Appropriately selecting and concisely reporting the outcome measures of randomized controlled trials of traditional Chinese medicine

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Abstract: Evaluating outcome is the primary means by which different medical modalities can be compared with regard to effectiveness. In traditional Chinese medicine (TCM), this focus has prompted practitioners to search for outcome measures that can objectively verify the effectiveness of TCM interventions, especially in the context of randomized controlled trials (RCTs). Commonly used indexes for outcome assessment in RCTs of TCM can be categorized into two types: TCM-specific outcomes such as tongue and pulse characteristics, and Western medicine (WM)-specific outcomes such as blood test and X-ray examination results. Some studies include both types of indicators. During the trial design, it is necessary to consider the rationales of selecting outcome assessments, the purpose and study approach, balance between objective and subjective indexes, standardization of outcome assessment, and standardized outcome indexes. We recommend to report the outcome assessment in RCTs of TCM in the following format: 1) identifying the primary and secondary outcomes based on the purpose and hypothesis of the trial; 2) defining the primary and secondary outcomes clearly; 3) presenting the rationale of selection; 4) presenting the method with aims to standardize the assessment process; 5) presenting the method to improve the reliability of assessment; and 6) stating the termination criteria in the trial.

Keywords: traditional Chinese medicine; Chinese herbal drugs; clinical research; randomized controlled trials; evidence-based medicine; outcome measure

恰当选取并清晰报告中医药临床研究的测量指标

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摘要：恰当选取方面是中医药临床研究的必要手段。在中医药临床研究中，常见测量指标包括中医药类指标如舌象、脉象及中医证候描述等；西医类指标如现代检验学方面的指标等。研究中测量指标的选择

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1 Introduction

Evaluating clinical outcomes is the primary means by which different interventions can be compared with regard to efficacy. In traditional Chinese medicine (TCM), this focus has prompted practitioners to search for outcome measures that can adequately assess the efficacy of TCM interventions, especially in the context of randomized controlled trials (RCTs).

Having the appropriate outcome measure is critical for an RCT because this is the yardstick against which success is measured and by which conclusions are reached with regard to the efficacy of the intervention under scrutiny. Using the wrong outcome measure could distort the results of a clinical trial and have serious repercussions when making recommendations for clinical practice. If the outcome measure fails to capture the intended changes in health or is not sensitive enough to determine clinically meaningful differences, important information about the efficacy of an intervention could be missed \[1\]. Therefore, careful, thorough consideration in choosing appropriate outcome measures is a prerequisite for obtaining valid, clinically useful evidence from RCTs.

With regard to the selection of outcome measures, the Draft Consolidated Standards for Reporting Trials of Traditional Chinese Medicine (CONSORT for TCM), published in Chinese and English in 2007 \[2,3\], suggested that one or two endpoint outcomes (e.g., mortality and survival) for which the definitions are the same in both TCM and conventional medicine should be selected as the primary outcomes. Further, the Draft suggested that any methods used to enhance the quality of measurement (e.g., multiple observation and training of assessors), when applicable, should be described in the report. Unfortunately, in trials involving TCM, finding a primary outcome measure with the same definition in both TCM and conventional medicine is a rarely realized, ideal scenario; other, more practical guidelines are needed.

This paper will address the appropriate selection and concise reporting of TCM outcomes by: 1) analyzing the current status of outcome types in RCTs of TCM; 2) presenting the rationale for selection of appropriate outcome measures, and 3) proposing a reporting structure of outcome measures in RCTs of TCM. The corresponding items in the Draft CONSORT for TCM checklist that require revision to incorporate these changes will also be discussed. Although reporting adverse events and harms may be considered an outcome measure in RCTs, this topic will be discussed separately in a future paper.

2 Types of outcomes

Commonly used outcomes in RCTs of TCM can be categorized into TCM-specific outcomes such as tongue and pulse characteristics, and Western medicine (WM)-specific outcomes such as blood tests and radiographic examination results. Some studies include both types of outcome measures.

