world populations.

The Zelen design improves patient acceptance on two levels. First, it directly avoids patient resistance to being randomized to a non-preferred treatment. In traditional RCTs, patients often refuse participation because they fear being assigned to the control group. By waiving informed consent in the single-consent design or delaying disclosure for control patients, the Zelen design removes the need for patients to decide under uncertainty, thereby substantially increasing recruitment efficiency. Second, the effectiveness of TCM interventions depends heavily on patients' long-term active cooperation, such as adherence to herbal decoctions, sustained practice of traditional exercises, or repeated acupuncture sessions. Even when the Zelen design successfully enrolls patients, ITT results may be diluted if patients discontinue treatment because of cognitive bias, discomfort, or lack of trust. For example, although high-level evidence supports Tai Chi for fall prevention in older adults,⁴⁰ adherence rates in community practice may remain low because participants find the movements difficult to sustain.

Beyond patient-related advantages, the applicability of the Zelen design also depends on the research question and disease context. The Zelen design has clear boundaries. It is unsuitable for explanatory studies that require strict bias control, such as placebo-controlled mechanistic studies, safety or dose-finding trials, or research on rare diseases. More specifically, the Zelen design is more suitable for chronic diseases and stable interventions than for acute diseases, rare diseases, or high-risk interventions. It is recommended that future methodological guidelines explicitly define eligible and ineligible scenarios.

4.3. Challenges of implementing the Zelen design in TCM research

In summary, while the Zelen design fits the real-world context of TCM, its

successful application demands rigorous ethical planning, methodological expertise, and careful handling of treatment complexity and patient behavior. The Zelen design offers clear advantages for TCM research, including lower recruitment barriers and better adherence. However, real-world implementation faces three main challenges.

First, ethical and regulatory uncertainty exists. The randomize-before-consent approach is novel in TCM. Investigators must consult ethics boards early, design appropriate consent procedures, and guarantee intervention safety.

Second, methodological development has not kept pace with research needs. Dedicated guidelines and statistical tools for applying the Zelen design in TCM research remain lacking. Researchers need skills to handle patient preference, crossover, and non-adherence, as well as to build outcome measures that accommodate pattern differentiation.

Third, TCM interventions are inherently complex. Herbal formulas and acupuncture are frequently modified during treatment, requiring protocols to specify core components, permitted adjustments, and process indicators. This complexity also heightens the risk of contamination. Control-group patients, unaware of their trial participation, may freely seek TCM therapies outside the study. Such co-intervention systematically dilutes the observed treatment effect, biases results toward the null, and may mask a truly effective intervention. To measure contamination, trial protocols must prospectively collect co-intervention data for all randomized participants through standardized therapy logs for consented patients and, where feasible, queries of claims databases, electronic health records, or patient-reported outcome diaries.

4.4. Methodological considerations for CACE analysis in TCM Zelen trials

The CACE approach, using randomization as an instrumental variable, is a key analytical tool for Zelen designs. However, its application in TCM trials raises several unique issues that warrant systematic discussion.

4.4.1. Exclusion restriction and its plausibility in TCM contexts

The exclusion restriction assumes that randomization affects the outcome only through actual receipt of the assigned treatment. In TCM trials, this assumption may be challenged by non-specific effects. For example, patients in the intervention group who are aware of receiving TCM may experience enhanced placebo or expectation effects, whereas control patients who remain unaware are not subject to such effects. Even if a control patient inadvertently learns of the trial, this could influence health-related behaviors or outcome reporting without actually receiving TCM. These pathways violate the exclusion restriction. This assumption is untestable but can be assessed through sensitivity analyses.

4.4.2. Monotonicity and contamination

Monotonicity requires that no control group patient receives experimental treatment. In the single-consent Zelen design, control patients are not informed and thus are unlikely to actively seek TCM, making monotonicity highly plausible. However, contamination may still occur if control patients obtain TCM through other channels. This would violate monotonicity, attenuate the ITT effect, and bias the CACE estimate. To detect contamination, trial protocols should prospectively collect co-intervention data for all randomized participants. For consented patients, standardized therapy logs can be used; where feasible, queries of claims databases, electronic health records, or patient-reported outcome diaries are also valuable. When contamination is present, standard CACE estimators are biased; alternative methods should be considered. The instrumental variable framework can be extended for statistical adjustment beyond standard CACE analysis. When co-intervention use is recorded as a binary or ordinal variable, methods such as principal stratification or multilevel instrumental variable models can separate the effect of the assigned treatment from that of self-sought therapies.

