EDITORIAL NOTES

Improving the quality of reporting of randomized controlled trial (RCT) of Chinese medicine has been embraced by the research community. A group of Chinese medicine researchers, practitioners, journal editors and epidemiologists have worked together since 2005 and published the Draft Consolidated Standards for Reporting Trials of Traditional Chinese Medicine (CONSORT for TCM) in 2007. The Draft revised the CONSORT items, adding some specific items to reflect the characteristics of TCM in clinical research. In order to enhance the reporting quality of RCT of TCM, the key elements about the trial involve the rationale of trial design, Chinese medicine intervention, outcome assessment and side effect. From Volume 6, Issue 7 of 2008, a series of papers will be published in Journal of Chinese Integrative Medicine to discuss how to enhance the reporting quality of these items, thus hope to consolidate the final version of CONSORT for TCM. And also, we hope that these papers can solicit more feedback from experts in different specialties to facilitate the discussion about the Draft, thus can consolidate the final version of CONSORT for TCM.

Precise reporting of traditional Chinese medicine interventions in randomized controlled trials

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Abstract: Traditional Chinese medicine (TCM) intervention should be concisely and precisely reported in randomized controlled trials (RCTs). Based on State Food and Drug Administration’s categories, we recommend reporting the interventions as follows; (1) Single Chinese herbal medicine-based/formula-based/extraction-based intervention includes 1) Name, dosage format and registration; 2) The composition and quality of intervention; 3) Pharmaceutical processing and quality control; 4) Stability of final product and quality control; 5) Function and safety description; 6) Dosage and treatment course; 7) Control group. (2) Active compound-based TCM drug intervention includes 1) Name of active compound(s); 2) Original source of active compound(s); 3) The brief process obtaining active compound(s); 4) Percentage of active compound(s) in final product; 5) Added materials and its quality and quantity control. Besides, the detailed information of intervention can be published as an online supplement in web site.

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

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清晰报告中医药随机对照试验中的干预措施

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摘要：中医药临床试验报告中，干预措施必须清晰报告，以便读者全面了解研究中所采用的干预措施的性质及其质量控制方法。按照中国食品药品监督管理局有关中药新药的分类方法，结合中药质量的控制要求，可以按照处方中药类及中药有效成分类进行干预措施的报告。对于单味中药/中药复方/中药有效成分提取物类中药，具体报告的方法应包括：①名称、剂型和注册号；②药物组成及其质量控制；③制剂程序及其质量控制；④终止产品的稳定性和质量控制；⑤药效和安全性的描述；⑥疗程和剂量；⑦对照组。对于中药活性成分类中药，具体报告的方法应包括：①活性成分名称；②活性成分的中药来源；③提取活性成分的方法；④活性成分在药物中的分量比例；⑤药物中的附加物及其质量控制。此外，干预措施的详细报告，可以考虑在网络版以附件形式发表。

关键词：中医学；中药；临床研究；随机对照试验；循证医学


1 Introduction

The number of randomized controlled trials (RCTs) evaluating traditional Chinese medicine (TCM) is increasing rapidly. However, the quality of their reports is not optimal [1-2]. Inadequate description of methodology is perhaps the most serious pitfall compromising the quality of many published RCTs of TCM [4]. The development of the Consolidated Standards of Reporting Trials (CONSORT) in the mid-1990s (subsequently revised in 2001) [5-6] was an attempt to help authors report the scientific details of how they conducted their RCTs. Use of the CONSORT reporting guideline is associated with increased quality of reporting RCTs [7]. The CONSORT Group has published several extensions (www. consort-statement.org) including one for reporting trials using a single unprocessed herbal intervention [8]. While this extension is useful, it is of more limited value when reporting interventions of TCM. Most TCM interventions contain multiple herbal and non-herbal ingredients with unique processing methods and formulations.

The Draft Consolidated Standards for Reporting Trials of Traditional Chinese Medicine (CONSORT for TCM) was published in Chinese and English in 2007 [9,10] for soliciting feedback from researchers and practitioners of relevant clinical specialties. In this draft, reporting requirements for three categories of TCM drug interventions are specified in detail, on the basis of formula format. For an intervention based on a formula(s), it is required that (i) for each ingredient, its cultivation location, processing method, and quality control method to be provided; while (ii) for the formula, its administration route, treatment regimen and dosage must be provided. As for patented or proprietary TCM interventions, it is required that the manufacturer, approval number (lot number), production date, expiry date and crude constituent contents to be specified. For self-designated or modified interventions, such as a new formula derived from an ancient one, it is required that the rationale of formulation and modification, dosage form, production process, constituent proportion, and quality control surveillance to be provided. For control interventions, the rationale for selecting the specific control group design should be given.