2.1 TCM-specific outcomes Symptoms and signs are critical elements for TCM practitioners because they are used to determine the pattern or syndrome of disease involving its cause, nature and location, and to assess the patient's overall health. Furthermore, these symptoms and signs are always used as outcomes to assess the efficacy of a particular therapy. Normally, symptoms and signs are assessed by TCM practitioners through inspection, auscultation, olfaction, interrogation, pulse-feeling and palpation. As in the WM system, symptoms are taken as exterior indicators of interior disease. However, in TCM, symptoms are considered to be sufficient for diagnosis if the practitioner can "read" and interpret the subtleties correctly. Thus, the nature of these symptoms and signs are described, mostly in subjective terms. Although in current TCM practice and research some examination results from laboratory tests are used to determine the pattern or syndrome, this is not generally considered mainstream TCM practice.

For example, Four-Gentlemen (Sijunzi)
Decoction is a classic formula to tonify the qi and strengthen the spleen. The indication for the usage of the formula is spleen and stomach qi deficiency with the symptoms of pallid complexion, low and soft voice, reduced appetite, loose stools, weakness in the limb, pale tongue body, and thin pulse. When the efficacy is evaluated, these symptoms are always used as outcome assessment indexes. While in theory these symptoms, as subjective indicators, are affected by the individual practitioner, in practice, the effectiveness of TCM suggests that the subjective variation may affect the results reported in RCTs.

2.2 WM-specific outcomes In WM, diagnosis and decisions about treatment are made based not only on the symptoms and signs but also on the results from examination with modern medical equipment, such as blood tests, X-rays, and computed tomography (CT), etc. For instance, CT is a medical imaging method employing tomography to generate a three-dimensional of the inside of the human body from a large series of two-dimensional X-ray images taken around a single axis of rotation. It is the gold standard in the diagnosis of many different disease entities. Modern medical equipment, with its inherently objective nature, can help practitioners fine-tune both diagnosis and treatment.

3 Outcome selection rationale

Selecting the most appropriate outcomes in an RCT of TCM remains controversial. Most of the concerns about assessing the efficacy and effectiveness of TCM have focused on the selection of TCM-specific indicators to reflect the syndrome- or pattern-based results. Recently, in a review of 18 Cochrane Systematic Reviews on Chinese herbal medicine (CHM) dated on or before September 2006, we found that no definite conclusion or specific clinical recommendation could be derived based on those evidences. One reason for this conclusion was that inappropriate outcome measures were used to assess the efficacy of TCM interventions. In our opinion, the selection of outcomes in RCTs of TCM should be based on the nature of the trial, with a balance between objectiveness and subjectiveness, and standardization of the outcome measures.

4 Purpose and study approach

The purpose and/or hypothesis of an RCT of TCM determines the study model, which can be categorized as either the WM disease-oriented model, the TCM syndrome-oriented model, or the integrated model. The selection of outcomes should reflect the purpose of the trial, and be consistent with the study model. For the WM disease-oriented model, the purpose of this study design is to evaluate whether the tested TCM can benefit the targeted disease. The outcomes selected should therefore be disease-oriented. The symptoms, signs and medical examination results could be used as primary and/or secondary outcome measures. In this situation, a TCM-specific outcome is not appropriate as the primary outcome, but it could still be reported as a secondary outcome. For the TCM syndrome-oriented model, the purpose of such design is to assess whether TCM intervention could improve the syndrome, therefore syndrome-oriented indexes could be selected as either the primary or secondary outcomes. For the integrated model, the ideal outcome is one or two endpoints for which the definitions are the same in both TCM and WM. Ideally, both TCM-oriented and WM-oriented outcomes should be included, and either could be defined as the primary and/or secondary outcomes.

5 Balance between objective and subjective outcomes

The results of an RCT based on objective outcomes are often considered more reliable than those based only on subjective outcomes. The most common objective outcomes include defined endpoints such as death or incidence of specific events, or surrogate response variables such as blood pressure or tumor size, which can be accurately evaluated with designated instruments. Common subjective outcomes include pain levels, function, overall health, and how patients feel during or at the end of treatment. It is often not practical to rely solely on objective outcomes in RCT with TCM given the nature of conditions being evaluated. Even in WM, subjective outcomes are commonly used as primary outcomes because they can give a more comprehensive picture of the effectiveness and safety of interventions, especially for functional or psychological disorders. Subjective indicators are valuable, and TCM researchers should be encouraged to quantify the subjective indicators.
they use, thereby improving the credibility and enabling independent verification of the results of RCTs of TCM.