4.4.3. Choice of CACE estimators for TCM outcomes

Several estimation approaches exist for CACE, including the Wald estima-

tor, 2SLS, two-stage residual inclusion (2SRI), and G-estimation with structural nested models. The choice depends on outcome type and whether covariate adjustment is needed. For binary outcomes, the Wald estimator using sample proportions is simple but cannot adjust for covariates; 2SRI is preferable when covariate adjustment is needed because 2SLS with a binary outcome may produce inconsistent estimates. For continuous outcomes, 2SLS is appropriate. G-estimation offers greater flexibility for time-varying compliance but requires larger sample sizes. We recommend that future TCM methodological guidelines provide a decision tree for selecting the appropriate CACE estimator based on outcome type and study design.

4.5. Limitations of the simulated trial and the present work

The example presented above is intentionally simplified to illustrate the CACE calculation transparently. In actual TCM trials, however, conditions are considerably more complex. Compliance is seldom constant at 70%; rather, it varies over time and can be influenced by multiple factors, including changes in patients' symptoms, tolerability of the herbal decoction, and treatment modifications made by the practitioner. Missing data are practically unavoidable. Moreover, the fundamental TCM principle of pattern differentiation and treatment entails that the herbal formula is not a fixed prescription but is adjusted within a predefined range for each patient. Although this flexibility reflects good clinical practice, it complicates the identification of compliers. Accordingly, the simplified example is best viewed as a pedagogical starting point. For an actual trial, a more comprehensive simulation study is needed. Sensitivity analyses can then be used to systematically examine how the CACE estimate responds under these varied and more realistic conditions. Such preparatory work contributes to producing more robust estimates that better capture the complexities of a real-world TCM trial.

In addition, there are some limitations in this methodological analysis. First, the proposed framework is primarily theoretical and based on simulated data, lacking empirical validation in completed TCM trials. Second, China's ethical regulations do not explicitly grant a general waiver of informed consent for prospective interventional studies such as the Zelen design, creating legal ambiguity that requires more detailed review by ethics committees. Third, key TCM-specific challenges, including contamination, time-varying compliance, pattern-driven modifications, and multi-component interventions, are not fully resolved by the current analytical framework. Although this paper provides a preliminary exploration of these issues, more systematic methods for statistical analysis are needed in the future. Finally, the claimed advantages of the Zelen design over traditional RCTs and TwiCs are based on conceptual comparisons rather than direct empirical evidence. Future studies should validate this approach through real-world TCM trials and develop tailored sensitivity analyses.

5. Conclusion

The Zelen design offers a methodological pathway for TCM clinical research that balances scientific rigor with clinical practicality. By carefully defining the research context, adhering to ethical standards, optimizing outcome selection, and applying rigorous statistical methods, this design can effectively evaluate the real-world effectiveness of TCM interventions and generate evidence that traditional RCTs often cannot provide. This article provides a preliminary framework for applying the Zelen design in TCM. Future work should focus on refining design strategies tailored to TCM characteristics, establishing standardized implementation protocols, and advancing methodological innovations to strengthen the scientific value of the Zelen design, thereby supporting the development and improvement of the TCM clinical evidence system.

Funding

This work was supported by the Backup Leader Support Program of Beijing University of Chinese Medicine (grant no.: 90010960920033); the Double First-Class Construction Support Program, Key Discipline of Traditional

Chinese Medicine Evidence-Based Medicine of Beijing University of Chinese Medicine, Evidence-Based Medicine in Traditional Chinese Medicine (grant no.: 90010951310169); the Beijing Municipal Science and Technology Rising Star Program Cross-Disciplinary Project (grant no.: 20240484546); and the National Natural Science Foundation of China (grant no.: 82374298).

Data Availability

Additional data related to this paper may be obtained from the corresponding author upon reasonable request.

Author Contribution Statement

Ya-qian Wen: Data curation, methodology, formal analysis, and writing – original draft. **Kai Liu:** Data curation, methodology, and validation. **Ying Zhang:** Data curation, investigation, validation, and writing – original draft. **Xiao-han Zhang:** Methodology, writing – review & editing, and validation. **Ting-xiu Liu:** Formal analysis, validation, and writing – review and editing. **Tae-Hun Kim:** Methodology and writing – review & editing. **Ze-yang Shi:** Investigation and writing – review and editing. **Yi-ke Song:** Writing – review and editing. **Zhao-lan Liu:** Conceptualization, funding acquisition, supervision, project administration, and writing – review and editing.

Use of AI Statement

None.

Declaration of Competing Interest

The authors have no competing interests to declare that are relevant to the content of this article.

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