Upon further consideration, it became apparent that these requirements were not adequate to fully convey the required information to readers of RCTs of TCM. Inadequate information about interventions may give rise to questions about their efficacy. For instance, it would be difficult for a researcher to follow the draft CONSORT for TCM in presenting the results of a clinical trial with a TCM intervention based on the active proportion extraction of a TCM formula. Therefore, this paper proposes a more precise way of reporting TCM drug
interventions. First, the paper proposes categorization of TCM drug interventions into four types. Second, within each type, the paper addresses the major factors affecting the quality of TCM drug interventions, and presents a precise framework for reporting RCTs using TCM drug interventions based on these main factors. Finally, the corresponding items on the draft CONSORT for TCM checklist that require revision are highlighted.

2 TCM drug intervention types

CONSORT's categories of TCM drug interventions should be consistent with the New Drug Registration Guidelines issued on 10 July 2007 by the State Food and Drug Administration of China [11]. According to these Guidelines, new drugs are now categorized into nine groups, summarized in Table 1 below.

<table>
<thead>
<tr>
<th>Category</th>
<th>TCM drug intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Active compounds and their pharmaceutical products, which are extracted from plants, animals or minerals, but not available in the domestic market</td>
</tr>
<tr>
<td>Category 2</td>
<td>Newly discovered Chinese materia medica (CMM) and their pharmaceutical products</td>
</tr>
<tr>
<td>Category 3</td>
<td>Replacements of old CMM</td>
</tr>
<tr>
<td>Category 4</td>
<td>New CMM and their pharmaceutical products</td>
</tr>
<tr>
<td>Category 5</td>
<td>Effective proportions of CMM and their pharmaceutical products, which are derived from plants, animals or minerals but are not available in the domestic market</td>
</tr>
<tr>
<td>Category 6</td>
<td>Formula-based pharmaceutical products of CMM or natural products, which are not available in the domestic market</td>
</tr>
<tr>
<td>Category 7</td>
<td>Pharmaceutical products that have an altered way of administering drugs available in the domestic market</td>
</tr>
<tr>
<td>Category 8</td>
<td>Pharmaceutical products that have an altered dosage form of CMM products available in the domestic market</td>
</tr>
<tr>
<td>Category 9</td>
<td>Generic drugs</td>
</tr>
</tbody>
</table>

3 Key characteristics of TCM drug interventions

3.1 Composition TCM drug interventions may comprise two parts: therapeutic components targeting the syndrome and/or disease, and added materials for maintaining the dosage form. The therapeutic materials are the fundamental elements determining the efficacy and safety of the TCM drug intervention. These materials could be a single CMM, a mixture of CMM in a recipe, an active compound of one CMM, or the effective extraction of a proportion from a single CMM or recipe. As for the CMM used in an intervention, it could be crude or prepared. The composition of the TCM drug intervention, and the selection of the crude or the prepared CMM, is normally based on TCM theories, pharmacological and pharmaceutical studies, and/or pilot clinical study results.

As regards the added materials, they are normally used to develop and fix the dosage form of the intervention. The quality of the added material itself and its percentage in the intervention affects the final quality of the pharmaceutical product, thereafter affecting the efficacy and/or safety via changing of the pharmacokinetic process to some degrees. The added materials, such as starch in granule, fructose in syrup, are always selected on the basis of the needs of the intervention.

3.2 Procedures for the processing of raw CMM

The CMMs used in a TCM drug intervention may be crude or processed. The objectives of processing crude CMMs could be simply physical (e. g. to make the plant parts of a more convenient size or shape) or chemical (e. g. to enhance its pharmaceutical properties). Processing procedures include cleaning, cutting, roasting and broiling. The roasting and broiling methods include stir-baking, scalding, calcining, carbonizing, steaming, boiling, stewing, blanching in boiling water, processing with wine, processing with
vapour or salt-water, stir-baking with ginger juice or honey, stir-baking with oil, frost-like powder, levigating and roasting. Because these procedures affect the function of raw CMMs, they must be standardized within any single RCT in order to maintain quality and consistency; and, equally importantly, they must be described accurately so that readers and other researchers can evaluate the work and either repeat or revise it as appropriate.

3.3 Pharmaceutical processing In an intervention, all CMMs, whether crude or processed, will undergo pharmaceutical processing so that they can be manipulated to the final intervention. The pharmaceutical process could be boiling, extraction by water or ethanol, etc. These procedures determine the nature of an intervention, and standardization is the only way to control the quality of the processes, thus keeping the quality and consistency of the intervention.

3.4 Quality control Quality control of TCM drug interventions involves a systematic procedure. The key steps involve: (1) the raw materials and added materials; (2) the processing procedure for raw CMMs; and (3) the pharmaceutical process of final products.