6 Standardization of outcome assessment

When the outcomes are selected, the assessment process should be standardized in order to minimize variation. Although it is not difficult to standardize outcomes based on modern medical examination such as blood tests, X-rays, or CT, it is more challenging to do so with subjective detection of the symptoms and signs of participants in TCM practice. Careful training of those who conduct RCTs and measure outcomes can improve data collection.

7 Standardized outcome measures

When standardized outcome measures are available for the outcomes selected by the researchers, they should be selected as the basis for defining the primary and secondary outcomes of RCTs of TCM. Unfortunately, no widely recognized standards related to TCM outcome assessment exist. Both Guidelines of Clinical Research on Chinese New Herbal Medicines (1) and Diagnostic and Therapeutic Effect Evaluation Criteria of Diseases and Syndromes in Traditional Chinese Medicine (2) were issued by Ministry of Health of the People's Republic of China and State Administration of Traditional Chinese Medicine in 1993 and 1994, respectively. The common diseases/syndromes covered in these texts include those pertinent to the fields of internal medicine, surgery, gynecology, pediatrics, ophthalmology, otolaryngology, colorectal surgery, dermatology, and traumatology and orthopedics. However, these should be considered an experience-based, rather than an evidence-based, approach to outcome measures in TCM. There is an urgency to develop widely accepted standards for outcome assessment in TCM practice and research.

8 Recommendations

Sharing the same goals as the original CONSORT, CONSORT for TCM aims to improve the reporting quality of RCTs with TCM. In order to produce an accurate report of RCTs of TCM, outcome assessment must be clearly and precisely presented. We recommend that outcome assessment in RCTs of TCM be reported in the following format.

I. Identifying the primary and secondary outcomes based on the purpose and hypothesis of the trial

II. Defining the primary and secondary outcomes clearly

III. Presenting the rationale of selection

IV. Presenting the method with aims to standardize the assessment process

V. Presenting the method to improve the reliability of assessment

VI. Stating the termination criteria in the trial

9 Recommendations for corresponding revisions

I. For the item of "outcomes and estimation" in the results section, the working group suggests that the results for each group be described according to the sequence of primary and secondary outcome measurements. Summarized in Table 1 below.

II. For the item of "interpretation" in the discussion section, the working group recommends that the CONSORT statement also be used in CONSORT for TCM, with the addition of discussion of the effectiveness of TCM for the disease, the syndrome, or both. Summarized in Table 1 below.

10 Conclusion

Outcomes are directly used to measure the efficacy, effectiveness and safety of an intervention in RCTs; careful selection of outcomes is the foundation to work out consolidated evidence to make clinical recommendation. Meanwhile, only total transparency in structured format reporting can make results comprehensible to international readers and foster further investigation. We hope that the development of CONSORT for TCM can specifically enhance the reporting quality of RCTs with TCM and, at the same time, generally improve the methodological quality.
Table 1  Recommendations for corresponding revisions

<table>
<thead>
<tr>
<th>Paper section and topic</th>
<th>Item</th>
<th>Description</th>
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<tbody>
<tr>
<td>Method</td>
<td>6</td>
<td>Clearly identify and define primary and secondary outcomes based on the study purpose and hypothesis, state their underlying selection rationales, specify the assessment method with aims (e.g. by whom, how and when) and standard (e.g. any available gold standard), and when applicable, any means used to enhance the quality of measurement (e.g. multiple observation and training of assessors). Set principle of study termination and assessment on safety issue.</td>
</tr>
<tr>
<td>Results</td>
<td>17</td>
<td>Describe the results for each group with the sequence of measurement of primary and secondary outcomes, and the estimated effect size and its precision (e.g. 95% confidence interval)</td>
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<tr>
<td>Outcomes and estimation</td>
<td></td>
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<tr>
<td>Discussion</td>
<td>20</td>
<td>Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analysis and outcomes. Discussions on the effectiveness and safety of TCM intervention based on the purpose and study approach are needed.</td>
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<tr>
<td>Interpretation</td>
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REFERENCES


5 Cheng CW, Bian ZX, Li YP, et al. CONSORT serial 1;