The quality of the crude herbs and inert materials is of paramount importance in TCM drug interventions. Elements affecting the quality of a crude herb include plant species, growth area, harvest season, part(s) used in the intervention, and possible contamination by pesticides, mycotoxins and heavy metals. General quality control methods for crude CMMs include description, identification, tests, determination of extractives, and chemical assays. For processed CMMs, in addition to the factors mentioned above, the processing method and its due course are relevant, especially when the processed CMM is to be used as the intervention in a single CMM-based, formula-based, and effective proportion-based intervention study. One challenge for quality control of the preparation process is that there are currently no widely recognized standards, although the Chinese Pharmacopoeia 2005 has set out common preparation processes in its appendix. The commonly used method is to select an active compound as a marker, and then to monitor its content throughout the processing of the TCM drug products.

With regard to quality control of the pharmaceutical process, it is necessary to standardize the procedure starting from crude CMMs or prepared CMMs through to the final product, regardless of whether the dosage form is pill, tablet, powder, granule, oral liquid, tea, syrup, capsule, etc. In order to control the quality of this process, it is recommended that the quality of TCM interventions be evaluated qualitatively and/or quantitatively on the basis of one or more selected biomarkers.

3.5 Quantity control Quantity control of TCM interventions involves as a minimum the amount of each CMM component or extraction in the intervention, the dosage of intervention administered to each patient in the trial, and basic concentration requirements of biomarkers during the quality control process and in the drug intervention.

Different from a single CMM-based TCM intervention, the efficacy and safety of a formula-based TCM drug intervention depends not only on its dosage, but also on that of each CMM in the formula. Changes in the amounts of any CMMs in the intervention could affect the clinical trial results even when the overall dosage of the entire intervention remains unchanged. The ratios of the components are crucial in the intervention that is based on the effective proportion extraction. Furthermore, the concentration of biomarkers selected for quality control of raw materials, the preparation process and the pharmaceutical process should be kept within a reasonable specific range. If the intervention is composed of active compound(s) only, then the concentration of these compound(s) in the intervention should be fixed.

3.6 Hypothetical action of the intervention in the trial In a randomized trial of TCM, the hypothesis usually concerns whether the selected intervention has the projected effect for the disease and/or syndrome. A single CMM or a formula normally results in more than one action. For example, ginseng not only nourishes the qi but also promotes the production of body fluid. Therefore, it is necessary to specify the kind(s) of effect(s) of the intervention that is (are) going to be tested in the trial and how these effects are going to be measured.

4 The need for precise reporting of interventions

When the efficacy and safety of an intervention is evaluated in an RCT, it is essential that all participants take the identical prescription in terms of quality and quantity during the whole treatment
course. Authors need to report this information in a complete, clear and transparent manner. Inadequate reporting of TCM interventions has been a major obstacle in the advancement TCM research for a long time. As mentioned before, the composition of the intervention, the processing procedures, the pharmaceutical process, the quality and quantity control of the intervention, and the hypothetical function of the intervention are the key factors in a TCM drug intervention; therefore it is crucial to monitor the factors/processes that convert the raw CMMs into dosage form, in order to ensure that the efficacy and safety results of the trial are actually derived from the intervention itself, not from variations in quality and/or quantity of the interventions. The factors/processes of the RCTs of TCM must be recorded and reported meticulously. Such information will help readers to properly understand the trial, to repeat it or to change it, as appropriate. Therefore, the readers require, and researchers in RCT of TCM have the obligation to provide, detailed information of TCM drug interventions, reported precisely and concisely.

5 Recommendations

Taking into consideration the types of TCM interventions and key factors relevant to a particular TCM drug intervention, we recommend that reporting of TCM interventions in RCT of TCM be described in the following format.

5.1 Single CMM-based/formula-based/extraction-based intervention

5.1.1 Name, dosage format and registration

Ⅰ. Name of intervention

Ⅱ. Dosage format (e.g. pill, tablet, capsule, decoction)

Ⅲ. Proprietary product name (i.e. brand name), if applicable

Ⅳ. Name of the manufacturer of the product, if applicable

Ⅴ. Registration number of product, if applicable

Ⅵ. Production data and expiry date, if applicable

5.1.2 The composition of intervention

Ⅰ. Common name of each CMM, together with the Latin binomial and family name

Ⅱ. Authentication method of each raw CMM (how it was done and by whom); if a voucher specimen was retained it is necessary to state where it is kept or deposited, and the reference number

Ⅲ. If the raw CMM came from a Good Agricultural Practice (GAP) farm, then the name and location of the GAP base should be given

Ⅳ. Quality control methods used for the raw CMM; whether any special screening tests, such as heavy metal screening, were undertaken

Ⅴ. Processing method and active biomarkers used in quality control for each crude CMM, if applicable

Ⅵ. Dosage of each CMM in the intervention and its proportion in whole formula

Ⅶ. Name of added materials in the intervention and method of controlling their quality, if applicable

Ⅷ. Percentage of added materials in the TCM intervention, if applicable

Ⅸ. The rationale of formula composition

5.1.3 Pharmaceutical processing

Ⅰ. The major pharmaceutical process used to convert the raw material to the final product, whether these processes are standardized and how, if applicable

Ⅱ. Biomarkers used for quality control of the pharmaceutical process, if applicable

Ⅲ. The quantitative or semi-quantitative requirements for the biomarkers in different steps of the process, if applicable

5.1.4 Stability and quality control of the final product

Ⅰ. Information of the stability test of the TCM drug intervention, if applicable

Ⅱ. Quality control methods and biomarkers used for the final product

Ⅲ. If Good Manufacturing Practice (GMP) standards was followed during the manufactory process, this should be mentioned

Ⅳ. Product’s chemical fingerprint and methods used (equipment and chemical reference standards with corresponding biomarkers) for evaluating the product stability, if applicable

5.1.5 Function and safety description

Ⅰ. Functions of TCM drug intervention

Ⅱ. Tested functions of the drug intervention in the trial

Ⅲ. Supporting data for hypothetical function(s), if applicable

Ⅳ. Safety data about the drug intervention (e.g. acute toxicity and chronic toxicity test data), if applicable

Ⅴ. Experimental pharmacological study data of the drug intervention, if applicable

5.1.6 Dosage and duration

Ⅰ. Dosage of the intervention in the trial

Ⅱ. Supporting evidence for dosage selection, if applicable
Ⅲ. Duration of the treatment course  
Ⅳ. Supporting evidence for the duration determination, if applicable  

5.1.7 Control group  
Ⅰ. Rationale for the selection of control used  
Ⅱ. Types of control group, e.g. drug, different types of TCM treatment such as acupuncture, massages, and placebo, etc.  
Ⅲ. The composition, dosage and duration of control intervention  

5.2 Active compound-based TCM drug intervention  
Although there are doubts as to whether interventions comprising only active compounds should be regarded as TCM drug interventions, they are still included in the TCM new drug registration system promulgated last year, and the Guidelines from the International Conference on Harmonization for Pharmaceutical Products should be followed. In light of this, the reporting method for this type of intervention could be different from those mentioned above. Basically, items 1, 4, 5, 6, 7 should be reported clearly as single CMM-based/formula-based/extraction-based intervention. In addition, the composition of intervention should be reported like this way:  
Ⅰ. Name of active compound(s)  
Ⅱ. Original source of active compound(s)  
Ⅲ. The brief process obtaining active compound(s)  
Ⅳ. Percentage of active compound(s) in final product  
Ⅴ. Added materials and its quality and quantity control  

6 Recommendations for corresponding revisions  
In addition to the above revisions with respect to the intervention, additional revisions concerning the title, abstract and introduction are also in order.  

6.1 Title and abstract  
Either the title, abstract, or both should state the name and brief description of the intervention (i.e. name of herbal formula, formula compositions and type of preparation for TCM intervention).  

6.2 Introduction  
As for the scientific background and explanation of rationale, authors should describe in complete and clear language: (1) TCM theory and scientific background (e.g. conventional medicine); (2) rationale of the choice of a TCM drug intervention (e.g. the origin of an herbal formula); (3) action of the individual herbal ingredients and combination formula(s) based on TCM theory; and (4) the active component(s) of individual herbal ingredients and combination formula(s) based on modern pharmacology.  

The requirement that a clinical trial report compiles so detailed information about the TCM drug intervention in a very limited length may invite lots of debate. The key is that the information is very important for the quality of reporting. With appearance of more and more web-based medical journals, an alternative is to publish the detailed information of intervention as a supplement of the article in the website of that journal, thus the readers can get, and also the authors can provide, all detailed information related with TCM drug intervention.  

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REFERENCES  
4 Bian ZH, Moher D, Dagenais S, et al. Improving the quality of randomized controlled trials in Chinese herbal medicine, part IV; applying a revised CONSORT checklist to measure reporting quality. Zhong Xi Yi Jie

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第三届全国中西医结合围手术期医学专题研讨会定于2008年10月在广州举行“第三届全国中西医结合围手术期医学专题研讨会”，会议主要围绕快速康复外科与围手术期中西医结合研究的进展进行交流。会议将邀请我国围手术期中西医结合研究领域的著名专家到会并进行专题讲座。会议结束后授予国家继续教育学分。欢迎踊跃投稿。截稿日期：2008年8月31日；来稿寄：广州市大德路111号广东省中医院科研部（邮政编码510120）；联系人：曹立新、周infra、老聬；电话：020-81887233-31225/31226；传真：020-81874903；E-mail：weishoushuxiqiangmu@126.com，luojing76@163.com，laoyr@yahoo.com.cn。

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